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Synthesis and Spectral Characterization of 6-*O*-Octanoyl-1,2-*O*-isopropylidene-α-D-glucofuranose Derivatives

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Abstract: Site selective acylation of monosaccharides and oligosaccharides is essential for the preparation of both natural and novel synthetic carbohydrate compounds, synthetic intermediates, postglycosylation modifications, and for the preparation of therapeutic agents, including research tools for glycobiology. Hence, site-selective octanoylation of 1,2-*O*-isopropylidene-α-D-glucofuranose was conducted. Under low temperature in anhydrous pyridine, direct unimolar octanoylation of this glucofuranose without any catalyst exhibited selectivity at the C-6 hydroxyl group. The C-6 *O*-octanoylglucofuranose, thus obtained, was then used to prepare three 3,5-di-*O*-acyl esters in a similar direct method to get novel esters of glucofuranose. Characterization of all the glucofuranose esters by 1D and 2D spectroscopic technique is also discussed herein.

Keywords: Bisacetone D-glucose, HMBC, Site-selective acylation, Sugar esters.

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INTRODUCTION

Carbohydrate-derived fatty acid esters, also known as sugar esters (SEs), have attracted interest due to their non-ionic surfactant (1) and biological activities (2-5). In general, the combination of hydrophilic sugar moieties and hydrophobic acid(s) produced the sugar esters and showed high stability, biodegradability under aerobic or anaerobic conditions, and low stimulatory effects with no taste (6-7). These properties attracted their use in food (e.g., gelatinization of starch), cosmetics, and pharmaceutical industries (8-9). One of the crucial features is their HLB (hydrophilic-lipophilic balance). This HLB can be manipulated, if necessary, via altering fatty acid(s) and monosaccharide moiety (glycon part) (10). Maintaining this HLB a plethora SEs has been synthesized for a long time, searching for effective bio-surfactant and potential biodegradable drugs (11-13). Their environmental acceptability, renewability, and low cost make SEs surfactants an excellent alternative to petrochemically derived similar types of products. Apart from the well-known surfactant and drug, SEs are found ubiquitously and well documented for other health-protective effects such as antimicrobial, anti-inflammatory, antimutagenic, etc. (14-16). In plants, SEs can carry not only sugars but also long-chain fatty acids into the plant cells. Thus, synthesis and application of monosaccharide-based SEs are essential for both medicinal and biological chemists (17-19).

Of the SEs, several glucofuranose esters of alkyl-fumarates were found suitable for use as active substances in treating psoriasis or other hyperproliferative, inflammatory, or autoimmune disorders (20). To control the solubility of SEs

sometimes sugar acetals and alkyl derivatives are also used (21). Protected glucofuranose, i.e., bisacetone D-glucose has been used as an intermediate for the synthesis of many natural and synthetic novel bioactive compounds (22-24). For example, D-glucofuranose-derived Seprilose (GW 80126) is used to inhibit prostaglandin E2 synthesis (25). Kobayashi and co-workers (26) also utilized D-gluco-1,4-furanose to synthesize its 6-*O*-palmitoyl derivative **1** (Figure 1) by enzymatic technique. Catelani et al. (27) synthesized several 3-*O*-acyl-1,2-*O*-isopropylidene-D-glucofuranose derivatives (**2a-c**) for bioactivity tests found that several such acyl glucofuranoses were highly potent enhancers for erythroid tumor cells. It was found that the combination of glucofuranose with various ester groups like acetyl and benzoyl groups increased its antimicrobial activities, and in some cases, the results are comparable to the standard drugs (28-29). Overall, an intrinsic interest was observed to synthesize glucofuranose derived compounds, many of which are used as drugs (e.g., Seprilose) (30-32).

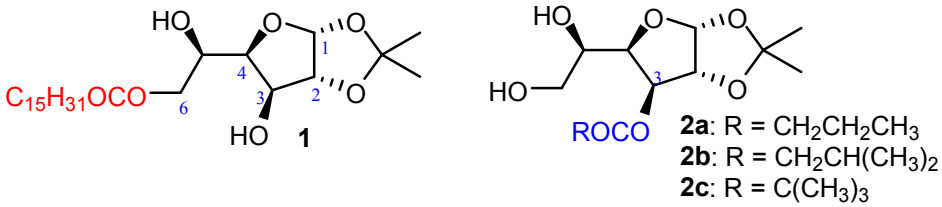


Figure 1. Structure of glucofuranose ester **1** and **2**.

Synthesis of site-selective monosaccharide esters faces unique synthetic difficulties as compared to other biomolecules. The basic problem is the availability of several hydroxyl (OH) groups in monosaccharides of almost the same reactivity as many reagents (33). Again, most of these secondary OH groups have similar reactivity and lead to mono-, di-, and poly-ester formation (34-36). Investigations for selective and site-selective conversion/protection of monosaccharides have been conducted for the last 100 years. Many methods were developed using a minor inherent reactivity variation of hydroxyl groups in useful ways (34, 37-38). For instance, in glucopyranoside and mannopyranoside, the OH group at C-4 was found intrinsically more reactive than the OH groups present in other positions under several conditions (39). However, in most cases, the 1° OH group showed higher reactivity than the 2° hydroxyl groups (40-41). The most common esterification/protection methods for monosaccharides are (i) direct method (42-43), (ii) catalyst mediated acylation (44-45), (iii) protection-deprotection method (46-47), (iv) enzymatic (48), and (v) microwave-assisted method (49). A direct acylation technique was employed in the present study, maintaining some important reaction conditions with some advantages over other methods (12-13).

Site-selective octanoylation of 1,2-*O*-isopropylidene-α-D-glucofuranose and its 3,5-di-*O*-acyl esters are described in the present article. Especial emphasis is given to their 1D and 2D spectroscopic characterization.

EXPERIMENTAL

Materials and general methods

All the reagents (D-glucose, octanoyl chloride, pentanoyl chloride, hexanoyl chloride, 4-chlorobenzoyl chloride etc.) and related solvents were purchased from a commercial supplier (analytical grade). Reduced pressure and temperature (40 °C, Büchi rotavopor, Switzerland) were maintained for evaporations. Electrothermal melting point apparatus is used for melting points and reported without corrections. Silica gel GF_{254} plates were used for thin-layer chromatography (TLC) detection. For purification, silica gel G_{60} was used in column chromatography (CC). During CC purification different proportion of *n*-hexane (PE)/ethyl acetate (EA) was used, and these solvents were distilled before use. FT-IR spectra were recorded on an FT-IR spectrometer (PerkinElmer, Spectrum Two) without solvent (neat). $CDCl_3$ solutions of the samples were used for scanning ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra. During characterization, the position of the proton and carbon signals for each compound was confirmed with the help of their different types of 2D spectra.

Preparation of 1,2-*O*-isopropylidene-α-D-glucofuranose (4)

Initially, bisacetone D-glucose **3** was prepared from the reaction of dry D-glucose with freshly dried CH_3COCH_3 and dry copper sulfate following reported method (50) in moderate yield (46%, solid, mp 107-109 °C [(50) mp. 108-109 °C]. The bisacetone D-glucose (5.0 g, 19.209 mmol) was then dissolved in a mixture of methanol-water (70:15 mL) with stirring followed by the addition of 10% H_2SO_4 (3.6 mL) at normal temperature. The stirring was continued for 5 h when the reaction mixture was neutralized with saturated aqueous potassium carbonate (K_2CO_3) solution. The reaction mixture was concentrated to dryness and slowly extracted with organic solvent (EA) with occasional heating. The combined EA layer was dried ($MgSO_4$) and

subjected for concentration. The thick syrup thus obtained was passed through the silica gel column. Elution with petroleum ether (PE)/EA (1:9) furnished the title compound **4** as a white solid (3.215 g, 76%), mp 158-160 °C [literature (51) melting point 159-160 °C].

Preparation of 1,2-*O*-isopropylidene-6-*O*-octanoyl-α-D-glucofuranose (5)

To a solution of monoacetonide **4** (1.5 g, 6.812 mmol) in dry C_6H_5N was slowly added octanoyl chloride (1.218 g, 7.488 mmol) at ice-cooled temperature. Stirring of the reaction mixture was continued at this temperature for 9 h and then at 22-25 °C temperature for 3 h. The reaction was quenched with ice-water. Then it was added with DCM for extraction (dichloromethane, 8×3 mL). The combined DCM solution was washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$ solution and NaCl solution followed by drying with $MgSO_4$, and concentration under diminished pressure. Purification of the thick residue thus obtained was achieved by passing the syrup through silica ge column (PE/EA, 1:1) and obtained a clear solid compound **5** (1.772 g, 73%) as needles, mp 90-92 °C (ethyl acetate-*n*-hexane). R_f = 0.66 (*n*-hexane/EA = 1/2); FT-IR (neat) $\blacktriangledown_{max}$ (cm^{-1}): 3180-3465 (OH), 1710 (CO), 1377 ($C(CH_3)_2$); ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm: 5.98 (d, *J* = 3.6 Hz, 1H, H-1), 4.55 (d, *J* = 3.6 Hz, 1H, H-2), 4.42–4.47 (m, 1H, H-6a), 4.38 (d, *J* = 1.6 Hz, 1H, H-3), 4.22–4.28 (m, 2H, H-5 and H-6b), 4.09-4.11 (m, 1H, H-4), 2.89-2.98 (br s, exchangeable with D_2O, 2H, 2×O*H*), 2.39 (t, *J* = 7.6 Hz, 2H, $CH_3(CH_2)_5CH_2CO$), 1.63–1.68 (m, 2H, $CH_3(CH_2)_4CH_2CH_2CO$), 1.51 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$), 1.26-1.32 (m, 8H, $CH_3(CH_2)_4(CH_2)_2CO$), 0.90 (t, *J* = 6.4 Hz, 3H, $CH_3(CH_2)_6CO$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm: 174.5 (*C*O), 111.9 ($C(CH_3)_2$), 105.0 (C-1), 85.2 (C-2), 79.3 (C-4), 75.6 (C-3), 69.4 (C-5), 66.0 (C-6), 34.2, 31.6, 29.0, 28.8, 24.8, 22.6 ($CH_3(CH_2)_6CO$), 26.8, 26.2 ($C(CH_3)_2$), 14.0 ($CH_3(CH_2)_6CO$). All the positions of proton and carbons were determined by combined analyses of 1D and several 2D spectra.

General procedure for preparation of 3,5-di-*O*-acyl derivatives 6-8 of 6-*O*-octanoyl-α-D-glucofuranose 5

Selected three acyl halides (2.2 eq.) were added separately drop-wise to an ice-cooled and well-stirred solution of diol **5** (0.2 g, 0.578 mmol) in dry C_6H_5N. A catalytic amount of DMAP was added to the solution. Stirring was continued, and reaction temperature was allowed to rise to 22-25 °C. Stirring continues for 10-12 h. Decomposition of excess acyl halide(s) was accomplished by the addition of a small amount of frozen water. An organic solvent like dichloromethane (DCM) was added and collected several times from a separating funnel. The combined DCM layer was washed with dilute aqueous HCl solution, then with aqueous $NaHCO_3$ solution, and finally with NaCl solution in water. This DCM layer was dried with $MgSO_4$ and concentrated in a rotavapor. This gave a thick syrup, which was finally purified employing column chromatography (CC). In CC, elution was performed with different proportions of *n*-hexane and ethyl acetate (10:0 to 6:1). After CC, the desired 3,5-di-*O*- acylates **6**-**8** were obtained in satisfactory yields.

