Configurational and Conformational Analysis of 5-deoxy-5-iodo-α,β-D-ribose with 3-Sphere Approach

Carmen-Irena Mitan*, **Emeric Bartha, Anca Hirtopeanu, Carmen Stavarache, Constantin Draghici, Miron Teodor Caproiu, Maria Maganu, Petru Filip**

"C. D. Nenitescu" Institute of Organic and Supramolecular Chemistry, Splaiul Independentei 202B, Bucharest, Romania

Email address:

cmitan@yahoo.com (Carmen-Irena Mitan)

*Corresponding author

Abstract: Configurational and conformational analysis with 3-Sphere approach on selective iodination of α, β-methyl D-ribofuranose (2-α:2-β) with iodotriphenilphosphonium iodide complex [Ph_3P^+I]I⁻ generated in situ, under RT, reflux, microwave and sonochemistry. Introduction of the unit and hypersphere trigonometric equations, under Hopf fibration and Lie algebra theories, on Lambert-Wu methods enable calculation of the dihedral angles from NMR data (^{13}C chemical shift, vicinal coupling constant $^3J_{HH}$[Hz]) and the ratio of anomers. The conformation/configuration at anomeric position is *cis*: *trans* with *axial*:*axial* 3-α:3-β ($^3J_{H1H2}$ 3 or 4.5:0[Hz]) or *equatorial*:*axial* 3-α:3-β ($^3J_{H1H2}$ 6 or 4.5:0[Hz]) as state based on dihedral angles θ_{H1H2}[deg], recorded carbon chemical shift δ_{Cn}[deg] and VISION molecular models. The conformation of 3-β anomer is ^3E, and in case of 3-α anomer $_3E$ on Altona's map, the last having the succession of sign (+, -, -) with $\theta_{H3H4}{}^{\alpha}$ *trans-ee*, or alternatively ^3_2T conformation having the succession of sign (-, +, -) with $\theta_{H3H4}{}^{\alpha}$ *trans-aa*. An equilibrium between $_3E^{\alpha}$ and $^3_2T^{\alpha}$ was confirmed by $^3J_{H1H2}$ of 4.5[Hz], *i.e.* negative $\theta_{H1H2}{}^{\alpha}$ with ^3_2T and *equatorial* OCH_3, or positive $\theta_{H1H2}{}^{\alpha}$ with $_3E$ and axial OCH_3. The APT experiment (attached proton test) demonstrated the formation of tetrahydro 2H-pyran-2-ol as side product after selective iodination of methyl 5-deoxy-*β*-D-ribofuranoside 2-β.

Keywords: 3-Sphere, Dihedral Angles, Configuration, Conformation, Selective Iodination

1. Introduction

The R-value method, known as Lambert's method for calculation of the torsional angles from the ratio of anomers and the vicinal coupling constant $^3J_{HH}$[Hz], gives information about the configuration at anomeric position (eq. 1-4). [1-3]

$$R = {}^3J_{trans}/{}^3J_{cis} = (1/2)x({}^3J_{aa} + {}^3J_{ee})/(1/2)x({}^3J_{ea} + {}^3J_{ae}) \quad (1)$$

$$R = [Acos^2(120 + \psi) + Acos^2(120 - \psi)]/2Acos^2\psi = 3 - 2cos^2\psi/4cos^2\psi \quad (2)$$

$$\psi = cos^{-1}\sqrt{\frac{3}{2+4R}} \quad (3)$$

$$\theta aa = 120 + \psi; \theta ee = 120 - \psi, \theta ae = \theta ea = \psi \quad (4)$$

where ψ – torsional angle[deg], θ_{aa} θ_{ee} θ_{ae} – dihedral angles for *trans-aa*, *-ee* and *cis* stereochemistry.

Wilson and Bazzone [4] proposed the equation 5 for the torsional angle under J_{trans}/J_{cis} rule assuming pseudo trigonal projection symmetry (θ = 120[deg]).

$$cos\psi = \sqrt{\frac{1-cos2\theta}{2(R-cos2\theta)}} \quad (5)$$

Our aim in this paper is to analyzed the anomeric position from the configurational and conformational point of view based on dihedral angles calculated with 3-Sphere along the Lambert-Wu methods from ratio of anomers, vicinal coupling constants and carbon chemical shift.

2. Method

2.1. Dihedral Angles θ_{HnHn+1}[deg] Calculated from Ratio of Anomers 3-α:3-β and Vicinal Coupling Constant $^3J_{HH}$[Hz]

Lambert eq. 6[1] is replaced by Lambert-Wu eq. 7[5] in this paper under 3-sphere method [6] for calculation of the dihedral angle in case of $^3J_{trans} > 0$(eq. 6) and $= 0$(eq. 7). Once calculated the angle ψ[deg] from the ratio of anomers, seven sets units U and S are builds, first angles on unit U higher as 5[deg] and smaller as 5[deg] in case of unit S. Dihedral angles of α and β anomers are chose almost equals with the dihedral angles predicted only from vicinal coupling constant $^3J_{HH}$[Hz] [6].

$$R = \,^3J_{cis}/^3J_{trans}: R = \frac{2A\cos^2\psi}{A\cos^2(120+\psi)+A\cos^2(120-\psi)} = \frac{2\cos^2\psi}{\cos^2 B + \cos^2 C}$$
$$= \frac{2x(1+\cos2\psi)}{(2+\cos2B+\cos2C)}$$

with $B = 120 + \psi, C = 120 - \psi$,

$$\cos2\psi = \frac{R-1}{BR+1}, \tag{6}$$

where $B = \cos240 = -0.809$[grad] $= -0.5$[deg].

