Supporting Information

Sassafras oil, carrot bits and microwaves: green lessons learned from the formal total synthesis of (-)-Talampanel

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1. Materials and Methods

All the reagents and chemicals were purchased from Sigma-Aldrich were used directly without further purification. Solvents (reagent grade) were used for extraction and flash chromatography. Reactions were monitored by analytical thin-layer chromatography (TLC, Merck silica gel 60 F-254 plates). The plates were visualized first with UV illumination followed by vanillin stain. Flash column chromatography was performed using silica gel (230-400 mesh). The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis. ¹H-NMR spectra were recorded at either 300 or 500 MHz and are reported in parts per million (ppm) on the δ scale relative to tetramethylsilane (TMS) as an internal standard.¹³C-NMR spectra were recorded at either 75 or 125 MHz and are reported in parts per million (ppm) on the δ scale relative to CDCl₃ (δ 77.00). Multiplicities are described as: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet); and coupling constants (J) are reported in Hertz (Hz). High resolution mass spectrometry (HRMS) data were reported in a MicroTOF (Bruker Daltonics) with ion mass/charge (m/z) ratios as values in atomic mass units. Optical Rotation values were measured in a Perkin-Elmer Polarimeter and P-2000 Jasco Polarimeter. The FT-IR spectra were recorded with the Bomem MB100 in wavenumber range from 4000 cm⁻¹ to 400 cm⁻¹. The microwave reactions were performed in a Discover[®] LabMate CEM Microwave. The conditions depend on each reaction.

2. Experimental Procedure and Characterization Data

3,4-methylenedioxyphenyl acetone (2). In a round-bottom flask, 36.4 mmol (4g) of safrole dissolved in methanol (2.3 ml) were added dropwise over 60 minutes to the flask containing 0.82 mmol (145 mg) of PdCl₂, 38,3 mmol (4.14 g) *p*-benzoquinone, 8 mL of methanol and 2 mL of deionized water. After the safrole addition was completed, the mixture was stirred for 6 hours. After this time, the mixture was filtered out and washed with 37 mL HCl 10% and extracted three times with dichloromethane (1 x 20 mL, 1 x 15 mL, 1 x 10 mL). The organic phases were combined and washed twice with 30 mL of saturated sodium bicarbonate, three times with 30 mL of saturated sodium chloride and three times with 30 mL of NaOH 5%. Then, the organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography. Elution with 40% hexane-10% ethyl acetate yielded 3.88 g (60%) as yellow oil.



¹H NMR (300 MHz, CDCl₃): $\delta = 6.77 - 6.62$ (m, 3H, H.C aromatic), 5.92 (s, 2H, H-C5), 3.59 (s, 2H, H-C8), 2.13 (s, 3H, H-C10). ¹³C NMR (75 MHz, CDCl₃): $\delta = 206.33$, 147.72, 146.51, 127.66, 122.32, 109.58, 108.27, 100.88, 50.32, 28.93. IR (cm⁻¹, KBr): 1714, 1492, 1356, 1246, 1038.

(S)- α -methyl-1,3-benzodioxole-5-ethanol (3). 1 mmol of 3,4 - methylenedioxypenyl acetone (1) (178 mg) was added to a suspension of cut carrot root (20 g) in 80 mL of distilled water, and the reaction mixtures were incubated in an orbital shaker (200 rpm) at room temperature for the time necessary until complete conversion as indicated by TLC. Then, the suspension was filtered off and extracted three times with ethyl acetate (3 x 125 mL). The organic phase was dried (Na₂SO₄) and then evaporated under reduced pressure. The final product was purified by flash chromatography. Elution with 30% hexane-10% ethyl acetate yielded 144 mg (80%) as brown oil.



¹H NMR (300 MHz, CDCl₃): $\delta = 6.64 - 6.76$ (m, 3H, H-C.aromatic), 5.92 (s, 2H, H-C.5), 3.92 - 3.98 (m, 1H, H-C.9), 2.56 - 2.73 (m, 2H, H-C.8), 1.78 (s, 1H, H-O), 1.22 (d, 3H, H-C10, J = 6.2 Hz). ¹³C NMR (75 MHz, CDCl₃): $\delta = 147.67$, 147.11, 132.18, 122.20, 109.61, 108.24, 100.80, 68.85, 45.33, 22.63. IR (cm⁻¹, KBr): 3397, 2991, 2890, 2790, 1490, 1244, 1039.[α]₅₈₉ = + 25.0°(*c*.1.36, CHCl₃) (Lit.¹: [α]₅₈₉ = + 34.0°

(*c*.1.0, CHCl₃).

(5RS,7S)-7,8-dihydro-7-methyl-5-(4-nitrophenyl)-5H-1,3-dioxolo-[4,5-G][2]-benzopyran

(4). 0.90 mmol of 2 (162 mg), 0.90 mmol of 4-nitrobenzaldehyde (136 mg) and a small amount of p-toluenesulfonic acid were added in a round-bottom flask. the flask is moved into microwave oven and irradiated at 150W for 10 minutes. At completion of the reaction, the resulting mixture of diastereisomers was purified by crystallization from EtOH yielded 203 mg (72%) as white solid.



