First Enantioselective Syntheses of (+) and (−)-Wilforonide by Using Chiral Auxiliaries Derived from the Same Chiral Source

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Supporting Information

General Procedures. All reactions were performed in oven-dried flasks. Air and moisture-sensitive compounds were introduced *via* syringes through a rubber septum. Radical cyclization reactions were carried out in the degassed acetic acid or 2,2,2-trifluoroethanol. THF was distilled from sodium metal-benzophenone ketyl before use. Dichloromethane and toluene were distilled from calcium hydride. Flash column chromatography was performed on E. Merck silica gel 60 (230−400 mesh ASTM) using ethyl acetate/*n*-hexane as eluting solvents. Nuclear magnetic resonance spectra were recorded on a Bruker Avance DPX 300 Fourier Transform Spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, or a Bruker Avance DRX 500 Fourier Transform Spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C.

Preparation of allylic alcohol 2. Magnesium turnings (6.95 g, 289.6 mmol) were stirred under argon for 2 d. Freshly distilled THF (80 mL) was added, and the mixture was cooled to 0 °C. 3-Chloro-2-methylpropene (9.8 mL, 97.0 mmol) was slowly added to the reaction over 12 h via an automatic syringe pump. The resulting reaction was slowly

warmed to room temperature during addition. The reaction was stirred for another 4 h at room temperature, and the mixture was cooled to −30 °C and allowed the dark grey precipitate to settle. The dark grey solution was cannulated to a precooled mixture of 2-methyl-2-vinyloxirane (5.0 mL, 48.4 mmol), CuI (460 mg, 2.42 mmol) in THF (100 mL) at −30 °C. The mixture was stirred for 2 h at −30 °C, and quenched with saturated NH_4Cl solution. The resulting mixture was extracted with ether, washed with dilute HCl, saturated $NaHCO_3$, water, and brine. The combined organic extracts were dried with anhydrous $MgSO_4$, and concentrated to give the crude residue, which was purified by flash column chromatography to provide allylic alcohol **2** (6.44 g, 46.0 mmol, 95% yield) as a colourless oil. Analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (dt, *J* = 1.2, 6.8 Hz, 1H), 4.72 (apparent s, 1H), 4.69 (apparent s, 1H), 3.99 (s, 2H), 2.22−2.17 (m, 2H), 2.06 (dd, *J* = 6.8, 7.3 Hz, 2H), 1.73 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 135.0, 125.7, 110.0, 68.9, 37.4, 25.8, 22.4, 13.7; IR (CH_2Cl_2) 3461, 2923, 1644 cm^{-1}; HRMS (EI) for $C_9H_{16}O$ (M^+): calcd 140.1201, found 140.1208; LRMS (EI, 20 eV) *m/z* 140 (M^+, 2), 97 (78), 71 (100); Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found C, 76.99; H, 11.41.

Preparation of allylic bromide 3. To a solution of allylic alcohol **2** (2.80 g, 20.0 mmol) and triethylamine (5.58 mL, 40.0 mmol) in dichloromethane (80 mL) at −40 °C was added methanesulfonyl chloride (3.13 mL, 40.0 mmol) dropwise. The mixture was warmed slowly to −20 °C over 1 h. A solution of LiBr (4.38 g, 50.0 mmol) in THF (30 mL) was added and the reaction mixture was warmed to room temperature over 4 h. The reaction was quenched with saturated NH_4Cl solution, and extracted with

dichloromethane. The organic extracts were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography to afford allylic bromide **3** (3.65 g, 18.0 mmol, 90% yield) as a colourless oil. Analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.82; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (t, J = 6.8 Hz, 1H), 4.73 (apparent s, 1H), 4.68 (apparent s, 1H), 3.97 (s, 2H), 2.17 (dt, J = 6.8, 7.7 Hz, 2H), 2.06 (t, J = 6.9 Hz, 2H), 1.77 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 132.2, 131.0, 110.3, 41.8, 36.9, 26.5, 22.5, 14.7; IR (CH_2Cl_2) 2972, 1636 cm^{-1}; HRMS (EI) for $C_9H_{15}Br$ (M^+): calcd 202.0357, found 202.0341; LRMS (EI, 20 eV) *m/z* 204 (M^+, 45), 202 (M^+, 45), 122 (49), 67 (100).

