STEREOSELECTIVE SYNTHESIS OF METHYL TETRA-O-METHYL α–AND β–D-GLUCO-AND MANNOPYRANOSIDES

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Abstract

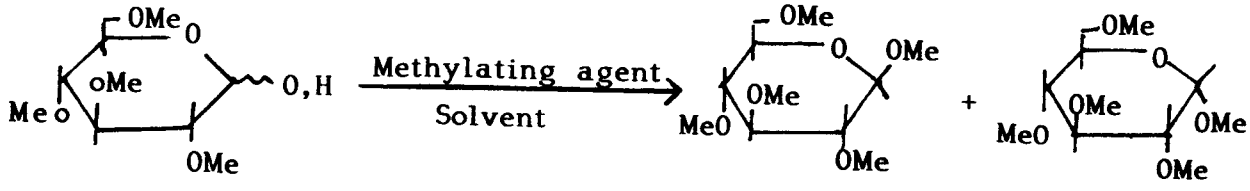
Methyl tetra - O-methyl- β–D- glucopyranoside is stereoselectively prepared from tetramethyl-D- glucopyranose by using (MeI+NaH) in toluene (86%) or cyclohexane (85%), while its α – isomer is best synthesized in hexamethyl phosphoramide (64%). Similarly, methyl tetra-O-methyl-β– D-mannopyranoside is synthesized in cyclohexane (80%), while its α– isomer is predominantly prepared by (MeI+n-BuLi) in cyclohexane (98%). The α–and β– isomers of these glycosides were identified and quantified by G.C.

Introduction

In most naturally occurring biologically active glycosides, the configuration at the anomeric position is quite distinct, that is either α– or β– isomer, and not a mixture of both exist [1,2]. Therefore, an understanding of factors which control the anomeric configuration in the stereospecific formation of the glycosides would be of great help towards synthesizing these active glycosides such as disaccharides. The ultimate aim of this work was to prepare either α–or β– glycosides depending on the solvent, type of metal alkoxide and on the addition of specific complexing agents such as dicyclohexyl-18-crown-6.

Results and Discussion

In this research a mixture of methyl 2,3,4,6- tetra-O methyl- α and β-D- glucopyranosides (2 and 3 respectively) were synthesized from 2,3,4,6- tetra- O-methyl glucopyranose (1) by 10 different procedures. The general method is shown below [3,4,5]:

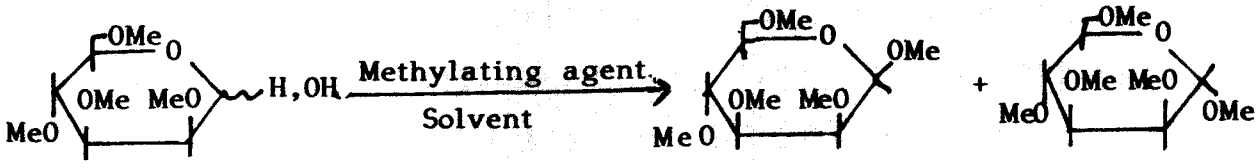


(1) α- isomer(2) β -isomer (3)

Keywords: Stereoselective synthesis, α and β– isomers, Glucopyranoside, Mannopyranoside

Similarly, the mixture of methyl 2,3,4,6- tetra-O-

methyl-α–and–β–D–mannopyranoside (**5** and **6** respectively) were prepared from 2,3,4, 6- tetra-**O**-methyl-**D**-mannopyranose (**4**):



(4) α – isomer (5) β– isomer (6)

The study of the stereoselective glycosides synthesis has been carried out on compounds (**1** and **4**) because a comparison can be made between two systems which differ only in configuration about C-2. The alkylation of these two compounds were investigated under a variety of conditions. The effect of alkylating agent, metal ion solvent and complexing agent were studied .

The mixtures of α-snd β- isomers of glycosides were separated, identified and quantified by using gas liquid chromatography (flame ionization technique). The ratios of α- and β- isomers (**2**,**3**) and (**5**,**6**) of the two sugars were summarized in tables (1 and 2) respectively.

Methylation of tetra-O-methyl-D-glucopyranose:

In theory, the highest amount of β- glycoside should be produced in HMPT (D.C.*=29.6) whereas the least of it should be produced in toluene (D.C.= 2.4). This is due to: 1. the effect of solvent polarity on the **anomeric effect** at the oxygen atom at C-1 which controls the α: β glycoside ratio [6,7]. 2. the presence of metal ion (i-e No^+, K^+, etc.) which forms a complex that controls the α: β glycoside ratio.

