Supporting Information for

Total Synthesis of Gelsemoxonine

Jun Shimokawa, Takaaki Harada, Satoshi Yokoshima and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo

7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

fukuyama@mol.f.u-tokyo.ac.jp

General. All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware unless otherwise noted. Dehydrated diethyl ether, tetrahydrofuran, methylene chloride and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Dehydrated *N,N*-dimethylformamide and dimethylsulfoxide were purchased from Kanto Chemicals Co., Inc. and stored over activated MS4A. Dehydrated methanol, ethanol and acetonitrile were also purchased from Kanto Chemicals Co., Inc. and stored over activated MS3A. Lipase AK was purchased from Amano Enzyme Inc. and lipase CR (*Candida rugosa*) was purchased from Sigma-Aldrich. IBX was prepared according to the literature procedure.¹ All other reagents were commercially available and used without further purification. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60F₂₅₄. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40-100 μ m) purchased from Kanto Chemical Co., Inc. ¹H and ¹³C NMR were recorded on a JEOL LA-400 spectrometer. All ¹H NMR spectra are reported in δ units, parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are indicated in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All ¹³C NMR spectra are reported in ppm relative to the central line of the triplet for CDCl₃ at 77.0 ppm. Infrared spectra (IR) were recorded on a JASCO FT/IR-410 or FT/IR-4100 Fourier Transform Infrared Spectrophotometer, and are reported in wavenumbers (cm⁻¹). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-T100LP AccuTOF LC-plus either in positive electrospray ionization (ESI) method or in positive direct analysis in real time (DART) ionization method, using PEG as the internal standard. Optical rotations were measured on a JASCO DIP-1000 or P-2200 Digital Polarimeter at room temperature, using the sodium D line. Melting points, determined on a Yanaco Micro Melting Point Apparatus, are uncorrected.

¹ Frigerio, M.; Santagostino, M; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538

6-Hydroxy-2H-pyran-3(6H)-one (**6**)²

To a stirred solution of furfuryl alcohol (43.0 g, 438 mmol) in CH_2Cl_2 (875 mL) was cooled to 0 °C and added *m*CPBA (65%, 128 g, 482 mmol) portionwise to the solution. The reaction was allowed to slowly warm to room temperature and stirring was continued for 2.5 h. After the consumption of the starting material was observed by TLC analysis, the resulting slurry was cooled to 0 °C for 30 min. The solid *m*CPBA was filtered through Celite and the filter cake was rinsed with cold CH_2Cl_2 (0 °C, 300 mL) five times. The filtrate was evaporated under the reduced pressure, and the residue was suspended in cold CH_2Cl_2 (0 °C, 300 mL). After 10 min, the suspension was filtered through Celite and the filter cake was rinsed with cold CH_2Cl_2 (0 °C, 50 mL). After the same suspension-filtration cycle was repeated, the filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (diameter = 10 cm, height = 13 cm, *n*-hexane/EtOAc = 2/1 (1% AcOH) to 1/1 (1% AcOH)) to afford **6** (36.3 g, 318 mmol, 73%) as a light-yellow amorphous solid.

R_f = 0.34 (*n*-hexane/EtOAc = 1:1, UV, Ce-PMA); IR (neat, cm^{-1}) 3417, 1757, 1682, 1626, 1428, 1376, 1268; ^1H NMR (CDCl_3 , 400 MHz) δ 6.96 (dd, J = 10.0, 2.7 Hz, 1H), 6.17 (d, J = 10.6 Hz, 1H), 5.64 (m, 1H), 4.58 (d, J = 17.0 Hz, 1H), 4.14 (d, J = 17.0 Hz, 1H), 3.26 (d, J = 5.0 Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 195.2, 146.5, 127.6, 88.0, 66.5; HRMS (DART) calcd for $\text{C}_5\text{H}_7\text{O}_3$ ($[\text{M}+\text{H}]^+$) 115.0395, found 115.0394.

² Jones, R.; Krische, M. *Org. Lett.* **2009**, *11*, 1849-1851.

(S)-5-oxo-5,6-dihydro-2H-pyran-2-yl acetate (7)

To a stirred solution of 6-hydroxy-2H-pyran-3(6H)-one (**6**) (29.8 g, 261 mmol) in vinyl acetate (300 mL) was added lipase AK (30% on Celite, 29.8 g) at room temperature. The mixture was vigorously stirred for 3 h, before the slurry was filtered through a Celite pad and the filter cake was rinsed with CH₂Cl₂ (300 mL) three times. The combined filtrates were concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 5/1 to 4/1) to afford (S)-5-oxo-5,6-dihydro-2H-pyran-2-yl acetate (**7**) (32.0 g, 205 mmol, 78%, 74% ee) as a light-yellow oil. The enantiomeric excess was determined by HPLC analysis with a chiral HPLC column (DAICEL CHIRALCEL AD-H, 1.0% 2-propanol in *n*-hexane, 1.0 mL/min at 25 °C, 210 nm). The retention times corresponding to **7** and its enantiomer are 31.8 and 26.6 min, respectively. To a stirred solution of **7** thus obtained (31.1 g, 199 mmol) in *n*-hexane (498 mL) and *n*-BuOH (166 mL) at rt was added lipase CR (3.11 g). After stirring for 4 h at the same temperature, the slurry was filtered through a Celite pad and the filter cake was rinsed with CH₂Cl₂ (300 mL) four times. The combined filtrates were concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 5/1 to 4/1) to afford (S)-5-oxo-5,6-dihydro-2H-pyran-2-yl acetate (**7**) (20.3 g, 130 mmol, 65%, >99% ee) as a light-yellow amorphous solid. Further elution (*n*-hexane/EtOAc = 1/1) afforded **6** (6.77 g, 43.4 mmol, 30%).

R_f = 0.62 (*n*-hexane/EtOAc = 1:1, UV, Ce-PMA); $[\alpha]_D^{25} +177$ (c = 1.00, CHCl₃); IR (neat, cm⁻¹) 1752, 1706, 1697, 1431, 1371, 1269, 1220, 1172, 1108, 1006, 932; ¹H NMR (CDCl₃, 400 MHz) δ 6.93 (dd, J = 10.1, 3.7 Hz, 1H), 6.50 (d, J = 3.7 Hz, 1H), 6.28 (d, J = 10.6 Hz, 1H), 4.52 (d, J = 17.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 1H), 2.15 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 193.3, 169.4, 142.2, 128.7, 86.5, 67.3, 20.8; HRMS (DART) calcd for C₇H₉O₄ ([M+H]⁺) 157.0501, found 157.0498.