Preparation of acyclic precursor 4a. To a suspension of sodium hydride (60% in mineral oil, 0.36 g, 8.84 mmol) in dry THF (20 mL) was added methyl acetoacetate (0.82 mL, 7.48 mmol) at 0 °C dropwise. After 10 min, *n*-butyllithium (1.6 M in *n*-hexane, 5.10 mL, 8.16 mmol) was slowly added to the mixture. The solution was stirred at 0 °C for 30 min. Then a solution of allylic bromide **3** (1.38 g, 6.80 mmol) in THF (15 mL) was transferred into the above mixture under argon. The reaction was stirred for 1.5 h at 0 °C, then quenched with saturated ammonium chloride solution. The resulting mixture was extracted with dichloromethane. The extracts were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography to afford acyclic precursor **4a** (1.09 g, 85% yield) as a colourless oil. Analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.47; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.01 (s, enol form, 0.10 × 1H), 5.14 (dt, J = 1.1, 6.9 Hz, 1H), 4.98 (s, enol form, 0.10 × 1H), 4.71 (apparent s, 1H), 4.67 (apparent s, 1H), 3.74 (s, 3H), 3.46 (s, keto form, 0.90 × 2H), 2.64 (t, J = 7.5 Hz,

2H), 2.27 (t, J = 7.5 Hz, 2H), 2.11 (dt, J = 6.3, 7.9 Hz, 2H), 2.02 (t, J = 7.1 Hz, 2H), 1.72 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 167.7, 145.6, 133.3, 125.0, 109.9, 52.3, 49.0, 41.7, 37.6, 33.2, 26.1, 22.5, 16.1; IR (CH_2Cl_2) 2929, 1744, 1714 cm^{-1}; HRMS (EI) for $C_{14}H_{22}O_3$ (M^+): calcd 238.1569, found 238.1572; LRMS (EI, 20 eV) *m/z* 238 (M^+, 1), 157 (53), 109 (58), 81 (100). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found C, 70.38; H, 9.28.

Preparation of acyclic precursor 4b. To a solution of ethyl 2-chloroacetoacetate (1.62 mL, 11.7 mmol) in THF (15 mL) was added a freshly prepared solution of LDA (1.0 M in THF and Hexane, 23.5 mL, 23.5 mmol) at −10 °C. The reaction was stirred for 1 h at −10 °C. Then a solution of **3** (1.59 g, 7.83 mmol) in THF (10 mL) was added and the mixture was stirred for another 2 h from −10 to 0 °C. Saturated NH_4Cl solution was added to quench the reaction and the mixture was extracted with ether. The combined organic extracts were washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated to give a yellow residue. The residue was purified by flash column chromatography to provide **4b** (1.57 g, 5.48 mmol, 70% yield) as a pale yellow oil; analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.65; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.39 (s, enol, 0.21 × 1H), 5.16 (m, 1H), 4.79 (s, keto, 0.79 × 1H), 4.71 (apparent s, 1H), 4.67 (apparent s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.80 (m, keto, 0.79 × 2H), 2.61 (dd, enol, J = 7.3, 8.3 Hz, 0.21 × 2H), 2.30 (m, 2H), 2.11 (m, 2H), 2.05 (m, 2H), 1.72 (s, 3H), 1.66 (s, enol, 0.21 × 3H), 1.62 (s, keto, 0.79 × 3H), 1.36 (t, enol, 0.21 × 3H), 1.32 (t, keto, J = 7.1 Hz, 0.79 × 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 165.1, 145.6, 133.0, 125.3, 110.0, 109.9, 63.1, 62.0, 61.0, 37.8, 37.6, 35.4, 33.2, 32.0, 26.2, 26.1,

22.5, 16.0, 15.9, 14.2, 14.0; IR (CH_2Cl_2) 2983, 1763, 1721 cm^{-1}; HRMS (EI) for $C_{15}H_{23}ClO_3$ (M^+): calcd 286.1336, found 286.1330; LRMS (EI, 20 eV) *m/z* 286 (M^+, 1), 233 (9), 205 (100).