But in **practice** as is revealed from table-1, the

Table-1

Percentage ratio of methyl tetra -**O**- methyl α and β-**D** glucopyranosides in reaction products

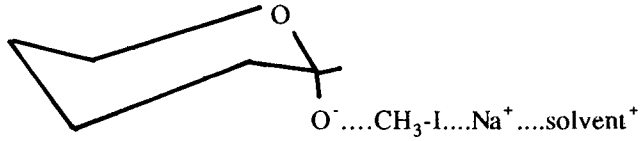
No.	Solvent	Reagent	α–glycosides	β–glycosides
1.	HMPT [a]	MeI + NaH	64%	36%
2.	DMSO [b]	MeI + NaH	57.4%	42.6%
3.	Toluene	MeI + NaH	14%	86%
4.	Cyclohexane	MeI + NaH	14.7%	85.3%
5.	DME [c]	MeI + NaH	51%	49%
6.	DME	MeI+NaH+dicyclohexy 18-crown-6(0.5 mM)	52.3%	47.7%
7.	DME	MeI+NaH+dicyclohexyl-18 crown-6(1.5 mM)	53%	47%
8.	MeI	MeI+$Ag2^O$	33%	67%
9.	DMF [d]	MeI+$Ag2^O$	54.5%	45.5%
10.	CH_2C1_2	(n-Bu)N^+Br^-+NaOH	55.5%	44.5%

a (HMPT)= Hexamethyl Phosphoramide b (DMSO) = Dimethyl Sulphoxide
c (DME)=1,2-Dimethoxyethane d(DMF)= N,N- Dimethylformamide

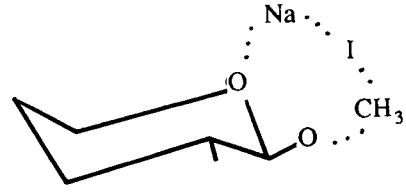
* D.C.= Dielectric constant

results were completely the opposite. The reaction affording the highest amount of β- glycoside was in toluene. This can be explained by that of the metal ion exerts an effect on the anomeric position [4,5], then the addition of dicyclohexyl-18-crown-6 which forms a complex with metal ions [8] that affects the α : β glycosides ratio. But, as shown in table-7, its addition to the methylation reaction in DME did not influence the α : β ratio. Therefore, there would be an explanation other than the metal ion of the solvent polarity.

This can be explained by the stereochemical control [9] which occurs along the reaction coordinate, and interprets these results in terms of formation of activated complex [10], which can be represented below:



∝ - form



β - form

The β- form of this activated complex is more stable (low energy) in low polarity solvent (low dielectric constant). Therefore, this explains the predominancy of the β- glycoside in toluene and cyclohexane, and the predominancy of α - glycoside in HMPT.

Methylation of tetra- O - methyl- D mannopyranose (Table-2)

The case was similar for methyl 2,3,4, 6- tetra- **O**-methyl α- and β - **D**- mannopyranoside (table-2) in which the - β glycoside was predominantly obtained in the less polar solvents, such as DME, cyclohexane and toluene (80%, 73% and 74% respectively).

It is very important to notice that the addition of dicyclohexyl -18 - crown-6 has greatly influenced the formation of the glycoside. This can be explained by the formation of the sugar alkoxide sodium salt as represented below:

By complexing Na^+ ion with dicyclohexyl - 18-crown-6, the α- isomer is greatly produced, while the B-isomer is best stabilized in low polarity solvents.

The last interesting result was the methylation in n-BuLi which predominantly produced the α- isomer (98%). This can be explained [11]by the small diameter of Li^+ ion (1.2A˚) which can easily form the sugar alkoxide- Li^+ complex [12]. This complex would afford the α- glycoside.

Experimental Section

GLC- measurements: These measurements were carried out on Perkin-Elmer F11 gas chromatography (flame ionization) on a carbowax 20M column, at 190°C with sensitivity of 20×10^2. The ratios of compounds analyzed by g.l.c. were determined from the relative area of the peaks.

The pure α- and β- glycosides of the two sugars (compounds **2**,**3**,**5**, and **6**) were synthesized and used as standards to identify the α- and β- glycosides mixtures resulted from different methylation procedures.

G.C. Analysis of these compounds showed that retention times of methyl 2,3,4,6- tetra-**O**-methyl α- and β -**D**- glucopyranosides (**2** and **3**) and methyl 2,3,4,6-tetra-**O**-methyl α- and β-**D**- mannopyranosides (5 and 6) were 22, 16, 30 and 21 minutes respectively.

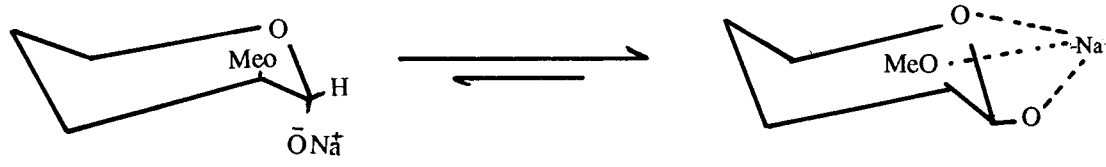


Table - 2

Percentage ratio of methyl tetra -O-methyl α - and β -D- mannopyranosides in reaction products

No.	Solvent	Reagents	α-glycosides	β-glycosides
1.	Toluene	MeI+NaH	26%	74%
2.	DME	MeI+NaH	27%	73%
3.	Cyclohexane	MeI+NaH	20%	80%
4.	DMSO	MeI+NaH	73%	27%
5.	Toluene	MeI+NaH=Dicyclohexyl 18-Crown-6	85%	15%
6.	Cyclohexane	MeI+NaH+dicyclohexyl 18-crown-6	84%	16%
7.	DME	MeI+NaH+dicyclohexyl 18-Crown-6	92.4%	7.6%
8.	Cyclohexane	$K^+O^-C(CH_3)_3$+MeI	29%	71%
9.	Cyclohexane	n-BuLi+MeI	98%	2%