(1*S*,2*S*,6*R*)-diethyl 2-acetoxy-5-oxo-3-oxabicyclo[4.1.0]heptane-7,7-dicarboxylate (9**)**

To a stirred solution of **7** (14.3 g, 91.6 mmol) and diethyl bromomalonate (**8**) (15.6 mL, 91.6 mmol) in THF (300 mL) at 0 °C was added DBU (14.4 mL, 96.2 mmol) dropwise through the dropping funnel over a period of 12 min. After 1 h, the reaction mixture was quenched with saturated NH₄Cl aq. (100 mL) and partitioned between 50% EtOAc in *n*-hexane (200 mL) and H₂O (25 mL). The organic phase was collected and the aqueous phase was extracted with 50% EtOAc in *n*-hexane (100 mL) once. The combined organic extract was washed with brine (100 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 5/1 to 4/1) to afford **9** (22.4 g, 71.3 mmol, 78%) as a pale yellow oil. The enantiomeric excess was determined by HPLC analysis with a chiral HPLC column (DAICEL CHIRALCEL AD-H, 1.0% 2-propanol in *n*-hexane, 1.0 mL/min at 25 °C, 210 nm). The retention time corresponding to **9** and its enantiomer are 37.3 and 27.5 min, respectively.

R_f = 0.39 (*n*-hexane/acetone = 2:1, Ce-PMA); $[\alpha]_D^{23}$ -61.3 (c = 1.00, CHCl₃); IR (neat, cm⁻¹) 2985, 1733, 1370, 1321, 1246, 1218, 1016, 958; ¹H NMR (CDCl₃, 400 MHz) δ 6.46 (s, 1H), 4.31–4.19 (m, 4H), 4.11 (d, J = 17.9 Hz, 1H), 3.92 (d, J = 18.4 Hz, 1H), 2.64 (d, J = 8.3 Hz, 1H), 2.58 (d, J = 8.3 Hz, 1H), 2.16 (s, 3H), 1.31 (t, J = 6.9 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 197.7, 168.9, 167.0, 164.0, 86.5, 66.0, 62.9, 62.5, 40.0, 33.9, 30.1, 20.8, 13.9, 13.7; HRMS (ESI) calcd for C₁₄H₁₈NaO₈ ([M+Na]⁺) 337.0899, found 337.0905.

(1*S*,6*R*)-diethyl 5-oxo-3-oxabicyclo[4.1.0]heptane-7,7-dicarboxylate (10**)**

To a stirred solution of **9** (22.4 g, 71.3 mmol) and triethylsilane (34.2 mL, 214 mmol) in MeCN (180 mL) at 0 °C was added TMSOTf (25.8 mL, 143 mmol) dropwise through a dropping funnel over a period of 30 min. After stirring for 2.5 h at room temperature, the reaction mixture was quenched with saturated NaHCO₃ aq. (50 mL). The mixture was concentrated to half the initial amount by rotary evaporation and partitioned between EtOAc (100 mL) and H₂O (10 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (50 mL) three times. The combined organic extract was washed with H₂O (50 mL), brine (50 mL) and dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 6/1 to 2/1) to afford **10** (15.1 g, 58.9 mmol, 82%) as a yellow oil.

R_f = 0.63 (*n*-hexane/EtOAc = 1:1, Ce-PMA); $[\alpha]_D^{22}$ +11.4 (c = 1.00, CHCl₃); IR (neat, cm⁻¹) 2982, 1727, 1371, 1310, 1241, 1181, 1125, 1096; ¹H NMR (CDCl₃, 400 MHz) δ 4.31 (d, J = 12.4 Hz, 1H), 4.28-4.18 (m, 4H), 4.03 (d, J = 17.8, 1H), 3.89 (dd, J = 12.4, 1.6 Hz, 1H), 3.74 (d, J = 17.8 Hz, 1H), 2.58 (d, J = 8.2 Hz, 1H), 2.46 (d, J = 8.2 Hz, 1H), 1.29 (t, J = 7.3 Hz, 3H), 1.28 (t, J = 7.3 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 199.7, 167.9, 165.0, 72.6, 62.7, 62.1, 61.5, 39.2, 34.9, 28.3, 13.9, 13.7; HRMS (ESI) calcd for C₁₂H₁₆NaO₆ ([M+Na]⁺) 279.0845, found 279.0838.

((1*S*,5*S*,6*R*)-5-hydroxy-3-oxabicyclo[4.1.0]heptane-7,7-diyl)dimethanol (11**)**

To a stirred solution of **10** (9.03 g, 35.2 mmol) in THF (176 mL) at room temperature was added sodium borohydride (13.3 g, 352 mmol). After stirring at 60 °C for 6 h, methanol (17.6 mL, 435 mmol) was added dropwise through a syringe pump over a period of 1 h. After stirring for an additional 10 min at the same temperature, the reaction mixture was cooled to 0 °C and diluted with methanol (100 mL). The reaction was quenched with acetic acid (20 mL, 350 mmol) and the cloudy slurry was concentrated *in vacuo*. Addition of methanol (300 mL) and evaporation was repeated three times to remove trimethyl borate. The residue was diluted with 10% methanol in CH₂Cl₂ (500 mL), filtered through a pad of silica gel, washed with 10% methanol in CH₂Cl₂ (500 mL) four times and concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (CH₂Cl₂/MeOH = 25/1 to 9/1) to afford **11** (5.13 g, 29.5 mmol, 84%) as a clear viscous liquid.

R_f = 0.21 (CHCl₃/MeOH = 9:1, Ce-PMA); $[\alpha]_D^{24}$ +52.2 (c = 1.00, CHCl₃); IR (neat, cm⁻¹) 3375, 2954, 2876, 1652, 1462, 1437; ¹H NMR (CDCl₃, 400 MHz) δ 4.24–4.21 (m, 1H), 4.15 (d, J = 11.9 Hz, 1H), 4.09 (d, J = 11.5 Hz, 1H), 3.96 (d, J = 11.9 Hz, 1H), 3.80 (dd, J = 12.0, 4.6 Hz, 1H), 3.67 (d, J = 11.0 Hz, 1H), 3.53 (d, J = 12.4 Hz, 1H), 3.37–3.33 (m, 1H), 3.21 (d, J = 11.0 Hz, 1H), 1.45 (dd, J = 9.2, 9.2 Hz, 1H), 1.06 (dd, J = 9.2, 4.6 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 71.5, 68.5, 64.2, 63.8, 59.6, 32.9, 22.1, 19.3; HRMS (ESI) calcd for C₈H₁₄NaO₄ ([M+Na]⁺) 197.0790, found 197.0793.

