African Journal of Pure and Applied Chemistry Vol. 7(1), pp. 31-34, January 2013
Available online at http://www.academicjournals.org/AJPAC
DOI: 10.5897/AJPAC11.007
ISSN 1996 - 0840 ©2013 Academic Journals

Full Length Research Paper

Synthesis of cholesteryl-(3,4-dihydroxy-5-methoxy tetrahydro-furan-2-yl) methanone

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Accepted 15 January, 2013

Various biological membranes are synthesized from sugars-based compounds. The hydrophobic groups of them made up the amphiphilic properties in the structure of membrane that consisted fatty acids, and long chain alkyl groups. It had established that cholesterol was an integral component and it affects the fluidity of membranes. We prepared the cholesteryl-(3, 4-dihydroxy-5-methoxy-tetrahydro-furan-2-yl)-methanone from reaction of N-methoxy-N-methyl amide as an effective acylating agent, Weinreb amide, with cholesteryl chloride. Spectroscopic methods elucidated the structure of these compounds.

Key words: Cholesterol, Weinreb, membrane, mannose.

INTRODUCTION

The biomembranes had been built from a water-induced self organized architecture of amphiphilic molecules. They are made from polar hydrophilic head groups and non-polar hydrophobic part like cholesterol. In prokaryotes, the triterpenoid compounds had been the membrane stabilizers (Dannenmuller et al., 2000). The efficiency of the stabilizers had been assigned to fit their dimensions and to their amphiphilic character locking them in the membrane (Pozzi et al., 1996). In the previous studies, it suggested that cholesterol were inserted perpendicularly to the surface of the membrane and that its inclusion improves the order of the chain (Sedaghat et al., 2004).

The present study shows that a new convenient strategy of synthetic route leads to the preparation of the triterpenoid compounds in good overall yields (Bourgeois and Gueyrard, 2005). In order to prepare the compound, we used the reaction of N-methoxy-N-methyl amide (Duvold, 2000) as a polyhydroxylated moiety with organolithium species in tetrahydrofuran solvent (Francais, 1991) to form ketones type bond between the hydrophilic and hydrophobic parts of molecule.

EXPERIMENTAL

The present study was a combinatorial synthesis method for preparation of biocompatible compound. All the reagents were purchased from Merck Chemical Company. The proton nuclear magnetic resonance (HNMR) and carbon NMR (CNMR) spectra (in $CDCl_3$, internal standard Me_4Si) were recorded on a Bruker 300 and 500 MHz spectrometers. The analytical thin layer chromatography (TLC) was performed on silica gel plate (Merck). Infrared spectra were recorded on a Perkin-Elmer 297 instrument. Reactions were monitored by TLC.

1-(6-Methoxy-2, 2-dimethyl-tetrahydro-furo [3, 4- d] [1, 3] dioxol-4-yl)-ethane-1, 2-diol

A mixture of D-mannose (5 g, 27.77 mmol), 2,2-dimethoxypropane (17 ml), acetone (16.5 ml), methanol (16.5 ml) and concentrated HCl (0.5 ml) was refluxed for 2 h. The cooled mixture was diluted with water (50 ml) and concentrated under reduced pressure at below 30°C. Methanol (50 ml) and concentrated HCl (1.25 ml) were then added. The reaction mixture was stirred at room temperature for 3 h, neutralized with a saturated solution of sodium hydrogen carbonate, and evaporated to dryness. The residue was taken in hot chloroform and solution was filtrated through the celite pad. The solvent evaporated to give methyl-2, 3-O-isopropylidene-mannofuranoside (Figure 1) as yellow oil (5.6 g, 85%).

6-Methoxy-2, 2-dimethyl-tetrahydro- furo [3, 4- d] [1, 3] dioxole-4-carbaldehyde

Sodium periodate (5.46 g, 25.52 mmol) dissolved in minimum of water was added to a solution of methyl-2, 3-O-isopropylidene-