$$R = \,^3J_{trans}/^3J_{cis}: R = \frac{A\cos^2(120+\psi)+A\cos^2(120-\psi)}{2A\cos^2\psi} = \frac{\cos^2 B + \cos^2 C}{2\cos^2\psi}$$
$$= \frac{(2+\cos2B+\cos2C)}{2x(1+\cos2\psi)},$$

with $B = 120 + \psi, C = 120 - \psi$,

$$2R + 2R\cos2\psi = 2 + \cos2B + \cos2C,$$

$$2R + 2R\cos2\psi = 2 + \cos(240 + 2\psi) + \cos(240 - 2\psi),$$

$$2R - 2 + 2R\cos2\psi = \cos240\cos2\psi - \sin240\sin2\psi + \cos240\cos2\psi + \sin240\sin2\psi,$$

$$R - 1 + R\cos2\psi = \cos240\cos2\psi,$$

$$R - 1 = \cos2\psi(-R + \cos240),$$

$$\cos2\psi = \frac{1-R}{B-R}, \tag{7}$$

where $B = \cos240 = -0.809$[grad] $= -0.5$[deg].

2.2. Dihedral Angles θ_{HnHn+1}[deg] Calculated from Carbon Chemical Shift $\Delta\delta_{CnCn+1}$[ppm] and Vicinal Coupling Constant $^3J_{HH}$[Hz]

From the differences between two atoms of carbon consecutives $\Delta\delta_{CnCn+1}$[ppm] transformed in gauss are calculated angles θ^A and θ^B and build units U^N or/and S^N (N = A, B, C, D, E, F, G) with trigonometric function sin and cos. The values of the dihedral angles at anomeric position will be equals with angles calculated from vicinal coupling constants $^3J_{HH}$[Hz]. [6]

2.3. Synthesis of Methyl 5-deoxy-α,β-D-ribose

NMR spectra were recorded on Varian Gemini 300 spectrometer. Sonication's were performed by using a Vibra-cell VCX-750 high intensity ultrasonic horn, alternatively Sono Swiss SW3H. The microwave heating was performed in a Biotage Initiator Plus microwave reactor with maximum power 120W. Anhydrous conditions were realized under argon, in dried flasks, and anhydrous solvents (dicloromethane (Fluka) and toluene (Fluka) were freshly distilled, anhydrous THF (Sigma-Aldrich)). TLC was performed on aluminum plates precoated with silica gel 60F$_{254}$ (Fluka) using EtOAc/MeOH 9/1 (vol/vol). Compounds were visualized by heating after dipping in basic solution of KMnO$_4$. The commercial D-ribose shown in the NMR (CD$_3$OD) spectra few characteristic signals (^{13}C NMR 103.8, 98.78, 96.8, 96.1 ppm); a mixture of α- and β-pyranoses and α- and β-furanoses with the β-pyranose in aqueous solution.

2.3.1. Fisher Type Glycosylation Catalyzed by Acetyl Chloride at RT

To a suspension of D-ribose (2.01 g, 0.014 moli) in 20 ml methanol dry was added 66 μL acetyl chloride. The reaction mixture was stirred at RT, then added NaHCO$_3$ solid and stirred 5 minutes. The solid was filtered and the solvent removed under reduced pressure. The mixture of the reaction was purified by short column chromatography (EtOAc, EtOC-MeOH 9:1): a. 4h: 1.8g, 83 %, b. 1h: 0.930 g, 43% yield.

2.3.2. Fisher Type Glycosylation Catalyzed by Dowex 50Wx8 RT

To a suspension of D-ribose (2.25 g, 0.015 moli) in 25 ml methanol dry was added Dowex acid 50Wx8. The reaction mixture was stirred at 20°C over night, and then was stirred 5 minutes with NaHCO$_3$ solid. The solid was filtered and the solvent removed under reduced pressure. The mixture of the reaction was purified by extraction with THF or short column chromatography (EtOAc, EtOC-MeOH 9:1): a. 14[°C], over night, extraction THF, 58[%], b. 20[°C], over night, EtOH:MeOH 9:1, 75[%].

2.3.3. Fisher Type Glycosylation Catalyzed by Dowex 50Wx8 Under Sweep Sonochem Conditions

To a suspension of D-ribose (2 g, 0.014 moli) in 50 ml methanol dried on molecular sieve 4[^{0}A] was added 0.2g Dowex acid 50Wx8. The reaction mixture after 1.5[h] under degas conditions at 30[°C] and 2[h] under sweep condition at 30 - 50°C (Sono Swiss SW3H) show complete consumption of the starting material. After filtered the resin was added NaHCO$_3$ and the reaction mixture stirred 10 minutes. The solid was filtered, the solvent evaporated and the product extracted in THF as a mixture of anomers, 90[%].

2.4. Synthesis of Methyl 5-deoxy-5-iodo-α,β-D-ribose

2.4.1. Synthesis of the Ph$_3$PII Complex First

To a mixture of PPh$_3$ in 10 ml dry solvent (THF, Toluene, CH$_2$Cl$_2$) at RT was added I$_2$ in the dark under argon. After 30 minutes were added imidazol (2 eq) and methyl-ribose **2** in solvent at RT, and the reaction mixture

stirred at reflux 2h and/or at RT overnight. The solid was removed by filtration and the solvent evaporated and purified by chromatography.

2.4.2. Synthesis of the Ph₃PII Complex in Situ

To a solution of methyl-ribofuranose (1 eq) in 10 ml dry solvent (THF, toluene, CH_2Cl_2) was added Ph_3P (x eq) and imidazole (y eq) under argon. Then a solution of I_2 (z eq) in 7 ml dry THF or solid I_2 was added under argon (30 minute) at RT, and the light-yellow reaction mixture refluxed 2h. The crystalline white/yellow solid formed in the reaction was dissolved with MeOH and the solvent removed under reduced pressure. To the reaction residue was added EtOAc and the crystalline white solid formed filtered of and washed twice with EtOAc and ether. The solvent was removed under vacuum, and ^1H NMR was performed on the reaction mixture. The mixture of the reaction was purified by short column chromatography (EtOAc, EtOC-MeOH 9:1).