((1*S*,5*S*,6*R*,7*R*)-5-hydroxy-7-(hydroxymethyl)-3-oxabicyclo[4.1.0]heptan-7-yl)methyl pivalate (S1)

To a stirred solution of **11** (5.00 g, 28.7 mmol), pyridine (8.1 mL, 100 mmol) and *N,N*-dimethylamino-4-pyridine (351 mg, 2.87 mmol) in CH_2Cl_2 (144 mL) at room temperature was added pivalic anhydride (9.6 mL, 47 mmol) and the reaction mixture was stirred at the same temperature for 15 h. The reaction mixture was quenched with saturated NaHCO_3 aq. (50 mL) and partitioned between EtOAc (150 mL) and H_2O (10 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (50 mL) twice. The combined organic extract was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/2) to afford **S1** (6.39 g, 24.7 mmol, 82%) as a pale yellow solid.

$R_f = 0.53$ (*n*-hexane/EtOAc = 1:1, Ce-PMA); $[\alpha]_D^{21} +40.0$ ($c = 1.22$, CHCl_3); IR (neat, cm^{-1}) 3360, 2961, 1726, 1481, 1461, 1398, 1365, 1285, 1161, 1033; ^1H NMR (CDCl_3 , 400 MHz) δ 4.39 (d, $J = 11.0$ Hz, 1H), 4.31 (m, 1H), 4.28 (d, $J = 11.4$ Hz, 1H), 4.00 (d, $J = 12.4$ Hz, 1H), 3.92 (d, $J = 12.0$ Hz, 1H), 3.79 (dd, $J = 12.4, 4.6$ Hz, 1H), 3.67 (d, $J = 12.4$ Hz, 1H), 3.66 (d, $J = 13.3$ Hz, 1H), 3.36 (dd, $J = 12.8, 4.1$ Hz, 1H), 1.59 (t, $J = 9.2$ Hz, 1H), 1.22 (s, 9H), 1.16 (dd, $J = 9.2, 4.6$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 178.8, 70.8, 69.2, 62.7, 62.4, 58.7, 38.8, 29.6, 27.1, 20.9, 18.8; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{22}\text{NaO}_5$ ($[\text{M}+\text{Na}]^+$) 281.1365, found 281.1365.

((1*S*,6*R*,7*S*)-7-formyl-5-oxo-3-oxabicyclo[4.1.0]heptan-7-yl)methyl pivalate (12**)**

To a stirred solution of **S1** (6.35 g, 24.6 mmol) in DMSO (123 mL) at room temperature was added IBX (10.3 g, 36.9 mmol) and warmed to 50 °C. After stirring for 1.5 h, another portion of IBX (10.3 g, 36.9 mmol) was added and stirred for an additional 3.5 h. The reaction mixture was partitioned between 50% EtOAc in *n*-hexane (150 mL) and H₂O (100 mL). The organic phase was collected and the aqueous phase was extracted with 50% EtOAc in *n*-hexane (70 mL) five times. The combined organic extract was washed with brine (70 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 3/1) to afford **12** (5.79 g, 22.8 mmol, 93%) as a white foam.

R_f = 0.38 (*n*-hexane/EtOAc = 1:1, Ce-PMA); $[\alpha]_D^{23}$ +25.9 (c = 1.00, CHCl₃); IR (neat, cm⁻¹) 2973, 2872, 1720, 1283, 1252, 1152; ¹H NMR (CDCl₃, 400 MHz) δ 9.71 (s, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.27 (d, J = 12.4 Hz, 1H), 4.09 (d, J = 18.3 Hz, 1H), 4.01 (d, J = 12.0 Hz, 1H), 3.96 (dd, J = 12.4, 1.4 Hz, 1H), 3.87 (d, J = 17.9 Hz, 1H), 2.40 (d, J = 8.2 Hz, 1H), 2.17 (dd, J = 7.8, 1.4 Hz, 1H), 1.19 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 201.2, 194.3, 178.1, 101.5, 72.4, 64.5, 62.0, 44.1, 33.5, 28.9, 27.0; HRMS (ESI) calcd for C₁₃H₁₈NaO₅ ([M+Na]⁺) 277.1052, found 277.1043.

((1*S*,6*R*,7*R*)-7-((*E*)-(1-methoxy-2-oxoindolin-3-ylidene)methyl)-5-oxo-3-oxabicyclo[4.1.0]heptan-7-yl)methyl pivalate (14**)**

To a stirred solution of *N*-methoxyindolin-2-one (**13**) (5.36 g, 32.9 mmol) and *i*-Pr₂NEt (5.7 mL, 33 mmol) in CH₂Cl₂ (60 mL) at $-78\text{ }^\circ\text{C}$ was added $n\text{-Bu}_2\text{BOTf}$ (1.0 M in CH₂Cl₂, 33 mL, 33 mmol) dropwise through a dropping funnel over a period of 30 min and stirred at the same temperature for an additional 75 min. A solution of the aldehyde **13** (5.56 g, 21.9 mmol) in CH₂Cl₂ (50 mL) was added dropwise through the dropping funnel over a period of 30 min and stirred at the same temperature for an additional 60 min. The reaction mixture was quenched with 1 M HCl aq. (20 mL) and extracted with EtOAc (150 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (20 mL) three times. The combined organic extract was washed with brine (50 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude aldol reaction adduct. The residue was dissolved in CH₂Cl₂ (110 mL) and MsCl (6.8 mL, 88 mmol) and TMEDA (21.9 mL, 146 mmol) was added at $-78\text{ }^\circ\text{C}$. After stirring for 2.5 h, the reaction mixture was quenched with saturated NH₄Cl aq. (30 mL) and partitioned between EtOAc (120 mL) and H₂O (10 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (30 mL) three times. The combined organic extract was washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/1) to afford **14** (7.67 g, 19.2 mmol, 88% for 2 steps) as a yellow foam.

R_f = 0.40 (toluene/acetone = 4:1, UV, Ce-PMA); $[\alpha]_D^{27} +19.2$ (c = 1.00, CHCl₃); IR (neat, cm⁻¹) 2974, 2871, 1724, 1615, 1460, 1320, 1281, 1146; ¹H NMR (CDCl₃, 400 MHz) δ 7.60 (d, J = 7.3 Hz, 1H), 7.33 (dd, J = 7.8, 7.8 Hz, 1H), 7.21 (s, 1H), 7.11 (dd, J = 7.8, 7.4 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 4.30 (s, 2H), 4.27 (d, J = 12.8 Hz, 1H), 4.04 (s, 3H), 3.95 (dd, J = 12.4, 1.8 Hz, 1H), 3.89 (d, J = 18.8 Hz, 1H), 3.72 (d, J = 18.3 Hz, 1H), 2.46 (d, J = 8.2 Hz, 1H), 2.15 (dd, J = 8.3, 1.8 Hz, 1H), 1.17 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 202.6, 178.0, 162.3, 139.8, 133.7, 130.1, 128.0, 124.2, 123.1, 116.9, 107.4, 72.0, 65.6, 63.8, 61.9, 38.9, 33.3, 27.0, 25.8; HRMS (ESI) calcd for C₂₂H₂₅NNaO₆ ([M+Na]⁺) 422.1580, found 422.1590.