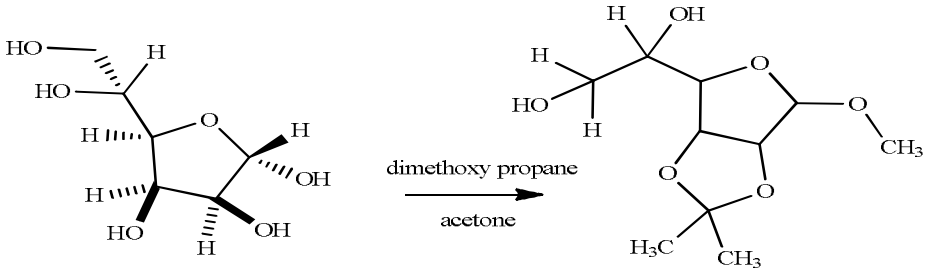

Figure 1. H-NMR (300 MHz, $CDCl_3$): δ = 4.87 (s, 1H), 4.72 (d, 1H), 4.49 (d, 1H), 3.12 (brs, 1H), 4,30 (dd, 1H), 3,57 (dd, 1H), 3.61 (dd, 1H), 3.32 (s, OCH_3, 3H), 1.37 (s, CH_3, 3H), 1.22 (s, CH_3, 3H); C-NMR (500 MHz, $CDCl_3$): 113, 107, 64.8, 80.4, 79.5, 70.7, 85.1, 54.9, 26.3, 25.1; FTIR: 3448, 1638, and 1084 cm^{-1}.

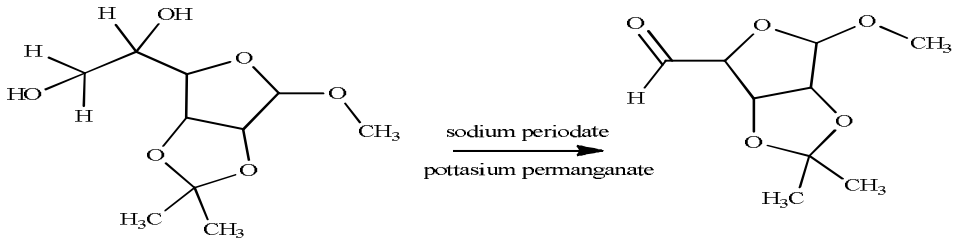

Figure 2. H-NMR (500 MHz, $CDCl_3$): δ = 9.5 (s, H fermyl), 5.1 (s, 1H), 5.08 (d, 1H), 4.63 (d, 1H), 4.38 (d, 1H), 3.36 (s, OCH_3, 3H), 1.44 (s, CH_3, 3H), 1.30 (s, CH_3, 3H); C-NMR (500 MHz, $CDCl_3$): 200.7, 109.1, 89.4, 84.4, 80.7, 55.6, 25.8, 24.8; FTIR: 3448, 1638, and 1088 cm^{-1}.

mannofuranoside (5.43 g) in methanol (150 ml). The mixture was stirred for 2 h at room temperature and the solvent was evaporated under reduced pressure (Duvold, 1995). The residue was taken in acetone and the solution was filtered through a celite pad. Thefiltrate was evaporated to dryness to give the intermediate aldehydes (Figure 2) (4.1 g, 75%).

6-Methoxy-2, 2-dimethyl-tetrahydro- furo [3, 4- d] [1, 3] dioxole-4-carboxylic acid or Methy-2, *3*-O-isopropylidene-a-D-lyxofuranosiduronic acid

The intermediate aldehydes dissolved in water (120 ml) and a solution of NaOH (0.23 g) in water (5 ml) and sodium permanganate (7.332 g, 46.4 mmol) in water (200 ml) were added at 0°C. The mixture was stirred at room temperature for 16 h. The excess of potassium permanganate was removed with a solution of H_2O_2 (33%) and the mixture filtered through a celite pad (Bourgeois and Gueyrard, 2005). The filtrate concentrated to 100 ml and washed twice with ethyl acetate (100 ml). The aqueous layer was acidified to pH 3 at 0°C with HCl and extracted with ether (2 × 100 ml). The organic layer was washed with a saturated sodium chloride solution, dried (Na_2SO_4), filtered and evaporated under reduced pressure to yield acid as a colorless oil (3.2 g, 68%) (Figure 3).

6-Methoxy-2,2-dimethyl-tetrahydro- furo [3, 4-d] [1, 3] dioxole-4-carboxylic acid methoxy-methyl-amide

The acid compound (3 g) dissolved in dichloromethane (30 ml) and 2.31 g of carbonyldiimidazole was added portion wise over 10 min at 22°C. The solution was stirred at room temperature for 30 min. N,O-dimethylhydroxylamine hydrochloride (4 g) was dissolved in water (17 ml) and 10 N sodium hydroxide (7 ml) was added to it. The solution was extracted with dichloromethane (3 × 17 ml) and the extract dried by $MgSO_4$. After stirring for 3 days, the solution was washed with 0.5 M citric acid, sodium bicarbonate solution, and evaporated in vacuum to give the compound as colorless oil (1.6 mg, 54) (Figure 4).

