Tikrit Journal of Pure Science 22 (9) 2017
ISSN: 1813 – 1662 (Print)
E-ISSN: 2415 – 1726 (On Line)

Synthesis and Characterization of 1,2,3- Triazole Derivatives from D-Mannitol

Ihmood Kh. Juber
Department of Chemistry, College of science, University of Tikrit, Tikrit , Iraq
ihmood.jebur@yahoo.com

Abstract

This research included the use of azido D-Mannitol (3) to synthesize 1,2,3 triazole derivatives. Azido D – Mannitol (3) itself used as an intermediate which was prepared from reaction of 1, 2:5, 6-Di-o-isopropylidene-3,4-di-p-tosyl-D-Mannitol (2) with sodium azide. The prepared compound (3) was allowed to react with alkenes for the formation of corresponding 1,2,3 triazole (4_{a-e}).

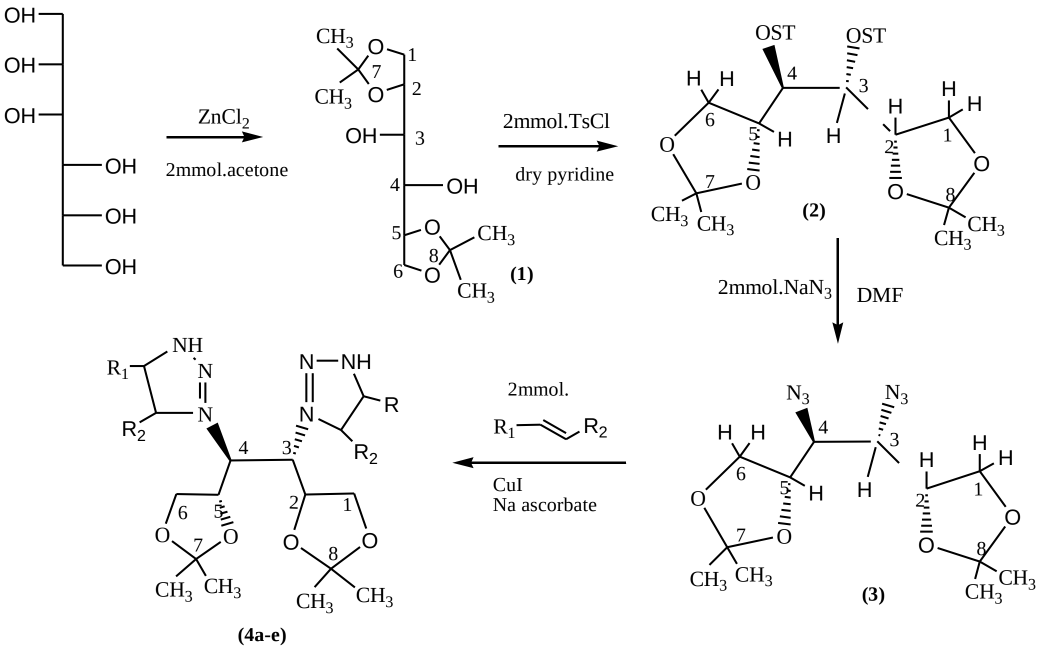
The structures of some prepared compounds were confirmed by physical properties and spectroscopic methods FT-IR , ^{1}H-NMR , ^{13}C-NMR and Mass spectra in addition to use TLC.

Key words: D-Mannitol, 1,2,3-triazole , azide , isopropylidene

Introduction

Cyclic acetals of sugars and alditols are important synthetic intermediates. Their preparation, chemistry, and physical properties have been comprehensively reviewed [1]. These compounds are generally prepared by acid-catalysed condensation of carbonyl compounds with suitable hydroxylic substrates. The final product's nature is thermodynamically controlled. Acetal exchange, which is frequently used to acetylates carbohydrates [2-5], is considered to be under kinetic control and has led to products not always available by direct methods. The most commonly used reagent is 2,2-dimethoxypropane in N,N-dimethyl formamide with toluene-p- sulphuric acid as catalyst. Acetonation under kinetic control may also be achieved by the use of 2-alkoxypropenes under similar conditions [6-7].

Huisgen 1,3-dipolarcycloaddition of azides and alkenes resulting in 1,2,3-triazoles are one of the most powerful preparation reactions. Several members of the 1,2,3-triazole family showed some interesting biological properties, including anti-allergic, anti-bacterial, and anti- HIV activity. In addition to that, 1,2,3-triazoles are found in herbicides, fungicides, and dyes [8-9].



TsCl = para toluene sulfonyl chloride

R	a	B	c	d	e
R_1	H	H	CH_3	CH_3	H
R_2	CH_2OH	3-methyl phenyl	Di CH_3	CH_3	Ph

(Scheme 1) (Preparation of compounds from 1----(4_{a-e}).

Experimental

Melting point was determined using a Linkam HF591. Digital series (TC92) melting point apparatus were uncorrected. Infra-Red (RX / FT-IR) spectra were recorded as (neat) disc using an ATR Perkin Elmer, RX / FT-IR Nicolet Model 205 FT-IR, spectrophotometer.

^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Bruker-Avance spectrometer AMX400 (H400MHz); with TMS as internal standard $CDCl_3$, as a solvent respectively at the chemistry department, University of Sheffield /UK. Thin layer chromatography (TLC) was on silica gel and used coated plates type Linear-K (20 x 20mm) Whatman com. Mass.