((1*S*,3'*S*,5*S*)-1'-methoxy-2',9-dioxo-6-oxaspiro[bicyclo[3.2.2]non[2]ene-4,3'-indolin]-2-yl)methyl pivalate (17**)**

To a stirred solution of **14** (7.67 g, 19.2 mmol) in THF (100 mL) at $-78\text{ }^{\circ}\text{C}$ was added chlorotrimethylsilane (7.3 mL, 58 mmol). LHMDs (1.6 M solution in THF, 30 mL, 47 mmol) was added dropwise through a dropping funnel over a period of 1.5 h. After stirring for an additional 1 h, the reaction mixture was quenched with NH_4Cl aq. (50 mL) and partitioned between EtOAc (50 mL) and H_2O (15 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (50 mL) three times. The combined organic extract was washed with brine (50 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was dissolved in toluene (96 mL) and the mixture was heated at $70\text{ }^{\circ}\text{C}$ for 140 min. After cooling to the room temperature, acetic acid (5.5 mL, 96 mmol) and TBAF (1.0 M solution in THF, 19 mL, 19 mmol) was added to the mixture. The reaction was quenched with NH_4Cl aq. and partitioned between EtOAc (40 mL) and H_2O (10 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (40 mL). The combined organic extract was washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 3/1 to 2/1) to afford **17** (6.81 g, 17.0 mmol, 89% for 2 steps) as a pale yellow foam.

$R_f = 0.42$ (*n*-hexane/EtOAc = 1:1, UV, Ce-PMA); $[\alpha]_D^{25} -57.7$ ($c = 1.00$, CHCl_3); IR (neat, cm^{-1}) 2973, 1742, 1729, 1615, 1478, 1464, 1317, 1281, 1211, 1149; ^1H NMR (CDCl_3 , 400 MHz) δ 7.39 (d, $J = 7.8\text{ Hz}$, 1H), 7.36 (dd, $J = 7.6, 7.6\text{ Hz}$, 1H), 7.14 (dd, $J = 7.1, 7.1\text{ Hz}$, 1H), 7.04 (d, $J = 7.8\text{ Hz}$, 1H), 5.31 (s, 1H), 4.65 (d, $J = 12.8\text{ Hz}$, 1H), 4.57 (d, $J = 12.8\text{ Hz}$, 1H), 4.34 (d, $J = 9.6\text{ Hz}$, 1H), 4.15 (dd, $J = 9.6\text{ Hz}, 3.2\text{ Hz}$, 1H), 4.03 (s, 3H), 3.77 (s, 1H), 2.99 (d, $J = 18.8\text{ Hz}$, 1H), 2.83 (m, 1H), 2.73 (dd, $J = 18.8, 5.5\text{ Hz}$, 1H), 1.21 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 202.9, 177.9, 168.6, 144.4, 139.2, 129.4, 126.3, 126.2, 124.2, 123.5, 107.7, 81.4, 69.9, 67.7, 63.8, 57.3, 42.6, 38.8, 32.6, 27.1; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{25}\text{NNaO}_6$ ($[\text{M}+\text{Na}]^+$) 422.1580, found 422.1574.

(1*S*,3'*S*,5*S*)-2-(hydroxymethyl)-1'-methoxy-6-oxaspiro[bicyclo[3.2.2]non[2]ene-4,3'-indoline]-2',9-dione (S2)

To a stirred solution of **17** (6.81 g, 17.0 mmol) in MeOH (85 mL) was added NaH (50 % in mineral oil, 838 mg, 17.4 mmol) in three portions at 0 °C, and stirred at room temperature for 3 h. The reaction mixture was quenched with saturated NH₄Cl aq. (30 mL) and partitioned between CH₂Cl₂ (150 mL) and H₂O (10 mL). The organic phase was collected and the aqueous phase was extracted with CH₂Cl₂ (30 mL) five times. The combined organic extract was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Toluene (20 mL) was added to the residue and triturated at 0°C for 2.5 h and the precipitate was filtered through the Büchner funnel to afford **S2** (4.71 g, 14.9 mmol, 88%) as white crystals.

R_f = 0.55 (*n*-hexane/EtOAc = 1:1, UV, Ce-PMA); Mp 216.5-217.5 °C; $[\alpha]_D^{23}$ -75.3 (c = 1.00, CHCl₃); IR (neat, cm⁻¹) 3422, 2939, 2884, 1740, 1713, 1615, 1463, 1320, 1212, 1134; ¹H NMR (CDCl₃, 400 MHz) δ 7.37 (d, J = 7.6 Hz, 1H), 7.36 (dd, J = 7.3, 7.3 Hz, 1H), 7.12 (dd, J = 7.6, 7.6 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 5.25 (s, 1H), 4.35 (d, J = 9.6 Hz, 1H), 4.19 (s, 1H), 4.17 (dd, J = 10.1, 3.7 Hz, 1H), 4.02 (s, 3H), 3.76 (s, 1H), 2.98 (d, J = 18.8 Hz, 1H), 2.90 (m, 1H), 2.74 (dd, J = 19.2, 5.5 Hz, 1H), 2.09 (br, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 203.4, 169.4, 149.2, 139.2, 129.3, 126.7, 126.4, 123.5, 120.8, 107.7, 81.6, 70.3, 66.9, 63.8, 57.4, 42.9, 32.2; HRMS (ESI) calcd for C₁₇H₁₇NNaO₅ ([M+Na]⁺) 338.1004, found 338.0992.

(1*S*,3'*S*,5*S*)-1'-methoxy-2',9-dioxo-6-oxaspiro[bicyclo[3.2.2]non[2]ene-4,3'-indoline]-2-carbaldehyde (18**)**

To a stirred solution of **S2** (4.63 g, 14.7 mmol) and $\text{PhI}(\text{OAc})_2$ (10.4 g, 32.3 mmol) in CH_2Cl_2 (73 mL) at room temperature was added TEMPO (461 mg, 2.94 mmol). After stirring for 3 h, the reaction mixture was diluted with 50% EtOAc in *n*-hexane (100 mL) and saturated NaHCO_3 aq. (50 mL). The slurry was filtered through a pad of Celite and the filter cake was washed with 50% EtOAc in *n*-hexane (20 mL) seven times and the filtrate was partitioned between 50% EtOAc in *n*-hexane (30 mL) and H_2O (25 mL). The organic phase was collected and the aqueous phase was extracted with 50% EtOAc in *n*-hexane (50 mL) twice. The combined organic extract was washed with brine (50 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 3/1 to 2/1) to afford **18** (4.15 g, 13.2 mmol, 90%) as a pale yellow foam.