[17-(1,5-Dimethyl-hexyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl]-(6-methoxy-2, 2-dimethyl-tetrahydro-furo [3, 4-d] [1, 3] dioxol-4-yl)-methanone

Lithium and di tert - butyl bromide were added to a flask and after 45 min of stirring, the flask cooled by cold acetone and ice. Cholesteryl chloride solution added to it and to continue stirring for 3 h until the lithium cholesteryl formed. The compound 4 (1.6 mg) were mixed into the flask and to continue stirring it for 3 h under the 0 degree. The organic layer washed, dried, filtered and evaporated under reduced pressure to yield the yellow solid (1.1 mg, 54%) (Figure 5).

RESULTS AND DISCUSSION

The purpose of the study was to synthesis the sugar-based membrane (Barton et al., 1994; Blunk and Bierganns, 2006; Tirnaksiz and Kalsin, 2005) and according to the results, carbon-carbon bond was formed by Weinreb method (Just and Martel, 1973; Nahm and Weinreb, 1981). The synthesis took place as a modified functional group in ribosyl portion of compound.

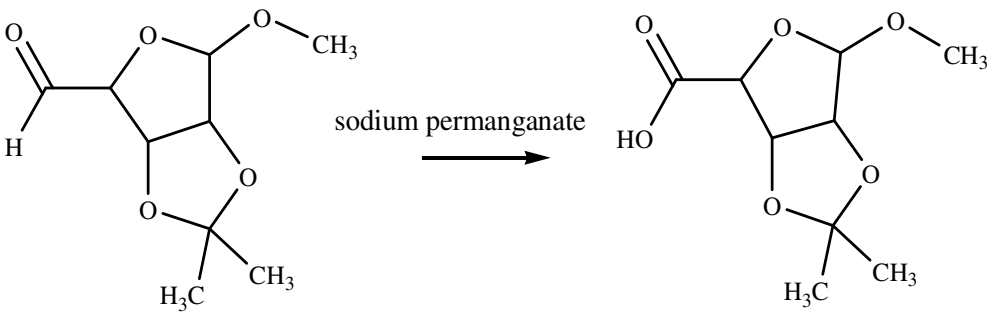

Figure 3. H-NMR (500 MHz, $CDCl_3$): δ = 5.1 (s, 1H), 5.07 (d, 1H), 4.9 (d, 1H), 4.67 (d, 1H), 3.35 (s, OCH_3, 3H), 1.50 (s, CH_3, 3H), 1.36 (s, CH_3, 3H); C-NMR (300 MHz, $CDCl_3$): 177, 113, 107, 83.9, 80.3, 79.1, 54.9, 25.7, 24.7.

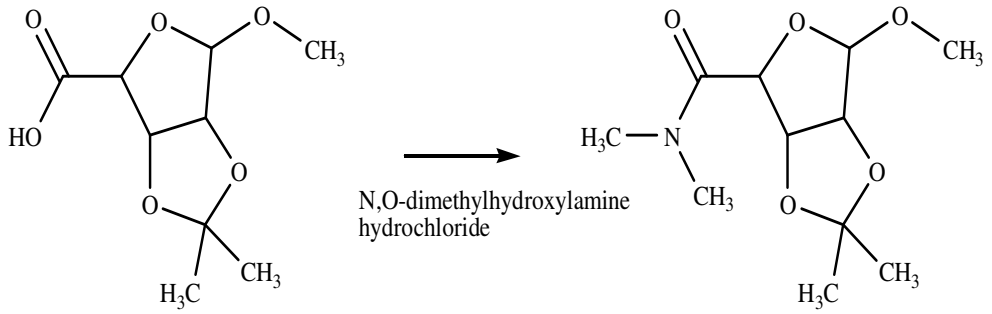

Figure 4. H-NMR (500 MHz, CDCl3): δ = 5.1 (s, 1H), 4.9 (d, 1H), 4.8 (brs, 1H), 4.6 (dd, 1H), 3.7 (s, 3H, OCH3), 3.38 (s, 3H, OCH3), 3.12 (s, 3H, OCH3), 1.43 (s, OCH3 , 3H), 1.35 (s, CH3, 3H); FTIR: 3400, 1638, 1062, 913, and 742 cm^{-1}.