1,2-*O*-Isopropylidene-6-*O*-octanoyl-3,5-di-*O*-pentanoyl-α-D-glucofuranose (6): Colorless thick mass; yield 91%; R_f = 0.50 (PE/EA = 5/1); FT-IR (neat) $\blacktriangledown_{max}$ (cm^{-1}): 1747, 1741, 1733 (CO), 1375 ($C(CH_3)_2$); ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm: 5.93 (d, *J* = 3.6 Hz, 1H, H-1), 5.33 (d, *J* = 2.4 Hz, 1H, H-3), 5.24 (ddd, *J* = 7.2, 5.6 and 2 Hz, H-5), 4.61 (dd, *J* = 12.4 and 2.0 Hz, 1H, H-6a), 4.47 (dd, *J* = 7.2 and 3.2 Hz, 1H, H-4), 4.44 (d, *J* = 2.8 Hz, 1H, H-2), 4.14 (dd, *J* = 12.4 and 5.6 Hz, 1H, H-6b), 2.30-2.34 (m, 4H, 2⟡$CH_3(CH_2)_2CH_2CO$), 2.26 (t, *J* = 7.5 Hz, 2H, $CH_3(CH_2)_5CH_2CO$), 1.54–1.62 (m, 6H, 2⟡$CH_3CH_2CH_2CH_2CO$ and $CH_3(CH_2)_4CH_2CH_2CO$), 1.53 (s, 3H, $C(CH_3)_2$), 1.25-1.39 (m, 15H, $C(CH_3)_2$, 2⟡$CH_3CH_2(CH_2)_2CO$ and $CH_3(CH_2)_4(CH_2)_2CO$), 0.88-0.94 (m, 9H, 2⟡$CH_3(CH_2)_3CO$ and $CH_3(CH_2)_6CO$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm: 173.3, 172.4, 172.3 (*C*O), 112.4 ($C(CH_3)_2$), 105.2 (C-1), 83.3 (C-4), 76.8 (C-2), 74.6 (C-3), 67.4 (C-5), 63.1 (C-6), 34.2, 33.8, 33.6, 31.7, 29.1, 28.9, 26.7, 26.6, 24.9, 22.6, 22.2(2) (2⟡$CH_3(CH_2)_3CO$ and $CH_3(CH_2)_6CO$), 26.8, 26.3 ($C(CH_3)_2$), 14.0, 13.7(2) (2⟡$CH_3(CH_2)_3CO$ and $CH_3(CH_2)_6CO$).

3,5-Di-*O*-hexanoyl-1,2-*O*-isopropylidene-6-*O*-octanoyl-α-D-glucofuranose (7): Clear syrup; yield 88%; R_f = 0.52 (PE/EA = 5/1); FT-IR (neat) $\blacktriangledown_{max}$ (cm^{-1}): 1736, 1739, 1722 (CO), 1374 ($C(CH_3)_2$); ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm: 5.91 (d, *J* = 3.2 Hz, 1H, H-1), 5.31 (d, *J* = 2.8 Hz, 1H, H-3), 5.23 (ddd, *J* = 7.0, 5.4 and 1.6 Hz, H-5), 4.59 (dd, *J* = 12.2 and 1.6 Hz, 1H, H-6a), 4.45 (dd, *J* = 7.1 & 3.2 Hz, 1H, H-4), 4.42 (d, *J* = 2.4 Hz, 1H, H-2), 4.12 (dd, *J* = 12.2 & 5.4 Hz, 1H, H-6b), 2.11-2.44 (m, 6H, 2⟡$CH_3(CH_2)_3CH_2CO$ and $CH_3(CH_2)_5CH_2CO$), 1.56-1.74 (m, 6H, 2⟡$CH_3(CH_2)_2CH_2CH_2CO$ and $CH_3(CH_2)_4CH_2CH_2CO$), 1.53 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$), 1.22-1.33 (m, 16H, 2⟡$CH_3(CH_2)_2(CH_2)_2CO$ and $CH_3(CH_2)_4(CH_2)_2CO$), 0.87-0.92 (m, 9H, 2⟡$CH_3(CH_2)_4CO$ and $CH_3(CH_2)_6CO$); ^1C NMR (100 MHz, $CDCl_3$) δ_C ppm: 173.3, 172.4, 172.3 (*C*O), 112.5 ($C(CH_3)_2$), 105.1 (C-1), 83.3 (C-4), 76.8 (C-2), 74.6 (C-3), 67.4 (C-5), 63.1 (C-6), 34.1, 34.0, 33.8, 31.6, 31.2(2), 29.1, 28.9, 24.8, 24.4, 24.2, 22.6, 22.2(2) (2⟡$CH_3(CH_2)_4CO$ and $CH_3(CH_2)_6CO$), 26.8, 26.2 ($C(CH_3)_2$), 14.0, 13.8(2) (2⟡$CH_3(CH_2)_4CO$ and $CH_3(CH_2)_6CO$).

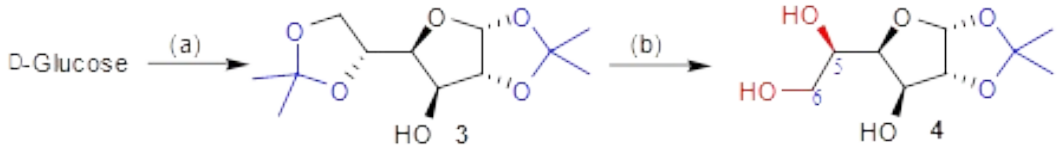
3,5-Di-*O*-(4-chlorobenzoyl)-1,2-*O*-isopropylidene-6-*O*-octanoyl-α-D-glucofuranose (8): Pale-yellow semi-solid; yield 94%; R_f = 0.59 (PE/EA = 5/1); FT-IR (neat) $\blacktriangledown_{max}$ (cm^{-1}): 1745, 1708, 1701 (CO), 1381 ($C(CH_3)_2$); ^1H

NMR (400 MHz, $CDCl_3$) δ_H ppm: 7.90 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.82 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.43 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.38 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.04 (d, *J* = 3.6 Hz, 1H, H-1), 5.60 (ddd, *J* = 7.2, 5.6 and 2.8 Hz, H-5), 5.54 (d, *J* = 2.8 Hz, 1H, H-3), 4.68-4.72 (m, 2H, H-4 & H-6a), 4.66 (d, *J* = 3.2 Hz, 1H, H-2), 4.37 (dd, *J* = 12.4 & 5.6 Hz, 1H, H-6b), 2.30 (t, *J* = 7.5 Hz, 2H, $CH_3(CH_2)_5CH_2CO$), 1.61 (s, 3H, $C(CH_3)_2$), 1.52–1.59 (m, 2H, $CH_3(CH_2)_4CH_2CH_2CO$), 1.37 (s, 3H, $C(CH_3)_2$), 1.19-1.29 (m, 8H, $CH_3(CH_2)_4(CH_2)_2CO$), 0.87 (t, *J* = 6.4 Hz, 3H, $CH_3(CH_2)_6CO$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm: 173.5 ($C_7H_{15}CO$), 164.2, 164.1 (2◈4-Cl.C_6H_4CO), 140.0, 139.9, 131.2(2), 131.0(2), 128.9(2), 128.8(2), 127.8, 127.4 (Ar-*C*), 112.7 ($C(CH_3)_2$), 105.2 (C-1), 83.2 (C-4), 76.9 (C-2), 76.1 (C-3), 68.8 (C-5), 63.1 (C-6), 34.1, 31.6, 29.0, 28.9, 24.9, 22.6 ($CH_3(CH_2)_6CO$), 26.8, 26.3 ($C(CH_3)_2$), 14.0 ($CH_3(CH_2)_6CO$).

RESULTS AND DISCUSSION

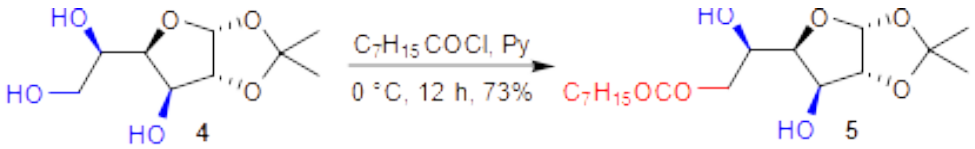
Regioselective octanoylation of monacetonide-α-D-glucofuranose 4

The present study mainly describes the synthesis and spectroscopic characterization of 6-*O*-octanoyl-α-D-glucofuranose **5** and its three derivatives **6**-**8**. In this respect, initially, 1,2:5,6-di-*O*-isopropylidene-α-D-gluco-1,4-furanose (**3**) was prepared from D-glucose. Treatment of D-glucose with anhydrous acetone, a catalytic amount of conc. H_2SO_4 and $CuSO_4$, according to the literature procedure (Scheme 1), gave **3** in moderate yield (46%) (19, 50). At this stage, removing the 5,6-*O*-acetonide group was conducted selectively by treating bisacetonide **3** with 15% H_2SO_4 in methanol for 5 h, which upon CC purification was furnished pure crystals of monoacetonide **4** (76%), mp 158-160 °C (Scheme 1). Its FT-IR, ^1H, and ^{13}C NMR showed similarity with the published data (51).



Scheme 1: (a) Dry acetone, anhydrous $CuSO_4$, conc. H_2SO_4, rt, 24 h, 46% (50); (b) 15% H_2SO_4, MeOH-H_2O, 25 °C, 5 h, 76% (51).

Having monoacetonide **4** in hand attempt was made for its mono-octanoylation. Thus, treating **4** with unimolar octanoyl chloride in basic pyridine at reduced temperature (0 °C) for 12 h followed by CC purification gave a solid mp 90-92 °C in 73% (Scheme 2). Its FT-IR showed one broad characteristic band at 3180-3465 cm^{-1} for the OH group. Also, a sharp characteristic band at 1710 cm^{-1} (CO) indicates the molecule's partial octanoylation.



Scheme 2. Selective octanoylation of glucofuranose **4**.

In its ^1H NMR spectrum, additional fifteen protons appeared at δ 2.39 (t, 2H), 1.63–1.68 (m, 2H), 1.26-1.32 (m, 8H), and 0.90 (t, 3H), which corresponded to an octanoyl group of protons. The appearance of a broad singlet at δ 2.89-2.98 corresponding to two protons of two OH groups supported the addition of only one octanoyl group in this solid. Also, the seven protons of glucofuranose skeleton appeared in their anticipated positions (Figure 2). In ^{13}C NMR eight extra carbons were found at δ 174.5 (CO), 34.2, 31.6, 29.0, 28.8, 24.8, 22.6 [$CH_3(CH_2)_6CO$] and 14.0 [$CH_3(CH_2)_6CO$]. The relative position of each proton and carbon signal was ascertained by analyzing its 2D COSY (Figure 3a), DEPT-135 (Figure 3b), and HSQC. Now, the position of attachment of the octanoyl group was ascertained in two ways. Firstly, reasonable downfield shifting of both the H-6 protons (δ 4.42–4.47 and 4.22–4.28) than that of its starting compound **4** (19, 51) suggested that an octanoyl group was added at the C-6 position of the glucofuranose skeleton. Secondly, in its HMBC spectrum (Figure 3c), the only carbonyl carbon interacts with both the protons of H-6a,b, which significantly confirmed that the $C_7H_{15}CO$ was added to the primary OH (C-6) position. Thus, corroboration of FT-IR, ^1H and ^{13}C NMR, DEPT-135, 2D COSY, HSQC, and HMBC spectra confirmed the structure assigned as **5**.