R_f = 0.41 (*n*-hexane/EtOAc = 1:1, UV, Ce-PMA); $[\alpha]_D^{23}$ -48.6 (c = 1.00, CHCl_3); IR (neat, cm^{-1}) 2925, 1742, 1688, 1645, 1614, 1464, 1320, 1213; ^1H NMR (CDCl_3 , 400 MHz) δ 9.46 (s, 1H), 7.44 (dd, 7.8, 7.8 Hz, 1H), 7.37 (d, J = 7.4 Hz, 1H), 7.16 (dd, J = 7.8, 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.25 (s, 1H), 4.22 (d, J = 10.1 Hz, 1H), 4.18 (d, J = 10.1 Hz, 1H), 4.06 (s, 3H), 3.89 (s, 1H), 3.76 (m, 1H), 2.86 (d, J = 19.2 Hz, 1H), 2.77 (dd, J = 19.2, 5.0 Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 202.3, 191.2, 167.1, 149.2, 146.1, 139.3, 130.0, 126.4, 124.8, 123.8, 108.1, 81.0, 69.8, 64.0, 58.3, 42.7, 26.1; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_5$ ($[\text{M}+\text{Na}]^+$) 336.0848, found 336.0845.

(1*S*,2*S*,3'*S*,5*S*)-1'-methoxy-2',9-dioxo-6-oxaspiro[bicyclo[3.2.2]nonane-4,3'-indoline]-2-carboxylic acid (22**)**

To a stirred solution of **21** (1.17 g, 3.15 mmol) and Pd(PPh₃)₄ (728 mg, 0.63 mmol) in MeCN (15 mL) was added pyrrolidine (520 μ L, 6.3 mmol) at 0 °C. After warming to room temperature and stirring for 3 h, the reaction mixture was quenched with 3% NaOH aq. (10 mL) and extracted with toluene (15 mL). The two phases were separated and the organic phase was extracted with 3% NaOH aq. (10 mL) five times. The combined aqueous phase was washed with *n*-hexane (10 mL) and the organic phase was discarded. The aqueous phase was acidified to pH = 1 with 3 M HCl aq. and extracted with CH₂Cl₂ (10 mL) five times. The combined organic extract was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford **22** (1.00 g, 3.02 mmol, 96%) as white crystals.

R_f = 0.27 (CHCl₃/MeOH = 9:1, UV, Ce-PMA); Mp 202.0-202.6 °C; [α]_D²⁵ -177 (*c* = 1.00, CHCl₃); IR (neat, cm⁻¹) 2940, 1737, 1617, 1463, 1119; ¹H NMR (CDCl₃, 400 MHz) δ 7.44 (d, *J* = 7.4 Hz, 1H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.14 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 4.20 (d, *J* = 10.5 Hz, 1H), 4.07 (dd, *J* = 10.6, 2.8 Hz, 1H), 4.01 (s, 3H), 3.76 (s, 1H), 3.27 (dd, *J* = 12.8, 4.6 Hz, 1H), 3.02 (d, *J* = 19.7 Hz, 1H), 2.97 (m, 1H), 2.58 (dd, *J* = 19.7, 5.5 Hz, 1H), 2.43 (dd, *J* = 15.1, 12.8 Hz, 1H), 2.05 (dd, *J* = 14.7, 4.6 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 203.4, 177.8, 170.2, 139.2, 129.1, 126.12, 126.08, 123.2, 107.8, 80.0, 69.9, 63.7, 51.8, 45.3, 37.6, 32.8, 31.0; HRMS (ESI) calcd for C₁₇H₁₇NNaO₆ ([M+Na]⁺) 332.1134, found 332.1121.

benzyl ((1*S*,2*S*,3'*S*,5*S*)-1'-methoxy-2',9-dioxo-6-oxaspiro[bicyclo[3.2.2]nonane-4,3'-indolin]-2-yl)carbamate (**23**)

To a stirred solution of **22** (994 mg, 3.00 mmol) in CH₂Cl₂ (15 mL) at 0 °C was added oxalyl chloride (1.0 mL, 12 mmol). After stirring at room temperature for 1 h, solvent was removed by rotary evaporation to give the crude carboxylic acid chloride as a white foam. The residue was dissolved in toluene (15 mL) and NaN₃ (780 mg, 12.0 mmol) in H₂O (15 mL) was added to the mixture at 0 °C. After 10 min, the reaction mixture was partitioned between EtOAc (20 mL) and H₂O (10 mL). The aqueous phase was extracted with EtOAc (20 mL) twice. The combined organic extract was washed with brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to afford the crude acyl azide. The crude mixture was dissolved in toluene (15 mL) and benzyl alcohol (930 μL, 9.0 mmol) was added. The mixture was heated at 80 °C for 30 min and the reaction mixture was partitioned between EtOAc (20 mL) and H₂O (15 mL). The aqueous phase was extracted with EtOAc (20 mL) once and the combined organic extract was washed with brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to afford the crude Cbz amine. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/0 to 2/1) to afford **23** (1.08 g, 2.47 mmol, 82%) as a pale yellow foam.

*R*_f = 0.41 (*n*-hexane/EtOAc = 1:1, UV, Ce-PMA); [α]_D²⁰ −12.1 (*c* = 1.00, CHCl₃); IR (neat, cm^{−1}) 3336, 2939, 2359, 1736, 1706, 1617, 1523, 1230; ¹H NMR (CDCl₃, 400 MHz) δ 7.44 (d, *J* = 7.3 Hz, 1H), 7.40–7.27 (m, 6H), 7.14 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.54 (m, 1H), 4.36 (d, *J* = 10.5 Hz, 1H), 4.13 (dd, *J* = 10.5, 3.2 Hz, 1H), 3.99 (s, 3H), 3.77 (s, 1H), 2.99 (d, *J* = 19.7 Hz, 1H), 2.88 (m, 1H), 2.57 (dd, *J* = 15.6, 6.4 Hz, 1H), 2.46 (dd, *J* = 15.6, 5.5 Hz, 1H), 1.91 (dd, *J* = 15.6, 4.1 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 204.8, 171.7, 155.8, 138.5, 136.4, 129.0, 128.4, 128.1, 128.0, 124.5, 123.9, 107.7, 82.5, 67.3, 66.7, 64.0, 53.1, 51.7, 36.2, 34.4, 34.0; HRMS (ESI) calcd for C₂₄H₂₄NNaO₆ ([M+Na]⁺) 459.1532, found 459.1531.