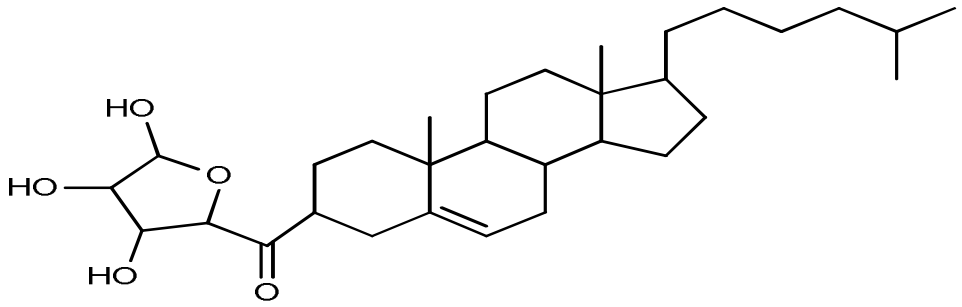

Figure 5. H-NMR (500 MHz, CDCl3): δ = 5.1 (s, 1H), 4.9 (d, 1H), 4.8 (brs, 1H), 4.6 (dd, 1H), 3.7 (s, 3H, OCH3), 3.12 (s, 3H, OCH3); FTIR: 3400, 1638, 1385, 1062, 913, and 742 cm^{-1}.

It started by protecting hydroxyl groups on sugar ring and these part of chain synthesis increased the yield of reaction (Petru, 2005). We applied the amide form of side carbohydrate to connect the cholesteryl group (Dual, 1995). This synthetic protocol represents a useful tool for the access to natural sugar derivatives of biological interest as well as to labeled ribose compounds for biosynthetic studies.

Conclusion

The synthesis is based on modifying functional group in ribosyl side group starting from protecting by hydroxyl groups on sugar ring and subsequent reaction of functional moieties. In a key step, an aldehyde is oxidized to the corresponding acidic group by means of an oxidant. This synthetic protocol represents a useful tool

for the access to natural sugar derivatives of biological interest as well as to label ribosyl compounds for biosynthetic studies.

REFERENCES

Barton DHR, Gero SD, Quiclet-sire B, Samadi M (1994). Stereocontrolled radical reaction in carbohydrate and nucleoside chemistry. Tetrahedron Asymmetry 5:2123-2136.

Blunk D, Bierganns P (2006). New speciality surfactants with natural structural motifs. New J. Chem. 30: 1705-1709.

Bourgeois MJ, Gueyrard D (2005). Exploration of Synthetic Pathways to Unprecedented TerpenylThioglycosides. Letts. Org. Chem. 2:665-669.

Dannenmuller O, Arakawa K, Eguchi T, Kakinuma K, Blanc S, Albrecht AM, Schmutz M, NakataniY, Ourisson G (2000). Membrane Properties of Archeal MacrocyclicDiether Phospholipids. Chem. Eur. J. 6:645-654.

Duvold T (1995). Benzyl 2,3-o-isopropylidene- b- D- ribo- 1,4-pentodialdofuranoside as a D-ribose Chiron for the synthesis of terpenyltetraols and aminotriols. Tetrahedron Letts. 36:3153-3157.

Duvold T, Rohmer M (2000). Synthesis of 3b-(5-D-ribityl) cholestane, a putative biological precursor for fossil 3-alkylsteranes. Tetrahedron Letts. 41:3875-3878.

Francais GW (1991). Approaches to the synthesis of terpenylcarbohydrate. Acta Chem. Scandinavica 45:18-23.

Just G, Martel A (1973). C-nucleosides and related compounds ,synthesis of D,L-3,4-Isopropylidene -2,5- anhydroallose: A novel periodate cleavage. Tetrahedron Letts. 17:1517-1525.

Nahm S, Weinreb S (1981). N-methoxy N-methylamide as effective acylating agents. Tetrahedron Letts. 22:3815-3818.

Petru ID (2005). Chemical synthesis of cholesteryl b-D-galactofuranoside and pyranoside. Carbohydr. Res. 340:2052-2058.

Pozzi G, Birault V, Werner B, Dannenmuller O, Nakatani Y, Ourisson G (1996). Single-Chain Polyprenyl Phosphates Form “Primitive” Membranes. Angewandte Chemie 35:177-180.

Sedaghat S, Désaubry L, Streiff S, Ribeiro N, Michels B, Nakatani Y, Ourisson G (2004). A Novel Type of Membranes Based on Cholesteryl Phosphate. Chem. Biodivers. 1:124-128.

Tirnaksiz F, Kalsin O (2005). A topical w/o/w multiple emulsions prepared with Tetronic 908 as a hydrophilic surfactant: Formulation, characterization. J. Pharm. Pharmaceut. Sci. 8:299-315.