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PREPARATION OF A BIS-MEM ASCORBIC ACID-LIPOIC ACID CONJUGATE

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Abstract: The preparation of a bis-MEM ascorbic acid-lipoic acid conjugate in support of pharmacodynamic and pharmacokinetic studies has been achieved through a four-step convergent synthesis.

Keywords: Ascorbic acid, lipoic acid, conjugation

Introduction

Reactive oxygen species (ROS) are reactive compounds suspected to cause damage to nucleic acids, proteins, and cells. In addition, there is evidence to support that ROS plays a role in the progression of Alzheimer's disease (AD).[I] Lipoic acid is well known as a dietary supplement and biological antioxidant and as such has been tested *in vitro* against ROS.[II] Additionally, other possible applications include treatment for type 2 diabetes,[III] multiple sclerosis,[IV] among other therapeutic applications.[V]

Our interest in conjugates of naturally occurring antioxidants as a putative treatment for AD and other diseases involving oxidative degradation has been described elsewhere.[VI,VII]

This report summarizes the synthesis of ascorbic acid – lipoic acid conjugate as shown in Scheme 1. In addition to the described protecting group strategy, a few other strategies were attempted prior the selection of the MEM group. Compound **6** with the corresponding benzyl protecting group in lieu of the MEM group was prepared; however, all attempts to afford the debenzylation failed. Also, protection of **1** with TBSCl afforded a mono-protected compound. Based upon these observations, the bis-MEM protecting group was determined to be optimal to prepare protected derivative **6**.

Ascorbic acid acetonide **1** was reacted with MEMCl in the presence of diisopropylethyl-amine in dichloromethane to afford compound **2**. Selective deprotection of compound **2** was attempted under various conditions and 80% aqueous acetic acid at 45 °C was finally selected

to afford compound **3**. The coupling reaction of acid chloride **5** with compound **3** in the presence of triethylamine afforded compound **6**.

Experimental

General

^{1}H NMR (300 MHz) data were obtained from a Varian Mercury 300MHz nuclear magnetic resonance spectrometer referencing tetramethylsilane. Preparative HPLC was performed on a Teledyne ISCO system using a gold column (125 g cartridge). Analytical HPLC analysis was performed on a Chemstation 1100 LC System using a Phenomenex Luna C18-2 column. All reagents were obtained from commercial sources and were used with further purification.

Synthesis of (*R*)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,4-bis((2-methoxyethoxy)methoxy)furan-2(5H)-one (2) A 1-L, 3-neck round bottom flask was charged with **1** (19.7 g, 91.2 mmol, 1 equiv.,)[VIII], anhydrous dichloromethane (400 mL, 20 vol) and diisopropylethylamine (28.3 g, 219 mmol, 2.4 equiv., Aldrich lot # 02696KMV). MEMCl (2-methoxyethoxymethyl chloride, 25 g, 200 mmol, 2.2 equiv.) was added dropwise maintaining the temperature at <30 °C. The mixture was stirred at room temperature for 1 h and TLC analysis indicated the reaction was complete. The mixture was washed with water (300 mL), dried (sodium sulfate, anhydrous), filtered, and concentrated under reduced pressure. The crude product was purified using a short silica gel column (100 g silica gel, 50-75% ethyl acetate/hexanes) to afford the product as a colorless oil (35.1 g, 98%,); ^{1}H NMR ($CDCl_3$) δ 5.55 (s, 2H, -O-CH_2-O-); 5.22 (dd, 2H, -O-CH_2-O-, *J* = 6.0 Hz); 4.57 (d, 1H, -OCH- , *J* = 3.0 Hz); 4.31 (m, 1H, -OCH-); 4.08 (dt, 2H, -CH_2-O-, *J* = 6.6 Hz); 3.88-3.80 (m, 4H, -CH_2-O-); 3.55-3.51(m, 4H, -CH_2-O-); 3.35 (s, 6H, -OCH_3 x 2); 1.35 (s, 3, acetal CH_3); 1.31 (s, 3, acetal CH_3).