Preparation of the 1,2:5,6-Di-o-isopropylidene-D-mannitol(1):[10]

A solution of zinc chloride (40g, 293 mmol.), in dry acetone (300 ml), was added to D-Mannitol (20 g, 110 mmol.). The mixture was shaken at 20^o C until solution was formed for 3 h, then it was allowed to stand for 16 h at room temperature, then poured into a solution of potassium carbonate (70 g, in 70 ml water), and covered by diethyl ether (300 ml). The prepared solution was shaken vigorously (acetone-ether) solution and poured off on the agglomerated pellets of zinc carbonate, later was washed twice with (100 ml) of solution (acetone/ether1:1). The filtrate was concentrated in vacuum at (60-70^{o}C), then the concentrate solution was heated until the residue was completely dry. The residue was further vigorously refluxed for 20 minutes each in (250ml) portions of petroleum ether (b. p 60-80^{o}C). The resulting solution was rapidly filtered through a steam–heated funnel on slow cooling long fine crystals of 1,2:5,6-diacetone D-Mannitol separated. Those were filtered off with suction after 2 hours in the refrigerator, recrystallization from isopropyl ether, m.p. = 117-119 ^{o}C, (Yield: 7.9 g, 55%),

Preparation of the 1,2:5,6-Di-o-isopropylidene-3,4-bis-*p*-tosyl-D-Mannitol (2) [10]

A solution of 1,2:5,6-Di-o-isopropylidene-D-Mannitol (1) (3.3 g, 12.5 mmol) in dry pyridine (65 ml) and *p*-toluene sulfonyl chloride (3.68 g, 23.7 mmol) was added at room temperature after 3h. The mixture was poured into ice-water (400ml) and the crystalline product separated out and filtrated off, washed carefully with cold water which dried over anhydrous calcium chloride in desiccators under reduced pressure. After two recrystallization from methanol, colourless crystals were obtained as m.p. 112-115^{o}C, (yield:44.1g, 84%).

Preparation of the 1,2:5,6-di-o-isopropylidene-3,4-diazido-D-Mannitol (3)[11]

To the solution of 1,2,5,6-Di-o-isopropylidene-3,4-bis -*p*-tolyl sulfonyl-d-mannitol(2) (1.2g ,2.5mmole) in N,N-Dimethyl formamide (2ml), water (1.5ml) , sodium azide (0.325, 5mmol), and urea (0.8 g, 10.5 mmole), were added. The mixture was heated for 19 h at 120^{o}C under nitrogen atmosphere. The cooled solution was poured into ice water (600ml), and then was extracted with chloroform (3x10ml). Organic Layers were combined and washed with aqueous sodium bicarbonate (10ml), and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure to give pale yellow oil (1.56 g, 84%).

Preparation of the 1,2:5,6-di-o-isopropylidene-1,2,3-triazole-D-Mannitol (4_{a-e}) [12]

A solution of 1,2:5,6-di-o-isopropylidene-3,4-diazido-D-Mannitol (3) (6.5g, 20.8mol) in anhydrous acetonitrile (15ml), was treated at room temperature with alkenes (41.6mmol) in anhydrous acetonitrile (5ml) in the presence of the sodium ascorbate (0.18 mmol) and $CuSO_4.5H_2O$ (0.09 m mol) in CH_3CN (10 ml). The mixture was stirred with heating at 60^{o}C for 6h.Diethyl ether (20 ml) was then added to the reaction mixture and then washed with water (3 x15 ml). Organic Layer was washed with water. The combined extracts were dried over magnesium sulphate. Solvent was evaporated under reduced pressure and the solid residue was collected to afford the 1,2,3-triazole (4_{a-e}). The reaction of azides (3) with propargyl alcohol was carried out in a similar manner to that already described above, and the resulting compounds (4a-e) were also identified as described below in Table (1).

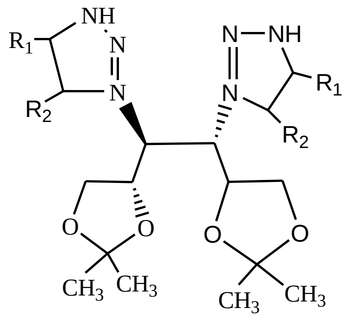


Table (1) Physical Properties melting point, Yield %, Recrystallization solvent and Molecular formula for compounds (4a-e).

Comp. No	R_1	R_2	M.P. ^{o}C	Molecular formula	Yield %	Rec. Sol.
4a	$-CH_2OH$	H-	Oily	$C_{16}H_{28}N_6O_6$	53%	------------
4b	3-methyl phenyl-	H-	112-114	$C_{28}H_{36}N_6O_4$	63%	DCM*
4c	Di CH_3-	CH_{3-}	132-135	$C_{20}H_{40}N_6O_4$	57%	MeOH
4d	CH_{3-}	CH_{3-}	103-107	$C_{18}H_{34}N_6O_4$	55%	90% MeOH
4e	Phenyl-	H	145-147	$C_{26}H_{30}N_6O_4$	61%	MeOH

*Dichloro methane

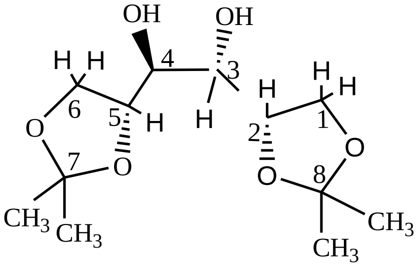
Results and Discussion

The compound (1) 1,2:5,6-Di-o-isopropylidene-D-mannitol, in 47% was yielded by cyclo addition of D-Mannitol with dry acetone in the presence of zinc chloride anhydrous at (20°C) according to the scheme (1). The structures of the synthesized compounds were confirmed by using IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral methods.

IR spectrum of compound (1) showed characteristic absorption bands in the regions (3422 - 3390) cm^{-1} for (O-H) stretching vibration. Also, it clearly showed two types of vibrating modes for (O-C-O) group asymmetric at 1212 cm^{-1} and symmetric at 1068cm^{-1} finally a band at 2941, 2840 cm^{-1} corresponding to $(CH_3)_2$ group of cycloisopropylidene. see figure (1).

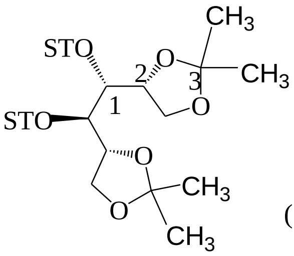
The **^{1}HNMR spectrum** of compound (1) shows the protons signals due to acetal groups which were recorded between 1.31–1.41 ppm integrating for six protons, and also it showed signals at 2.72 ppm for methylene (CH_2) group and one triplet at 3.71 ppm for CH group, as well as CH group appears as multiplet at 4.10 ppm. Attributed to CH-OH group.

^{13}CN.M.R spectrum of the compound (1) showed the following characteristic chemical shifts ($CDCl_3$,ppm), the carbon of two methyl group appeared singlet at δ 25.19, 26.71 ppm and it showed CH_2 group(C_1&C_6) at 66.73 ppm, while it showed bands singlet at δ 71.19, 76.26, 109.38 ppm for the C_5, C_4 and C_7 respectively .see figure (2). The **Mass spectrum** showed peak due to the molecular ion m/z (TOF MS ES+) M^+ = 263.1493 (M+), $C_{12}H_{22}O_6$, Calc. Mass, 263.1495. see figure (1).



