Synthesis and characterization of Some Mannose Esters at C_1 as a Prodrugs

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الخلاصة

حضرت في هذه الدراسة مشتقات جديدة للمانوز كأسترات عند الموقع الانومري . تؤدي معاملة السكر الحر المحتوي على مجاميع هيدروكسيل مثل المانوز مع الاسيتون باستعمال حامض الكبريتيك المركز كعامل مساعد الى تكوين حلقتي اسيتال خماسية ؛ 2,3:5,6-O-diisopropyldine-D-Mannose .ان معاملة حامض الفا – (٤-ايزوبيوتيل)فنيل مثيل ايثانويك، حامض ديكانويك وحامض سز-٩-اوكتاديكينيويك مع كلوريد الثايونيل تعطي كلوريدات الحوامض. يعطي تفاعل كلوريدات الحوامض الكاربوكسيلية مع-2,3:5,6-O-diisopropyldine-D-Mannose استرات المانوز.

Abstract

In this study, new derivatives of D-Mannose have been synthesized . These derivatives are esters of D-Mannose at anomeric center .Treatment of free sugar containing hydroxyl groups such as D-Mannose with acetone using sulfuric acid (Conc.)as catalyst lead to the formation of two five membered acetal rings ; 2,3:5,6-*O*-diisopropyldine-D-mannofuranose.

Treatment of α-(4-isobutyl)phenyl methyl ethanoic acid,decadecanoic acid and *cis*-9-octadecenoic acid with thionyl chloride give their carboxylic acid chlorides.

Reaction of carboxylic acid chlorides with 2,3:5,6-*O*-diisopropyldine-D-mannose give Mannose esters.

Introduction

1-1 Mannose:

Mannose is a constituent of many glycoproteins, and after absorption or release following the recycling of glycoproteins mannose can be converted to mannose -6-phosphate by hexokinase. Action of phosphomannose isomerase then permits the sugar to enter glycolysis at the level of fructose-6- phosphate, before the phosphofructokinase control point figure (1).[(1)]

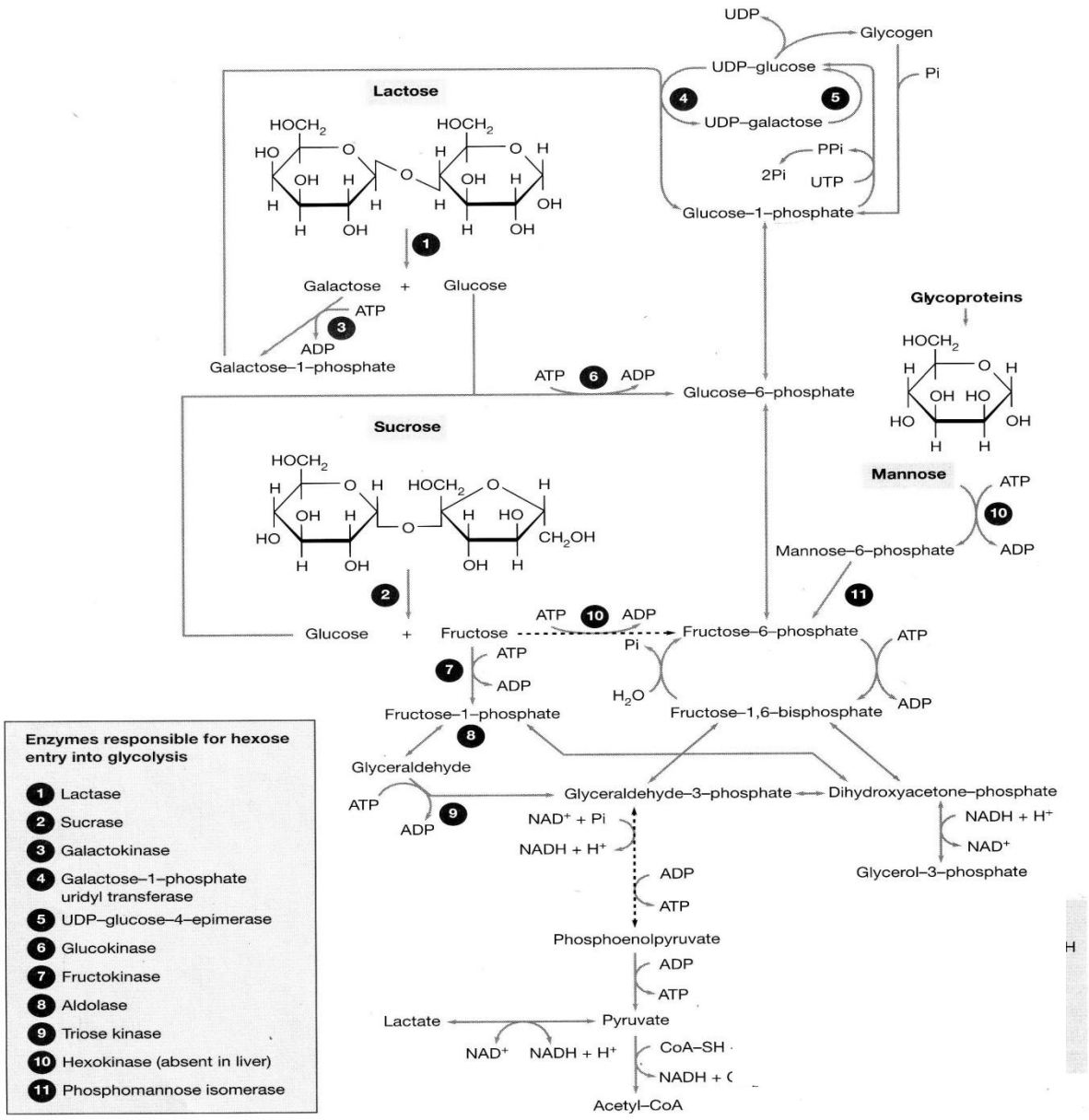
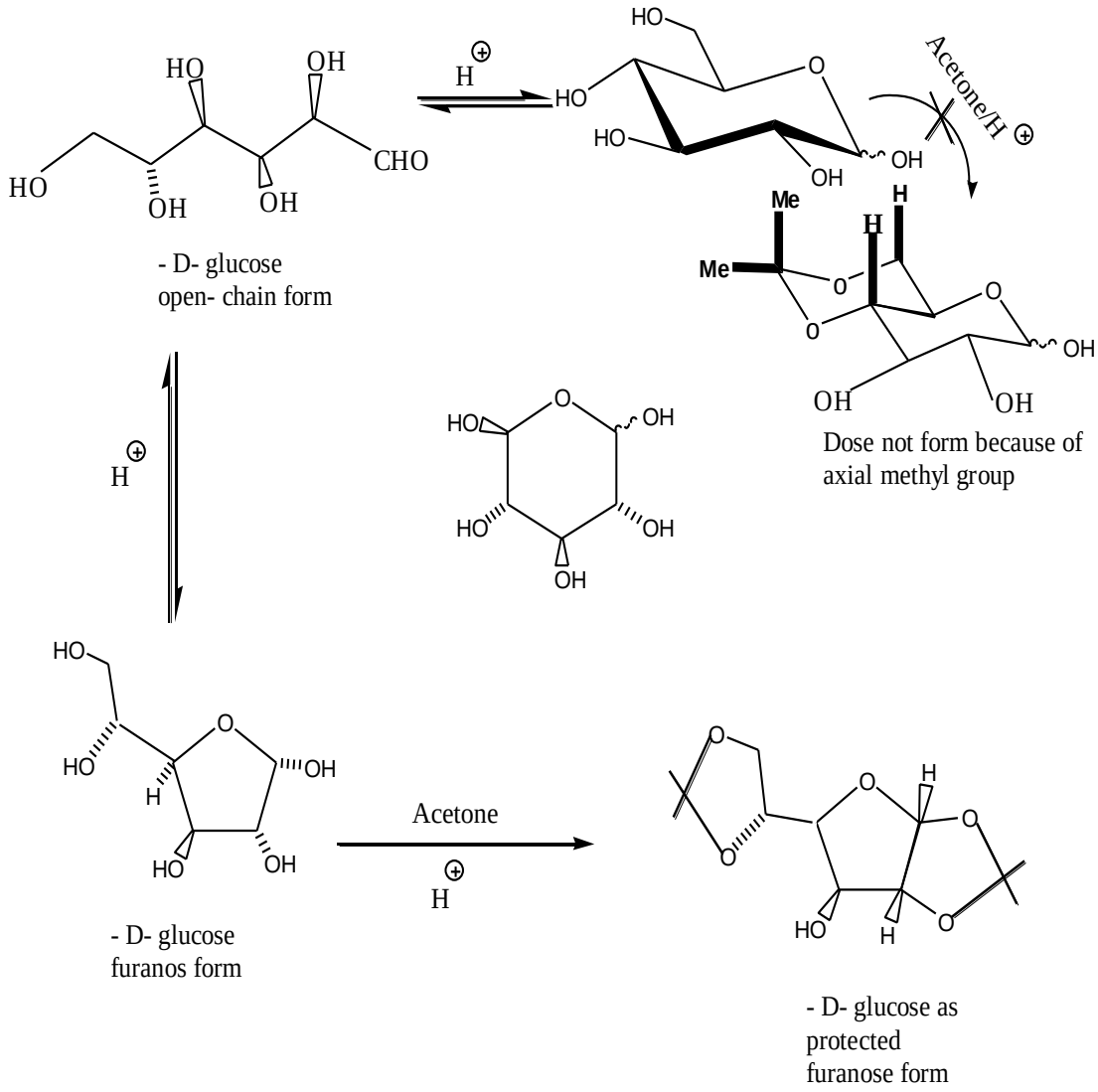