benzyl ((1*S*,2*S*,3'*S*,5*S*,*E*)-8-((dimethylamino)methylene)-1'-methoxy-2',9-dioxo-6-oxaspiro[bi-cyclo[3.2.2]nonane-4,3'-indolin]-2-yl)carbamate (**25**)

To a stirred solution of **23** (1.05 g, 2.41 mmol) in toluene (12 mL) was added *t*-butoxy bis(dimethylamino)methane (**24**) (2.48 mL, 12.0 mmol) and heated to 70 °C. After 2 h, the reaction mixture was quenched with saturated NH₄Cl aq. (10 mL) and partitioned between EtOAc (20 mL) and water (5 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (15 mL) twice. The combined organic extract was washed with brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH₂Cl₂/MeOH = 1/0 to 50/1) to afford **25** (1.15 g, 2.34 mmol, 97%) as a pale yellow foam.

R_f = 0.31 (EtOAc, UV, Ce-PMA); $[\alpha]_D^{21}$ -134 (c = 1.00, CHCl₃); IR (neat, cm⁻¹) 3325, 2938, 1712, 1663, 1567; ¹H NMR (CDCl₃, 400 MHz) δ 7.70 (s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.40–7.27 (m, 6H), 7.10 (dd, J = 7.3, 7.3 Hz, 1H), 6.97 (d, J = 10.1 Hz, 1H), 5.23 (d, J = 11.9 Hz, 1H), 4.89 (d, J = 12.4 Hz, 1H), 4.44 (m, 1H), 4.34 (d, J = 9.6 Hz, 1H), 4.08 (dd, J = 9.6, 2.8 Hz, 1H), 4.03 (s, 3H), 3.86 (s, 1H), 3.75 (m, 1H), 2.85 (s, 6H), 2.68 (dd, J = 15.1, 6.0 Hz, 1H), 1.81 (d, J = 13.8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 191.1, 172.2, 155.7, 149.6, 138.5, 136.8, 130.5, 128.5, 128.4, 128.0, 123.6, 123.5, 107.4, 99.5, 84.3, 68.0, 66.2, 64.1, 53.2, 50.8, 35.7, 34.8; HRMS (ESI) calcd for C₂₇H₂₉N₃NaO₆ ([M+Na]⁺) 514.1954, found 514.1934.

benzyl ((1*S*,2*S*,3'*S*,5*S*)-9-chloro-8-formyl-1'-methoxy-2'-oxo-6-oxaspiro[bicyclo[3.2.2]non[8]-ene-4,3'-indolin]-2-yl)carbamate (**26**)

To a stirred solution of **25** (1.11 g, 2.26 mmol) in DMF (11 mL) at 0 °C was added oxalyl chloride (570 μL , 6.8 mmol) at 0 °C and stirred at 70 °C for 10 min. The reaction was quenched with saturated NH_4Cl aq. (10 mL) and diluted with 50% EtOAc in *n*-hexane (15 mL). The two phases were partitioned and the aqueous phase was extracted with 50% EtOAc in *n*-hexane (15 mL) four times. The combined organic extract was washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 2/1 to 1/1) to afford **26** (875 mg, 1.81 mmol, 80%) as a white foam.

R_f = 0.50 (toluene/acetone = 4:1, UV, Ce-PMA); $[\alpha]_D^{20}$ -238 (c = 1.00, CHCl_3); IR (neat, cm^{-1}) 3337, 2939, 1714, 1680, 1519, 1240; ^1H NMR (CDCl_3 , 400 MHz) δ 10.18 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.40–7.27 (m, 6H), 7.16 (dd, J = 7.8, 7.8 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.55 (d, J = 8.7 Hz, 1H), 5.10 (d, J = 12.4 Hz, 1H), 5.06 (d, J = 12.4 Hz, 1H), 4.39 (d, J = 9.6 Hz, 1H), 4.34 (m, 1H), 4.22 (s, 1H), 4.04 (s, 3H), 3.90–3.82 (m, 2H), 2.67 (dd, J = 15.6, 6.4 Hz, 1H), 1.82 (dd, J = 15.1, 3.6 Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 186.6, 171.1, 155.7, 146.4, 138.6, 136.5, 134.9, 129.2, 128.7, 128.3, 128.0, 127.9, 124.4, 124.0, 107.8, 81.6, 66.6, 66.5, 63.9, 51.2, 48.4, 35.6, 35.1; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{23}\text{ClN}_2\text{NaO}_6$ ($[\text{M}+\text{Na}]^+$) 505.1142, found 505.1166.

benzyl ((1*S*,2*S*,3'*S*,5*R*)-8-formyl-1'-methoxy-2'-oxo-6-oxaspiro[bicyclo[3.2.2]non[8]ene-4,3'-indolin]-2-yl)carbamate (**27**)

To a stirred solution of **26** (875 mg, 1.81 mmol) in DMF (9.1 mL), Et_3SiH (1.45 mL, 9.06 mmol) and Et_3N (505 μL , 3.62 mmol) was added $\text{Pd(PPh}_3)_4$ (419 mg, 0.36 mmol) in one portion. After stirring at 80 $^\circ\text{C}$ for 4.5 h, the reaction was quenched with saturated NH_4Cl aq. (10 mL), and 50% EtOAc in *n*-hexane (40 mL) was added. The mixture was filtered through Celite and washed with EtOAc (5 mL). The two phases were partitioned and the aqueous phase was extracted with 50% EtOAc in *n*-hexane (15 mL) twice. The combined organic extract was washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/0 to 3/2) to afford **27** (812 mg, 1.81 mmol, quant.) as a white foam.

