An Improved Synthesis of the ‘Miracle Nutrient’ Coenzyme Q_{10}

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Supporting Information

2,3,4-Trimethoxybenzaldehyde and 2-hydroxy-3,4-dimethoxybenzaldehyde (**11**) were prepared by literature procedures.[1] Spectroscopic data matched that of previously reported material.

Solanesyl chloride: PCl_3 (180 µL, 2.10 mmol) and DMF (110 µL, 2.10 mmol) were added to a 25 mL pear-shaped flask and stirred slowly at rt for 10 min until the solution solidified into a white solid. Solanesol (2.20 g, 3.50 mmol) was dissolved in 7.0 mL THF and added *via* cannula to the PCl_3/DMF reagent. The heterogeneous reaction was stirred at rt for 2.0 h, and then the solvent was completely removed *in vacuo* to produce a yellow oil. Absolute ethanol (10.0 mL) was added, and the flask was agitated. The white precipitate was filtered from solution to yield 2.16 g (95.1%) solanesyl chloride as an off-white solid. Spectroscopic data matched that of previously reported material.[1]

2-Chloromethyl-5,6-dimethoxy-3-methyl-[1,4]benzoquinone (1): A flame-dried 10 mL round-bottomed flask was equipped with a magnetic stir bar and purged with argon. DMF (88 µL, 1.13 mmol) and PCl_3 (99 µL, 1.13 mmol) were combined and stirred vigorously until the solution completely solidified to a white solid, *ca.* 5 min. In a separate 10 mL flask 2-hydroxymethyl-5,6-dimethoxy-3-methyl-[1,4]benzoquinone (240 mg, 1.13 mmol) was dissolved in THF (5.0 mL). This solution was transferred to the preformed Vilsmeyer reagent *via* cannula, and the bright red heterogeneous solution was stirred at rt for 3 h. The reaction was then diluted with Et_2O (10 mL), washed with H_2O (10 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo,* and chromatographed using 50% EtOAc/hexanes to afford a red oil (240 mg, 93% yield). $R_f = 0.64$ (50% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (s, 2 H), 4.04 (s, 3 H), 4.02 (s, 3 H), 2.16 (s, 3H, CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 184.1, 182.0, 145.1, 144.6, 142.7,

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[1] Lipshutz, B. H.; Mollard, P. M.; Pfeiffer, S. S.; Chrisman, W. *J. Am. Chem. Soc.* **2002**, *124*, 14282.

137.1, 61.5, 61.4, 35.3, 12.2; HRMS *m/z* (EI, 70 eV) calcd for $C_{10}H_{11}O_4Cl$ 230.0346, found 230.0348.

Solanesyl alkyne (8): A solution of *n*-butyllithium (30 mL, 75 mmol, 2.5 M in hexanes, 3.75 equiv) was added slowly to dry THF (60 mL), and then cooled to –7 °C. Gaseous propyne (670 mL, 30 mmol, 1.5 equiv) was added at –7 °C. After complete addition of the propyne gas, the mixture was stirred for 1 h at –5 to 0 °C, warmed to rt and stirred at that temperature for further 80 min. A solution of solanesyl chloride **(6)**, (purity 75.5% by weight, 17.3 g, 20 mmol, 1.0 equiv) in THF (80 mL) was then added dropwise to the aforementioned solution at temperatures between 0 and 2 °C. The reaction mixture was then stirred at 0 °C for 90 min and then poured into aqueous NH_4Cl solution. The organic phase was separated, the water phase was extracted once with ethyl acetate (60 mL), the combined organic phases were washed with brine, and then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure to give 17.6 g of a light brown oil, containing 60.0 weight-% of solanesyl alkyne substrate (80.9% yield). Spectroscopic data matched that of previously reported material.[1]

2-Hydroxymethyl-5,6-dimethoxy-3-methylphenol (12): To a 250 mL round-bottomed flask was added 2-hydroxy-3,4-dimethoxy-6-methylbenzaldehyde (9.81 g, 50.0 mmol) and MeOH (100 mL). The resulting pale-yellow solution was cooled to 0 ºC and $NaBH_4$ (495 mg, 13.0 mmol) was added in three portions over the course of 5 min. The reaction was complete within minutes (as determined by TLC analysis) to give a colorless solution. The reaction was quenched by addition of *ca.* 1 mL H_2O and the solvent was removed under reduced pressure to yield a colorless oil. The viscous oil was subjected to a silica gel filtration to remove residual borate salts, using straight EtOAc as eluent. Concentration afforded a white crystalline solid (9.40 g, 95% yield). R_f = 0.34 (50% EtOAc/hexanes); mp = 87-88 ºC; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 6.31 (s, 1 H), 6.22 (s, 1 H), 4.73 (d, *J* = 6 Hz, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.34 (s, 3 H), 2.11 (d, *J* = 7Hz, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 151.6, 148.4, 133.8, 132.8, 118.2, 61.2, 57.7, 55.9, 19.3; HRMS *m/z* (EI, 70 eV) calcd for $C_{10}H_{14}O_4$ 198.0892, found 198.0892.

2-Hydroxymethyl-5,6-dimethoxy-3-methyl-[1,4]benzoquinone (13): A 25 mL round-bottomed flask was charged with 2-hydroxymethyl-5,6-dimethoxy-3-methylphenol (100 mg, 0.50 mmol), *N,N´*-bis(salicylidene)-ethylenediaminocobalt(II) (8.1 mg, 0.025 mmol, 5.0 mol %), DMF (3.0 mL), and toluene (2.0 mL). Oxygen gas was continuously bubbled through the stirring mixture. DMF was added as needed over time to keep the volume at ~5 mL; and an additional 8.1 mg catalyst was added after 8 h. The reaction was complete after 16 h as judged by TLC. The reaction mixture was concentrated under reduced pressure to a volume of *ca*. 1 mL, and then dissolved in 5 mL CH_2Cl_2. The organics were washed with H_2O (2x 5 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and chromatographed using 50% EtOAc/hexanes to afford a red oil (96 mg, 91% yield) which solidified upon standing to a bright red crystalline solid. $R_f = 0.28$ (50% EtOAc/hexanes); mp = 45-46 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (d, *J* = 7 Hz, 2H, $C\underline{H}_2OH$), 4.01 (s, 6H, $OC\underline{H}_3$), 2.52 (t, *J* = 7 Hz, 1H, $CH_2O\underline{H}$), 2.10 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 185.5, 184.7, 145.0, 144.4, 140.6, 138.9, 61.5, 61.4, 57.3, 11.9; HRMS *m/z* (EI, 70 eV) calcd for $C_{10}H_{12}O_5$ 212.0685 found 212.0684.