Figure (1-1): Entry points for monosacchrides into glycolysis[1].

1-2- Acetals formation [2]: -

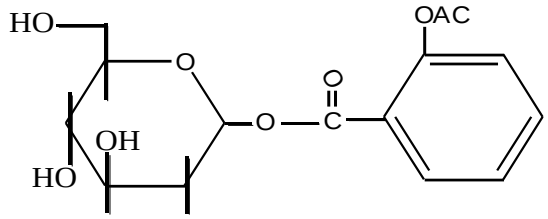
Acetals formed from sugars and acetone have a quite different selectivity. For a start, cyclic acetals of acetone prefer to be five – rather than six- membered rings. In a six – membered ring, one of the acetone's methyl groups would have to be axial, so the five- memebered ring is preferred.



Scheme (1): - shown the selectivity of acetone to formation the cyclic acetals in glucose [2].

1-3- Novel Aspirin prodrug:-

In 1980 1-*O*-(2-actoxy) benzoyl-α- D-2-deoxy glucopyranose [1] was prepared as aspirin prodrug by J.E. Truelove. A.A. Hussain, and H.B. Kosten - bauder.[3]



[1]

Aspirin, probably the most widely used drug in the world, is potent effective, and low cost medicament. However, it produces occult GI blood loss in a large percentage of patients. [4,5,6]

1-4. prodrugs:

The term "prodrug" or "proagent" was first introduced by Albert [7] to signify pharmacologically inactive chemical derivatives that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness and/ or to decrease associated toxicity. Since Albert discussed the concept of prodruges in the late 1950_s, such compounds have also been called "ateutiated drugs" , "biorevesible derivatives" , and "congeners" , but " prodrug" is now the most commonly accepted term [8-10] . Usually, the use of the term implies a covalent link between a drug and a chemical moiety.

Generally, prodrugs can be defined as pharmacologically inert chemical derivatives that can be converted in vivo to the active drug molecules, enzymatically or nonenzymatically, to exert a therapeutic effect. Ideally, the prodrug should be converted to the original drug as soon as the goal is achieved, followed by the subsequent rapid elimination of the released derivatizing group [10,11] .

2-proccedurs

2-1.**Method of preparation of carboxylic acid chlorides [12].**

To a dry powder of carboxylic acid (0.024 mole) in claisen Flask was added excess redistilled thionyl chloride and the mixture was refluxed for one hour or until the evolution of hydrogen chloride ceases .The reaction mixture was left to cool, then condenser was removed and the flask was heated at $60c^o$ for five minutes with occasional shaking to give a yellow oily product.

FTIR spectra (cm^{-1}) for [3] show stretching bands at 1780 –1801 for (Carbonyl group) carboxylic acid chloride figure(3-1).

2-2. 2,3: 5,6- di- *O*- isopropyl dine - D- mannofuranose [1] [13].

To a solution of one liter acetone containing(15 ml) sulfuric acid (conc.), was added, (22g) anhydrous D- mannose the mixture was stirred vigorously, with exclusion of moisture, for five hours. Anhydrous sodium carbonate was added until the solution was neutral, the mixture was filtered and the residues extracted with several lots of hot acetone, and filtered.

The combined filtrate and were evaporated on rotary evaporator and the residue dissolved in sodium- dried ether, filtered, and precipitated with thrice the volume of petroleum ether.

The precipitate was separated, and the mother liquor partially evaporated to give a further crop of crystals; total yield (24 gm), literature; (26 gm). After recrystallization from hot petroleum ether, yield (23 gm, 71.8%), melting point (128-$130C^o$), literature; (25 gm, m.p 122-$123C^o$, 78-6%)[12]. Rate flow (benzene ; methanol , 9:1 ; 0.36) , table (2). Infrared spectra (cm-1) shows at ; 3436 (OH)stretching band,

2985-2904 (CH- aliphatic), figure (4) .Elemental analysis ; calculation for C_{12} H_{20} O_6, C 55.38; H 7.69 .found; C 55.60; H 7.77.

2-3. **1-*O*- α¯-(4- isobutyl) phenyl methyl ethanoyl –2,3; 5,6 – di -*O*-isopropylidine – D- mannofuranose [4].**

A solution of derivative [39] (3.144 gm, 0.012 mole) in dichloromethane (35 mL) was added to a solution of [35] (2.688 gm, 0.012 mole) in dichloromethane (10mL) and pyridine (1mL) , the mixture was stirred at (30 C^o) for (24 hours) .Added (25 gm) of ice was added to a mixture and left for an additional one hour. The dichloromethane layer was separated and washed with distilled water. The organic layer dried over ($MgSO_4$), solvent was removed by rotary evaporator to give a waxy solid product, which washed with benzene (30 ml) . Removed solvent under reduced pressure, gave syrup .The syrup purified on a silica gel column eluent with chloroform to give (3.764 gm, 69%) . Rate flow (benzene ; methanol , 9;1 , 0.85) table (2) . Infrared spectrum (cell, cm^{-1}) 4049 (C-H, aromatic), 2983-2869 (C-H, aliphatic), 1745 (carbonyl group) , 1512, 1600 (-C=C-) aromatic figure (3-2) .Elemental analysis; calculation for C_{25} H_{36} O_7, C 66.96 ; H 8.03 , found: C 65.15 ; H 6.98.