2.4.3. Purification of the Reaction Mixture

Methyl 5-deoxy-5-iodo-α,β-D-ribose anomeric mixture of the selective iodination can be separated by selective precipitation. The triphenylphosphine oxide was removed in H₂O/HCl pH~1 solution after stirring 10 minutes at RT, and solvent of reaction dried with Na_2SO_4. The solid obtained after evaporation of the solvent was refluxed in hexanes for 15 minutes and cooled at 0°C. The hexane solution contains triphenylphosphine Ph_3P. The classic method, extraction with aqueous thiosulfate solution and water should be used carefully because unprotected furanose are soluble in water.

In table 1 are presented the vicinal coupling constants of 2b and 3b recorded experimentally in comparation with the literature data.

Table 1. The vicinal coupling contants $^3J_{HH}[Hz]^a$ of methyl-furanosides (2b) and methyl-iodofuranosides (3b).

Entry	Product	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5}$
1.	2b-β^b	1.2	4.5	6.9	6.6	3.1	12.2
2.	2b-β	0	3	6	6	3	12
3.	2b-β^c	0	4.6	6.9	6.43	3.35	11.58
4.	3b-β^c	0	5.1	5.6	6.0	7.7	9.8
5.	3b-β	0	6	6	6	7.2	10
6.	3b- β^c	0	4.95	5.5 (5.7)	6.04	7.1	

a. 300[MHz] in CD₃OD 2b and CDCl₃ 3b, ~25°C; b. data from *J. Am. Chem. Soc.* 1990, *112*, 7373[26], 600[MHz] in ^2H_2O solvent, ~25°C; c. data from *Synthesis* 2002, *12*, 1721[10]: 500[MHz] in CDCl₃.
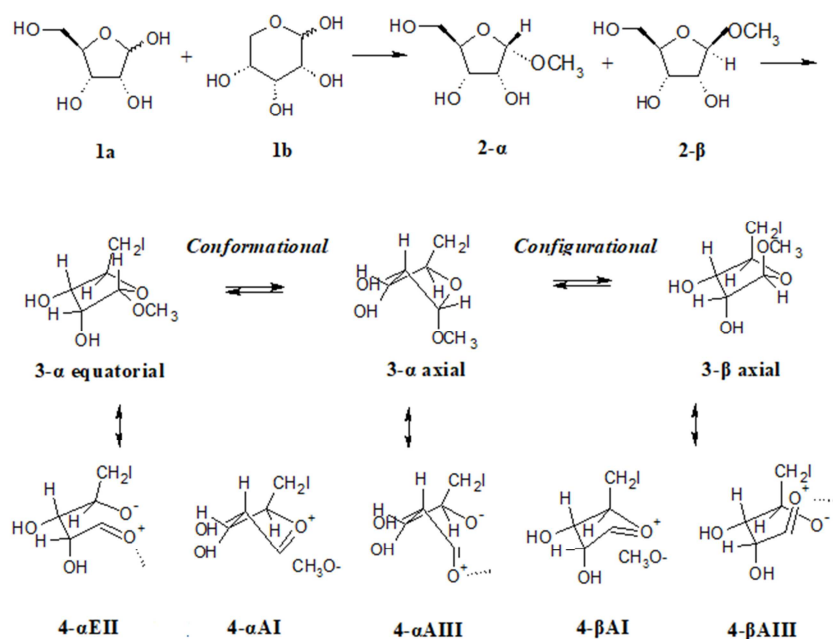

Figure 1. Conformational and configurational equilibrium of selective iodination of methyl D-ribofuranose primary alcohols 2-α:β.

3. Results

Fisher type glycosylation [7] of D-ribose 1, commercially as a mixture of α- and β-pyranoses (1b) and α- and β-furanoses (1a), with major product β-pyranose, catalyzed by acetyl chloride or Dowex 50Wx8 in dry MeOH at RT or sweep Sonochem conditions (Figure 1), was considerably optimized under sonochem conditions of reaction. The anomeric mixture (2-α:2-β 1:0.9) of 5-deoxy-α,β-D-ribose in polar protic solvent (MeOH dielectric constant 33, dipole moment 1.70D) is slightly increased in favor of 2-α. The mixture of the reaction was purified by chromatography (EtOAc:MeOH 9:1) or by extraction with THF. The yield of the glycosylation reaction with acetyl chloride [8] was increased after 4h (83%) at RT, relative to 1h (43%).

Selective iodination [8, 9] of methyl D-ribofuranose primary alcohol 2, [10] in the presence of two unprotected secondary hydroxyl groups, with ratio of anomers 2-α:2-β 0.52:0.47 (Table 2, Figure 1), gives 3-α *cis*:3-β *trans* anomeric mixtures with 3-α *axial:* 3-β *axial* (3:0 or 4.5:0[Hz]) or 3-α *equatorial:* 3-β *axial* (6:0 or 4.5:0[Hz])

stereochemistry in function of the reaction conditions (Table 2): reflux, microwave and sonochemistry, with triphenylphosphine/iodine/imidazole or Py, in THF, toluene or CH_2Cl_2, as demonstrated with 3-Sphere-Lambert-Wu approach [6, 11]. The anomeric mixture (3-α, β) was separated by selective precipitation [12] and short chromatography (EtOAc, EtOC-MeOH 9:1).

The yield of the reaction and the ratio of the anomers is endorsed by the equilibrium $[Ph_3P^+I]OR^-$ - $[Ph_3P^+OR]I^-$ - $[PhP^+R]OH^-$ under the reaction conditions [6], leading to side products formation along the stereochemical outcome. Furanose, pyranose, acyclic or bicyclic side products [13], occurs through endocyclic (4-αEII, 4-αAIII, 4-βAIII) or exocyclic conjugate acids (4-αAI, 4-βAI) (Figure 1) [14, 15].