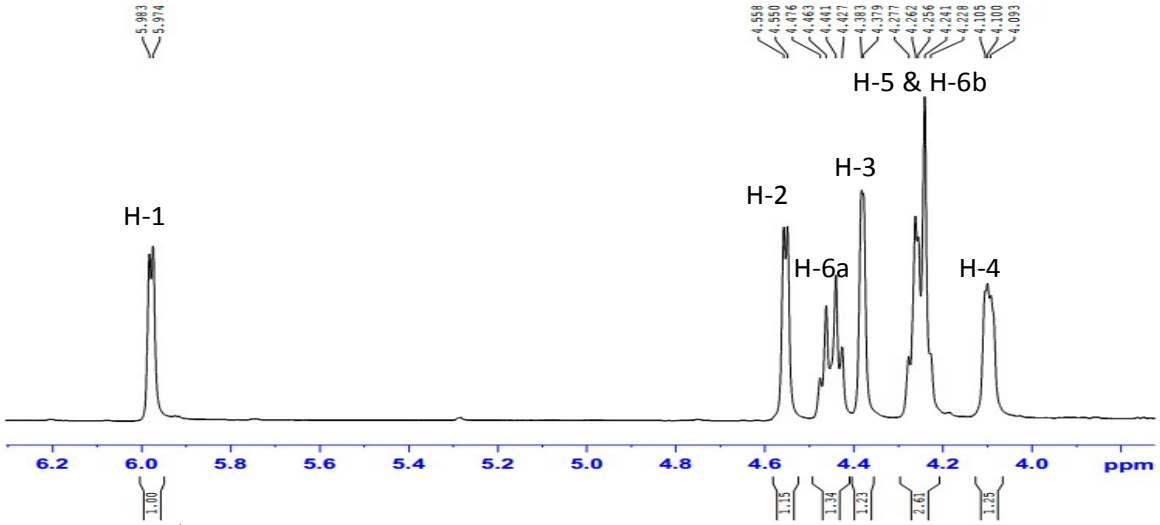
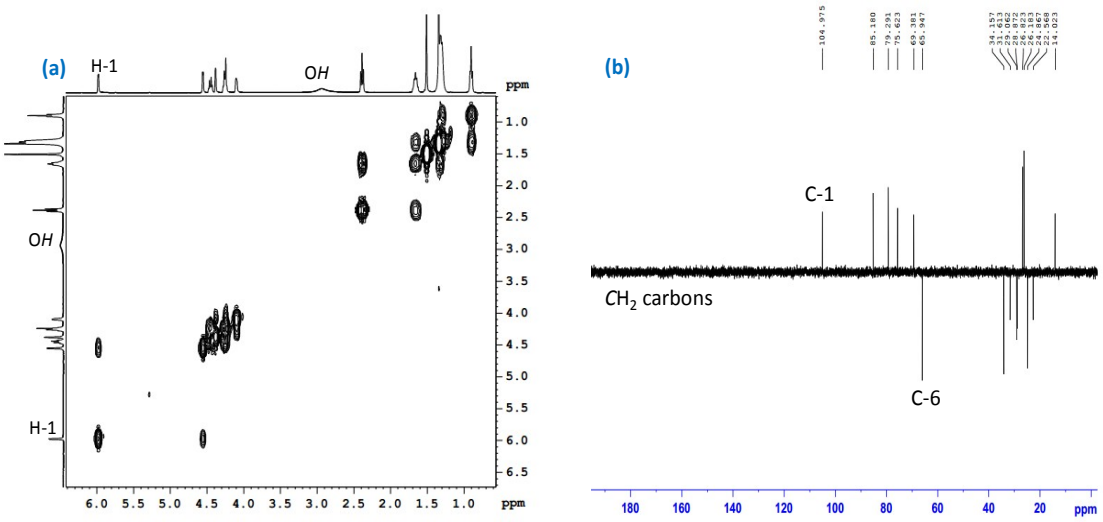


Figure 2. ^{1}H NMR spectrum of 6-*O*-octanoate **5** indicating glucofuranose proton signals.



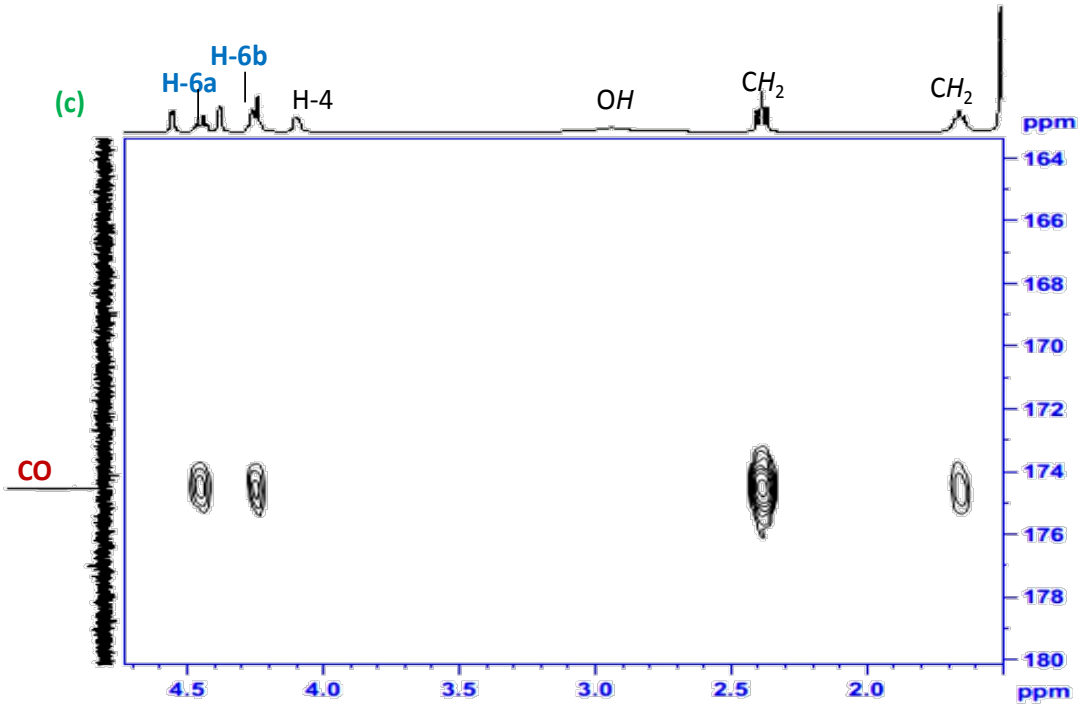
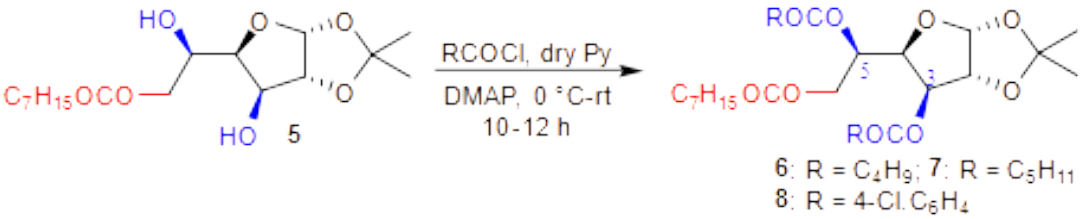


Figure 3: (a) 2D COSY, (b) DEPT-135, and (c) HMBC spectra of 6-*O*-octanoate **5**.

The successful synthesis of compound **5** thus indicated that the necessary conditions for site-selective 6-*O*-octanoylation in the direct method are- (i) use of bulky acylating agent, (ii) use of unimolar acylating agent, and (iii) reaction need to conduct at low temperature (0 °C). An analogous methodology has also been reported by Sindona et al. (52) with other acylating agents and yields vary from 15% to 93%.

Synthesis of 2,5-di-*O*-acyl esters 6-8 of octanoate 5

For more evidence in favor of 6-*O*-octanoate **5** formation and to prepare newer glucofuranose esters, **5** was converted into three 3,5-di-*O*-acyl esters using three different acylating agents. First of all, dihydroxy compound **5** was reacted with pentanoyl chloride in dry C_6H_5N for 10 h, and a thick syrup was obtained in 91% (Scheme 3).



Scheme 3. Derivatization of octanoate **5** (**6** = 91%; **7** = 88%; **8** = 94%).

In its FT-IR spectrum, carbonyl characteristic peaks appeared at 1747, 1741, and 1733 cm^{-1} while the hydroxyl stretching band completely disappeared (Figure 4), indicating the pentanoylation of the molecule. A total of thirty-nine protons resonated in the aliphatic region of its ^1H NMR spectrum. Of these 6 protons are due to one isopropylidene group, and fifteen protons are for one octanoyl group that already exists in the molecule. The additional eighteen protons than its starting **5** were indicative of the attachment of two C_4H_9CO groups in the molecule.

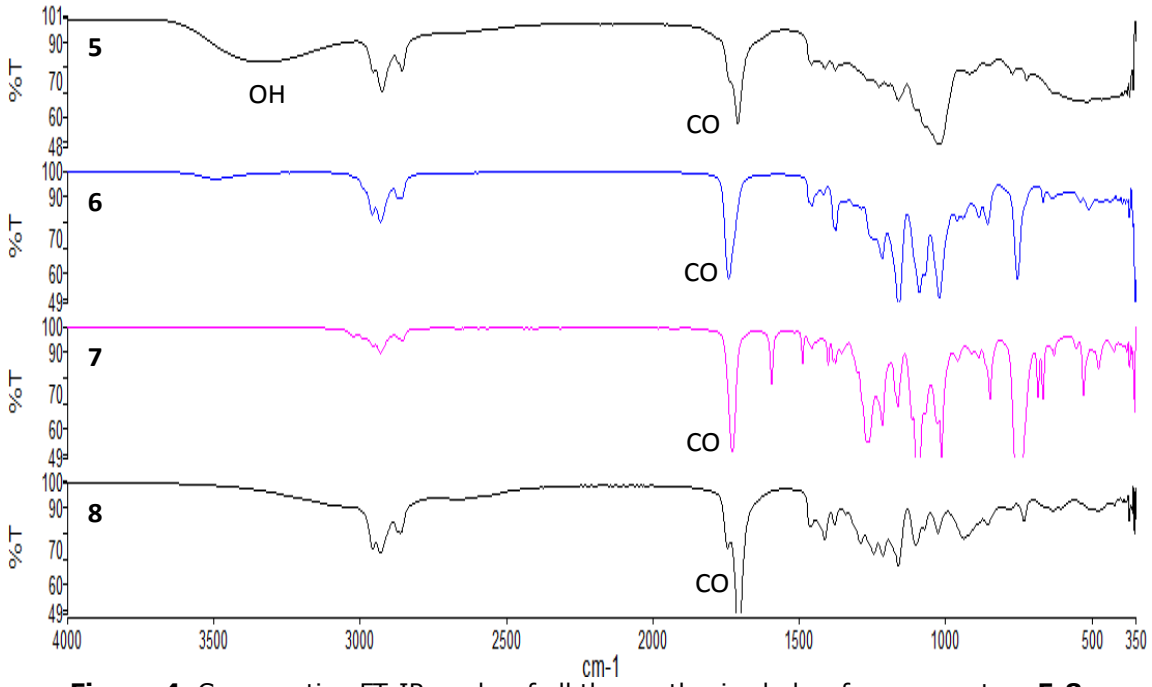


Figure 4. Comparative FT-IR peaks of all the synthesized glucofuranose esters **5**-**8**.