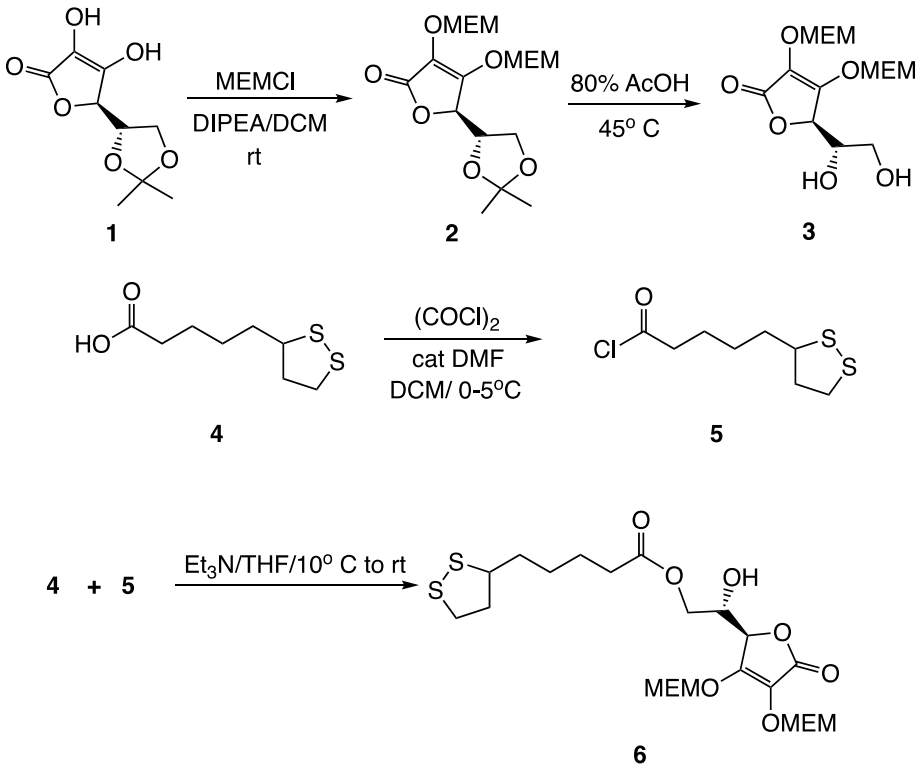
Synthesis of (*R*)-5-((*S*)-1,2-dihydroxyethyl)-3,4-bis((2-methoxyethoxy)methoxy)furan-2(5H)-one (3). A 250-mL, 3-neck round bottom flask was charged with compound **2** (10 g, 39.2 mmol) and 80% aq. acetic acid (60 mL, 6 vol). The mixture was heated at 45 °C for 2 h. TLC analysis indicated the reaction was complete. The mixture was concentrated under reduced pressure in the presence of toluene as the azeotrope. The crude was combined with two similar batches and purified by two consecutive column chromatography (1-5% MeOH/DCM) to afford product **3** as a colorless viscous oil (6.5 g, 24%,); ^{1}H NMR ($CDCl_3$) δ 5.66 (d, 1H, -OCH, *J* = 5.7 Hz); 5.42 (d, 1H , -OCH, *J* = 6.0 Hz); 5.21 (q, 2H, -OCH- , *J* = 6.0 Hz); 4.74 (s, 1H, -OH); 3.95 (br s, 1H, -OH); 3.88-3.57 (m, 7H, -OCH_2CH_2O-; -OCH3); 3.57-3.53(m, 4H, -CH_2-O-); 3.37-3.35 (m, 7H, -OCH_2CH_2O-; -OCH_3).

Synthesis of (*S*)-2-((*R*)-3,4-bis((2-methoxyethoxy)methoxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl 5-(1,2-dithiolan-3-yl)pentanoate (6). A 50-mL, 3-neck round bottom flask was charged with DL-lipoic acid (1.17 g, 5.7 mmol, 1 equiv., Toronto Research Chemicals lot # 6-XYZ-87-1), anhydrous dichloromethane (20 mL, 18 vol) and anhydrous *N*,*N*-dimethylformamide (5 drops, catalytic) then cooled to <5 °C. Oxalyl chloride (0.79 g, 6.3 mmol, 1.1 equiv., Aldrich lot # 46296KMV) was added dropwise at <5 °C. The mixture was stirred for 2 hours while allowed to warm to room temperature. The solution was directly used for the coupling reaction without further characterization.

A separate 250-mL, 3-neck round bottom flask was charged with **3** (2 g, 5.7 mmol, 1 equiv.), anhydrous tetrahydrofuran (40 mL, 20 vol) and triethylamine (0.97 g, 17 mmol, 3 equiv.,

Aldrich lot # 44596DM) then cooled to <10 °C. The acid chloride solution was added dropwise at <10 °C and the mixture stirred at room temperature for 3 hours. TLC analysis indicated the reaction was complete. The mixture was diluted with MTBE (50 mL) and washed with 5% aq. citric acid (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL) and the combined organic phases were dried (anhydrous sodium sulfate) then filtered. The crude product was purified by silica gel column (30-40% ethyl acetate/hexanes) to afford product **6** as a light-yellow oil (1.9 g, 62%). A catalytic amount of cysteine methyl ester as the stabilizer was added to the pure fractions before concentration). ^{1}H NMR ($CDCl_3$) δ 5.77 (d, 1H, -OCH, *J* = 6.0 Hz); 5.38 (d, 1H , -OCH, *J* = 6.0 Hz); 5.26 (d, 2H, -OCH-, *J* = 1.5 Hz); 4.73 (s, 1H, -OH); 4.35-4.15 (m, 3H, $-OCH_2$, -OCH); 3.89-3.87 (br m, 4H, $-OCH_2CH_2O$-); 3.58 (br m, 5H, $-CH_2$-O-, $-OCH_3$); 3.38 (br m, 6H, $-OCH_2CH_2O$-; $-OCH_3$); 3.14 (m, 2H $-SCH_2$-); 2.45 (sextet, 1H, -SCH-, *J* = 5.1 Hz); 2.38 (t, 2H, -C**H$_2$**-CH_2-, *J* = 7.3 Hz); 1.93 (sextet, 1H, -SCH-, *J* = 5.1 Hz); 1,69 (br m, 5H, $-CH_2-CH_2$-); 1.48 (br m, 2H, -C**H$_2$**-CH_2-, diastereotopic -CH). LC-MS exact mass = 540.17 amu; 96% pure.

Scheme 1



Conclusion

The bis-MEM ascorbic acid-lipoic acid conjugate **6** was successfully prepared by a convergent synthesis in four total steps. In addition to rat brain homogenate assays to determine brain uptake, future work will also include a study to optimize the deprotection step to form **3**.

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