¹H NMR (500 MHz, CDCl₃): $\delta = 8.22$ (d, J = 8.75Hz, 2H), 7.52 (d, J = 8.75Hz, 2H), 6.61 (s, 1H), 6.05 (s, 1H), 5.87 (dd, J = 1.3Hz, J = 11.15Hz, 2H), 5.74 (s,1H), 4.03 - 3.96 (m,1H), 2.86 - 2.81 (m, 1H), 2.69 (dd, J = 1.7Hz, J = 14.4Hz, 1H) 1.39 (d, J = 6.3 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): $\delta = 149.63$, 147.77, 146.67, 146.16, 129.51, 129.31, 127.31, 123.85, 108.45, 108.14, 106.09, 100.95, 79.87, 71.48, 36.38, 21.70. IR (cm⁻¹, KBr): 1606, 1519,1475, 1355, 1235, 1039. HRMS calcd. for C₁₇H₁₅NNaO₅ 336.0848, found 336.0841 [(M + Na)⁺].

(*5RS*, *7S*)-7,8-dihydro-7-methyl-5-(4-nitrophenyl)-5H-1,3-dioxolo-[4,5-G][2]-benzopyran-5ol (5). A solution of 3 (200 mg, 0.64 mmol) in 50 mL of dichloromethane and 2.5 mL of deionized water was stirred for 15 minutes. 0.64 mmol of 2,3-Dichloro-5,6-dicyano-1,4benzoquinone (145 mg) was added and the mixture was stirred for 3 hours. The reaction mixture was washed with solution of NaOH (1 mol.L⁻¹) and water, extracted three times with ethyl acetate and dried over sodium sulfate anhydrous; the organic layer was filtered by gravity and evaporated under reduced pressure. The final product was purified by flash chromatography. Elution with 40% hexane-10% ethyl acetate yielded 152 mg (72%) as an oil.



¹H NMR (500 MHz, CDCl₃): $\delta = 8.18$ (d, J = 9Hz ,2H), 7.76 (d, J = 9Hz, 2H), 6.57 (s, 1H), 6.40 (s, 1H), 5.88 (d, J = 1,25Hz, 1H), 5.84 (d, J = 1.5Hz, 1H), 4.43 - 4.36 (m, 1H), 3.36 (br s, 1H), 2.85 -2.78 (m 1H), 2.71 - 2.68 (m, 1H), 1.42 (d, J = 6.2Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): $\delta = 147.28$, 146.27, 145.31, 136.21, 130.96, 127.02, 123.27, 123.13, 111.49, 107.68, 107.25, 100.84, 97.46, 69.06, 65.56, 35.94, 30.63. IR (cm⁻¹, KBr): 3439, 3114, 3076, 2978, 2897, 1605, 1519, 1475, 1355, 1235, 1028. HRMS calcd. for C₁₇H₁₅NNaO₆ 352.0797, found 352.0791 [(M + Na)⁺].

(S)-acetic acid-[[6-(2-hydroxypropyl)-1,3-benzodioxol-5-yl] (4-nitrophenyl) methylene] hydrazide (6). To a round bottom flask were added 0.68 mmol (223 mg) of 4 and 0.68 mmol (50 mg) of acetylhydrazide. The mixture was stirred under microwave irradiation (200 W) for 5 minutes. The mixture was then cooled to room temperature. The final product was purified by flash chromatography. Elution with 100% ethyl acetate yielded 214 mg (82%) as a yellow foam.



¹H NMR (500 MHz, CDCl₃): $\delta = 9.00(s, 1H)$, 8.18 (dd, J = 9 Hz, J = 3Hz, 2H), 7.74 (dd, J = 2Hz, J = 9 Hz, 1H), 6.95 (d, J = 15,5Hz, 1H), 6.51 (d, J = 18.3Hz, 1H), 6.03 (ddd, J = 6.4Hz, J = 8Hz, J = 5.5Hz, 2H), 2.39 (d, J = 15Hz, 3H), 1.08 (dd, J = 2Hz, J = 6Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): $\delta = 173.42$, 170.56, 149.54, 148.25, 147.46, 142.95, 142.44, 132.88, 132.57, 127.13, 123.71, 122.80, 112.17, 107.96, 101. 98, 68.01, 67.41, 43.00, 20.54. IR (cm⁻¹, KBr): 3421, 3297, 2962, 2913, 1670, 1523, 1481, 1340. HRMS calc. for C₁₉H₁₉N₃NaO₆ 408.1172, found 408.1174 [(M + Na)⁺]

(*S*) - aceti acid - [[6 - [2 - [(methanessulfony)oxy]propyl] - 1,3 - benzoioxol - 5 - yl](4 - nitrophenyl) methylene]hydrazide (7). 1.55 mmol (596 mg) of 5 was solubilized with 15 mL of dichloromethane, and the resulting mixture was cooled to -10° C. 0.5 mL of triethylamine and 1.9 mmol of mesyl chloride (150 µL) were added respectively. After stirring for 30 minutes, the reaction mixture was washed with solution of HCl (2 mL, 1 mol.L⁻¹), water (2 mL) and brine (2 mL) and the organic phase was separated and dried over sodium sulfate anhydrous; the organic layer was filtered by gravity and evaporated under reduced pressure. The final product was purified by flash chromatography. Elution with 10% hexane-40% ethyl acetate yielded 640 mg (89%) as a yellow solid.