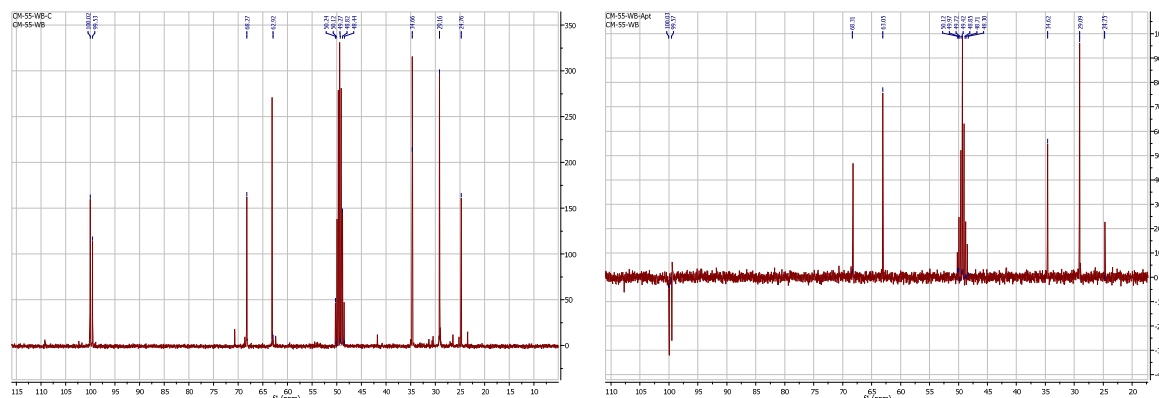*Table 2. Selective iodination of methyl D-ribofuranose primary alcohols 2-α:β.*

Entry[a]	$PPh_3:I_2:B$ 2:1:2	Reaction conditions	Solvent	η [%]	$H_1^\alpha:H_1^\beta$	α:β d:s	$^3J_{H1H2}$ [Hz]	θ_{H1H2}^{LW} [deg] 3-α:β	$\delta_{Cn}^{\alpha}:\delta_{Cn}^{\beta}$ [ppm]	θ_{H1H2}[deg] 3-α:β	$^3J_{H1H2}$ [Hz]
1.	Imidazol	Reflux, 2[h]	THF[b]	48	4.99:4.85	1:5.3	3:0	57.58:87.58 55.16:88.79	C_1: 102.98:108.21 C_2: 73.84:75.66	54.71: 87.12	2.94 0.847
2.	Py	Reflux, 2[h]	THF[b]	50	4.98:4.85	1:2.64	3:0	55.72:85.72	C_1: 103.12:108.74 C_2: 73.95:75.59	54.79:85.89	2.96 1.01
3.	Imidazol	MW	THF[b]	17	4.94:4.80	1:6.39	6:0	-56.53:86.53	C_1: 103.01:108.67 C_2: 74.25:75.88	-53.31:86.64	5.98 0.91
4.	Imidazol	US	THF[b]	20	4.94:4.80	1:3	3:0	55.16:85.16 59.02: 89.62	C_1: 102.99:108.34 C_2: 73.85:75.66	54.71:86.86	2.97 0.88
5.	Py	US	THF[b]	40	5.03:4.88	1:5.9	6:0	-53.80:83.80 -52.82:82.83	C_1: 102.88:108.28 C_2: -:75.73	-54.24:87.12	6.0 0.84
6.	Imidazol 1.5: 1.4: 3	Reflux, 3[h] Reflux, 2[h]	Toluene[c]	33 48	4.9:4.8 4.84	1:8.8 β	4.5:0 -	+/-10.65[f]:88.64	C_1: 108.28, C_2: 75.63	6.14:86.92	4.57: 0.87
7.	Imidazol 1.5: 1.4: 3	US 10[min] 2-puls	Toluene[c]	50	4.99:4.82	1:4.8	4.5:0	+/-10.35[f]:88.94	-	-	-
8.	Py 1:1	Reflux, 6h	CH_2Cl_2[d]	10	5.00:4.86	1:30.4[e]	3:0	52.57:89.68	C_1: -, 108.26, C_2: -, 75.73	54.32:87.16	2.98: 0.84

a. δ[ppm], [1]H 300[MHz], [13]C 75[MHz], CDCl3; b. THF - borderline polar aprotic solvent: dielectric ct. 7.5, dipol moment 1.75D; c. toluene - nonpolar solvent: dielectric ct. 2.3, dipol moment 0.36D, d. CH_2Cl_2 - borderline polar aprotic solvent: dielectric ct. 9.1, dipol moment 1.60D; e. after purification; f. negative sign result from Torus inversion to Dupin ciclide with $cis^{5,2}$ -44.87[deg] and from Dupin cyclide to Torus $cis^{6,1}$ -9.113[deg] [23].

Ring-opened oxocarbenium ion (4-αAIII, 4-βAIII) and oxocarbenium ion (4-αAI, 4-βAI) intermediates are predicted for axial anomer and only ring-opened oxocarbenium ion (4-αEII) for equatorial anomer. [6] The protonation of 2 at the anomeric –OMe group is followed by *exo*-cyclic –C-O bond cleavages with the formation of the oxocarbenium ion intermediate, according to the SN_1 mechanism; or the protonation of 2 at the internal oxygen atom is followed by *endo*-cyclic C-O bond cleavage with the formation of a ring-opened oxocarbenium ion intermediate, according to the SN_2 mechanism. The solvolysis products occurs when alcohol or water is the trapping nucleophile from both pathways.