A. Methylation of 2,3,4,6- tetra-O- methyl-D glucopyranose(1): a. Through sodium salt in various solvents (table-1 entries 1-5):

Compound (1) (O.12 gm, O.5mM) was dissolved in the required solvent (2ml), and treated with sodium hydrid NaH (O.O24 gm, 1mM) to form sodium alkoxide. After evolution of hydrogen had ceased, methyl iodide (1.2 ml, 19.2mM) was added and the mixture was stirred at room temperature for 48 hrs. The mixture was diluted with chloroform (15ml) and washed with water (3×10ml).

The organic layer was then dried and concentrated to yield a thick yellow oil which was analyzed by g.l.c. to obtain the α : β-glycosides ratio.

b. Through sodium salt in the presence of dicyclohexyl-18-crown-6 (table-1 entries 6-7):

Compound (1) (O.12gm, O.5mM) was dissolved in DME (2ml) and treated with NaH (O.O24 gm, lmM). After evolution of hydrogen had ceased, MeI (0.16 ml, 2.5 mM) and dicyclohexyl 18- crown-6 (O.186 gm, O.5 mM) were added, and the mixture was stirred at room temperature for 48 hrs. The product was diluted with chloroform (15 ml) and washed with water (3 × 10 ml).

The organic layer was dried and concentrated to yield a thick yellow oil which was analyzed by g.l.c. The above procedure was repeated in the presence of dicyclohexyl-18-crown-6(O.56 gm, 1.5mM) The product was analyzed by g.l.c to obtain the α : β- glycosides ratio.

c. Purdie methylation conditions [1,2] (table-1 entry-8):

Compound (1) (0.12 gm, 0.5 mM) was dissolved in MeI (2ml). Silver oxide (O.23gm, lmM) was added portionwise, and the mixture was stirred at room temperature for 48 hrs, the progress of the reaction was monitored by t.l.c (chloroform: methanol 14:1). The product was centrifuged, and the clear solution was diluted with chloroform (15ml), and washed with water (3× 10 ml). The organic layer was dried and concentrated to give a thick oil which was analyzed by g.l.c

d. Kuhn methylation [13] conditions (table-7 entry-9):

Compound (1) (0.12 gm, 0.5 mM) was dissolved in DMF (2ml), MeI (0.16 gm, 2.5 mM) and silver oxide (O.23 gm, 1mM) were added and the mixture was worked up exactly as in (c) to give the product as a thick oil which was analyzed by g.l.c to obtain α : β - glycosides ratio.

e. Methylation with phase transfer catalysis (table-1 entry-10):

To a solution of compound (1) (0.12 gm, 0.5mM)

and $(n\text{-}B)_4 N^+ Br^-$ (0.16gm, 0.5m) in dichloromethane (20 ml), 20% NaH solution (5 ml) was added. The mixture was stirred vigorously at room temperature for 48 hrs, and worked up as in (c) to yield the product as a thick oil which was analyzed by g.l.c.

B. Methylation of 2,3,4,6- tetra-0- methyl-D- mannopyranose (4)

a. Through sodium salt in various solvent (table-2 entries 1-4): A solution of compound (**4**) (0.12 gm, 0.5mM) in the required solvent (3ml) was treated with NaH (O.024 gm, lmM) and MeI (1.4ml, 22.5mM) as described for the methylation of compound (1). A thick yellow oil was analyzed by g.l.c to obtain the $\alpha : \beta$ – glycoside ratio.

b. Through sodium salt in the presence of dicyclohexyl -18-crown-6 (entries 5-7): Compound (4) (0.12gm, 0.5mM) was dissolved in the required solvent (3ml) and treated with NaH (0.024 gm, lmM). After evolution of hydrogen had ceased, dicyclohexyl-18- crown-6 (O.4gm, 1.07mM), MeI (1.2ml, 18.42 mM) were added, and the mixture was stirred at room temperature for 48 hrs. The product was diluted with chloroform (15ml) and washed with water (3×10ml). The organic layer was dried and concentrated to yield a thick oil which was analyzed by g.l.c

c. Through potassium salt in cyclohexan (table-2 entry-8) :

To a solution of compound (**4**) (0.12gm , 0.5mM) in cyclohexane (3Ml) , potassium t- butoxide (0.112gm, 1mM), and MeI (1.2ml, 18.45mM) were added.

The mixture was worked up exactly as described for compound (**1**) in (a,c) to yield the product as a thick oil which was analyzed by g.l.c

d. Through lithium salt in cyclohexane (table-2 entry -9):

Treatment of compound (**4**) (0.12gm, 0.5mM) with n-butyl lithium (n-BuLi) (1.6ml of 1.6M solution in hexane, 2.5mM) and MeI (1.2ml, 18.45mM) as described in (C) gave a yellow oil which was analyzed by g.l.c

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