Preparation of cyclization products 5a and 6a. To a solution of precursor **4a** (163 mg, 0.68 mmol) in degassed acetic acid (7 mL) were added $Mn(OAc)_3 \cdot 2H_2O$ (383 mg, 1.43 mmol) and $Cu(OAc)_2$ (136 mg, 0.68 mmol). The reaction was stirred at room temperature under argon for 24 h, then quenched with 10% $NaHSO_3$ solution, and extracted with ether three times. The combined organic extracts were washed with saturated $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. Removal of the solvent gave a yellow residue which was purified by flash column chromatography to provide the cyclization products **5a** and **6a** (ratio 2.5:1) as a mixture (78 mg, 0.33 mmol, 50% yield). Characterization data of compound **5a**: analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.33; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (apparent d, *J* = 1.8 Hz, 1H), 4.67 (apparent d, *J* = 1.9 Hz, 1H), 3.76 (s, 3H), 3.17 (d, *J* = 12.9 Hz, 1H), 2.30–2.54 (m, 3H), 1.93–2.11 (m, 3H), 1.46–1.78 (m, 4H), 1.32 (m, 1H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 170.3, 144.9, 118.4, 110.3, 60.1, 52.0, 49.2, 46.3, 39.9, 37.8, 33.8, 28.0, 16.2; HRMS (EI) for $C_{14}H_{20}O_3$ (M^+): calcd 236.1412, found 236.1412; LRMS (EI, 20 eV) *m/z* 236 (M^+, 19), 205 (25), 130 (93), 107 (100). Partial data of compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (br. s, 1H), 3.18 (d, *J* = 12.9 Hz, 1H), 1.05 (s, 0.18 × 3H), 1.08 (s, 0.82 × 3H).

Preparation of compounds 5c and 6c. To a solution of **4b** (267 mg, 0.93 mmol) in degassed acetic acid (9.3 mL) were added $Mn(OAc)_3 \cdot 2H_2O$ (524 mg, 1.96 mmol) and $Cu(OAc)_2$ (186 mg, 0.93 mmol). The mixture was stirred at room temperature under argon for 5 h. A solution of $NaHSO_3$ was added to quench the reaction and the mixture was extracted with ether. The combined organic extracts were washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated to give the yellow residue. The residue was purified by flash chromatography to provide a mixture of **5b** and **6b** (186 mg). To a solution of **5b** and **6b** (186 mg) in acetic acid (3.3 mL) was added zinc powder (85 mg, 1.3 mmol). After stirred for 1 h at room temperature, the reaction was extracted with ether. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography to provide **5c** and **6c** (ratio 3.1:1) as a mixture (144 mg, 0.576 mmol, 62% yield in two steps). Data of **5c**: a colorless oil; analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.42; ^{1}H NMR (300 MHz, $CDCl_3$) 4.77 (m, 1H), 4.66 (m, 1H), 4.22 (m, 2H), 3.14 (d, J = 12.9 Hz, 1H), 2.29–2.57 (m, 3H), 1.92–2.18 (m, 4H), 1.64–1.89 (m, 3H), 1.49 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.7, 169.9, 145.0, 110.3, 60.9, 60.1, 49.2, 46.2, 39.9, 37.8, 34.5, 33.8, 27.9, 16.3, 14.2; IR (CH_2Cl_2) 1746, 1709 cm^{-1}; HRMS (EI) for $C_{15}H_{22}O_3$ (M^+): calcd 250.1569, found 250.1555; LRMS (EI, 20 ev) *m/z* 250 (M^+, 18), 217 (29), 144 (100). Partial data of **6c**: 5.32 (br. s, 0.23 × 1H), 5.24 (br. s, 0.05 × 1H), 3.16 (d, J = 12.5 Hz, 1H), 1.08 (s, 0.05 × 3H), 1.05 (s, 0.23 × 3H).