R_f = 0.42 (toluene/acetone = 4:1, UV, Ce-PMA); $[\alpha]_D^{21}$ -189 (c = 1.00, CHCl_3); IR (neat, cm^{-1}) 3335, 2937, 1717, 1686, 1521, 1228, 1077; ^1H NMR (CDCl_3 , 400 MHz) δ 9.77 (s, 1H), 7.47 (d, J = 7.4 Hz, 1H), 7.40–7.26 (m, 7H), 7.15 (dd, J = 7.6, 7.6 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 5.29 (d, J = 7.8 Hz, 1H), 5.07 (s, 2H), 4.37 (d, J = 6.0 Hz, 1H), 4.30 (d, J = 9.6 Hz, 1H), 4.22 (m, 1H), 4.00 (s, 3H), 3.69 (dd, J = 9.6, 2.8 Hz, 1H), 3.51 (m, 1H), 2.06 (dd, J = 14.2, 5.0 Hz, 1H), 1.71 (dd, J = 14.2, 10.1 Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 190.2, 171.3, 155.4, 146.6, 140.7, 139.0, 136.3, 128.9, 128.4, 128.04, 127.98, 126.7, 126.1, 123.7, 107.5, 72.3, 67.1, 66.7, 63.6, 52.7, 48.9, 36.4, 35.6; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{NaO}_6$ ($[\text{M}+\text{Na}]^+$) 471.1532, found 471.1523.

benzyl ((1*S*,2*S*,3'*S*,5*R*)-1'-methoxy-2'-oxo-8-propionyl-6-oxaspiro[bicyclo[3.2.2]non[8]ene-4,3'-indolin]-2-yl)carbamate (**28**)

To a stirred solution of ethylmagnesium bromide (2.4 M solution in Et₂O, 4.53 mL, 10.9 mmol) in THF (32 mL) at -78 °C was added dropwise **27** (812 mg, 1.81 mmol) in THF (6.0 mL + 4.0 mL wash) through a gastight syringe over a period of 1.5 h. After 15 min, the reaction mixture was quenched with saturated NH₄Cl aq. (10 mL) and EtOAc (20 mL) was added. The two phases were partitioned and the aqueous phase was extracted with EtOAc (20 mL) once. The combined organic extract was washed with brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude secondary alcohol. The residue was dissolved in DMSO and IBX (1.52 g, 5.43 mmol) was added at room temperature. After stirring at 50 °C for 1.5 h, H₂O (10 mL) and 50% EtOAc in *n*-hexane (15 mL) were added to the reaction. The mixture was filtered through Celite and washed with EtOAc (5 mL). The two phases were partitioned and the aqueous phase was extracted with 50% EtOAc in *n*-hexane (15 mL) three times. The combined organic extract was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/0 to 3/1) to afford **28** (561 mg, 1.18 mmol, 65%) as a pale yellow foam.

R_f = 0.49 (toluene/acetone = 4:1, UV, Ce-PMA); $[\alpha]_D^{23}$ -208 (c = 1.00, CHCl₃); IR (neat, cm⁻¹) 3343, 1718, 1673, 1517; ¹H NMR (CDCl₃, 400 MHz) δ 7.45 (d, J = 7.8 Hz, 1H), 7.38-7.26 (m, 7H), 7.13 (dd, J = 7.6, 7.6 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 5.62 (d, J = 7.8 Hz, 1H), 5.05 (s, 2H), 4.28 (d, J = 6.0 Hz, 1H), 4.25 (d, J = 9.6 Hz, 1H), 4.17 (m, 1H), 3.98 (s, 3H), 3.69 (dd, J = 9.2, 2.7 Hz, 1H), 3.40 (m, 1H), 3.01 (dq, J = 17.9, 7.3 Hz, 1H), 2.76 (dq, J = 17.4, 7.3 Hz, 1H), 2.01 (dd, J = 13.8, 5.0 Hz, 1H), 1.67 (dd, J = 13.7, 10.5 Hz, 1H), 1.19 (t, J = 7.3 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 200.5, 171.5, 155.4, 139.4, 139.0, 137.2, 136.5, 128.7, 128.4, 128.0, 126.6, 126.4, 123.6, 107.4, 71.8, 67.5, 66.6, 63.5, 52.9, 48.9, 38.2, 35.7, 30.4, 8.2; HRMS (ESI) calcd for C₂₇H₂₈N₂NaO₆ ([M+Na]⁺) 499.1845, found 499.1826.

benzyl ((1*S*,2'*S*,3*S*,4'*R*,5'*S*,6'*S*)-1-methoxy-2-oxo-4'-propionyl-3',9'-dioxaspiro[indoline-3,8'-tricyclo[3.3.2.0^{2,4}]decan]-6'-yl)carbamate (29)

To a stirred solution of **28** (558 mg, 1.17 mmol) in THF (11.7 mL) at $-20\text{ }^{\circ}\text{C}$ was added *tert*-butyl hydroperoxide (70% in H_2O , 1.62 mL, 11.7 mmol) and Triton B (40% in H_2O , 925 μL , 2.34 mmol). After 1 h, the reaction was quenched with saturated NH_4Cl aq. (5 mL) and saturated NaHSO_3 aq. (3 mL) and diluted with 50% EtOAc in *n*-hexane (10 mL) and the organic phase was collected. The aqueous phase was extracted with 50% EtOAc in *n*-hexane (15 mL) twice. The combined organic extract was washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/0 to 4/1) to afford **29** (545 mg, 1.11 mmol, 95%) as a white foam.

Rf = 0.60 (toluene/acetone = 4:1, UV, Ce-PMA); $[\alpha]_D^{21} -135$ ($c = 1.00$, CHCl_3); IR (neat, cm^{-1}) 3389, 2939, 1716, 1617, 1507, 1463, 1223; ^1H NMR (CDCl_3 , 400 MHz) δ 7.43 (d, $J = 7.3$ Hz, 1H), 7.38–7.27 (m, 6H), 7.14 (dd, $J = 7.6, 7.6$ Hz, 1H), 7.01 (d, $J = 7.8$ Hz, 1H), 6.97 (d, $J = 9.2$ Hz, 1H), 5.09 (d, $J = 12.4$ Hz, 1H), 5.04 (d, $J = 12.4$ Hz, 1H), 4.53 (ddd, $J = 12.8, 9.6, 4.2$ Hz, 1H), 4.39 (d, $J = 2.8$ Hz, 1H), 4.31 (dd, $J = 9.8, 2.8$ Hz, 1H), 4.00 (d, $J = 2.8$ Hz, 1H), 3.99 (s, 3H), 3.88 (d, $J = 9.2$ Hz, 1H), 2.75 (m, 1H), 2.62 (dq, $J = 19.2, 7.4$ Hz, 1H), 2.47 (dq, $J = 19.2, 7.4$ Hz, 1H), 2.12 (dd, $J = 13.8, 12.8$ Hz, 1H), 1.82 (dd, $J = 13.8, 4.2$ Hz, 1H), 1.10 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 210.6, 171.4, 155.4, 138.7, 136.5, 128.8, 128.4, 128.02, 127.99, 126.8, 126.5, 123.8, 107.4, 70.1, 68.3, 66.6, 63.5, 59.2, 58.7, 53.0, 52.2, 40.3, 35.4, 28.9, 7.1; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{NaO}_7$ ($[\text{M}+\text{Na}]^+$) 515.1794, found 515.1769.