2-4. 1-*O*-Decadecanoy1-2,3:5,6-di-*O*-isopropylidine-D-mannofuranose [5].

To a solution of [39] (1.572gm, 0.006 mole) in dichloromethane(12m1) was added a solution of [36] (1.983gm, 0.006 mole) in dichloromethane (5m1) and pyridine (0.5ml). The mixture was stirred at (33C^0) for (24 hours). (15gm)of Ice was added and the mixture left for an additional one hour. Organic layer was separated, washed with distilled water (25ml) and dried over anhydrous ($MgSO_4$). Solvent was removed by evaporation under reduced pressure, to leave thick oil; purified on silica gel column with chloroform eleuent to give (3.275gm, 97.77%)rate flow (benzene; methanol, 9; 1,0.91) table [2]. Infrared spectrum (cell, cm^{-1}) 2975-2852 (C-H, aliphatic), 1739(carbonyl group) figure (14).

Elemental analysis, calculation for $C_{32}H_{58}$ O_7, C 69.31; H 10.46 found C 68.43;H 9.52, table (2).

2-51-*O*-*cis*-9-Octadecenoyl-2,3:5,6-di-*O*-isopropylidine-D-mannofuranose [6].

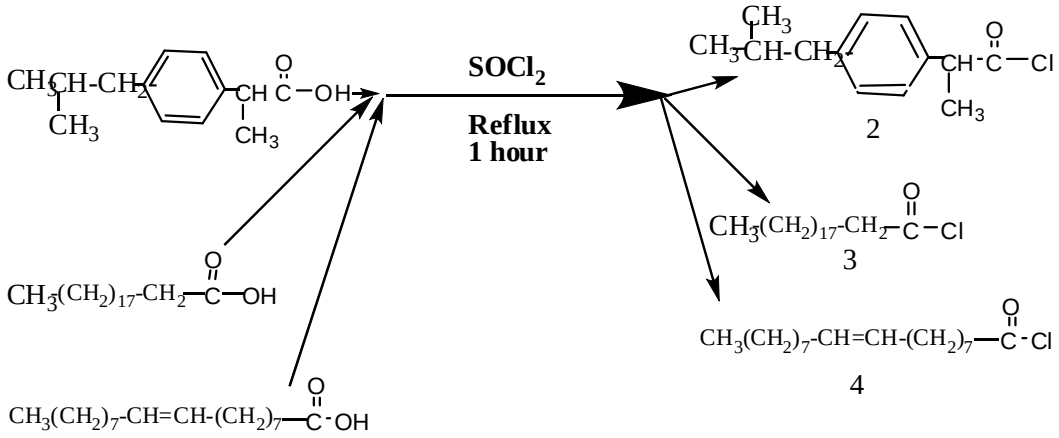
A mixture of compound [39](1.83gm,0.007mol) in dichloromethane (15ml), compound [37](2.1gm,0.007mole) in dichloromethane (5ml)and pyridine(0.5ml) was stirred at (34C°) for (24 hours).

Twenty grams of ice was added and the mixture left for an additional one hour. Dichloromethane layer was separated, washed with distilled water (50ml), dried over anhydrous ($MgSO_4$) and evaporated under reduced pressure to yield thick oil.

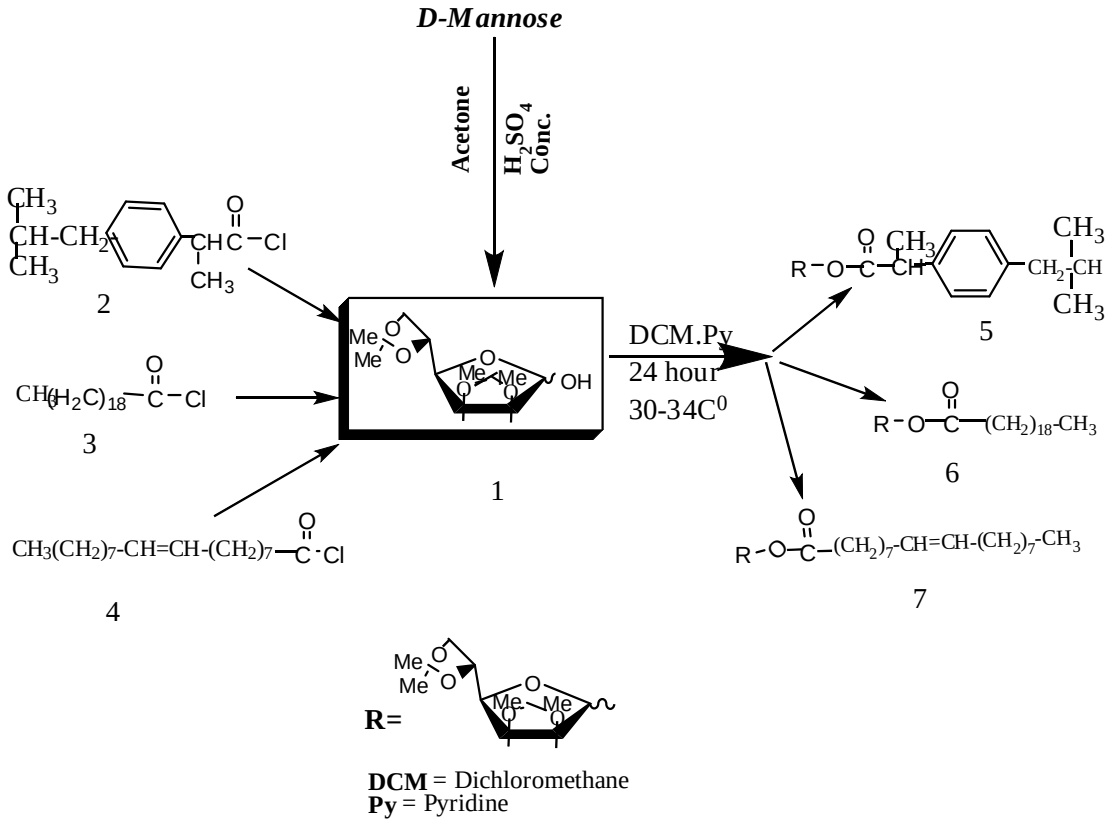
The crude product was purified on silica gel column using chloroform as eleuent to give (2.857gm,77.3%). Rate flow (benzene; methanol, 9;1, 0.88) table

(2). Infrared spectrum (cell, cm^{-1}) 2921-2852 (C-H, aliphatic),1739(carbonyl group) 1690(-C=C-),figure (16) .

Elemental analysis, calculation for $C_{30}H_{52}O_7$, C 68.70; H 9.92.found C 67.14, H 10.28, table (2).



Scheme (2) Synthetic route used for the preparation of acid chlorides [,2,3,4].