The most frequent method of preparation of 1,2:5,6-Di-O-isopropylidene-D-Mannitol (1) was treated by an excess amount of p-toluene sulphonyl chloride in the presence of anhydrous pyridine to yield the corresponding bistosylate **(2)** in good yield 75%.

The structure of the desired bistosylate (**2**) was confirmed by Infrared spectrum. The IR spectrum showed the disappearance of the OH bond absorption at 3406 cm^{-1}, usually present in the IR spectrum of D-mannitol. The IR spectrum also showed two types of vibration, symmetric at 1372 cm^{-1} and asymmetric at 1160 cm^{-1} for the $-SO_2$ group. see figure (4). The Mass spectrum showed peak due to the molecular ion m/z (TOF MS ES+) M^+ = 570.9471 (M+), $C_{20}H_{38}N_6O_4$, Calc. Mass, see figure (5).



(2)

Compound (3) was prepared by reaction of compound (2) with sodium azide in presence of anhydrous N,N`-dimethyl formamide which was heated for 19 h at 120°C under nitrogen gas.

The displacement of a sulfonate group by a good nucleophile such as azide ion is an important route to organic azide [13-15]. Azides are versatile intermediates in organic synthesis, since they can be used for the preparation of a variety of triazoles compounds. The diazide (**3**) was prepared in two subsequent steps starting from D-mannitol, the first one was a condensation reaction to form the di-OTs compound (2) while the second was an SN^2 reaction. The formation of the diazide (3) was followed by FTIR technique because there were essential changes in functional groups. The disappearance of (O-H) stretching band is a good proof of formation of the di-OTs (2**)** while the presence of the ($-N_3$) stretching band at 2100 cm^{-1} is an excellent evidence of the preparation of the diazide (3).Cu(I) catalyzed 1,3-dipolarcycloaddition reaction of the terminal alkenes with the diazido sugar (3) .

IR spectrum of diazide (**3**) compound showed the very strong stretching band of azide group at 2100 *cm^{-1}* and another stretching one of C-N at 1258 *cm^{-1}* in which it indicated that bistosylate group have been substituted. see figure (6).

1, 2:5,6-Di-o-isopropylidene3,4-di(-1,2,3-triazolo)-D-Mannitol ($4_{a\text{-}C}$)

As a part of our interest in the synthesis of some new heterocyclic compounds, new series of 1,2,3-triazoline ($4_{a\text{-}e}$) scheme-(1) were achieved by the 1,3-dipolar cycloaddition reaction of azide (4) with substituted (alkene or propargyl alcohol) in the presence of the copper (I) and catalysed sodium ascorbate to give the corresponding 1,2,3-triazoline ($4_{a\text{-}e}$).

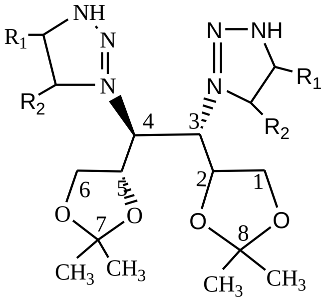
IR infrared spectra of compounds ($4_{a\text{-}e}$) as shown in figure (7), and table (2), the appearance of absorption bands (1447-1440cm^{-1}) which could be assigned to (-N=N-) stretching. The characteristic of IR absorption bands (KBr, disc) showed the appearance of absorption bands at (3420 cm^{-1}) due to (-N-H). It also showed stretching bands around (3255 cm^{-1}) which was assigned to (N_3) as characteristic bands of compounds ($4_{a\text{-}e}$).

^{1}HNMR spectrum of compound (4a-e) as shown in figure (8,9), and table (3), the protons signals due to CH_3 groups which were recorded between 1.43 – 1.47 ppm integrating for six protons, and also it showed signals at 2.65-2.88 ppm for methylene group and one triplet at 3.71-3.76 ppm for CH group, as well as C-H Aromatic group due to compound (4b, 4d) appears as multiplet at 7.13 – 7.91 ppm .

^{13}C N.M.R spectrum of compounds (4a-e) figure (11,12) and table (4), showed the following characteristic chemical shifts, the carbon of two methyl group appeared singlet at δ 26.1, 27.65 ppm and it showed CH_2 group at 67.33 ppm, while it showed bands singlet at δ 71.19, 76.26, 109.38 ppm for the C_1, C_2 and C_3 respectively.

The spectroscopic data were in agreement with the expected structure.

Finally, thin layer chromatography (T.L.C) measurement clearly indicated the formation of the product by comparing its (R_f) values with those of the starting material.



(4a-e)

Table (2) infrared spectra data for compounds (4a-e)

Comp. No	R_1	R_2	IR (υ cm^{-1},KBr)						
			NH	ν (C-H) Aliph.	ν (C=C) *Arm.*	ν (N=N)	ν (C-N)	ν (C-O-C) Asym, sym
4a	$-CH_2OH$	H-	3243	2850	-	1470	1210	1223 1068
4b	3-methyl phenyl-	H_-	3265	2879	1550,1445	1465	1230	1236 1055
4c	Di CH_3-	CH_{3-}	3267	2880	-	1455	1211	1212 1076
4d	CH_{3-}	CH_{3-}	3254	2875	-	1445	1223	1223 1069
4e	Phenyl-	H	3287	2883	1555,1449	1440	1225	1245

Table (3) ^{1}HNMR data for compounds (4a-e).