The mechanism of reaction depends mostly on the structure of the carbohydrate that allows both exocyclic and endocyclic pathways, [14, 15] as well as from the selective iodination reaction conditions (pH and solvent). The higher moment of dipole at the anomeric center (RCO ~ 2.69) relatives to the primary alcohol (ROH 1.69) groups is a plausible explanation for the observed selectivity at the reaction center (primary alcohol, secondary alcohols, anomeric center). The competition between the selective iodination at C_5 or C_2/C_3 should be determined by the pH of the reaction media (~4.5). [16]

Figure 2. The ^{13}C-NMR spectra and the APT experiment.

The ^{13}C NMR spectra of the side product formed after   selective iodination of methyl 5-deoxy-*β*-D-ribofuranoside (2-β),

in THF and imidazole as base at reflux, shown two characteristic signals at lowest field (99.9 and 99.5 ppm) attributed to the anomeric position of the six membered rings α-, β-ribopyranose, along the other five signals at 68.3, 63.1 (C-5), 34.7 (C-2), 29.1 (C-4), 24.7 (C-3) ppm. The APT experiment (attached proton test) confirms the presence of five CH_2 and two CH groups at 99.9 and 99.5 ppm (ratio 1:0.46), probably $^4C_1$ axial and the $^1C_4$ equatorial anomers (Figure 2) of tetrahydro 2H-pyran-2-ol. [17] Axial methyl 5-deoxy-*β*-D-ribofuranoside (2-β) gives through oxocarbenium ion intermediate the six membered ring side product, or from open ring oxocarnenium ion through the acyclic hemiacetal intermediate, in case of five membered ring preferably SN2 mechanism.

Dihedral angles can be calculated with Lambert-Wu methods from the ratio between two anomers and vicinal constant couplings [1, 5], introduction of the 3-sphere approach [6, 11], *N*-unit rule and trigonometric equations, enable calculation of the dihedral angles with right sign and stereochemistry a way to obtain valuable information about configuration at anomeric position (Table 2).
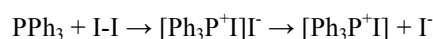
4. Discussions

Two green activation techniques, microwave heating (MW) and ultrasonic waves (US), known as the most simple and inexpensive methods, which promote faster and more selective transformations, are applied in comparison with thermic reaction on solvents with different dielectric constants (Table 2). The *anomeric effect* increases once the dielectric constant values decreased. A mixture of three anomers was recorded once 3:6:0[Hz] in THF at reflux with Py as base, and second 6:6:0[Hz] in THF under MW with imidazole as base, but isolated as a mixture of two anomers (3-α:β) after purification. Madsen [10] reported 80% yield in 3-β anomer after generation the iodotriphenoxyphosphonium iodide complex $(Ph_3P^+I^-I)$ in situ using the Ph_3P/imidazole/I_2 system with ratio 1.5:2:1.5 in dry THF, 2h at reflux. From the mixture of the reaction was remove imidazole hydroiodide [Im.HOI] formed as a white precipitate, and product purified by reverse phase column chromatography (H_2O:MeOH 9:1, m.p. 70-71°C). The melting point is comparable with the melting point reported by Anderson et. al. (68-70°C). [18] Han et. al. synthesized 3β in 60.9% yield using a mixture Ph_3P/Py/I_2 in dioxane as solvent at 25°C after 24h. [19]

Two methods are used to generate the iodotriphenoxyphosphonium iodide complex ($Ph_3P^+I^-I$) for regioselective synthesis of the 5-iodo-methyl-D-ribofuranose (3): 1. preparation of the triphenyl phosphite dihalide complex in situ (Met. 2.4.1), 2. first preparation the triphenyl phosphite dihalide complex following by its addition to a solution of the alcohol and base in the solvent under argon (Met. 2.4.2). With first method (Table 2), product **3** result in THF (48% reflux) and toluene (48% reflux, 50% ultrasonic conditions) after purification by chromatography (EtOAc:Hexane 6:4), in CH_2Cl_2 only
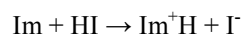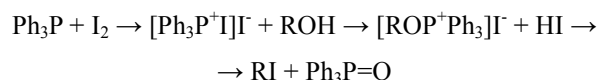
with Py as base result **3** after 6h at reflux 10% product (Table 1, entry 8). The THF was preferred as solvent due to high solubility of both the methyl-D-ribofuranose and I_2, in dichloromethane or toluene I_2 was added as solid in small portions. The heterogeneous reaction in toluene with PPh_3/I_2/imidazole was performed using a procedure reported by Garegg and Samuelsson [9]. The yield was also around 48%, in fact the authors reported the combination PPh_3 and 2,4,5-tri-iodoimidazole as more efficient in converting the secondary hydroxyl-group into iodides with inversion of configuration. [9]

In situ, in the presence of imidazole, two quasiphosponium halides: $[Ph_3P^+I]I^-$ and $[Ph_3P^+Im]I^-$, are in competition for the conversion of the hydroxy-groups into the iodo-groups. In the mechanism proposed by Mandal the imidazole act as a proton trap for the hydrogen ions with the generation of the nuclophile (I^-) (Scheme 1, path. 1). [20] Garegg et. al. [9] and Classon et. al. [21] claim the implication of the imidazole at the phosphorus center (Scheme 1, path. 2, path 3). In the Garegg's mechanism [9] the imidazole leaves the complex with the formation of the $Ph_3P=O$, alternatively the formation of the $Ph_2ImP=O$ can be possible after displacement one of the Ph group, process reported in the case of the triphenyl phosphite methiodide (($PhO)_3PCH_3I$) [22].