Scheme (3): - Synthetic route used for the preparation derivatives [5,6,7]

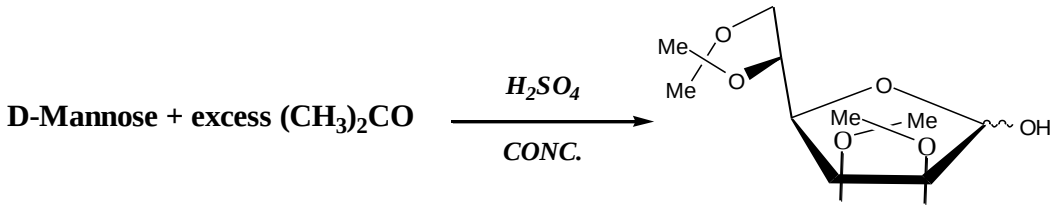
3-Results and discussion

Two principles approaches have been used for construction of the carbohydrate portion for prodruges. The first approach utilized a suitable sugar, while the second one started with simple non- carbohydrate compound [(14)].D- maunose has been chosen as a starting material since it is readily available and comparatively inexpensive compound. The strategy used for the synthesis of [1] as the carbohydrate moiety and derivatives [2,3,4] as the acid chlorides for the synthesis of prodrugs [5,6,7] was started with D-mannose in a series of reactions schemes (2,3).

Treatment of free sugar containing hydroxyl group such as D-mannose with acetone using sulfuric acid (conc.) as catalyst lead to the formation of two five membered acetal rings, one acetal having cis-fused 5/5rings and other being on the side chain [(2)].

A cetals are stable in alkaline conditions but are readily hydrolyzed by dilute aqueous acids, hence, they were very useful in our synthetic route as blocking groups and were used in case of D-mannose for protecting the hydroxyl groups at C-2,C-3, C-5,C-6, leaving the (1-OH) free for further chemical modification[(12)].

A number of procedures using different acid catalysts were available for the acetonation of D- mannose but generally they are time consuming and require large quantities of reagents. These methods include the use of mineral acids (conc.) such as sulphuric acid (H_2SO_4) [(12)] as catalyst and acetone. The 2,3; 5,6-di-*O*-isopropylidine - D-mannofuranose [1] was synthesized using (conc.H_2SO_4)as catalyst[(12)].



[1]

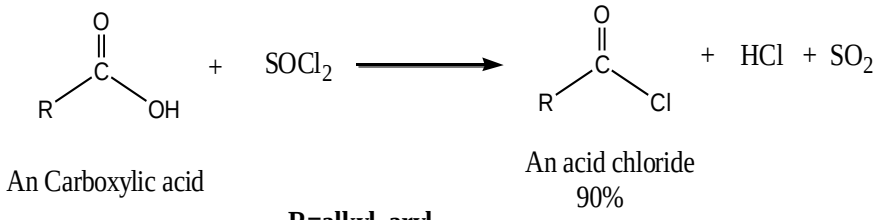
The derivative [1] was characterized by FTIR spectroscopy (cm^{-1}) which showed stretching band at 3436 for hydroxy group, 2985-2904 (C-H aliphatic) figure (3-2), and elemental analysis table (3-2).

H^1NMR($CDCl_3$)δ;1.2-1.5(12H,s,4CH_3,iso.),3.6(1H,s,H-OHgroup)3.9-4.8 (6H,m,H-2,H-3-~~H~~-4,~~H~~-5,~~H~~-6[a],~~H~~-6[b]~~)~~,5.3~~5~~(1H,H-1) Fig~~ur~~e(3-3).

C^{13}NMR($CDCl_3$)[(2)] ;24.5-26.8(carbons, 4CH_3, iso.),66.55-85.56 (carbons, sugar~~,2,3,4,5,6)~~, 77.11-77.58 (carbon, solvent, $CDCl_3$), ,101.1, (carbon- 1). Figure FTIR spectrum (cm^{-1}) for [2], showed stretching bands at 1780-1801, for (carbonyl group) carb~~o~~xylic acid chloride figure (3-4)

After purification of the derivatives [5,6,7] on silica column chromatography, [5,6] are a crystaline product in 69.44%,97.77% yield respectively, and [7]is yellow oil in 77.3% yield .

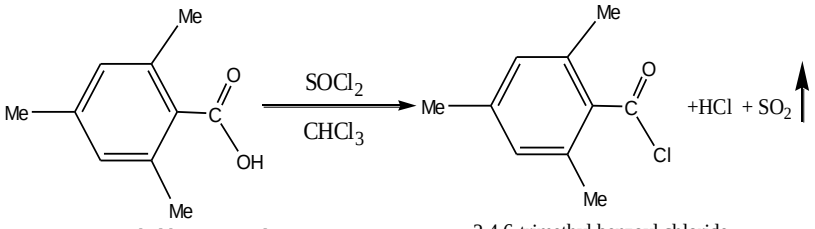
Treatment of carboxylic acid with thionyl chloride, $SOCl_2$, or phosphorus penta chloride, PCl_5, gives acid chloride:-[15,16]



An Carboxylic acid

An acid chloride
90%

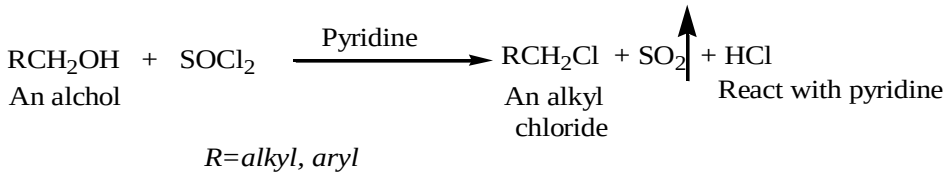
R=alkyl ,aryl



2,4,6-trimethyl benzoic acid

2,4,6-trimethyl benzoyl chloride

Thionyl chloride is the same reagent that is used for making alkyl chorides from alcohols:-



Thionyl chloride is adense, fuming liquid (bp75-76°) that commerically available.

The FTIR spectrum $cm^{-1}$of [1-*O*-α-(4-isobutyl) phenyl methyl ethanoyl- 2,3: 5,6-di-*O*-isopropylidine –D-mannofuranose][5] showed astretching band at 3049; (C-H, aromatic) 2983-2869, (C-H, aliphatic) 1745,for carbonyl group, 1512,1600, (-C=C-) aromatic, and the absorption band at 700-800 was assigned to aromatic bending figure (3-5).

H^1NMR ($CDCl_3$) δ ;0.9-1.0(6H,s, $4CH_3$,isobutyl group), 1.44 (12H,s $4CH_3$,2iso), 1.1-1.2(3H,d, CH_3 of ethanoate group),1.8-1.84(1H,t,C-H, isobutyl group),2.41-2.43(2H,d,methylene group, isobutyl group) 3.49-3.67 (1H,q, C-H, ethanoic acid). 3.98-4.67 (6H,m,H-2,H-3,H-4,H-5,H-6^a,H-6^b) 5.1-5.27(1H,t,H-1),7-7.24(4H,q,C-H,aromatic),Figure(3-6)

C^{13}NMR (CDCl3)δ ; 18(carbon methyl group , ethanoate group), 22.46 (carbons, 2 methyl group, isobutyl group), 30.26 (carbons, 4 methyl group ,2iso group), 30.5(carbon, C-H isobutyl group,), 45.11 (carbon, methylen group, isobutyl group), 76.65-77.58(carbone,solvent, $CDCl_3$). 69-78 (carbons,sugar,C-2,C-3,C-4,C-5,C-6), 101 (carbon,C-1),114 (carbons, -C-, 2 iso), 128-131(carbons,-C=C-, aromatic), 173(carbon, carbonyl group, ester)figure (3-7)

The FTIR spectrum $cm^{-1}$of [1-*O*-Decadecanoyl—2,3: 5,6-di-O-isopropylidine –D-mannnofuranose][6] showed 2975-2852, for (C-H, aliphatic), 1739 for carbonyl group), figure (3-8)

