Efforts Directed Toward the Synthesis of Colchicine; Application of Palladium-Catalyzed Siloxane Cross-Coupling Methodology

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SUPPLEMENTAL MATERIAL

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^a CHBr_3 , KOt-Bu , pentane, 61%. ^b AgOAc , HOAc , I_2 , H_2O , 81%. ^c PCC , CH_2Cl_2 , 90%. ^d K_2CO_4 , MeOH , H_2O , then HCl , 74%. ^e Me_2SO_4 , K_2CO_4 , acetone/ H_2O , 89%.

7,7-Dibromo-bicyclo[4.1.0]hept-3-ene (S1). The dibromide was prepared using a modified procedure of Hofmann.¹ To 300 mL of *tert*-butyl alcohol was added 10.0 g of potassium. Upon dissolution of all of the potassium, excess alcohol was removed *in vacuo*. The resulting white potassium *tert*-butoxide was dried *in vacuo* for 12 h. The dry potassium *tert*-butoxide (14.6 g, 130 mmol) was added to 250 mL of pentane. The suspension was cooled to 0 °C and 25.0 mL (260 mmol) of 1,4-cyclohexadiene was added. With stirring, 11.0 mL (130 mmol) of bromoform was added over 30 min at a rate to maintain an internal temperature between 0 °C and 5 °C. The reaction was stirred for an additional 30 min at 0 °C followed by the addition of 200 mL of water. The organic layer was separated, and the aqueous fraction extracted with pentane (100 mL x2). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo* to give a pale yellow oil. Column chromatography (pentane, TLC R_f = 0.59) yielded colorless crystals (60%) mp 36-37 °C (lit. 36.8-37 °C).² The IR matched that reported by Coates.² The ^1H NMR and ^{13}C NMR match that reported by Rigby.³

(1 α , 3 β , 4 β , 6 α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-ol (S2). The hydroxyacetate was prepared using a modified procedure of Banwell.⁴ Iodine (4.47 g, 17.6 mmol) was added over a 30 min period to a stirred mixture of 7,7-Dibromo-bicyclo[4.1.0]hept-3-ene (4.00 g, 16.0 mmol), and silver

S3 acetate (5.34 g, 32.0 mmol) in acetic acid (70 mL). Upon completion of the addition of the iodine, water was added (0.288 mL, 16.0 mmol). The reaction was stirred in the dark for 3 days. The mixture was then filtered through celite and diluted with 100 mL of CH₂Cl₂. Water (100 mL) was added, followed by solid Na₂CO₃ until all of the acetic acid had been consumed. The layers were separated and the aqueous layer was washed with 75 mL of CH₂Cl₂ twice. The combined organic layers were washed with successively with saturated NaHCO₃ (100 mL), 20% NaHSO₃ (100 mL), water (100 mL), and brine (100 mL), dried with MgSO₄, and concentrated *in vacuo*. Column chromatography (1:1 hexanes/EtOAc, TLC R_f = 0.39) yielded a white solid (81%) mp 82.6-83.8 °C (lit. 82-83 °C).⁴ The IR, ¹H NMR, and ¹³C NMR matched that reported by Banwell.⁴

(1 α , 4 β , 6 α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-one (S3). The α -acetoxy ketone was prepared according to a modified procedure of Banwell.⁴ (1 α , 3 β , 4 β , 6 α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-ol (3.91 g, 9.50 mmol) was added to 100 mL of CH₂Cl₂. Pyridinium chlorochromate (5.11 g, 24.0 mmol) was then added in one portion. The reaction was stirred at room temperature until TLC indicated the all of the starting alcohol had been consumed (2 h). The reaction was concentrated to 1/5 of the original volume and 100 mL of ether was added. The mixture was then filtered through a short pad of silica gel using 500 mL of 1:1 ether/CH₂Cl₂. The solvents were removed *in vacuo* to produce a light brown solid. Column chromatography (3:1 hexanes/EtOAc, TLC R_f = 0.39) yielded a white solid (90%) mp 119.6-120.3 °C (lit. 118-120 °C).⁴ The IR, ¹H NMR, and ¹³C NMR matched that reported by Banwell.⁴

5-Bromo-2-hydroxycyclohepta-2,4,6-triene-1-one (S4). 5-Bromotropolone was prepared according to a literature procedure.⁴

5-Bromo-2-methoxy-cyclohepat-2,4,6-trien-1-one (S5). Dimethyl sulfate (0.283 mL, 2.99 mmol) was added to a stirred solution of K₂CO₃ (1.03 g, 7.47 mmol) and 5-Bromo-2-hydroxycyclohepta-2,4,6-triene-1-one (500 mg, 2.49 mmol) in 10 mL of 90:10 acetone/water. The bright yellow suspension was refluxed for 4 h to produce a cloudy white mixture. The acetone was then removed *in vacuo* and the remaining mixture extracted with CH₂Cl₂ (30 mL x3). The combined organic extracts were dried

^{S4} (MgSO₄) and concentrated *in vacuo* to produce pale yellow needles (89%) mp 136.2-137.0 °C (lit. 135-137 °C).⁴ The IR, ¹H NMR, and ¹³C NMR matched that reported by Banwell.⁴

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