Preparation of compounds 9 and 10. To a solution of compounds **5a** and **6a** (0.944 g, 4.0 mmol) in dry THF (60 mL) was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 9.6 mL, 4.8 mmol) at −78 °C dropwise. The mixture was warmed to −20 °C in a period of 2 h, then cooled down to −78 °C. A solution of 1,1,1-trifluoro-*N*-phenyl-*N*-[trifluoromethyl)sulfonyl]methanesulfonimide (1.73 g, 4.8 mmol) in THF (10 mL) was cannulated to the above solution, and the mixture was warmed to room temperature overnight. The mixture was diluted with ether, washed with water followed by a citric acid solution (10%). The organic layers were dried, filtered, and concentrated. The residue was purified by flash column chromatography to afford a mixture of compounds **7a** and **8a** (1.30 g, 88% yield), which was used in the next step directly. To a solution of compounds **7a** and **8a** (1.30 g, 3.52 mmol) in CH_2Cl_2 (17 mL) at −78 °C was added diisobutylaluminum hydride (1.0 M solution in CH_2Cl_2, 14.0 mL, 14.0 mmol) dropwise. The solution was warmed to room temperature overnight. The reaction was quenched with small amount of water, dried with Na_2SO_4, and filtered through a short pad of silica gel. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to afford **9** (741 mg, 55% yield in two step, 72% yield based on **5a** consumed) and **10** (238 mg, 70% yield based on **6a** consumed). The same result was obtained by using **5c** and **6c** (3.1:1) as the starting materials. Data of compound **9**: a colourless oil; analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (apparent s, 1H), 4.65 (apparent s, 1H), 4.35 (d, *J* = 12.3 Hz, 1H), 4.09 (dd, *J* = 2.0, 12.3 Hz, 1H), 2.31–2.57 (m, 4H), 2.08 (m, 2H), 2.02 (dd, *J* = 1.6, 13.0 Hz, 1H), 1.93 (d, *J* = 13.0 Hz, 1H), 1.52–1.67 (m, 2H), 1.62 (br. s, 1H), 1.39 (ddd, *J* = 4.3, 13.0, 13.1 Hz, 1H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

145.3, 145.0, 130.9, 118.4 (q, J = 319 Hz), 110.4, 56.8, 48.3, 44.6, 36.9, 34.0, 25.6, 24.6, 16.0; IR (CH_2Cl_2) 3610, 2934, 1410 cm^{-1}; HRMS (EI) for $C_{14}H_{19}F_3O_3S$ (M^+): calcd 340.0956, found 340.0963; LRMS (EI, 20 eV) *m/z* 340 (M^+, 3), 322 (71), 189 (100), 119 (82). Data of compound **10** (major isomer a : minor isomer b = 5:1): a colourless oil; analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.38; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (br. s, 1H, a), 5.25 (br. s, 1H, b), 4.37 (d, J = 5.4 Hz, 1H, a), 4.34 (d, J = 5.4 Hz, 1H, b), 4.15 (d, J = 12.3 Hz, 1H, b), 4.10 (dd, J = 1.3, 12.3 Hz, 1H, a), 2.26–2.59 (m, 4H), 1.67 (s, 2H), 1.51–1.91 (m, 4H), 0.90 (s, 3H, b), 0.84 (s, 3H, a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 144.9, 132.6, 131.3, 130.9, 130.8, 119.8, 118.4 (q, J = 319 Hz), 56.9, 45.1, 42.7, 40.6, 36.3, 35.4, 33.5, 31.6, 31.1, 30.8, 25.7, 25.4. 25.3, 23.6, 23.2, 20.4, 19.5, 16.4; IR (CH_2Cl_2) 2968 cm^{-1}; HRMS (EI) for $C_{14}H_{19}F_3O_3S$ (M^+): calcd 340.0956, found 340.0960; LRMS (EI, 20 eV) *m/z* 340 (M^+, 2), 189 (100).

Preparation of lactone 11. Carbon monoxide was bubbled through a mixture of compound **9** (280 mg, 0.82 mmol), $Pd(PPh_3)_4$ (95 mg, 0.1 mmol), triethylamine (0.228 mL, 1.64 mmol), and lithium chloride (35 mg, 0.82 mmol) in acetonitrile (21 mL) for 20 min. Then the reaction was charged with a carbon monoxide balloon and heated to 65 °C overnight. Diethyl ether was added to the cooled solution, and the mixture was filtered through a pad of celite and rinsed with diethyl ether. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to give **11** (171 mg, 0.74 mmol, 94% yield) as a white solid: colourless crystal, m.p. 108–109 °C (*n*-Hexane/CH_2Cl_2); analytical TLC (silica gel 60), 50% EtOAc in *n*-Hexane, R_f = 0.54; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (apparent s, 1H), 4.70 (apparent s, 1H), 4.68 (m, 2H),