H^1NMR ($CDCl_3$) δ; 0.86-0.89 (3H,t, methyl group, C_{20}), 1.17-1.42 (30H, s, methylen group ,C_4-C_{19}.), 1.66 (2H, t, methylen group C_3), 2.27-2.30 (2H,q, methylen group,C_2), 3.66-3.68 (12H, s, 4 methylen group, 2 iso) 4.0-4.12(6H,q,H-2,H-3,H-4,H-5,H-6^a,H-6^b). Figure (3-9)

The FTIR spectrum cm^{-1} of 1-*O*-*cis*-9-Octadecenoy-2,3:5,6 –di-*O*- isopropylidine –D-mannofuranose[7]showed, 2921-2852,(C-H, aliphatic), 1739 (carbonyl group), 1680, (-C=C-), allkene, figure (3-10)

H^1NMR($CDCl_3$) δ ;0.8-0.9(3H,t,methylgroupC_{18}),1.2-1.5(26H,m,methylen group,C_3-C_8 ,C_{11}-C_{17}), 2.2 (12H,s,4methyl group ,2 iso), 3.6 (1H, s,H-OH group,),4-4.9 (6H,m,H-2,H-3,H-4,H-5,H-6^a,H-6^b), ,5.3-5.4(1H,s,H-1), 6.1-6.2(2H,s,H-olefinic), 7.3 (3H,s,H $CDcl_3$), figure(3-11)

C^{13}NMR ($CDCl_3$) δ; 14(carbon, CH_3,C_{18}), 23-30 (carbons, methylen group ,C_3-C_8,C_{11}-C_{17}),33(carbons, 2iso), 35 (carbon, methylen group,C_2), 70-85 (carbons, sugar,C-2,C-3,C-4,C-5,C-6),77(solvent, $CDCl_3$) 101 (carbons, C-1) 109,114(carbons, -C-,2iso.), 131 (carbons, olefinc , C_9-C_{10}), 172-180(carbon, carbonyl group, ester) figure(3-12)

Table(1):- show yield (gm%) for the prepared acid chlorides [2,3,4].

Comp. No.	***Acid chloride***	Formula	Physical Properties	Yield	
				gm.	%
2	α–(4-isobutyl) phenyl methyl ethanoyl chloride	$C_{13}H_{17}OCl$	Yellow oil	5.11	95.2
3	Decadecanoyl chloride	$C_{20}H_{40}OCl$	Yellow oil	7.73	97.5
4	*cis*-9-octadecenoyl chloride	$C_{18}H_{33}OCl$	Yellow oil	6.75	94.25

Table (2) :-physical properties for Derivatives [1,5,6,7].

Compound number	Formula	Physical state	Melting point c°	Rate of flow in thin layer chromatography (T.L.C), R_f (Solvent)	Elemental analysis calculated (found)		Yield %
					C %	H %	
1	$C_{12}H_{20}O_6$	White hte crystals	128-130	(benzene :methanol, 9:1 ,0.36)	55.38 (55.60)	7.69 (7.77)	78
5	$C_{25}H_{36}O_7$	White crystals	86-88	(benzene :methanol, 9:1 ,85)	66.96 (65.15)	8.03 (6.98)	69.44
6	$C_{32}H_{58}O_7$	Waxy yellow crystals	49-51	(benzene :methanol, 9:1 ,0.91)	69.31 (68.43)	10.46 (9.52)	97.77
7	$C_{30}H_{52}O_7$	Yellow oil	-	(benzene :methanol, 9:1 ,88)	68.70 (67.14)	9.92 (10.28)	77.3

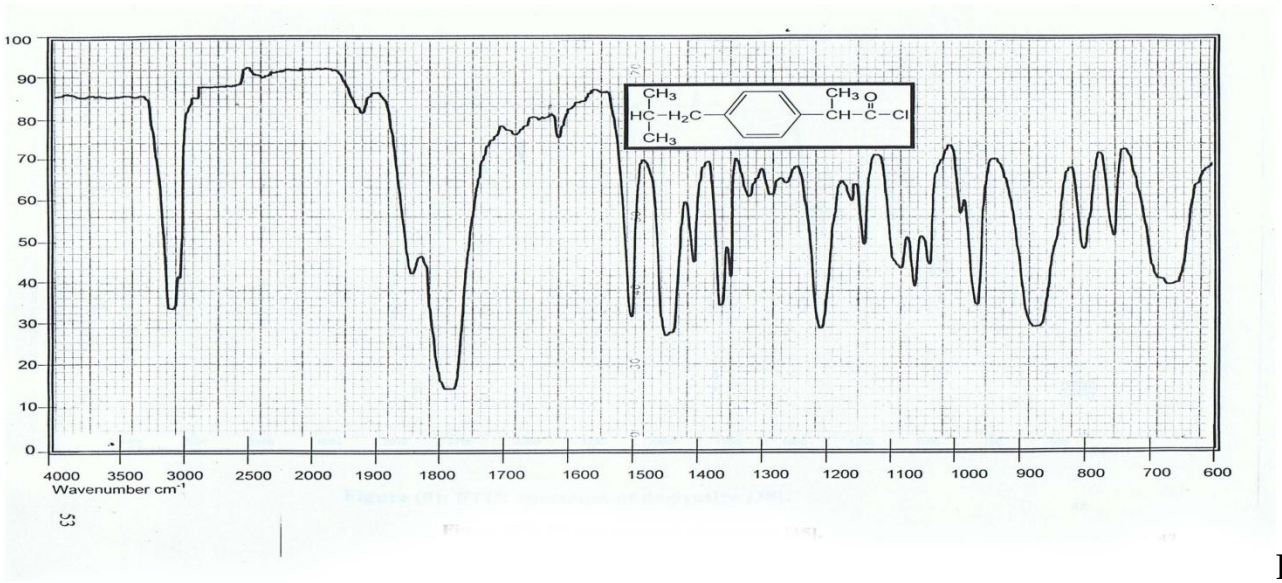


Figure (3-1) IR spectrum of derivative [2]

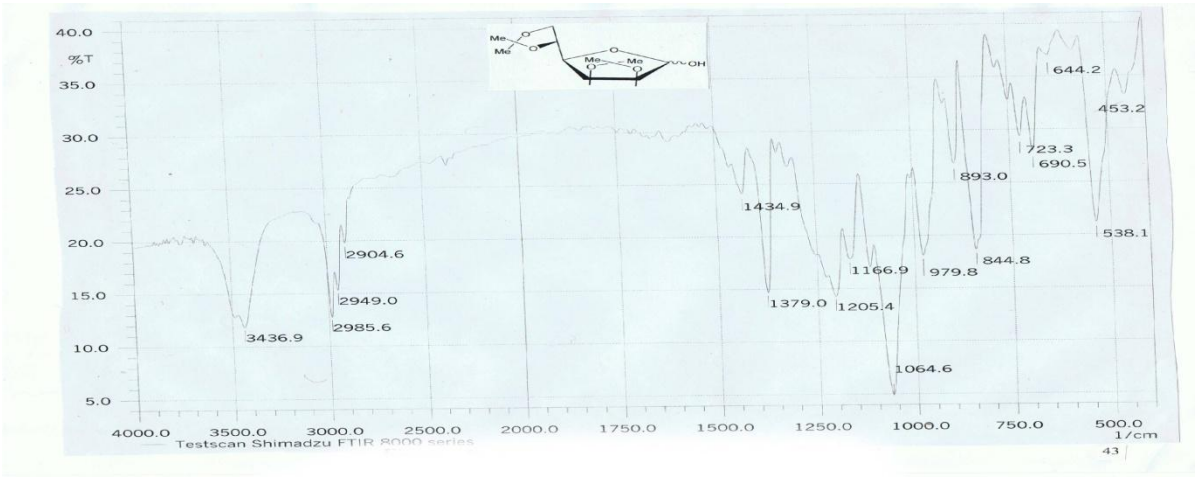


Figure (3-2) FT- IR spectrum of derivative [1]