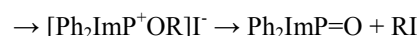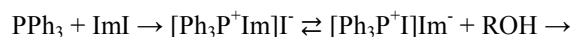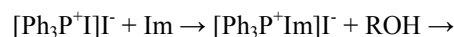Scheme 1. The proposed mechanisms for the generation of the triphenyl phosphite dihalide complex in situ.

$$PPh_3 + I\text{-}I \rightarrow [Ph_3P^+I]I^- \rightarrow [Ph_3P^+I] + I^-$$

$$PPh_3 + I\text{-}I + 2Im \rightarrow [Ph_3P^+Im]I^- \rightarrow [Ph_3P^+Im] + I^-$$

Pathway 1:

$$Ph_3P + I_2 \rightarrow [Ph_3P^+I]I^- + ROH \rightarrow [ROP^+Ph_3]I^- + HI \rightarrow$$
$$\rightarrow RI + Ph_3P=O$$
$$Im + HI \rightarrow Im^+H + I^-$$

Pathway 2:

$$[Ph_3P^+I]I^- + Im \rightarrow [Ph_3P^+Im]I^- + ROH \rightarrow$$
$$[ROP^+Ph_3]I^- + Im^+H \rightarrow RI + Ph_3P=O$$
$$PPh_3 + ImI \rightarrow [Ph_3P^+Im]I^- \rightleftarrows [Ph_3P^+I]Im^- + ROH \rightarrow$$
$$\rightarrow [Ph_2ImP^+OR]I^- \rightarrow Ph_2ImP=O + RI$$

Pathway 3:

$$Ph_2ImP + ROH \rightarrow Ph_2POR + Im$$
$$Ph_2POR + I_2 \rightarrow [Ph_2IPOR]I^- \rightarrow RI + Ph_2IP=O$$

Side reactions:

$$Im + I_2 \rightarrow Im\text{-}I + HI \rightarrow I_2Im^+ + 2HI$$
$$ImI + Im^+H \rightarrow HI + 2Im$$
$$HI + Ph_3P=O \rightarrow Ph_3PI(OH) \rightleftarrows [Ph_3POH]I^-$$
$$[ROPh_3P^+] \rightarrow ROPPh_2 + Ph$$
$$2[ROPh_3P^+] \rightarrow Ph_3P^+OP^+Ph_3$$
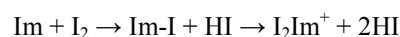
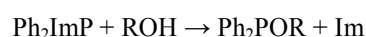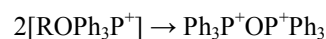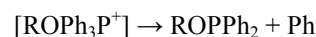Scheme 2. The proposed mechanisms for the generation of the triphenyl phosphite dihalide complex first.

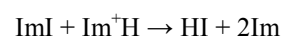$$:PPh_3 + I\text{-}I \longrightarrow PPh_3^+I\text{-}I \longrightarrow PPh_3^+I + I^-$$

$$ROH + B: \rightleftharpoons RO^- + BH^+$$

$$PPh_3^+I + BI \qquad\qquad Ph_3P^+OR + HI + B:$$

$$RO^-$$

$$+I^-$$

$$[Ph_3P^+I]RO^- \rightleftharpoons [Ph_3P^+OR]I^- \longrightarrow RI + O=PPh_3$$

B – base
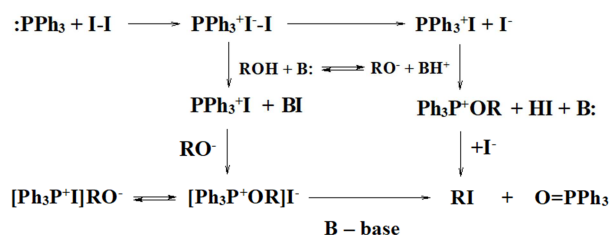
In the Scheme 2 the electrophilic attack of the $[Ph_3P^+I]$ on the RO^- gives the $[ROP^+Ph_3]I^-$ intermediate, and then is followed by the nucleophilic attack of the I^- on the intermediate $[Ph_3P^+OR]$. The role of base seems to be in the direct connection with the generation of the electrophile $[Ph_3P^+I]$ and free nucleophile I^-.

The experimental data presented in Table 2 shown that the higher yields 48-50% of the required product was obtained with different ratio of the reagents (PPh_3:I_2:imidazole): 1.5:1.4:3 in toluene and 2:1:2 in THF, at reflux and sonochem (US) conditions. Replacing the imidazole with Py under reflux the yield is 50%, but the ratio of the anomers 3-α:β 1:2.64, resulting a considerable decreased of the 3-β anomer, relative to reaction under US condition with 1:5.9 ratio of anomers and 40% yield. In our case, lower dielectric constant of toluene decreases the 3-β anomer under US (1:4) relative to reflux (1:8.8), and higher dielectric constant of CH_2Cl_2 increased the 3-β anomer at reflux (1:30.4) only with Py as base. In THF the 3-β anomer increased (1:6.39) under MW with 17% yield, resulting that along the solvent polarity or dielectric constant the reaction conditions (*i.e.* reflux, US,

MW, pH of reaction, base) have significative influence on the yield and the ratio of anomers.

The configuration/conformation of the anomeric mixture was analyzed introducing the hypersphere trigonometric equations and seven sets unit on Lambert-Wu method for calculation torsional angles. Dihedral angles at anomeric position are calculated from the ratio of the anomers and vicinal coupling constant with 3-Sphere-Lambert-Wu (eq. 7) [5], or from carbon chemical shift with 3-Sphere approach (Table 2): 1. anomeric mixture with vicinal couplings constants of 3:0[Hz] *axial:axial* 3-α-3-β result at reflux with imidazole (0.15:0.84, 48%) and Py (0.27:0.72, 50%) as base, or under ultrasonic irradiation (US) with imidazole as base (0.25:0.75, 20%); 2. anomeric mixture with vicinal couplings constants of 6:0[Hz] *equatorial:axial* 3-α-3-β result under ultrasonic irradiation (US) in Py (0.14:0.85, 40%), and microwave (MW) with imidazole as base (0.13:0.86, 17%); 3. at border line are reactions in toluene (Table 1, entry 6, 7) with vicinal coupling constants 4.5:0[Hz], since positive θ_{H1H2}^α result from 3[Hz] and negative from 6[Hz], and both from 4.5[Hz]. Considering all four equations for calculation of the dihedral angles from vicinal coupling constant (circle of torus and torus inversion to Dupin cyclide and *viceversa*) [23] all vicinal coupling constant gives positive and negative angles resulting two possible conformations.