Comp No	R_1	R_2	^{1}HNMR
4a	$-CH_2OH$	H-	(CH_3) 1.33 – 1.550 , (CH2) 2.75-2.88 , CH (3.65-3.74) , NH 9.4
4b	3-methyl phenyl-	H_-	(CH_3) 1.31 – 1.51 ,(CH2) 2.75-2.66 , CH (3.62-3.73) , C-H Ar.(7.13 – 7.91 ppm), NH 9.5
4c	Di CH_3-	CH_{3-}	(CH_3) 1.23 – 1.50 , (CH2) 2.65-2.58, CH (3.66-3.71) , C=H (5.3) , NH 9.75.
4d	CH_{3-}	CH_{3-}	(CH_3) 1.29 – 1.50 , (CH2) 2.72-2.85 , CH (3.65-3.73) , C=H (5.6) , NH 9.7
4e	Phenyl-	H	(CH_3) 1.28 – 1.49 , (CH_2) 2.69-2.76, C-H , CH (3.67-3.73) , NH 9.5 , C-H Ar .(7.10 – 7.90 ppm)

Table (4) ^{13}C N.M.R **data for compounds (4a-e).**

Comp No	R_1	R_2	^{1}HNMR
4a	$-CH_2OH$	H-	(CH_3) δ 26.1 , 27.65,(CH2) 67.33 – 67.47 ppm, δ (71.19, 76.26, 109.38)C_1, C_2 and C_7
4b	3-methyl phenyl-	H_-	(CH_3) δ 26.1 , 27.63,(CH2) 67.31 – 67.43 ppm, C-H Ar.(112 – 129 ppm), δ (71.21, 76.25, 109.36)C_1, C_2 and C_7
4c	Di CH_3-	CH_{3-}	((CH_3) δ 26.1 , 27.65,(CH2) 67.66 – 67.50 ppm, δ (71.18, 76.27, 109.37)C_1, C_2 and C_7
4d	CH_{3-}	CH_{3-}	(CH_3) δ 26.13 , 27.56,(CH2) 67.45 – 67.53 ppm, δ (71.18, 76.24, 109.35)C_1, C_2 and C_7
4e	Phenyl-	H	(CH_3) δ 26.12 , 27.55,(CH2) 67.43 – 67.29 ppm, C-H Ar .(112 – 129 ppm), δ (71.20, 76.27, 109.35)C_1, C_2 and C_7

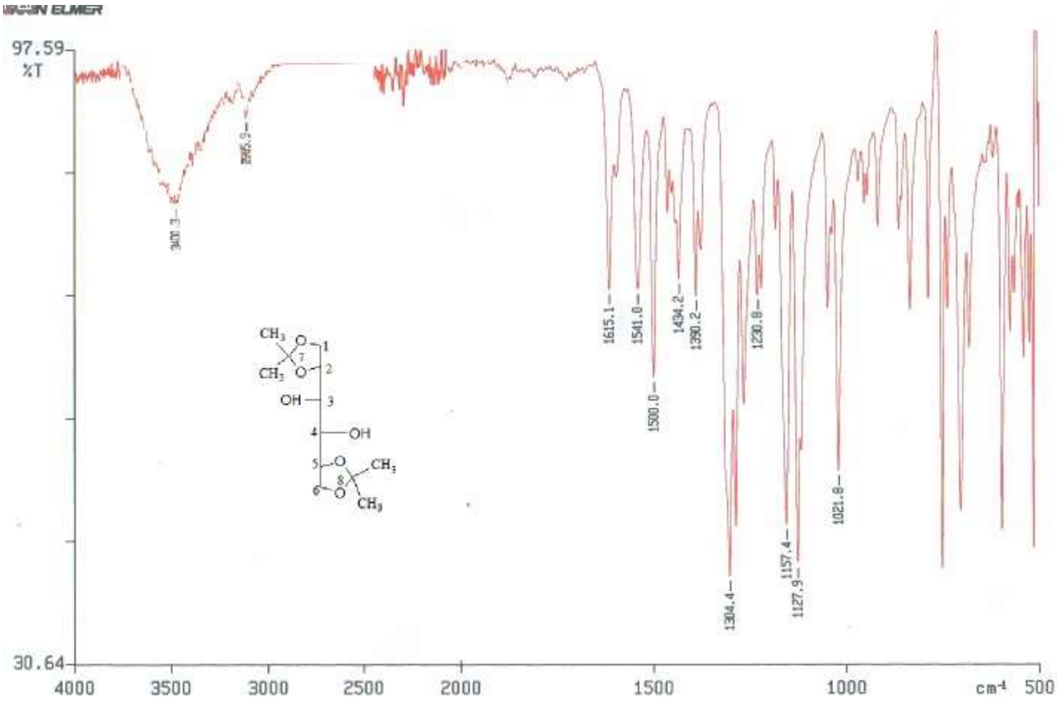


Fig (1) I.R. spectrum of compound (1)