For confirmation, its ^{13}C NMR was analyzed, where an additional two CO and fourteen aliphatic carbon signals were present. In its HMBC, protons present at 3 and 5 positions were found to interact with two carbonyl carbons at δ 172.4 and 172.3, respectively, and thus, the new two pentanoyl groups must be attached at the same 3 and 5 positions. The considerable downfield shift of H-3 (δ 5.33) and H-5 (δ 5.24) as compared to its precursor **5** (δ 4.38 and 4.22–4.28, respectively) confirmed this fact. Thus, the structure of this compound was unambiguously assigned as **6**.

In the next step, dimolar hexanoylation of octanoate **5** in dry DMF for 12 h (Scheme 3) furnished a syrup in 88% yield. No band in the OH was observed in its FT-IR spectrum. Instead, it exhibited characteristic bands at 1736, 1739, and 1722 cm^{-1} (CO) (Figure 4). The ^{1}H NMR spectrum gave peaks for additional characteristic twenty-two protons compared to its precursor compound **5**. In its ^{13}C NMR carbonyl carbon signals at δ 173.3, 172.4 and 172.3, and aliphatic carbon signals at δ 34.1, 34.0, 33.8, 31.6, 31.2(2), 29.1, 28.9, 24.8, 24.4, 24.2, 22.6, 22.2(2), 26.8, 26.2, 14.0 and 13.8(2) were confirmative of the addition of two $C_5H_{11}CO$ groups in this compound in addition to one isopropylidene and one octanoyl group. HMBC spectrum showed multiple bond correlations between carbonyl carbons and H-3, H-5, and H-6a,b (Figure 5). As the octanoyl group is already attached to the C-6 position, hexanoyl groups must be attached with 3 and 5 positions. Complete analysis of its all 1D and 2D spectra established its structure as **7**.

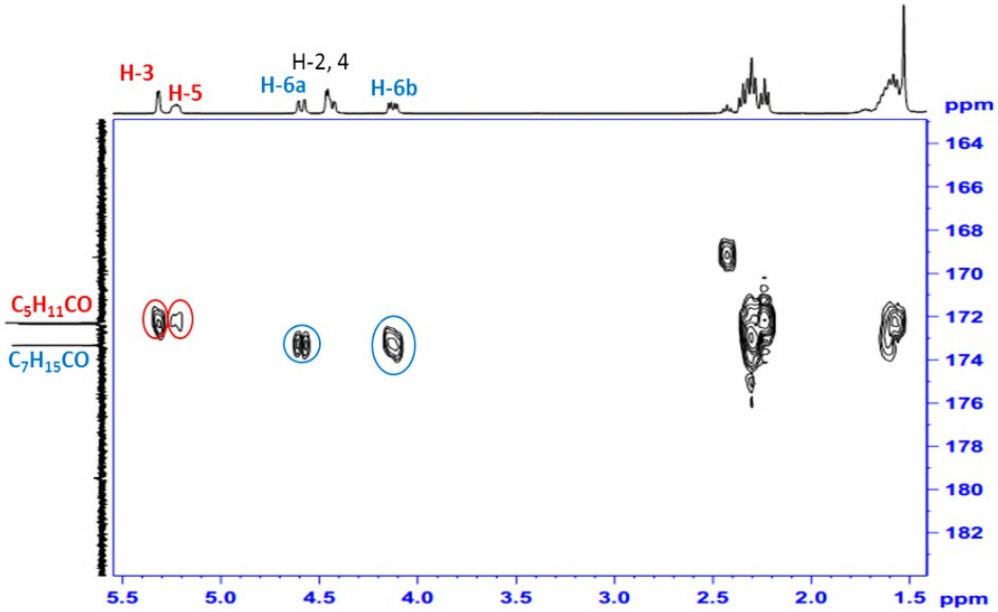


Figure 5. HMBC correlation between CO and H-3, H-5 and H-6a,b in **7**.

Finally, dimolar 4-chlorobenzoylation of octanoate **5** in dry pyridine for 10 h gave a semi-solid which resisted crystallization (Scheme 3). The disappearance of OH band and presence of CO characteristic bands at 1745, 1708, and 1701 cm^{-1} were informative of the desired di-chlorobenzoylation of this compound (Figure 4). To confirm this observation, initially, its proton NMR spectrum was analyzed, where new eight aromatic protons resonated at δ 7.90 (2H), 7.82 (2H), 7.43 (2H), and 7.38 (2H) indicating the attachment of two 4-chlorobenzoyl groups in the molecule. A doublet at δ 6.04, assigned for H-1, with small coupling constant 3.6 Hz indicated *cis*-relationship with H-2. As H-2 is β-oriented H-1 must be β-oriented i.e. above the plane. Also, C-3 and C-5 protons resonated at highly down fields (at δ 5.54 and 5.60, respectively). Like compound **6**-**7**, its carbonyl signals at δ 164.2 and 164.1 showed heteronuclear multiple bond correlation with H-3 and H-5, respectively, thereby confirming that 4-chlorobenzoyl groups were added at these C-3 and C-5 positions. Thus, its structure was established as **8**.

CONCLUSION

A convenient and straightforward site-selective octanoylation method for monoacetonide protected α-D-glucofuranose is described. The necessary condition for such a reaction was using an unimolar acylating agent and a lower reaction temperature, and the absence of any catalyst. The regioselective 6-*O*-octanoate **5**, thus obtained, was converted into corresponding three di-*O*-acyl esters **6**-**8** successfully. All these synthetic compounds were characterized well with 1D and 2D spectroscopic techniques. The biological activities, computer-aided *in silico* thermodynamics, binding energy and ADMET properties, and structural basis for such bioactivities will be reported shortly.

ACKNOWLEDGMENT

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SUPPLEMENTARY DATA

Synthesis, and Spectral Characterization of 6-*O*-Octanoyl-1,2-*O*-isopropylidene-α-D-glucofuranose Derivatives

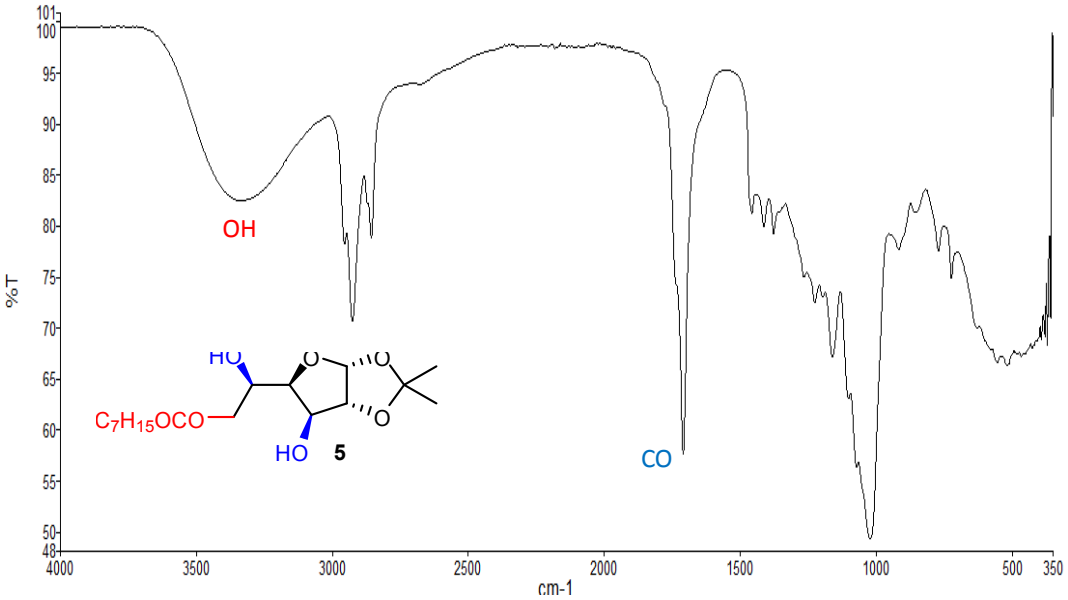

Figure S1. FT-IR (neat) spectrum of compound **5**.

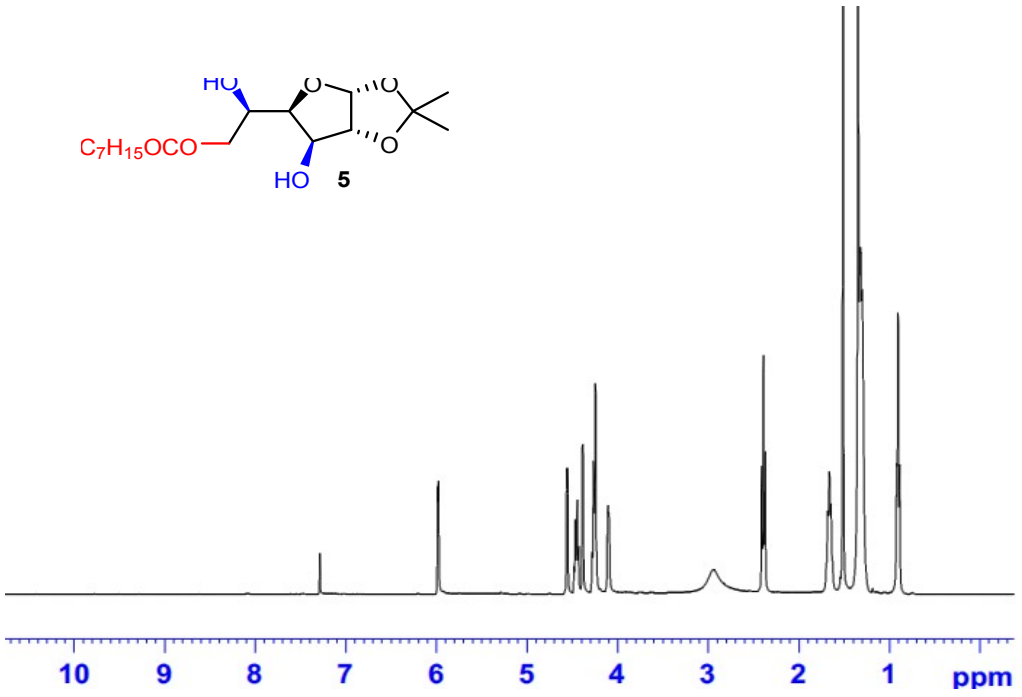

Figure S2. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5**.