Dihedral angles calculated from ratio of anomers are found on six sets units build with angle Ψ of eq. 7. Angles almost equals with the angles results from the vicinal coupling constant [24] are required dihedral angles with right stereochemistry and sign.
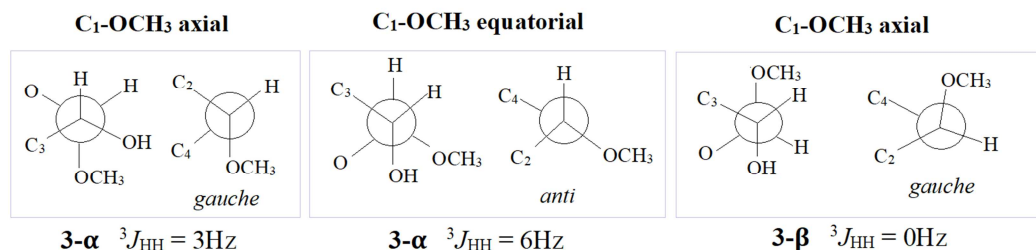
C_1-OCH_3 axial   **C_1-OCH_3 equatorial**   **C_1-OCH_3 axial**

3-α $^3J_{HH} = 3$Hz   **3-α** $^3J_{HH} = 6$Hz   **3-β** $^3J_{HH} = 0$Hz

Figure 3. *Newman projection of C_2C_1 and C_1O.*

The angles results from differences between two atoms of carbon consecutives [25] are in case of 3-α the required dihedral angles with values around 53-54[deg], and in case of 3-β angles around 65-68[deg]. The vicinal coupling constants of 3 and 6[Hz] confirming the values of the dihedral angles 3-α, much more giving the sign positive for 3[Hz] and negative for 6[Hz]. Positive *trans*-aa[5,2] dihedral angle θ_{H1H2}^α 126[deg] was excluded by the values of carbon chemical shift: δ_{C1}^α 102[ppm], relative to δ_{C1}^β 109[ppm]. The NMR spectra in case of 3-β shown singlet, thus the vicinal coupling constant 0[Hz]. In seven sets 3-β unit are remarkable two vicinal angles 5.7-8.7[UA1] and 2.8 – 4.1[USD1], the last giving angles around 0[Hz] (0.8-1.0[Hz]). Seven sets unit ensure in this case calculation of the dihedral angles of 3-α and 3-β anomers, with values very

close between the unit of 3-α and 3-β, as well as in the absence of C_2 of 3-α anomer dihedral angles can be predicted from the unit of 3-β anomer (Table 2, entry 5). Usually are used six sets angles on two units, [25] the first one with angles higher as 5[deg] and the second with angles smaller as 5[deg]. In this case was observed that units with angles very close to borderline have set D and set F on unit S (namely unit S of unit U, θ^{USNi}, N = A, B, C, D, E, F, G, i = 1-6), the transformation U1 to S1 leading to U2. The anomeric mixture 3:0[Hz] ensure *cis*:*trans-ee*[3,2] stereochemistry, also 6:0[Hz] but with negative *cis* dihedral angle θ_{H1H2}^α -53[deg], instead of *trans*:*trans* or *gauche*:*trans*. The conformation/configuration at anomeric position is *axial:axial* (3 or 4.5:0[Hz]) or *equatorial:axial* (6 or 4.5:0[Hz]) as state based on dihedral angles H_1H_2, recorded

carbon chemical shift and VISION molecular models (Figure 3).

The conformation of 3-β anomer is ^3E in N-E side of the Altona's map [13] with phase angle of the pseudorotation P ~ 18[deg]. The values and the sign of the calculated dihedral angles from the vicinal coupling constants (Table 2, entry 4, 5) are: trans-θ_{H1H2} ~ 90[deg], cis-θ_{H2H3} 46[deg] or 14.48[deg], trans-θ_{H3H4} -149.5 (-133.4) or -152.51 (-142.4) [deg]. Negative dihedral angle θ_{H2H3}^β required a dihedral angle θ_{H1H2}^β higher as 90[deg], ~120[deg].

In case of 3-α anomer the specific D-ribose stereochemistry with θ_{H3H4}^α negative and θ_{H1H2}^α positive or negative on molecular models shown $_3E$ conformation having the succession of sign (+, -, -) with θ_{H3H4}^α trans-ee, and ^3_2T conformation having the succession of sign (-, +, -) with θ_{H3H4}^α trans-aa. An equilibrium between $_3E$ and ^3_2T should exist: 1. negative θ_{H1H2}^α with $^3J_{H1H2}$ 3[Hz] leading to ^3_2T conformation with OCH_3 in equatorial position, 2. positive θ_{H1H2}^α with $^3J_{H1H2}$ 6[Hz] $_3E$ with axial OCH_3, 3. both conformation in case of $^3J_{H1H2}$ 4.5[Hz].

5. Conclusions

The conformation and configuration of 5-iodo-α and β-methyl-D-ribofuranose (3-α:β) at anomeric position after selective iodination with iodotriphenylphosphonium iodide complex ($Ph_3P^+I^-I$), under reflux, MW, US, was analyzed with 3-sphere and Lambert-Wu methods for calculation dihedral angles from NMR data. The conformation/configuration at anomeric position: cis:trans with axial:axial 3-α:3-β ($^3J_{H1H2}$ 3 or 4.5:0[Hz]) or equatorial:axial 3-α:3-β ($^3J_{H1H2}$ 6 or 4.5:0[Hz]) was estbilised based on dihedral angles θ_{H1H2}[deg], recorded carbon chemical shift δ_{Cn}[deg] and VISION molecular models.