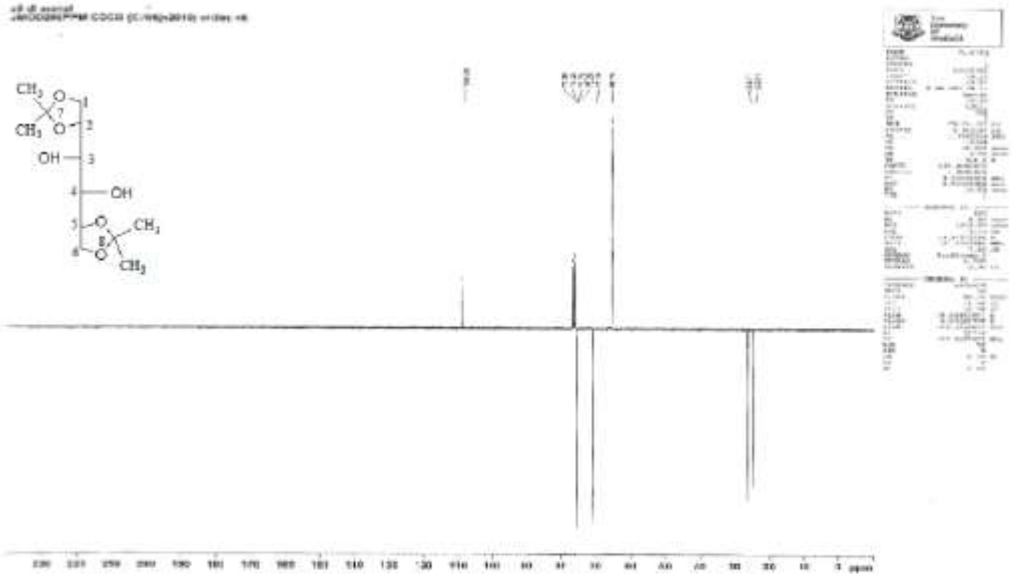
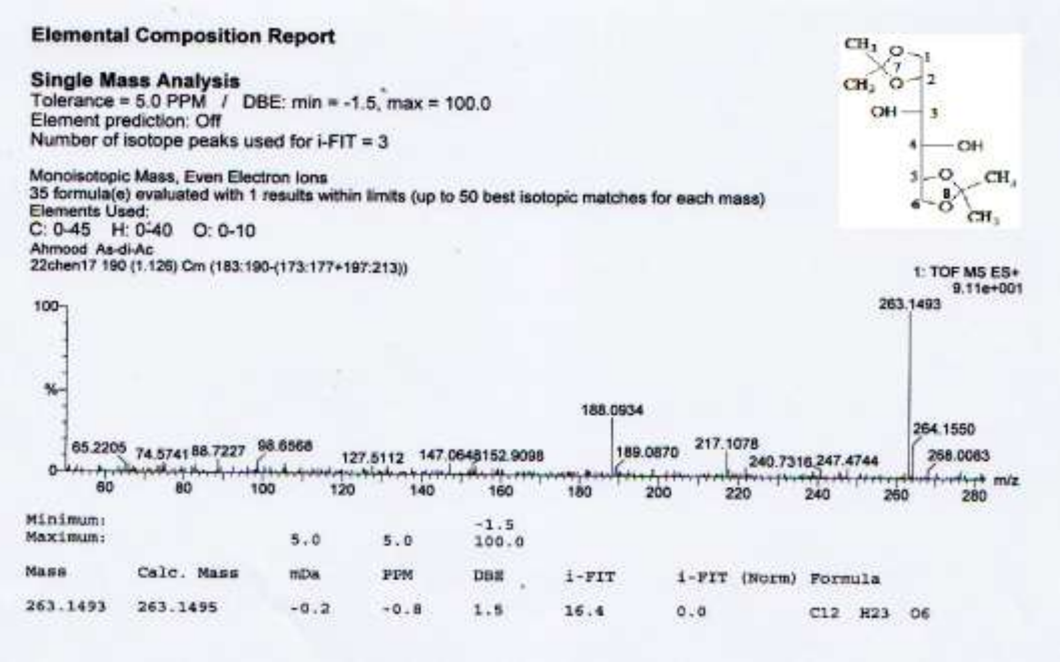


Fig (2) ^{1}H-NMR spectrum of compound (1)



Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
35 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-45 H: 0-40 O: 0-10
Ahmood As-di-Ac
22chen17 190 (1.126) Cm (183:190-(173:177+197:213))

```
Minimum:                                  -1.5
Maximum:                 5.0      5.0    100.0

Mass      Calc. Mass     mDa      PPM     DBE     i-FIT     i-FIT (Norm) Formula

263.1493  263.1495      -0.2     -0.8     1.5     16.4      0.0          C12  H23  O6
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Fig (3) Mass spectrum of compound (1)

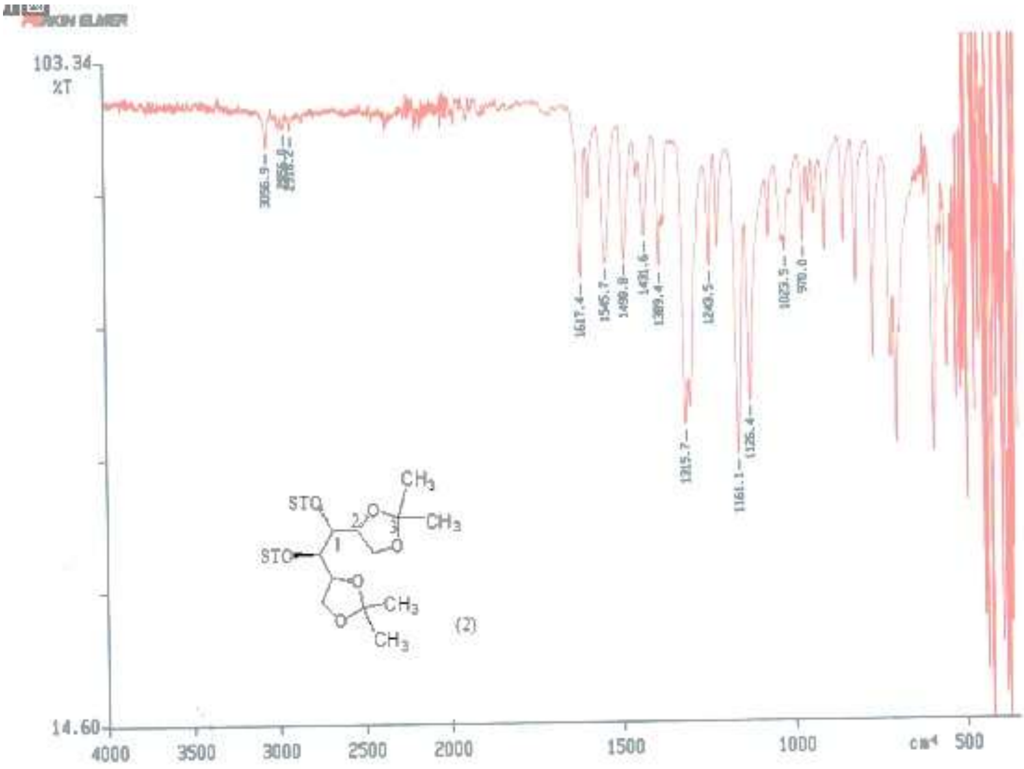
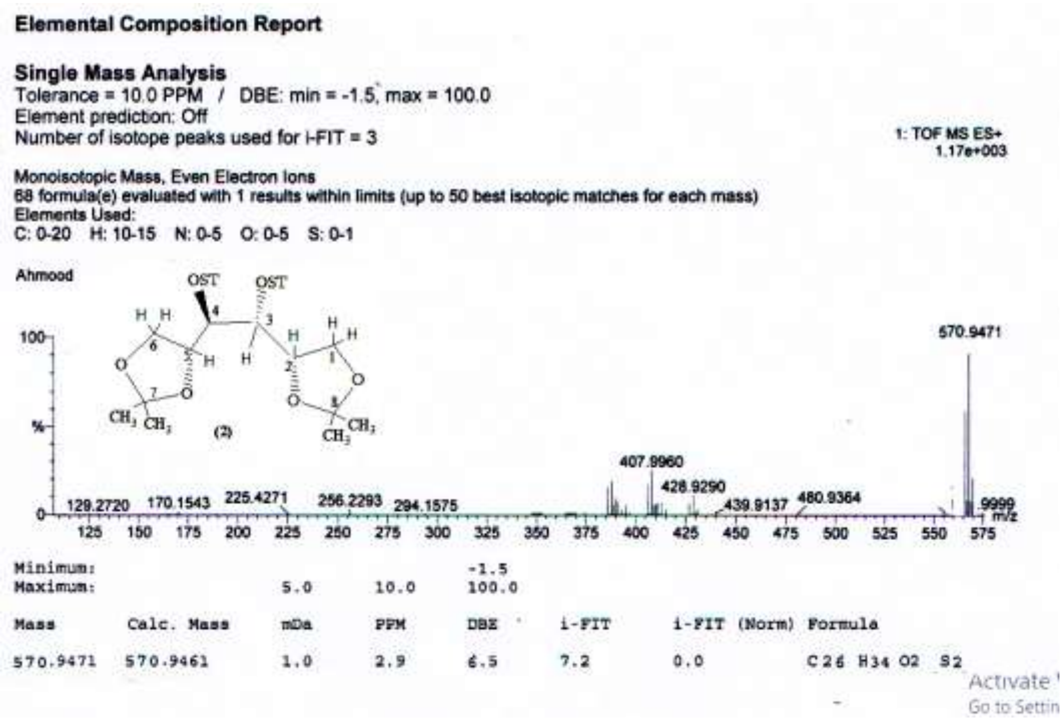


Fig (4) I.R. spectrum of compound (2)



Elemental Composition Report

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Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
68 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-20 H: 10-15 N: 0-5 O: 0-5 S: 0-1