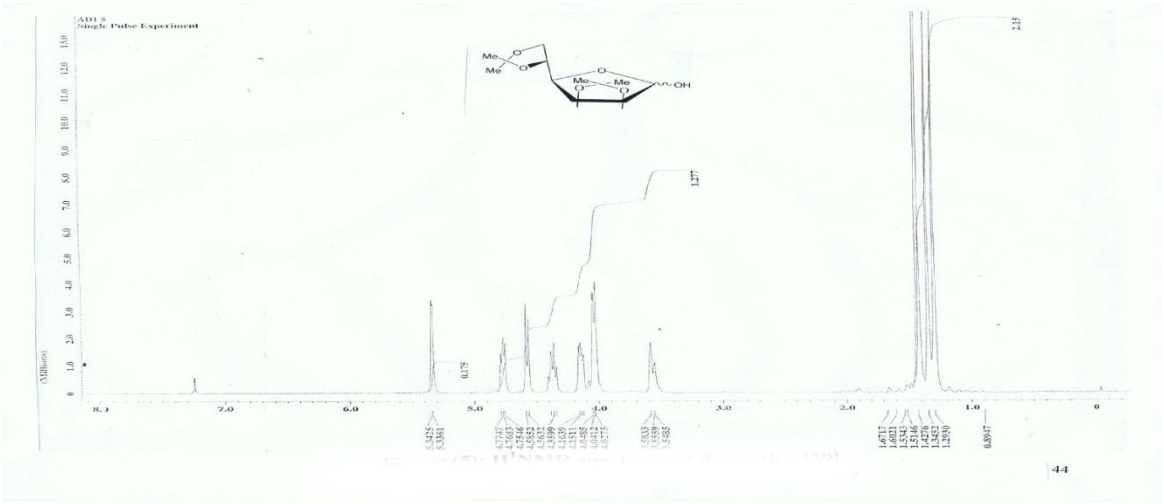


Figure (3-3) H^1NMR spectrum of derivative [1]

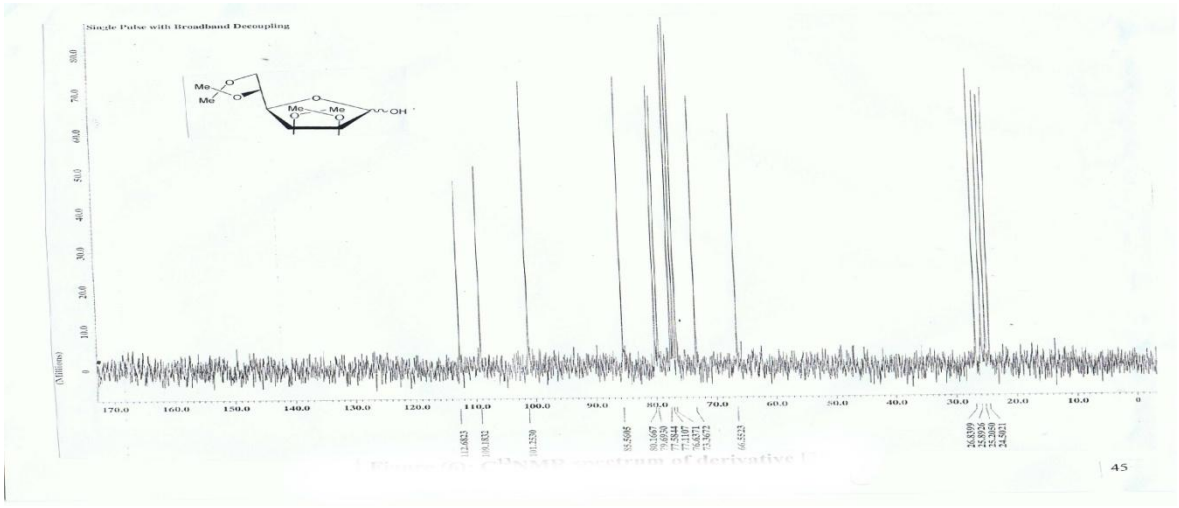


Figure (3-4) C^{13}NMR spectrum of derivative [1]

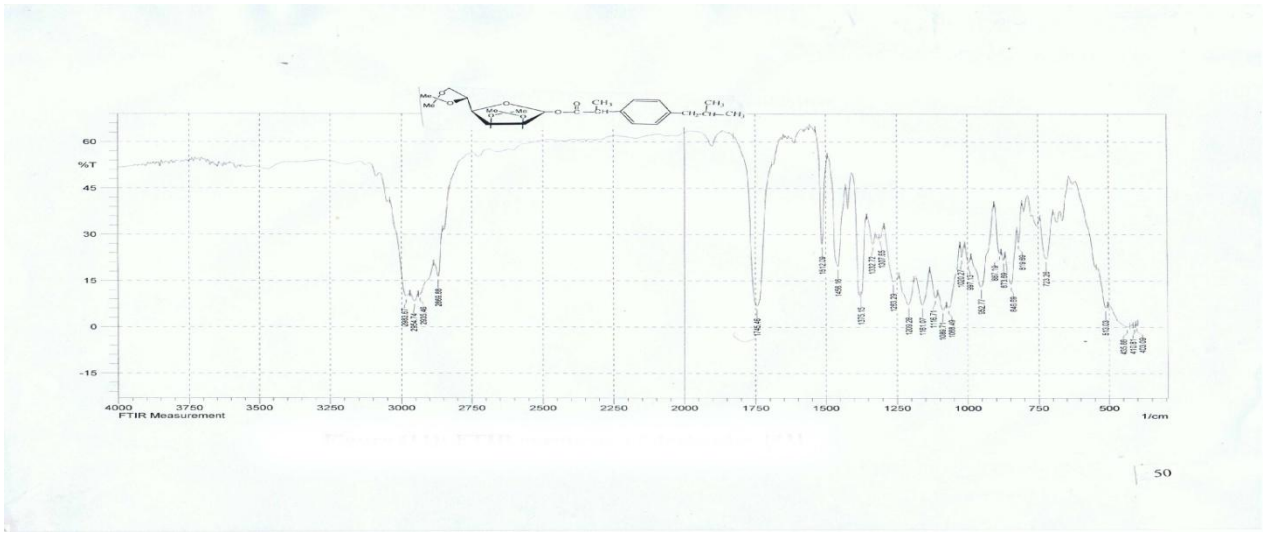


Figure (3-5) FT-IR spectrum of derivative [5]