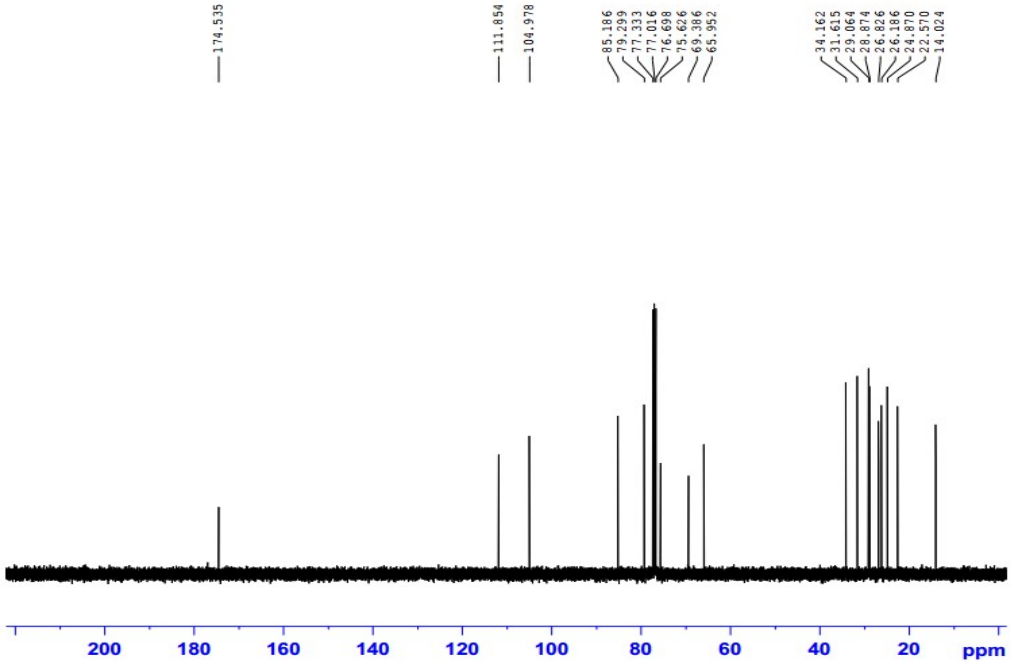

Figure S3. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5**.

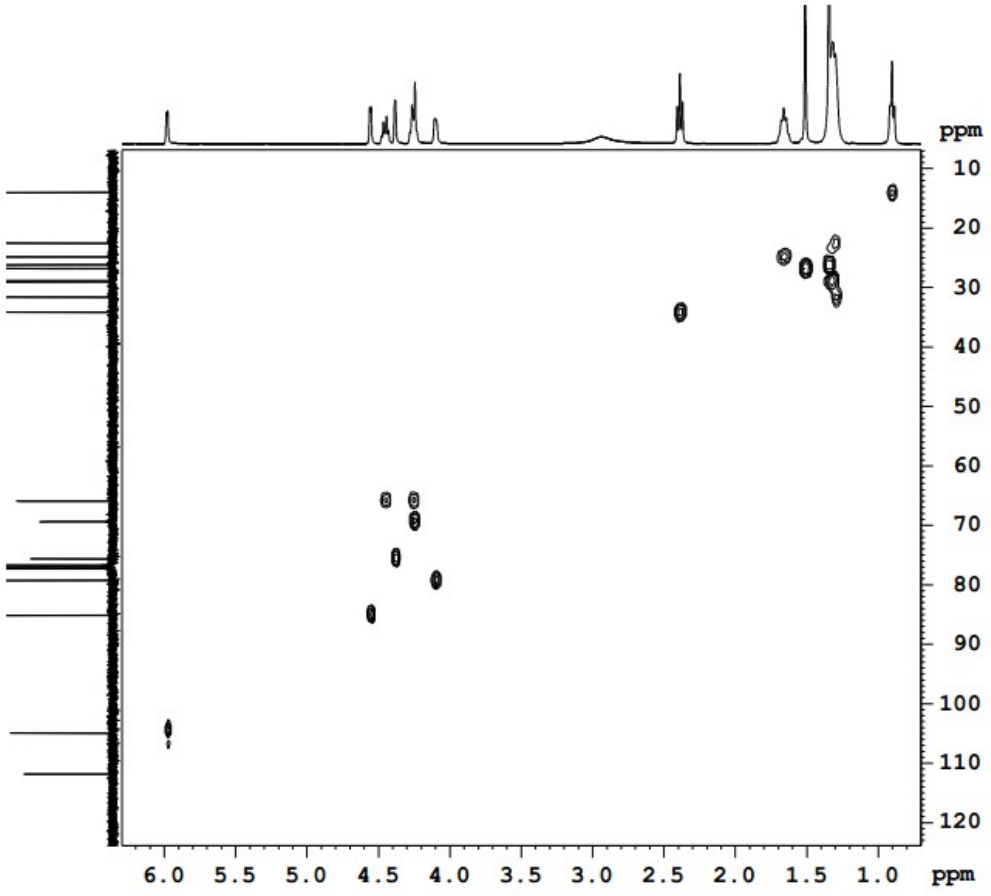

Figure S4. 2D HSQC spectrum of compound **5**.

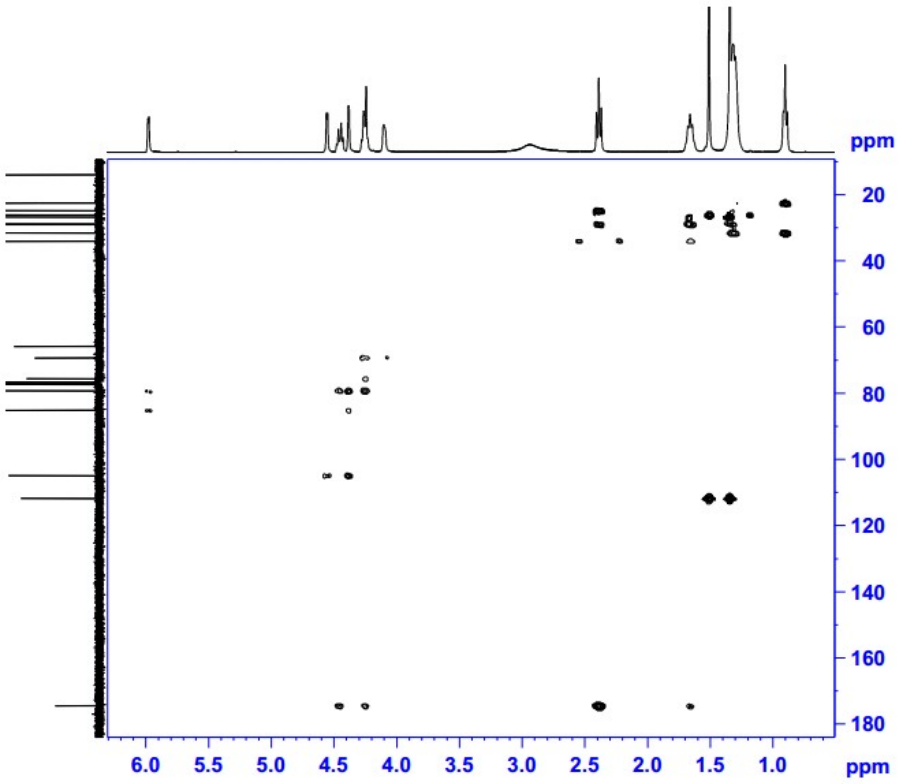

Figure S5. 2D HMBC spectrum of compound **5**.

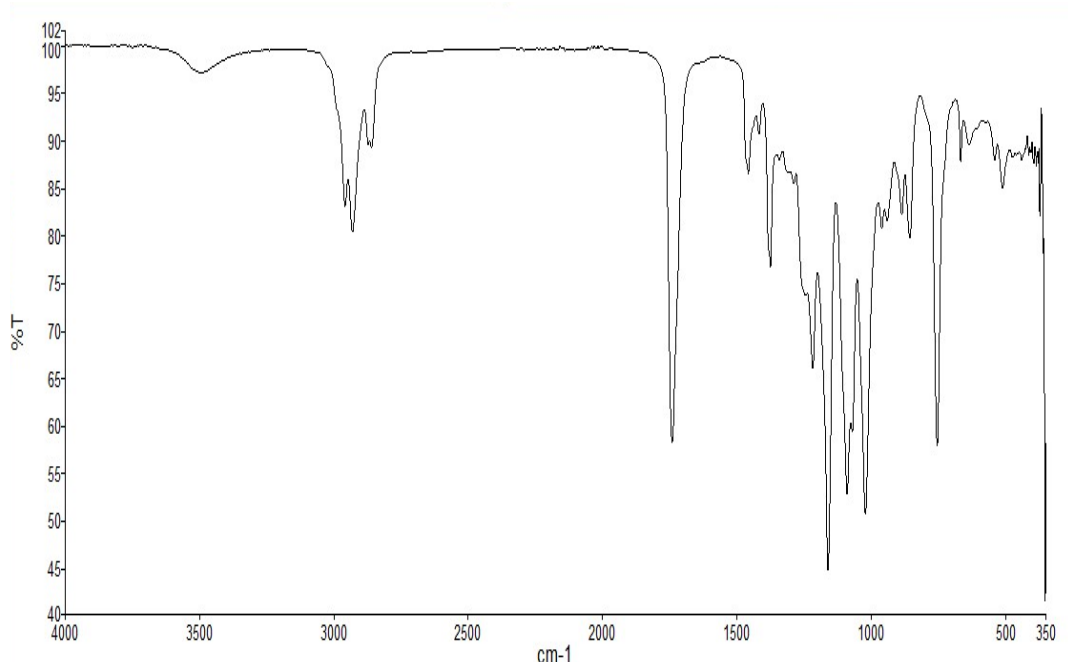

Figure S6. FT-IR (neat) spectrum of compound **6**.

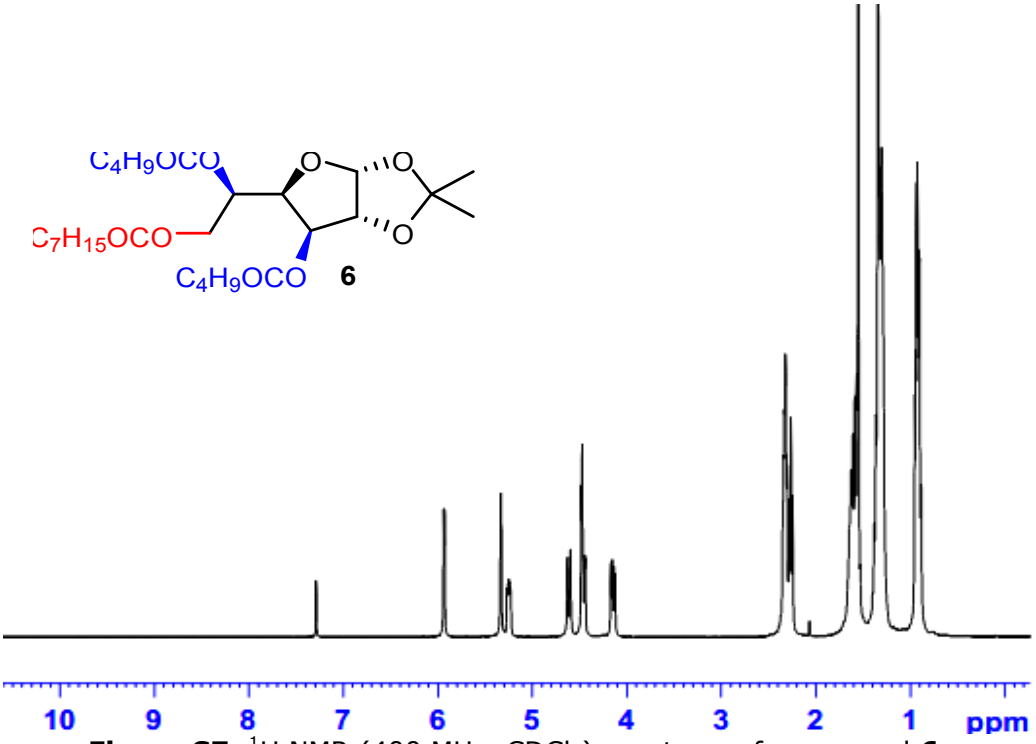

Figure S7. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **6**.