¹H NMR (300 MHz, CDCl₃): $\delta = 8.45$ (s, 1H), 8.21 (d, J = 9Hz, 2H), 7.75 (d, J = 9 HZ, 2H), 6.95 (d, J = 3Hz, 1H), 6.56 (d, J = 3Hz, 1H), 6.01 (d, J = 6Hz, 2H), 4.78 (m, 1H), 2.69 - 2.55 (m, 2H), ¹H NMR (300 MHz, CDCl₃): $\delta = 8.46$ (d, J = 6Hz, 1H), 8.22 (d, J = 9Hz, 2H), 7.76 (d, J = 9 HZ, 2H), 6.97 (d, J = 3Hz, 1H), 6.57 (d, J = 3Hz, 1H), 6.11 (d, J = 6Hz, 2H), 4.80 (m, 1H), 2.93 (s, 2H), 2.86 (s, 1H), 2.69 -2.55 (m, 2H), 1.28 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): $\delta = 206.96$, 172.86, 149.81, 148.28, 146.64, 129.39, 127.53 (2C), 123.86 (2C), 122.87, 111.26, 108.32, 108.19, 102.11, 39.91, 38.89, 30.91, 21.28, 20.95. IR (cm⁻¹, KBr): 1706, 1494, 1344, 1173, 1038, 924. HRMS calcd. for $C_{20}H_{21}N_3NaO_8S$ 486.0947, found 486.0944[(M + Na)⁺].

(R)-7-acetyl-8,9-dihydro-8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo[4,5-

h][2,3]benzodiazepine (8). To a sealed tube were added 0.215 mmol of **6** (100 mg), 0.236 mmol (77 mg) of Cs_2CO_3 and 0.5 mL of dimethylformamide. The reaction mixture was irradiated for 10 minutes at 200 W and heated at 70°C. The final product was purified by flash chromatography. Elution with 10% hexane-40% ethyl acetate yielded 74 mg (94%).



¹H NMR (300 MHz, CDCl₃): $\delta = 8.27$ (d, J = 9Hz, 2H), 7.75 (d, J = 9Hz, 2H), 6.76 (s, 1H), 6.48 (s, 1H), 6.02 (s, 2H), 5.39 (m, 1H), 3.02 (dd, J = 3Hz, J = 11.4Hz, 1H), 2.80 (dd, J = 6Hz, J = 6Hz, 1H), 2.33 (s, 3H), 1.07 (d, J = 9 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): $\delta = 206.95$, 149.34, 148.07, 146.28, 135.47, 130.03 (2C), 127.56, 125.42, 123.47 (2C), 109.97, 109.66, 101.76, 57.70, 38.37, 30.92, 22.90, 18.77. IR (cm⁻¹, KBr): 1681, 1693, 1518, 1344, 1235, 1036. HRMS calcd. for C₁₉H₁₇N₃NaO₅ 390.1066, found 390.1067 [(M + Na)⁺]. [α]₅₈₉ = +54° (*c*. 1.0, CHCl₃) (Lit.²: [α]₅₈₉ = + 67.7° (*c*.1.0, CHCl₃) for >99.9% ee)

(-)-7-acetyl-5-(4aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-Dioxolo-[4,5-

h][2,3]benzodiazepine (1). To a 2 mL eppendorf, 0,11 mmol (40 mg) of 7 was suspended in 0.5 mL of vinegar and 30 mg of steel wool. After sonication for 1 hour, the mixture was filtered in a Pasteur pipette and extracted with ethyl acetate. The organic phase was separated and dried over sodium sulfate anhydrous; the organic layer was filtered by gravity and evaporated under reduced pressure. The final product was purified by flash chromatography. Elution with 10% hexane-90% ethyl acetate yielded 60% (22 mg).



¹H NMR (300 MHz, CDCl₃): $\delta = 7.53$ (d, J = 9Hz, 2H), 6.92 (s, 1H), 6.69 (d, J = 6 Hz, 2H), 6.59 (s, 1H), 6.01 (d, J = 9Hz, 2H), 5.26 - 5.18 (m, 1H) , 4.03 (br , 2H - NH₂), 2.69 - 2.63 (m, 2H), 2.02 (s, 3H), 1.31 (d, J = 6Hz, 3H). ¹³C NMR: according to literature.² IR (cm⁻¹, KBr): 3444, 2925, 1605, 1486, 1375. m/s [(M + Na)⁺]. [α]₅₈₉ = -22° (*c*. 1.43, MeOH) (Lit.²: [α]₅₈₉ = -303.7° (*c*.1.0, MeOH) for >99.9% *ee*).

































Figure 1. GC chromatograms from the reduction reaction of compound **(2**) with (A) NaBH₄ and (B) carrot bits.Chiral GC column : Chirasil-Dex CB-β-cyclodextrin 25 m x 0.25 mm.

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