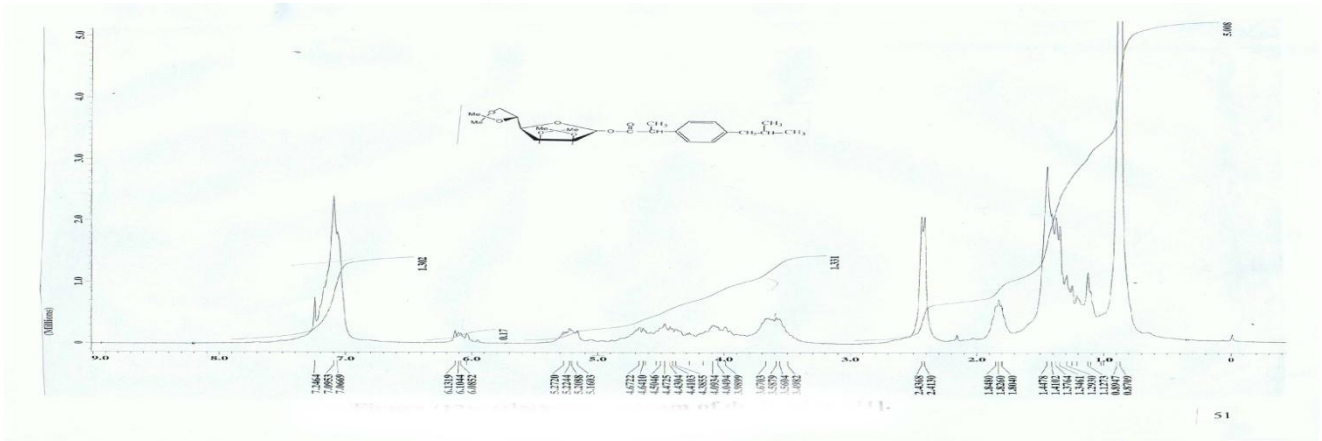


Figure (3-6) H^{1}NMIR spectrum of derivative [5]

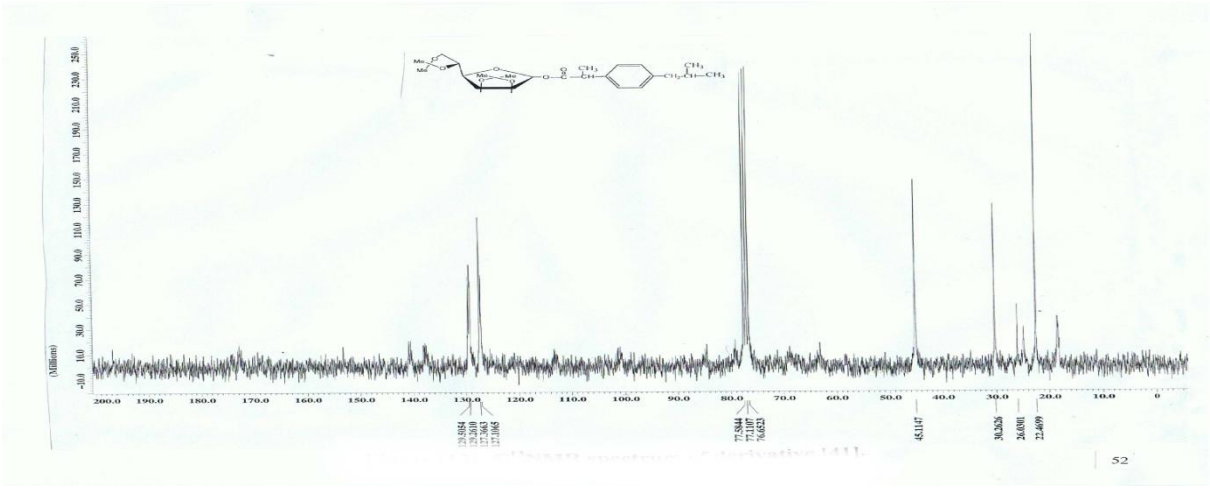


Figure (3-7) C^{13}NMIR spectrum of derivative [5]

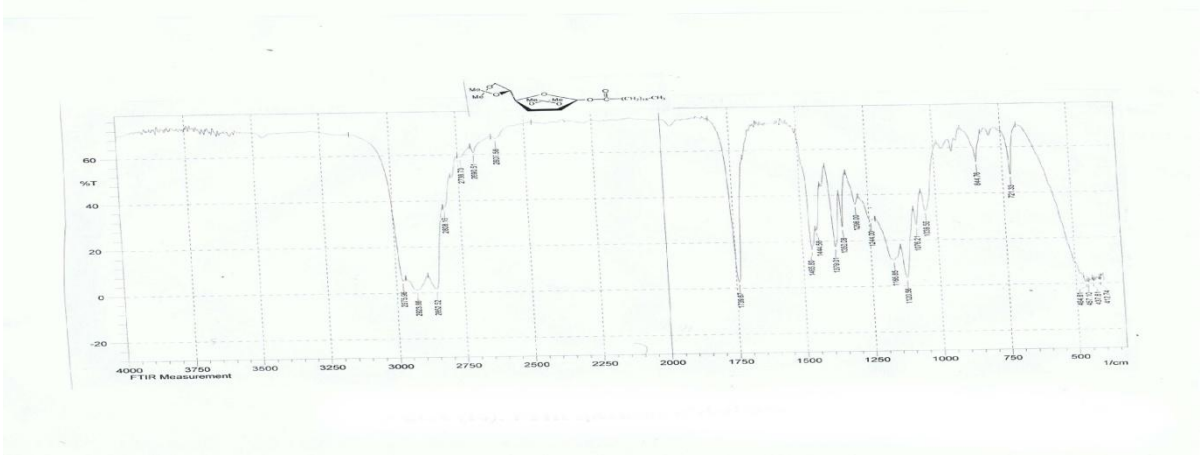


Figure (3-8) FT-IR spectrum of derivative [6]

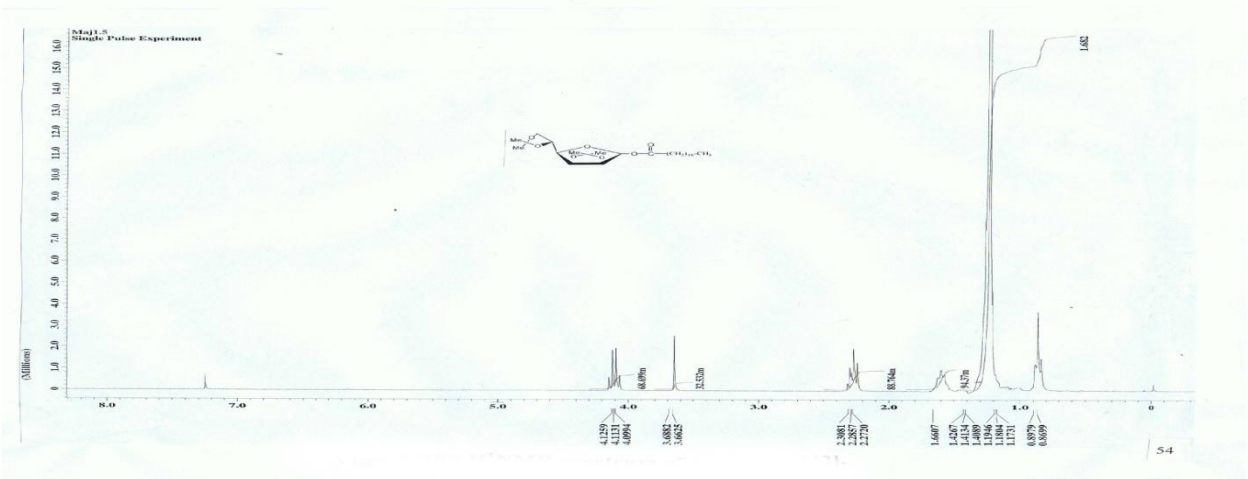


Figure (3-9) H^{1}NMIR spectrum of derivative [6]