2.33–2.48 (m, 3H), 2.26 (m, 1H), 2.13 (m, 1H), 2.11 (dd, *J* = 1.2, 13.1 Hz, 1H), 2.02 (d, *J* = 13.1 Hz, 1H), 1.69 (dddd, *J* = 3.2, 5.4, 7.8, 12.7 Hz, 1H), 1.52–1.64 (m, 2H), 1.44 (ddd, *J* = 4.3, 12.8, 12.9 Hz, 1H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 163.0, 144.8, 124.8, 111.4, 70.4, 48.2, 43.9, 36.5, 34.71, 34.67, 24.1 17.9, 16.1; IR (CH_2Cl_2) 2940, 1752, 1015 cm^{-1}; HRMS (EI) for $C_{14}H_{18}O_2$ (M^+): calcd 218.1307, found 218.1309; LRMS (EI, 20 eV) *m/z* 219 (M^+ + 1, 20), 218 (M^+, 100), 203 (42), 105 (59).

Preparation of (±)-wilforonide. OsO_4 (10 μL, 4% solution in water, 1.57×10^{-3} mmol) was added to a mixture of **11** (18 mg, 0.082 mmol), $NaHCO_3$ (96 mg, 1.14 mmol), and $NaIO_4$ (145 mg, 6.68 mmol) in *tert*-butyl alcohol (2.5 mL) and water (0.5 mL) at room temperature. The reaction was stirred for 4 h, and another portion of OsO_4 (10 μL) was added. The resulting mixture was stirred overnight and then quenched with 10% $Na_2S_2O_3$. After stirred for 0.5 h, the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, and dried with anhydrous $MgSO_4$. Removal of the solvent gave the crude residue which was purified by flash column chromatography to provide (±)-wilforonide (15 mg, 85% yield) as a white solid: m.p. 185–187 °C (*n*-Hexane/CH_2Cl_2), (lit,[1] 187–189 °C); analytical TLC (silica gel 60), 70% EtOAc in *n*-Hexane, R_f = 0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (m, 2H), 2.79 (m, 1H), 2.57 (dd, *J* = 5.0, 15.1 Hz, 1H), 2.34 (br. s, 2H), 1.67–2.47 (m, 7H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 173.6, 160.7, 125.8, 76.6, 70.2, 54.7, 40.8, 36.8, 36.2, 23.2, 17.5, 17.1; HRMS (EI) for $C_{13}H_{16}O_3$ (M^+): calcd 220.1099, found 220.1095; LRMS (EI, 20 eV) *m/z* 220 (M^+, 100), 191 (27), 152 (31).

(+)-**Wilforonide**: $[\alpha]_D^{20}$ +25.1 ° (*c* 0.18, CH_2Cl_2).

(–)-**Wilforonide**: $[\alpha]_D^{20}$ –26.6 ° (*c* 0.14, CH_2Cl_2). [natural (–)-wilforonide: $[\alpha]_D^{20}$ –26.8 ° (*c* 0.045, CH_2Cl_2)].

General Procedure for Preparation of Chiral Precursors 12 and 17

To a flame-dried round-bottom flask equipped with a reflux condenser were added (–)-8-phenylmenthol **16** (0.232 g, 1.0 mmol), 4-(dimethylamino)pyridine (0.073 g, 0.6 mmol), and β-keto ester **4a** (0.250 g, 1.05 mmo1) in anhydrous toluene (15 mL) under argon. The mixture was stirred under reflux for 30 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to afford chiral precursor **12** (0.416 g, 0.95 mmol, 95% yield) as a pale yellow oil; analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.65; $[\alpha]_D^{20}$ +17.3 ° (*c* 1.47, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.07 (s, enol, 0.27 × 1H), 7.25–7.29 (m, 4H), 7.14 (m, 1H), 5.16 (apparent t, enol, *J* = 6.6 Hz, 0.27 × 1H), 5.09 (apparent t, keto, *J* = 6.5 Hz, 0.73 × 1H), 4.82 (m, 1H), 4.71 (s, enol , 0.27 × 1H), 4.67 (br. s, 1H), 4.41 (s, enol, 0.27 × 1H), 2.78 (d, keto, *J* = 15.6 Hz, 0.73 × 1H), 2.63 (d, keto, *J* = 15.6 Hz, 0.73 × 1H), 2.43 (dd, *J* = 6.2, 8.1 Hz, 1H), 1.78–2.20 (m, 9H), 0.85–1.64 (m, 6H), 1.59 (s, 3H), 1.30 (s, 3H), 1.20 (s, 3H), 0.88 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 177.8, 171.9, 166.6, 151.9, 151.2, 145.6, 133.6, 133.4, 127.9, 125.5, 125.4, 125.1, 124.99, 124.76, 109.9, 89.7, 75.0, 74.1, 50.7, 50.2, 49.0, 41.8, 41.6, 41.4, 39.8, 39.5, 37.7, 36.0, 34.5, 33.8, 33.0, 31.31, 31.26, 29.1, 26.7, 26.6, 26.3, 26.2, 26.1, 23.5, 22.5, 21.8, 16.1, 15.9; IR (CH_2Cl_2) 1727, 1704 cm^{-1}; HRMS (EI) for $C_{29}H_{42}O_3$ (M^+): calcd 438.3134, found 438.3145; LRMS (EI, 20 eV) *m/z* 438 (M^+, 0.5), 215 (7), 143 (42), 119 (100).