```
Minimum:                                    -1.5
Maximum:                  5.0       10.0    100.0

Mass      Calc. Mass      mDa       PPM     DBE      i-FIT     i-FIT (Norm) Formula

570.9471  570.9461        1.0       2.9     6.5      7.2       0.0          C26 H34 O2  S2
```

Fig (5) Mass spectrum of compound (2)

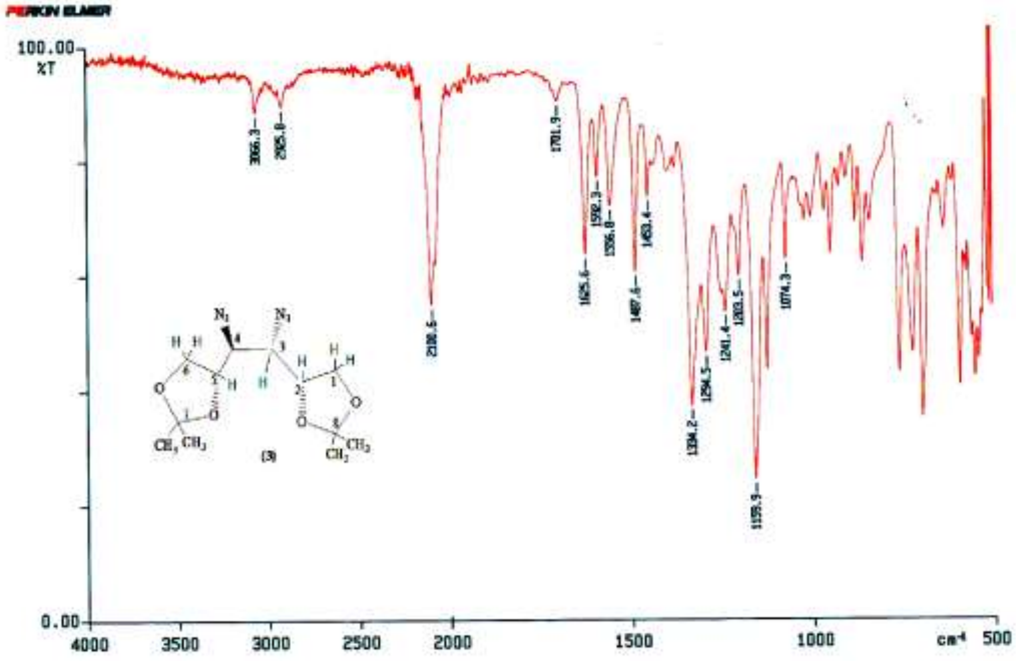


Fig (6) I.R. spectrum of compound (3)

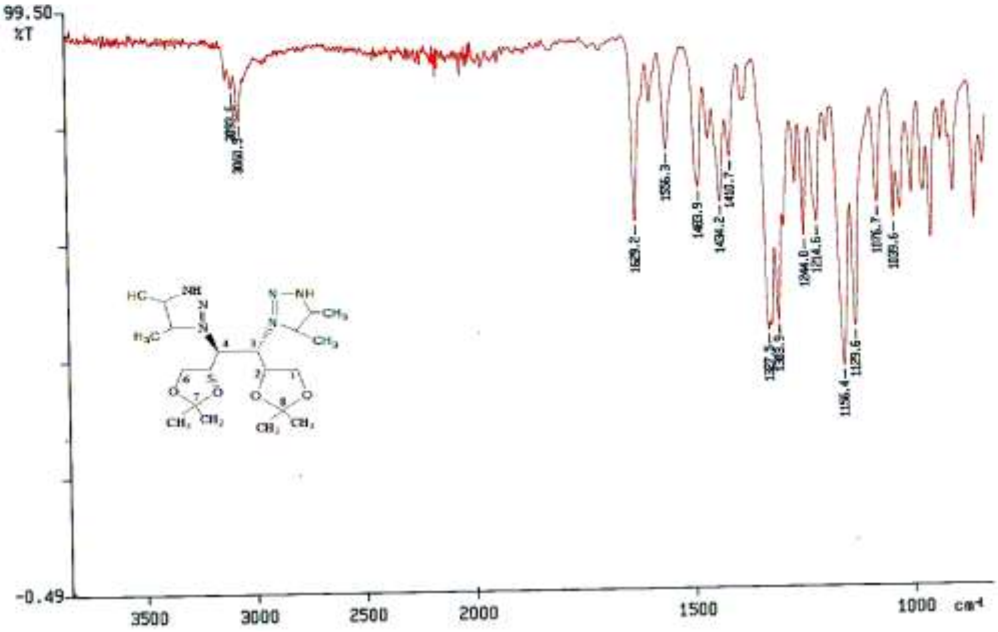