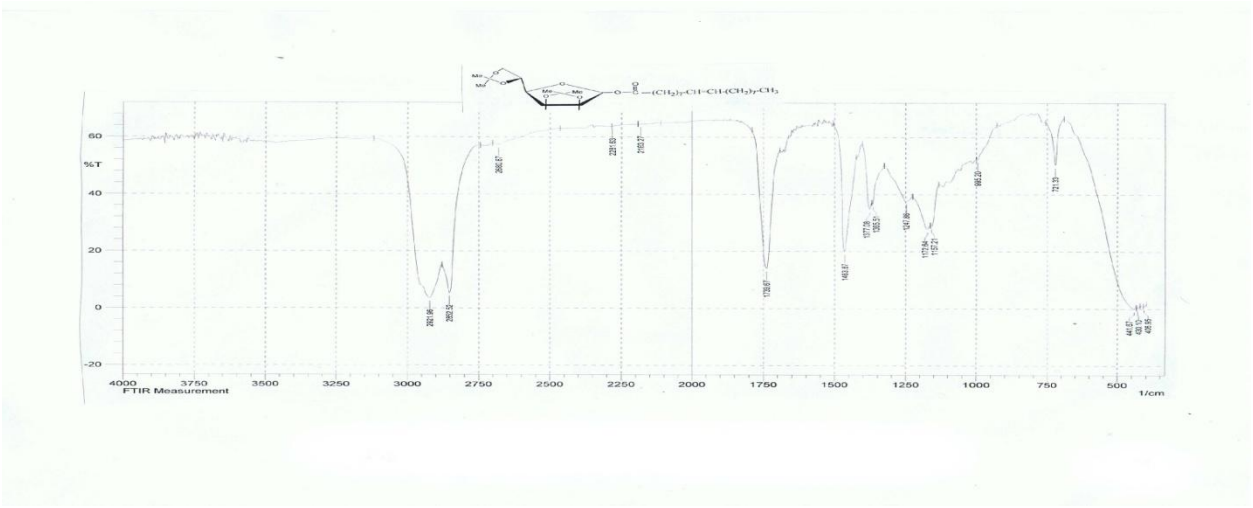


Figure (3-10) FT-IR spectrum of derivative [7]

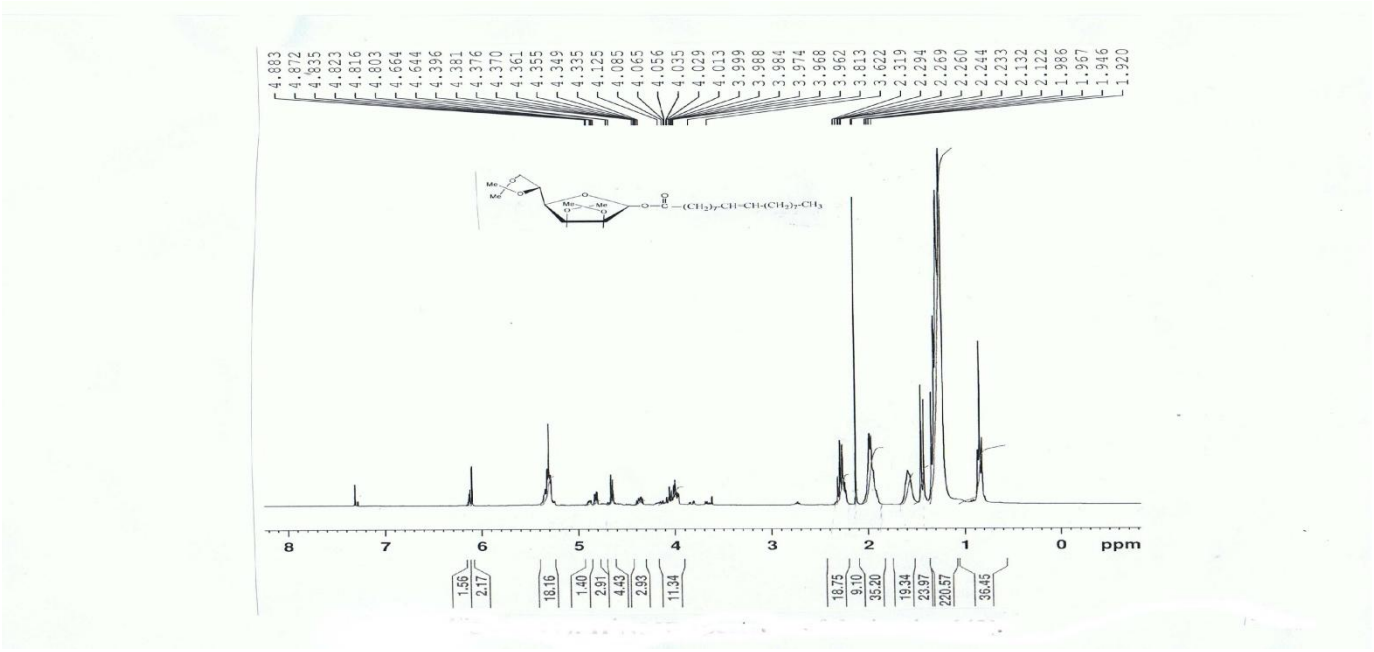


Figure (3-11) H^{1}NMIR spectrum of derivative [7]

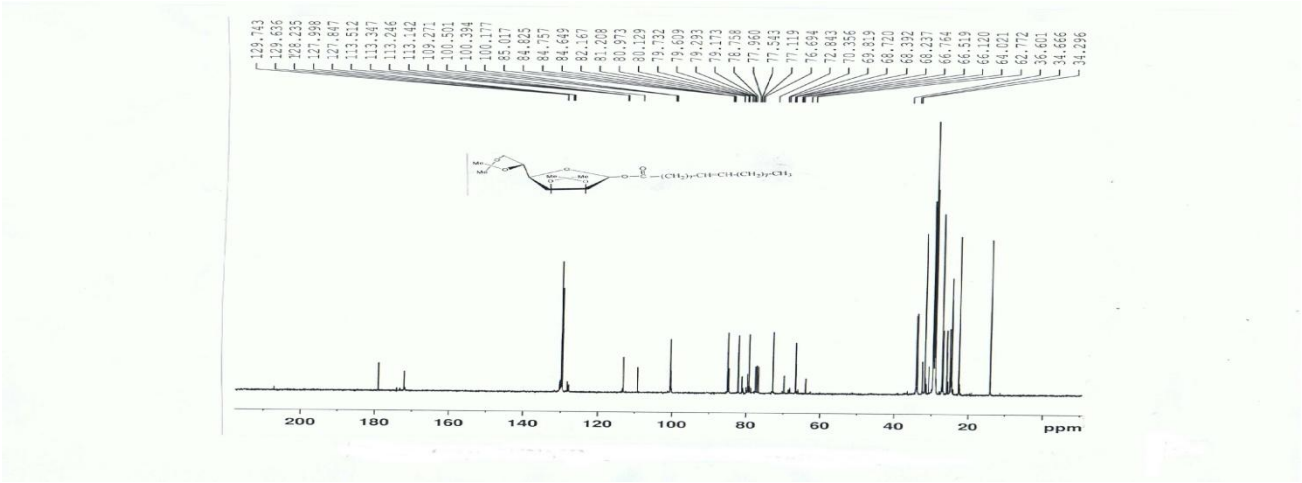


Figure (3-12) C^{13}NMIR spectrum of derivative [7]

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