Compound **17**: a pale yellow oil; analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.41; $[\alpha]_D^{20}$ +28.9 ° (*c* 0.86, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.19 (s, enol, 0.12 × 1H), 6.43 (d, *J* = 2.2 Hz, 2H), 6.29 (dd, *J* = 2.1, 2.2 Hz, 1H), 5.13 (m, 1H), 4.99 (s, keto, 0.88 × 1H), 4.94 (s, enol, 0.12 × 1H), 4.92 (br. s, enol, 0.12 × 1H), 4.70 (br. s, 1H), 4.66 (br. s, 1H), 3.77 (s, keto, 0.88 × 3H), 3.75 (s, enol, 0.12 × 3H), 3.35 (s, keto, 0.88 × 2H), 2.59–2.64 (m, 2H), 2.23–2.30 (m, 2H), 2.08–2.13 (m, 2H), 1.92–2.03 (m, 2H), 1.88 (m, 1H), 1.71 (s, 3H), 1.50–1.74 (m, 4H), 1.60 (s, 3H), 1.26 (s, 6H), 0.79–1.02 (m, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 166.4, 160.4 (× 2), 152.0, 145.6, 133.6 (enol), 133.4, 125.1 (enol), 124.9, 109.9, 105.0 (× 2), 104.9 (enol), 96.8, 89.5 (enol), 72.7, 55.2 (× 2), 55.1 (enol), 51.1, 49.7, 41.9, 40.4 (enol), 40.3, 39.7, 37.6, 36.1 (enol), 35.2, 33.2, 31.6 (enol), 26.9, 26.8, 26.1, 25.9, 22.7 (enol), 22.5, 22.3, 22.0, 16.0, 15.9 (enol), 14.1 (enol); IR (CH_2Cl_2) 1735, 1706 cm^{-1}; HRMS (EI) for $C_{31}H_{44}O_3$ (M^+): calcd 498.3345, found 498.3356; LRMS (EI, 20 eV) *m/z* 498 (M^+, 4), 275 (43), 259 (100), 180 (24).

Compounds **13** and **14** (prepared following the procedure for compound **5a** and **6a** by using CF_3CH_2OH as a solvent instead of HOAc at 0 °C): a semi solid; analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.48. Partial data of compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08–7.27 (m, 5H), 4.67–4.74 (m, 1H), 4.71 (br. s, 1H), 4.62 (br. s, 1H), 1.32 (s, 3H), 1.22 (s, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 169.3, 152.1, 145.0, 127.5 (× 2), 125.7 (× 2), 118.3, 110.1, 76.3, 59.6, 50.5, 46.5, 43.2, 41.2, 39.9, 39.6, 37.8, 34.7, 34.5, 33.7, 31.6, 31.3, 27.6, 26.6, 22.7,

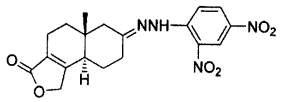
21.8, 16.1; IR (CH_2Cl_2) 1733, 1708 cm^{-1}; HRMS (EI) for $C_{29}H_{40}O_3$ (M^+): calcd 436.2977, found 436.2970; LRMS (EI, 20 eV) *m/z* 436 (M^+, 1), 214 (27), 119 (100). Partial data of compound **14**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.08−7.27 (m, 5H), 5.24 (br. s, 1H), 1.62 (br. s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 132.3, 124.5, 76.2, 49.1, 28.5, 27.5, 24.9, 23.6, 16.5.