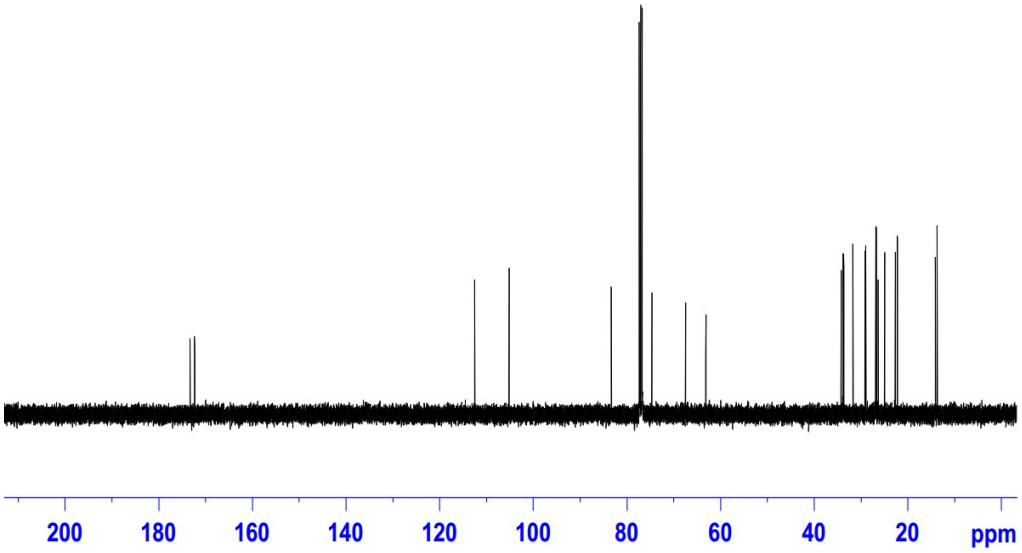

Figure S8. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **6**.

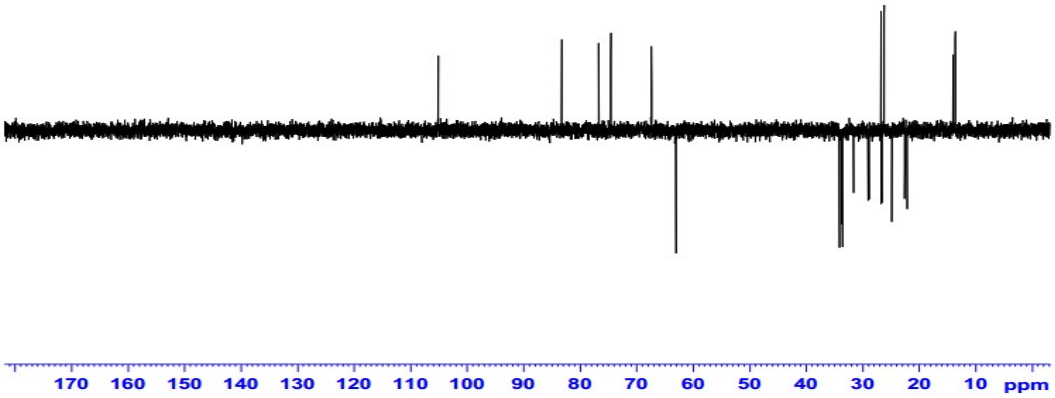

Figure S9. DEPT-135 spectrum of compound **6**.

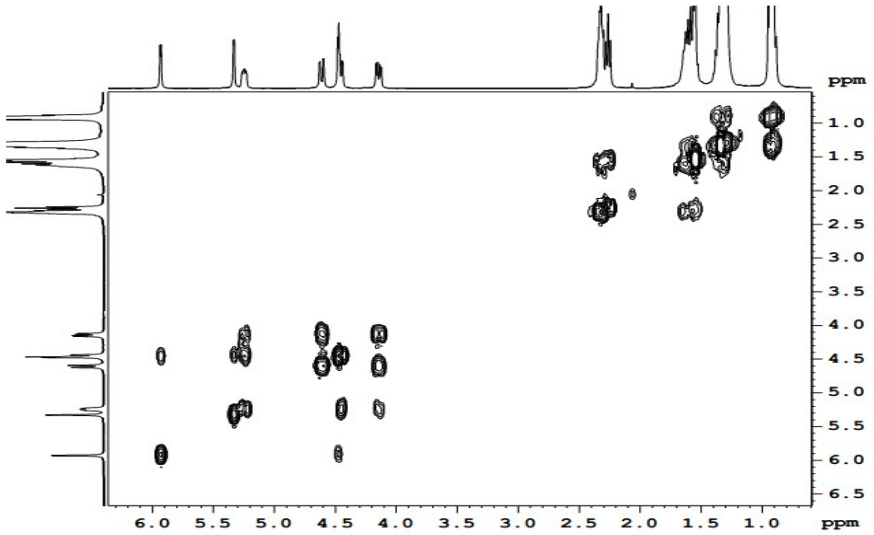

Figure S10. 2D COSY spectrum of compound **6**.

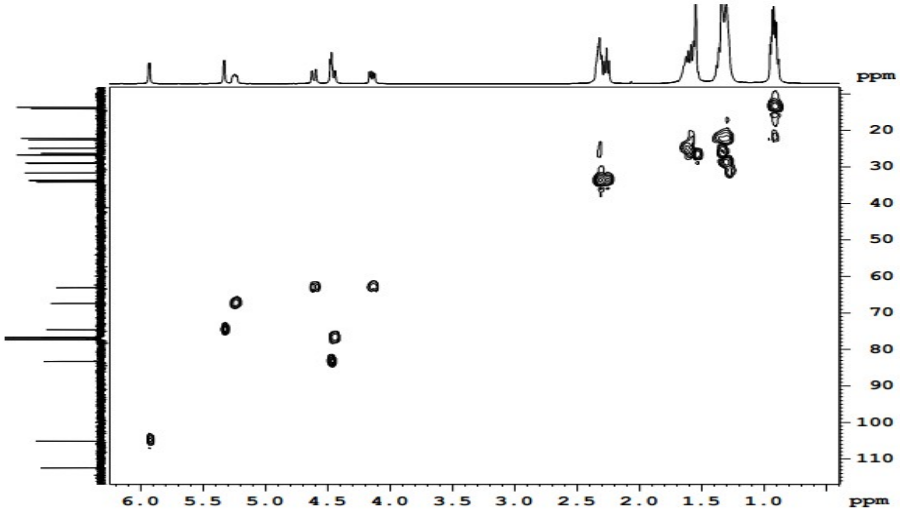

Figure S11. 2D HSQC spectrum of compound **6**.

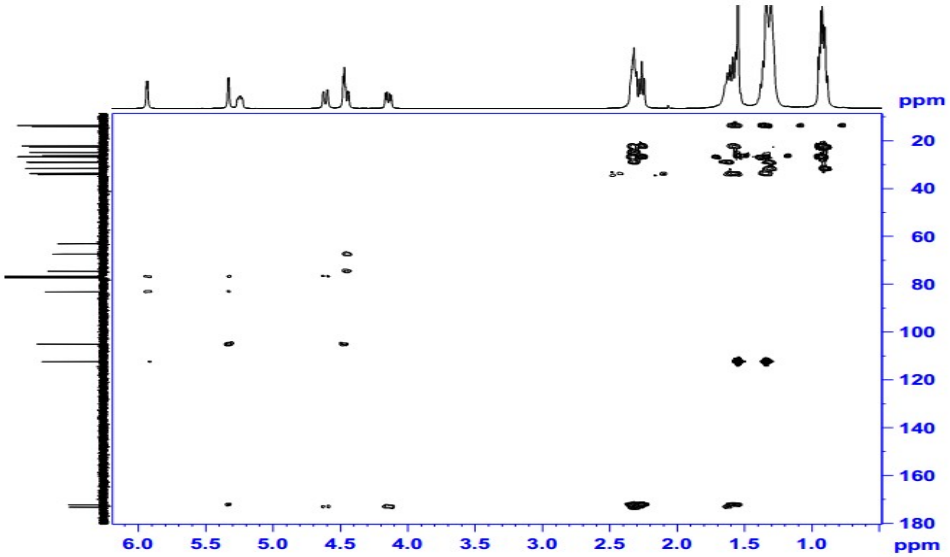

Figure S12. 2D HMBC spectrum of compound **6**.

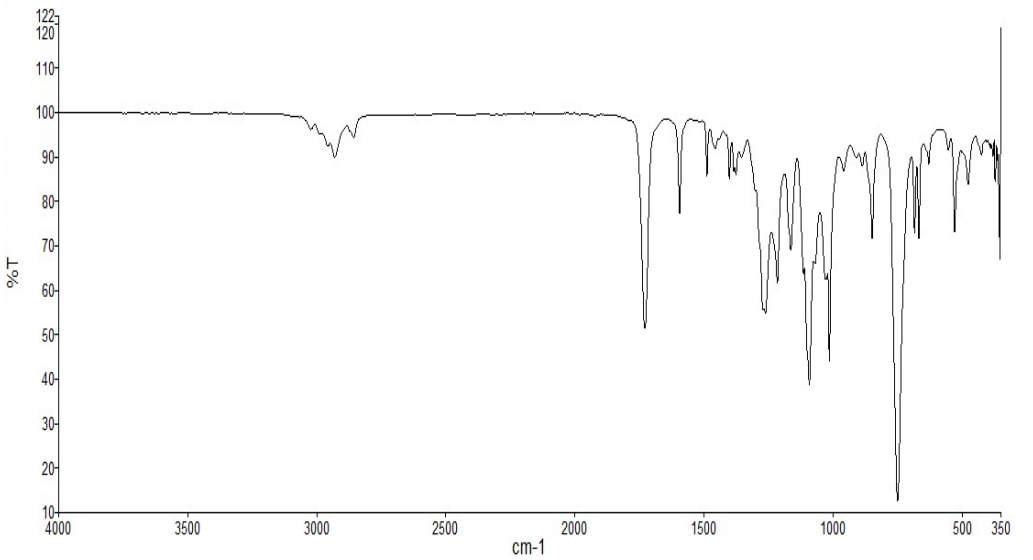

Figure S13. FT-IR (neat) spectrum of compound **7**.