(-)-gelsemoxonine (1)

To a stirred solution of **29** (545 mg, 1.11 mmol) in CH_2Cl_2 (11 mL) was added freshly-prepared trimethylsilyl iodide³ (2.0 M solution in CH_2Cl_2 , 4.45 mL, 8.91 mmol) at 0 °C. After 1.5 h, the reaction mixture was quenched with saturated NaHCO_3 aq. (1.5 mL) and saturated NaHSO_3 aq. (4 mL). The mixture was acidified with 3 N HCl aq. (6.0 mL) to pH = 2, extracted with 25% EtOAc in *n*-hexane (30 mL) and the organic phase was discarded. The aqueous phase was then basified with 3% NaOH aq. (15 mL) to pH = 8 and extracted with 17% MeOH in CH_2Cl_2 (40 mL) seven times. The combined organic extract was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude amino epoxide. The residue was dissolved in EtOH (11 mL) and refluxed for 12 h. The solvent was removed by rotary evaporation and the residue was purified with flash column chromatography on silica gel (toluene/acetone = 1/0 to 5/1) to afford gelsemoxonine (**1**) (312 mg, 0.871 mmol, 79% for 2 steps) as colorless crystals.

Synthetic: R_f = 0.53 (toluene/acetone = 1:1, UV); Mp 161.0-162.0 °C (benzene); $[\alpha]_D^{25}$ -61.4 (c = 1.00, MeOH); IR (neat, cm^{-1}) 2936, 1699, 1617; ^1H NMR (CDCl_3 , 400 MHz) δ 7.48 (d, J = 7.8 Hz, 1H), 7.36 (dd, J = 7.8, 7.8 Hz, 1H), 7.18 (dd, J = 7.8, 7.8 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 4.51 (d, J = 6.9 Hz, 1H), 4.27 (dd, J = 11.9, 4.1 Hz, 1H), 4.19 (d, J = 2.8 Hz, 1H), 4.17 (d, J = 11.9 Hz, 1H), 4.06 (s, 3H), 3.89 (ddd, J = 8.2, 6.9, 4.6 Hz, 1H), 3.80 (d, J = 2.8 Hz, 1H), 3.35 (dd, J = 8.2, 4.1 Hz, 1H), 2.83 (dq, J = 18.3, 7.3 Hz, 1H), 2.52 (dq, J = 18.3, 7.3 Hz, 1H), 2.40 (d, J = 16.5 Hz, 1H), 2.30 (dd, J = 16.0, 4.6 Hz, 1H), 1.11 (t, J = 7.3 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 211.7, 173.4, 138.0, 130.3, 128.7, 125.2, 124.0, 107.4, 78.5, 68.6, 67.1, 63.7, 61.7, 55.5, 53.9, 34.7, 33.6, 28.8, 7.0; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{NaO}_5$ ($[\text{M}+\text{Na}]^+$) 381.1426, found 381.1409.

Natural (lit.)⁴: Mp 171-172 °C (benzene); $[\alpha]_D^{22}$ -41.3 (c = 0.988, MeOH); IR (KBr, cm^{-1}) 3410, 3250, 2936, 1698, 1616; ^1H NMR (CDCl_3 , 500 MHz) δ 7.47 (dd, J = 7.6, 0.6 Hz, 1H), 7.36 (1H, ddd, J = 7.6, 7.6, 0.9 Hz, 1H), 7.18 (ddd, J = 7.6, 7.6, 0.9 Hz, 1H), 7.02 (dd, J = 7.6, 0.6 Hz,

³ Sakurai, H.; Shirahata, A.; Sasaki, K.; Hosomi, A. *Synthesis* 1979, 740-741.

⁴ Kitajima, M.; Kogure, N.; Yamaguchi, K.; Takayama, H.; Aimi, N. *Org. Lett.* **2003**, 5, 2075-2078.

1H), 4.51 (br-d, $J = 6.1$ Hz, 1H), 4.26 (dd, $J = 12.0, 4.1$ Hz, 1H), 4.17 (d, $J = 12.0$ Hz, 1H), 4.05 (s, 3H), 3.89 (br-ddd, $J = 8.2, 4.6, 1.5$ Hz, 1H), 3.80 (d, $J = 2.4$ Hz, 1H), 3.34 (br-dd, $J = 8.2, 4.0$ Hz, 1H), 2.82 (dq, $J = 18.3, 7.3$ Hz, 1H), 2.52 (dq, $J = 18.3, 7.3$ Hz, 1H), 2.39 (dd, $J = 16.2, 1.5$ Hz, 1H), 2.29 (dd, $J = 16.2, 4.6$ Hz, 1H), 1.11 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 211.8, 173.4, 138.0, 130.3, 128.8, 125.2, 124.1, 107.5, 78.6, 68.7, 67.2, 63.7, 61.8, 55.6, 53.9, 34.7, 33.6, 28.9, 7.0; HRMS (FAB) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_5$ ($[\text{M}+\text{H}]^+$) 359.1607, found 359.1611.

^1H NMR (400 MHz) in CDCl_3

^{13}C NMR (100 MHz) in CDCl_3

¹H NMR (400 MHz) in CDCl₃

^{13}C NMR (100 MHz) in CDCl_3

¹H NMR (400 MHz) in CDCl₃

^{13}C NMR (100 MHz) in CDCl_3

¹H NMR (400 MHz) in CDCl₃

¹³C NMR (100 MHz) in CDCl₃

^1H NMR (400 MHz) in CD_3OD

¹³C NMR (100 MHz) in CD₃OD

¹H NMR (400 MHz) in CDCl₃

¹³C NMR (100 MHz) in CDCl₃

^1H NMR (400 MHz) in CDCl_3

^{13}C NMR (100 MHz) in CDCl_3

^1H NMR (400 MHz) in CDCl_3

14 OMe
¹³C NMR (100 MHz) in CDCl₃

^1H NMR (400 MHz) in CDCl_3

17

^{13}C NMR (100 MHz) in CDCl_3

¹H NMR (400 MHz) in CDCl₃

^{13}C NMR (100 MHz) in CDCl_3

¹H NMR (400 MHz) in CDCl₃

^{13}C NMR (100 MHz) in CDCl_3

^{13}C NMR (100 MHz) in CDCl_3

^1H NMR (400 MHz) in CDCl_3

^{13}C NMR (100 MHz) in CDCl_3

^{13}C NMR (100 MHz) in CDCl_3

^1H NMR (400 MHz) in CDCl_3

^1H NMR (400 MHz) in CDCl_3

^{13}C NMR (100 MHz) in CDCl_3

28

^{13}C NMR (100 MHz) in CDCl_3

gelsemoxonine (**1**)

^1H NMR (400 MHz) in CDCl_3