Compounds **18** and **19** (prepared following the procedure for compounds **13** and **14** by using 1.0 equiv of $Yb(OTf)_3$ and 0.5 equiv of $Cu(OAc)_2$ at −10 to 0 °C): a semi-solid; analytical TLC (silica gel 60), 20% EtOAc in *n*-Hexane, R_f = 0.37. Partial data of compound **18**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.0 Hz, 2H), 6.31 (dd, *J* = 0.7, 0.8 Hz, 1H), 5.10 (br. s, 1H), 4.76 (br. s, 1H), 4.67 (br. s, 1H), 3.80 (s, 3H), 3.09 (d, *J* = 12.8 Hz, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.01 (s, 3H), 0.81 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 169.3, 160.2, (× 2), 152.7, 144.8, 110.2, 104.9 (× 2), 97.1, 72.8, 60.4, 55.3 (× 2), 51.3, 49.2, 46.3, 40.5, 39.9, 39.6, 37.7, 35.3, 34.4, 33.8, 27.8, 26.8, 26.3, 25.4, 22.2, 22.1, 16.4; IR (CH_2Cl_2) 1738, 1703cm^{-1}; HRMS (EI) for $C_{31}H_{44}O_5$ (M^+): calcd 496.3189, found 496.3188; LRMS (EI, 20 eV) *m/z* 497 (M^+ + 1, 6), 496 (M^+, 18), 275 (30), 259 (20), 180 (100). Partial data of compound **19**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (br. s, 1H), 3.11 (d, *J* = 12.6 Hz, 1H), 1.06 (s, 3H), 0.83 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 152.9, 132.4, 118.3, 55.1, 45.6, 43.0, 40.3, 37.7.

Preparation of the 2,4-DNP derivative of wilforonide: To a solution of (+)-wilforonide (4 mg, 0.018 mmol) in 95% ethanol (1 mL) was added the freshly prepared 2,4-dinitrophenylhydrazine solution (0.2 mL, 0.2 N in ethanol). After stirred at room

temperature for 1 h, the reaction was extracted with EtOAc. The combined organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated. The resideu was purified by flash column chromatography to afford compound **21** (4.3 mg, 0.011 mmol, 60% yield) as a yellow solid: m.p. > 180 °C; analytical TLC (silica gel 60), 70% EtOAc in *n*-Hexane, R_f = 0.39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.27 (s, 1H), 9.14 (d, *J* = 2.2 Hz, 1H), 8.32 (dd, *J* = 2.4, 9.6 Hz, 1H), 7.99 (d, *J* = 9.7 Hz, 1H), 4.75 (m, 2H), 3.01–3.10 (m, 3H), 2.02–2.69 (m, 6H), 1.62–1.82 (m, 2H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 160.7, 156.7, 145.2, 138.0, 130.2, 129.2, 125.9, 123.6, 116.4, 70.2, 51.2, 48.4, 43.2, 36.1, 35.7, 22.8, 17.8, 16.7; IR (CH_2Cl_2) 1752, 1619 cm^{-1}; HRMS (EI) for $C_{19}H_{20}N_2O_6$ (M^+): calcd 400.1383, found 400.1381; LRMS (EI, 20 eV) *m/z* 401 (M^+ + 1, 21), 400 (M^+, 100), 340 23), 153 (59).

HPLC Analysis of 2,4-DNP Derivative of (±)-Wilforonide



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Sample: xm-7-149f1, racemic wilforonide-2,4-DNP Compd.

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Sample Name : xm-7-149f1 Vial : 1
Acq. Operator : xuming Inj : -

Method : C:\HPCHEM\1\METHODS\XU.M
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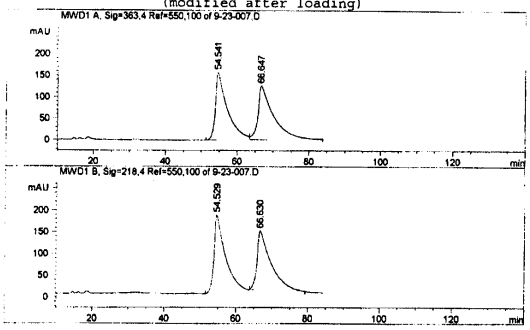