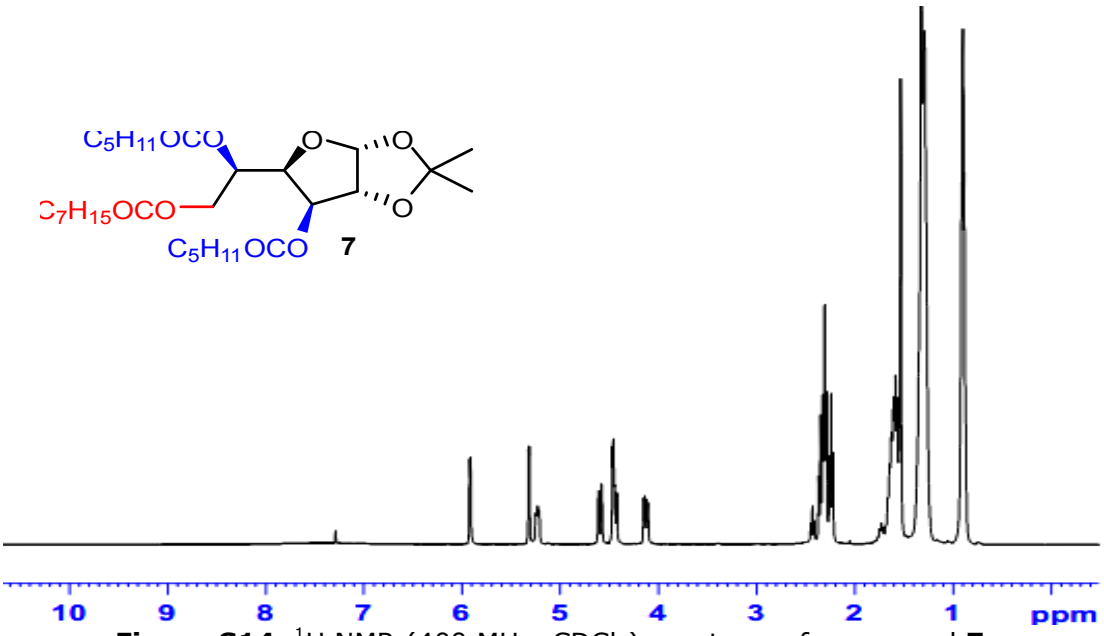

Figure S14. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **7**.

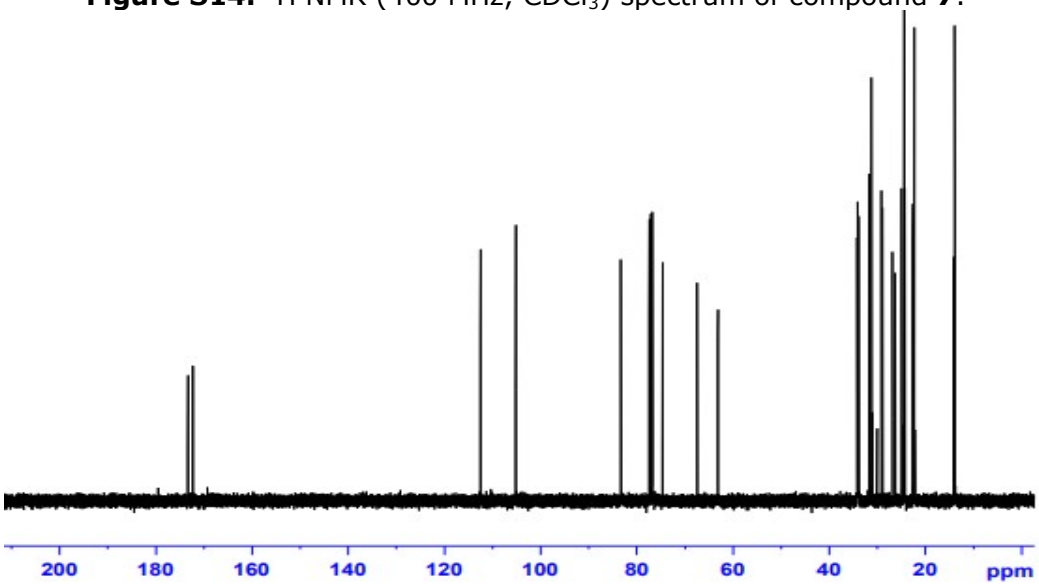

Figure S15. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **7**.

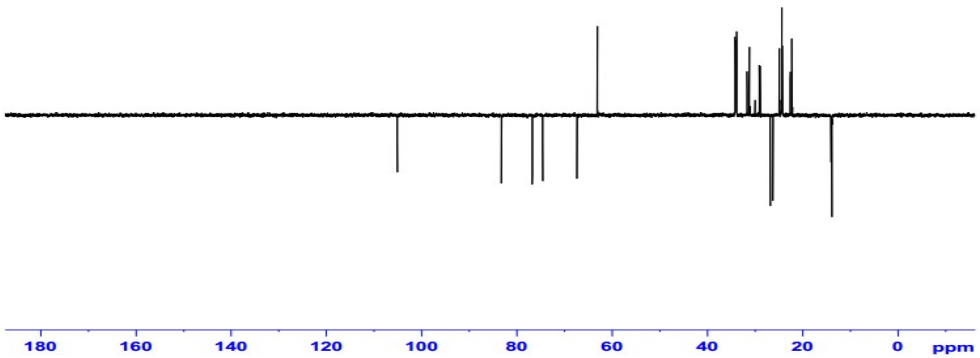

Figure S16. DEPT-135 spectrum of compound **7**.

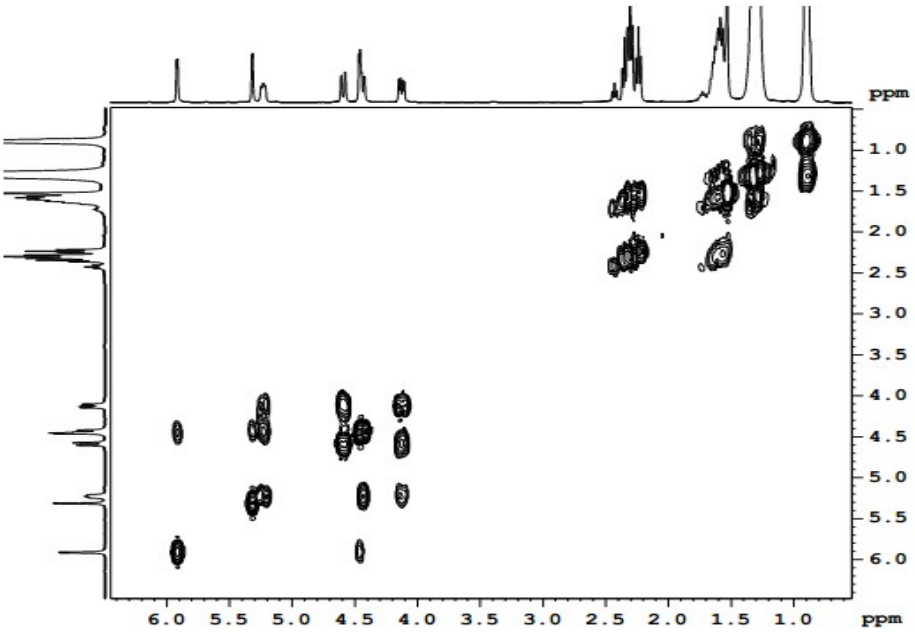

Figure S17. 2D COSY spectrum of compound **7**.

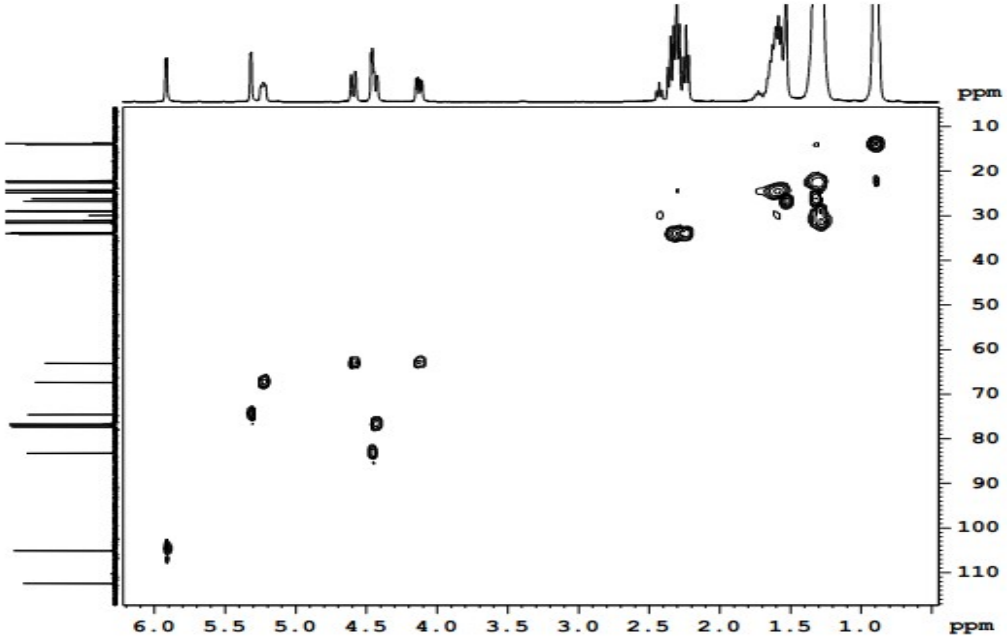

Figure S18. 2D HSQC spectrum of compound **7**.

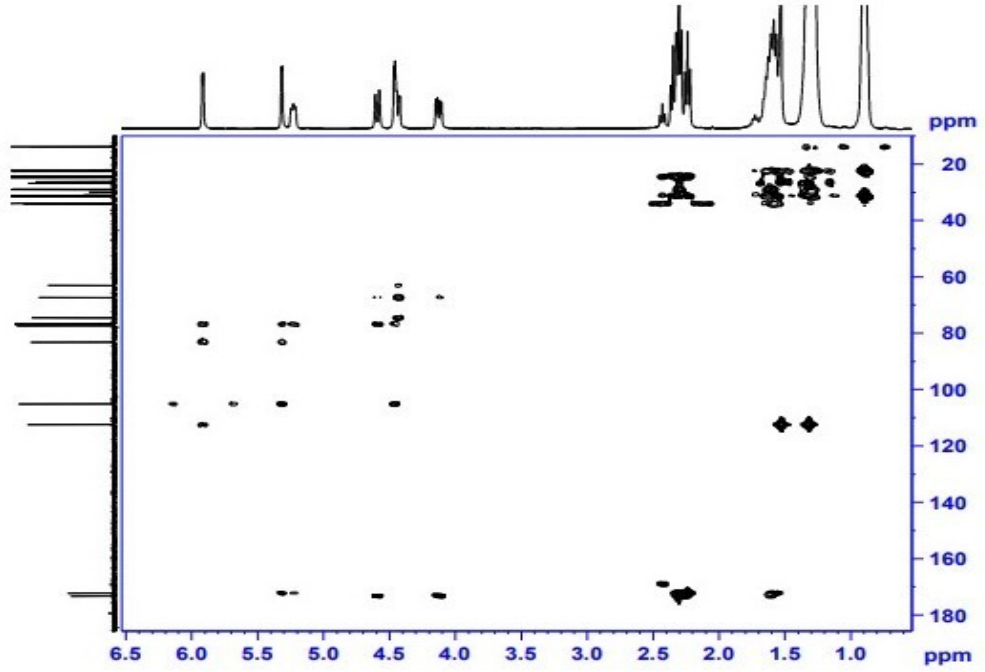

Figure S19. 2D HMBC spectrum of compound **7**.