Fig (7) I.R. spectrum of compound (4a)

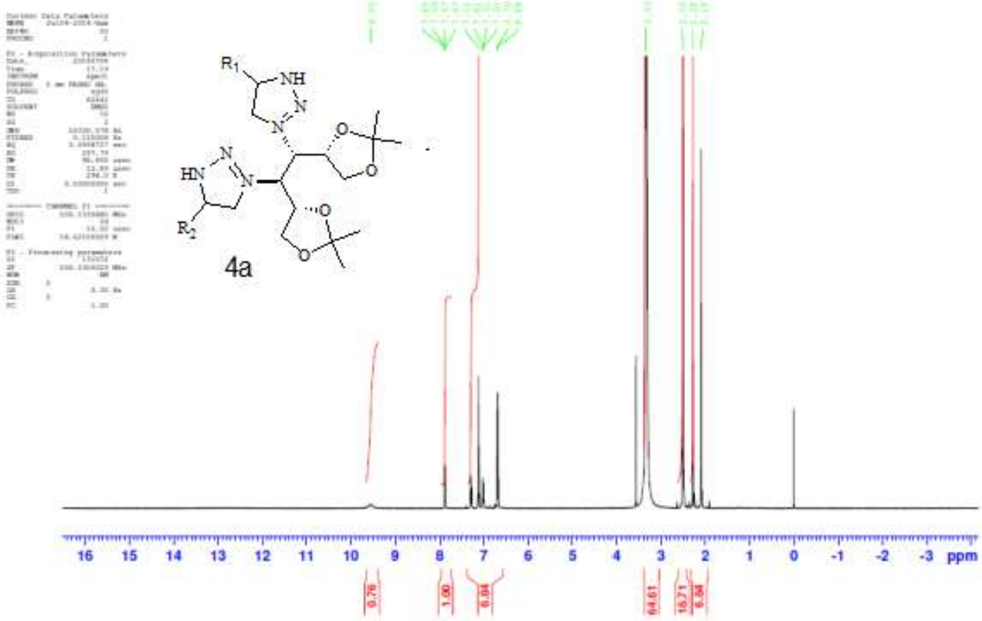


Fig (8) ^{1}H-NMR spectrum of compound (4a)

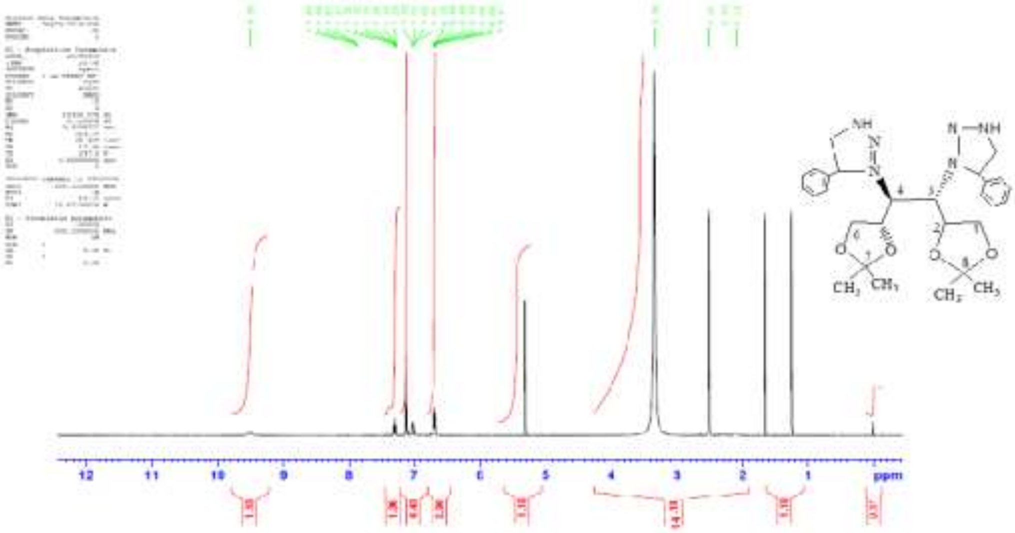
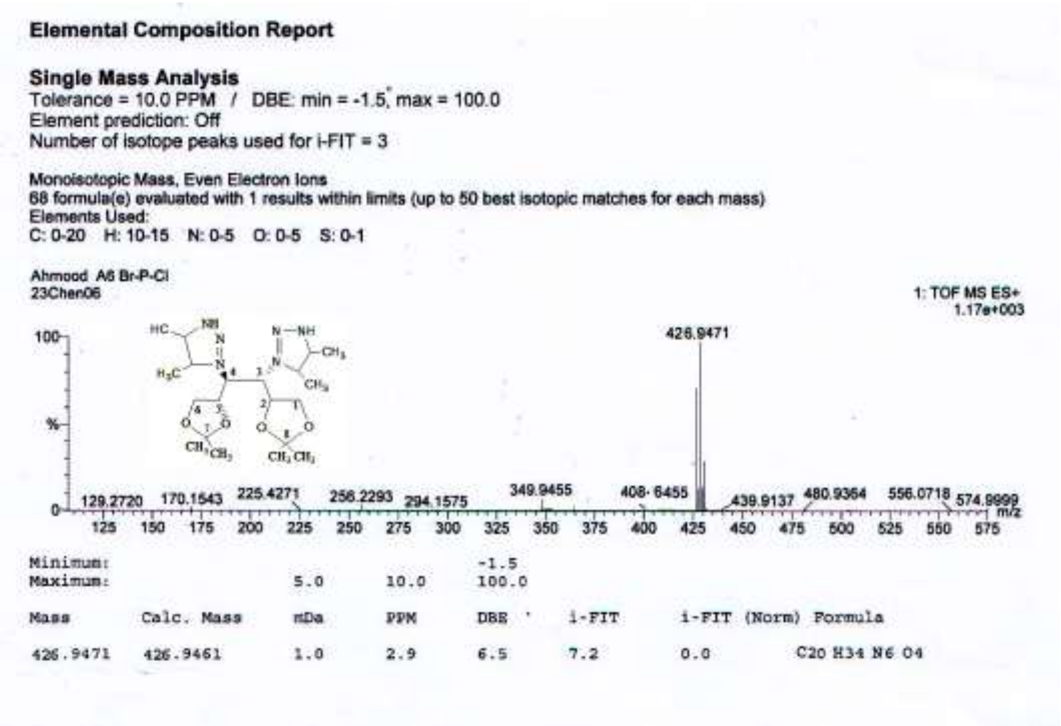


Fig (9) ^{1}H-NMR spectrum of compound (4b)



Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
68 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-20 H: 10-15 N: 0-5 O: 0-5 S: 0-1

Ahmood A6 Br-P-Cl
23Chen06

1: TOF MS ES+
1.17e+003