Area Percent Report

Sorted by Signal
Multiplier : 1.000000
Dilution : 1.000000

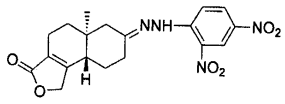
Signal 1: MWD1 A, Sig=363,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	54.541	BV	2.982	36048.52344	157.11449	49.0945
2	66.647	VBA	3.877	37378.28516	125.04062	50.9055
Totals :				73426.81250	282.15509	

Signal 2: MWD1 B, Sig=218,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.825	BB	0.312	63083.51562	3297.65747	45.7803
2	54.529	BB	2.728	38314.64844	178.79196	27.8053
3	66.630	BB	3.403	36398.03125	135.94778	26.4144
Totals :				137796.18750	3612.39722	

HPLC Analysis of 2,4-DNP Derivative of (+)-Wilforonide



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Sample: xm-7-151f1, (+)-wilforonide-2,4-DNP Compd.

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Acq. Operator : xuming Inj : -

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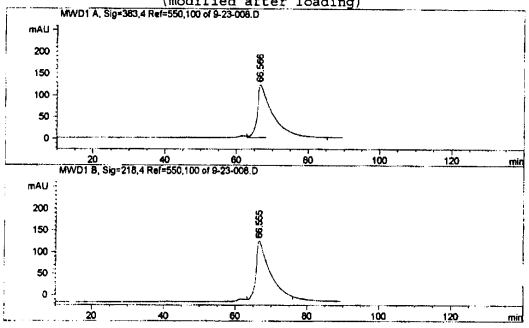


Area Percent Report

Sorted by Signal
Multiplier : 1.000000
Dilution : 1.000000

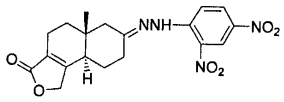
Signal 1: MWD1 A, Sig=363,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	66.566	VB	3.852	35842.44531	121.11443	100.0000
Totals :				35842.44531	121.11443	

Signal 2: MWD1 B, Sig=218,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.866	BB	0.346	16196.46289	740.90021	32.2115
2	66.555	BB	3.260	34085.16016	134.31332	67.7885
Totals :				50281.62500	875.21350	

HPLC Analysis of 2,4-DNP Derivative of (–)-Wilforonide



Column: (s,s)whelk-o1 No.786101
Solvent: n-hex/IPA=72/28; Flow: 1.1 mL/min;
Sample: xm-7-150f1, (-)-wilforonide-2,4-DNP Compd.

Injection Date : 9/25/01 11:00:14 AM Seq. Line : -
Sample Name : xm-7-150f1 Vial : 1
Acq. Operator : xuming Inj : -

Method : C:\HPCHEM\1\METHODS\XU.M
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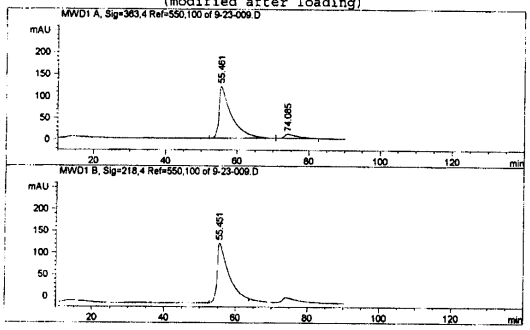


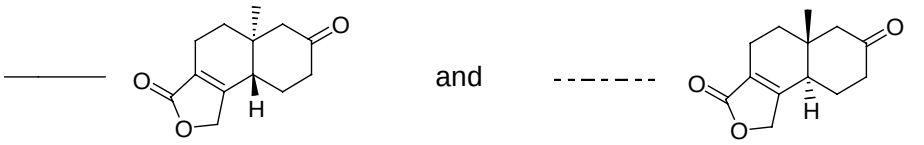
Area Percent Report

Sorted by Signal
Multiplier : 1.000000
Dilution : 1.000000

Signal 1: MWD1 A, Sig=363,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	55.461	BV	3.203	29026.74414	119.54575	92.0160
2	74.085	VB	3.427	2518.59424	9.73949	7.9840
Totals :				31545.33789	129.28525	

The CD spectra of synthetic (+) and (–)-wilforonide



(+)-**wilforonide** (–)-**wilforonide**