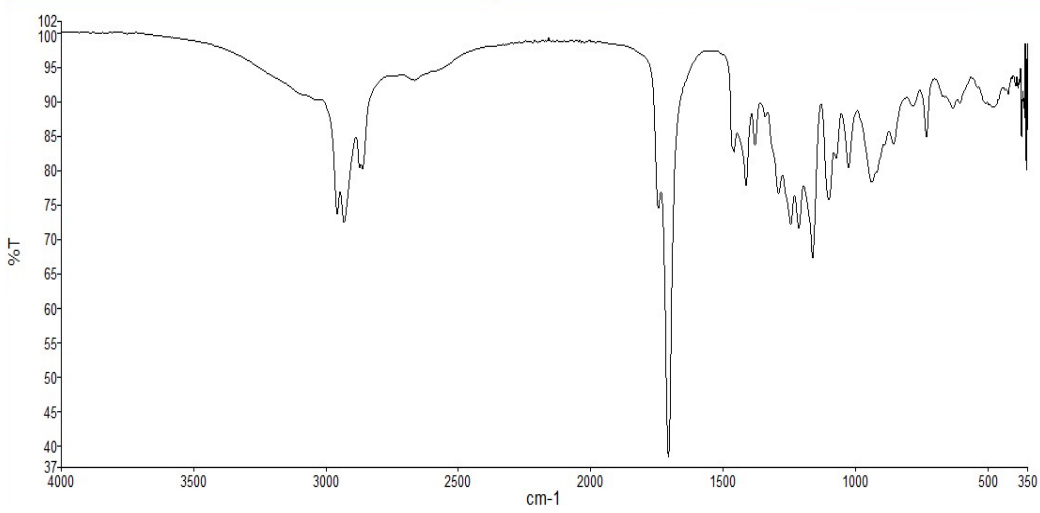

Figure S20. FT-IR (neat) spectrum of compound **8**.

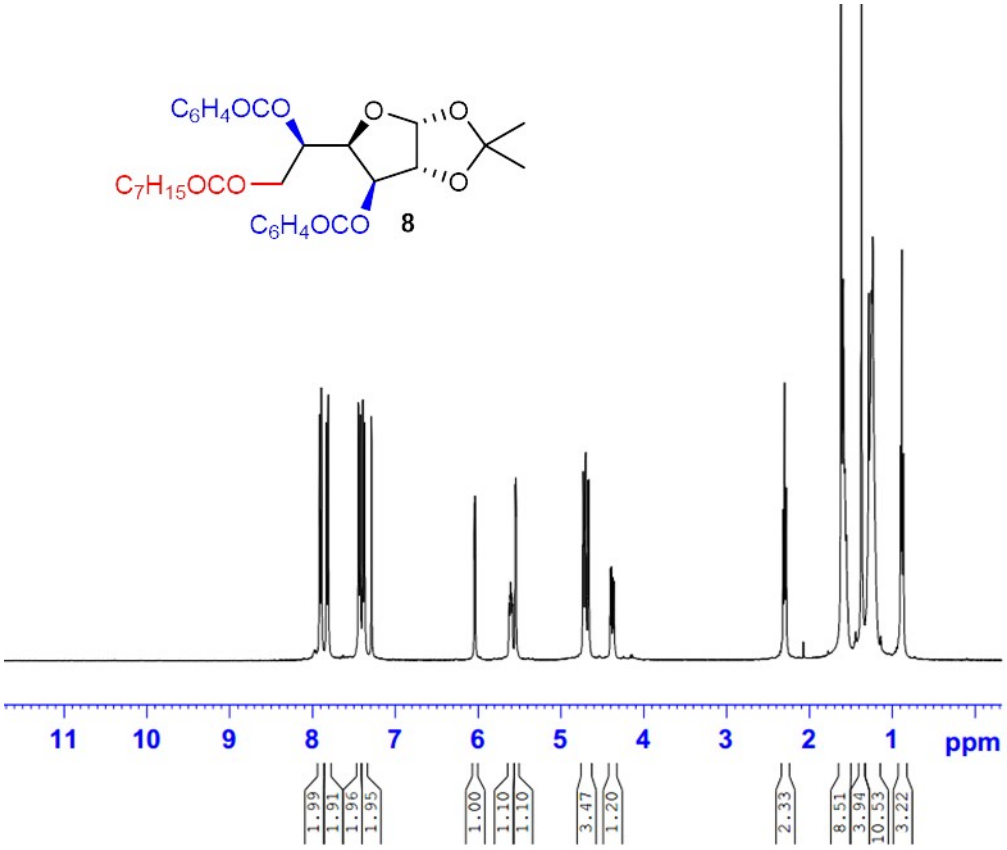

Figure S21. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8**.

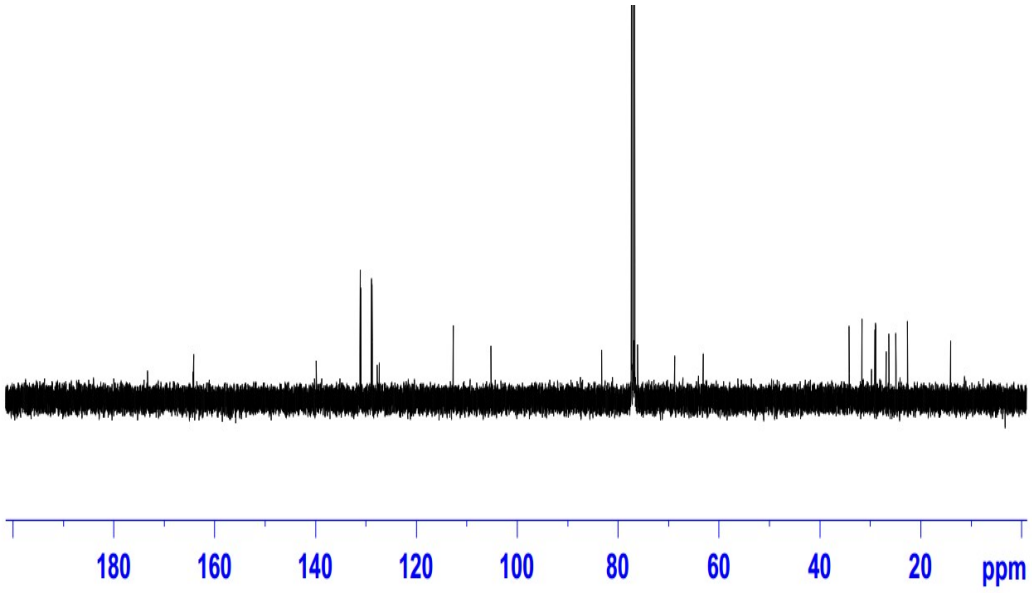

Figure S22. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **8**.

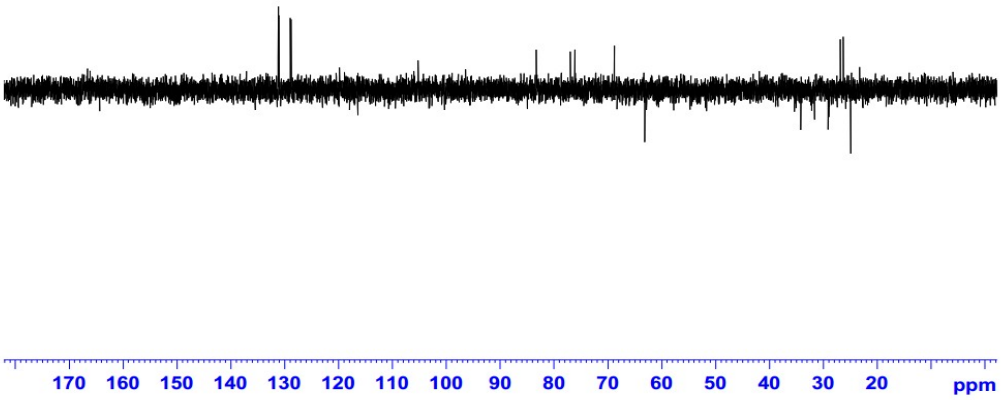

Figure S23. DEPT-135 spectrum of compound **8**.

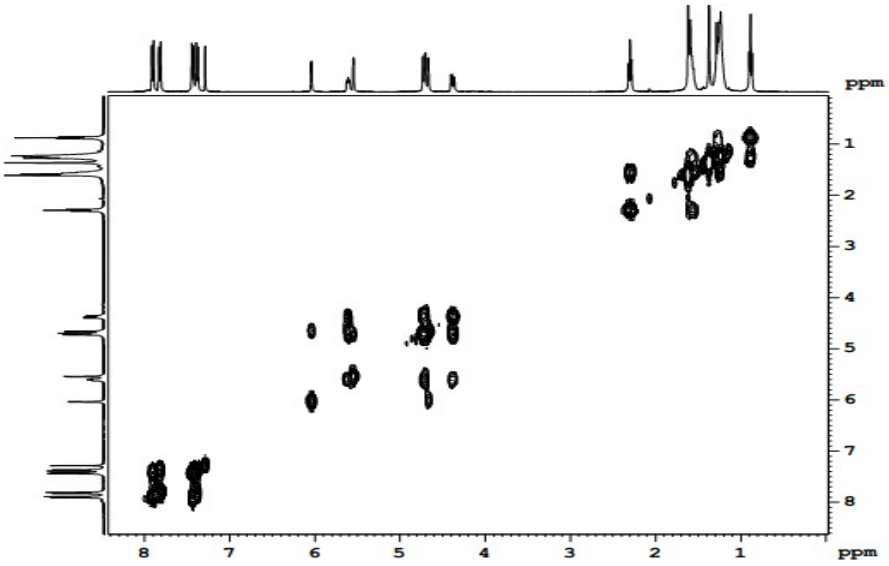

Figure S24. 2D COSY spectrum of compound **8**.

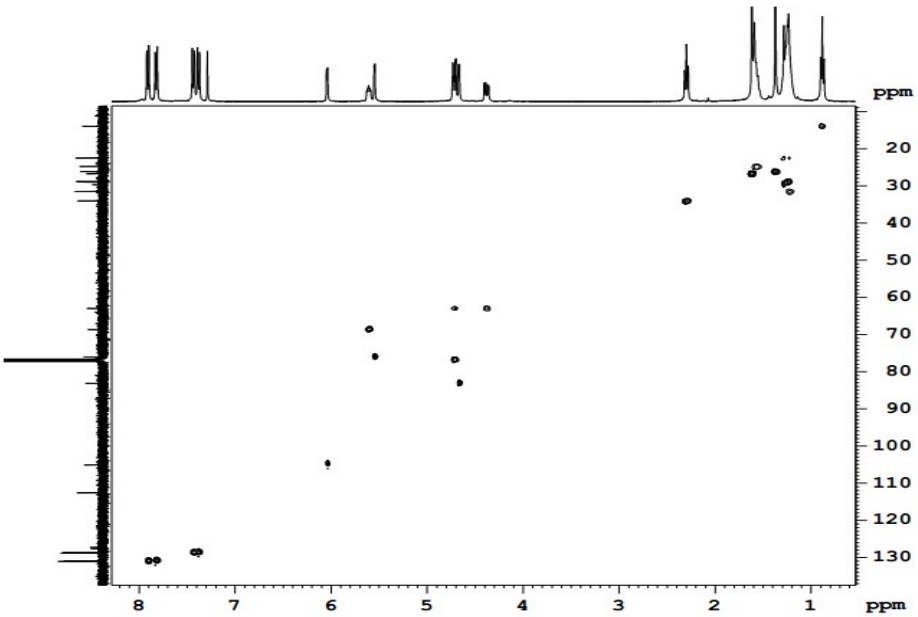

Figure S25. 2D HSQC spectrum of compound **8**.