```
Minimum:                            -1.5
Maximum:           5.0      10.0    100.0

Mass      Calc. Mass   mDa   PPM    DBE    i-FIT    i-FIT (Norm) Formula

426.9471  426.9461     1.0   2.9    6.5    7.2      0.0          C20 H34 N6 O4
```

Fig (10) Mass spectrum of compound (4a)

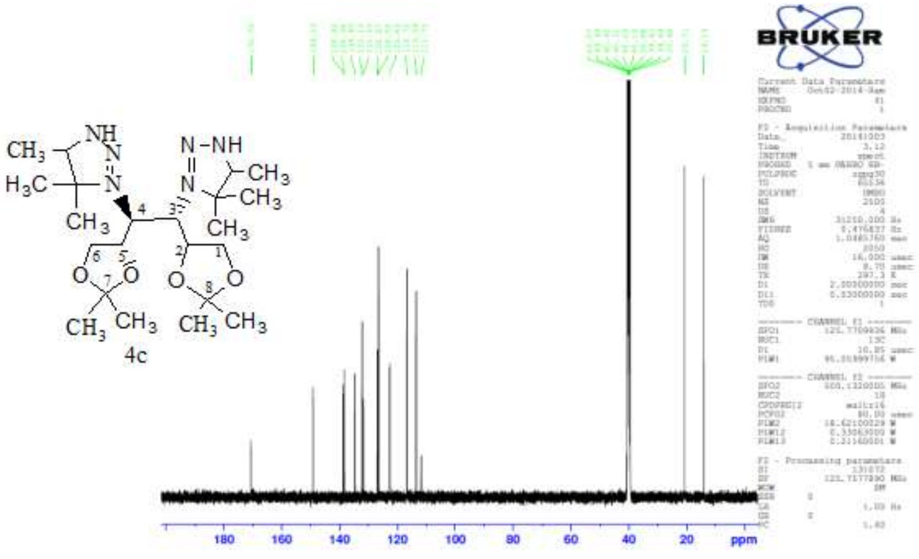


Fig (11) ^{13}C- -NMR spectrum of compound (4c)

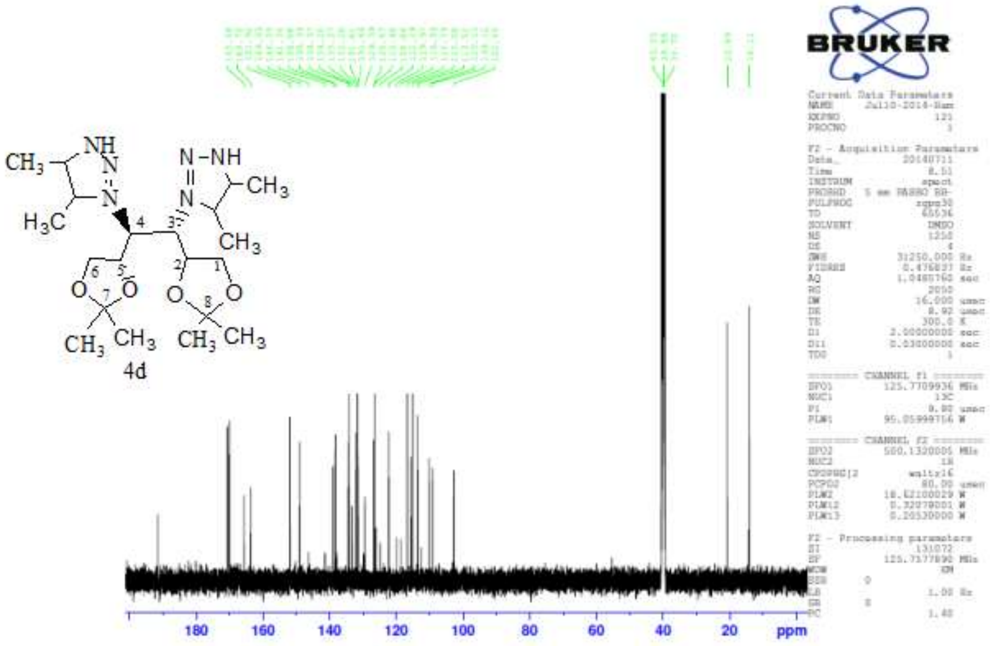


Fig (12) ^{13}C-NMR spectrum of compound (4d)

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تحضير وتشخيص بعض المشتقات 1 , 2, 3− ترايزول مشتق سكر ازايد مانيتول

احمود خلف جبر

قسم الكيمياء ، كلية العلوم ، جامعة تكريت ، تكريت ، العراق

الملخص

البحث يتضمن استخدام ازايد مانيتول (3) Azide D – Mannitol لتحضيرمشتقات 1, 2 3− ترايزول مشتق سكر ازايد مانيتول (3) كوسطي فعال والذي يحضر من تفاعل (2) 1, 2:5, 6-Di-o-isopropylidene-3,4-di-p-tosyl-D-Mannitol مع أزيد الصوديوم, المركب(3) الناتج سمح له بالتفاعل مع الألكينات لتكوين الترايازولات (4_{a-e}) .

شخصت بعض تراكيب االمركبات المحضرة بوا سطة الخواص الفيزيائية والطيفية كطيف FT-IR وطيف الرنين النووي المغناطيسي ^{1}H-NMR, ^{13}C-NMR , وطيف الكتلة Mass Spectra فضلا عن استخدام T.L.C .

الكلمات المفتاحية: المانيتول وترايزول والازايد,ايزوبروبليدين.