Higher yield of the cis:trans 3-α-axial:3-β-axial anomeric mixture result at reflux (48-50%) in toluene (1:8) and THF (1:5.3), or in toluene (1:4) under US conditions of reaction (50%) with imidazole as base, and with 50% yield but 1:2.6 ratio of anomers in THF and Py as base. Higher dielectric constant of CH_2Cl_2 at reflux with Py as base giving 3-α-axial:3-β-axial anomeric mixture 1:28 with only 10% yield. The yield of the cis:trans 3-α-equatorial:3-β-axial anomeric mixture was advantaged by the US and Py as base (40%), relative to MW and imidazole (17%), both in THF ~1:6. Tetrahydro 2H-pyran-2-ol was identified as side product after selective iodination of methyl 5-deoxy-β-D-ribofuranoside 2-β, as demonstrated with APT experiment (attached proton test).

The conformation of 3-β anomer is ^3E on Altona's map, and in case of 3-α anomer $_3E$ with axial OCH_3 in case of positive θ_{H1H2}^α[deg] or ^3_2T with equatorial OCH_3 in case of negative θ_{H1H2}^α[deg], as confirmed by $^3J_{H1H2}$ of 4.5[Hz].

References

[1] J. B. Lambert, Structural chemistry in solution. R value, Acc. Chem. Res. 1971, 4, 87; doi.org/10.1021/ar50039aoo2.

[2] H. R. Buys, Conformation of nonaromatic ring compounds LIV†: The calculation of dihedral angles from vicinal coupling constants is six membered ring compounds, Recl. Trav. Chim. Pays-Bas 1969, 1003; doi.org/10.1002/recl.19690880814.

[3] J. B. Lambert, J. J. Papay, E. S. Magyar, M. K. Neuberg, Conformations of five membered rings. Limitations of the R-value methods, J. Am. Chem. Soc. 1973, 4458; doi.org/10.1021/ja007940073.

[4] G. E. Wilson, T. J. Bazzone, Conformational studies of 1,3-thiazolidines, J. Am. Chem. Soc. 1974, 1465; doi.org/10.1021/ja00812a032.

[5] A. Wu, D. Cremer, A. A. Auer, J. Gauss, Extension of the Karplus relationships for NMR Spin-Spin coupling constants to nonplanar ring systems: Pseudorotation of cyclopentane, J. Phys. Chem. A. 2002, 106, 657; doi.org/10.1021/jp013160l.

[6] C.-I. Mitan, E. Bartha, A. Hartopeanu, C. Stavarache, C. Draghici, M. T. Caproiu, M. Manganu, I. Man, L. Tarko, F. Teodorescu, C. Deleanu, Anomeric ratio and dihedral angles of α,β-iodo-methyl-D-ribofuranose, ACS National Meeting, San Francisco, CA, 16-20 August 2020, ANYL 49 (poster) ID: 3396478; Demo - Morressier. Publisher: American Chemical Society, Washington, D. C; doi.10.1021/Scimeetings.Oc00571.

[7] E. Fischer Ber. 1893, 26, 2400; doi.10.1002/cber.18930260327.

[8] E. D. Dangerfield, S. A. Gulab, C. H. Plunkett, M. S. M. Timmer, B. L. Stocker, Carbohydrate Research 2010, 345, 1360; doi.org/10.1016/j.carres.2010.03.016.

[9] P. J. Garegg, B. Samuelsson, Novel reagent for converting a hydroxy group into an iodo-group in carbohydrates with inversion of configuration, Perkin Trans 1, 1980, 2866; doi.org/10.1039/P19800002866.

[10] P. R. Skaanderup, C. S. Poulsen, L. Hyldtoft, M. R. Jørgensen, R. Madsen, Regioselective conversion of primary alcohols into iodides in unprotected methyl furanosides and pyranosides, Synthesis 2002, 12, 1721; DOI: 10.1055/1-2002-33641.

[11] C.-I. Mitan, E. Bartha, P. Filip, C. Draghici, M. T. Caproiu, R. Moriarty, Calculation of the dihedral angles of 1-α,-β-R-5-O-methanesulfonyl-2,3-O-isopropilidene-L-lyxose from NMR data with 3-sphere approach and Lambert-Wu R value. ACS National Meeting, Atlanta, GA, 22 - 26 August 2021, CARB (poster) ID: 3582748; Demo - Morressier. Publisher: American Chemical Society, Washington, D. C; doi.10.1021/Scimeetings.1c00922.

[12] F.-H. Hu, L.-S. Wang, S.-F. Cai, Solubilities of triphenylphosphibe oxide in selected solvents, J. Chem. Eng. Data 2009, 54, 1382; doi.org/10.1021/je800842z.

[13] J. Kennedy, J. Wu, K. Drew, I. Carmichael, A. S. Serianni, Carbohydrate reaction intermediates: Effect of ring oxygen protonation on the structure of conformation of aldofuranosyl rings, J. Am. Chem. Soc. 1997, 119, 8933; doi.org/10.1021/ja963727p.

[14] J. L. Liras, V. M. Lynch, E. V. Anslyn, The ratio between endocyclic and exocyclic cleavage of pyranoside acetals is dependent upon the anomer, the temperature, the aglycon group, and the solvent, J. Am. Chem. Soc. 1997, 119, 8191; doi.org/10.1021/ja963807t.

[15] O. St.-Jean, M. Prévost, Y. Guidon, Study of the endocyclic versus exocyclic C-O bond cleavage path ways of α- and β-methyl furanosides, J. Org. Chem. 2013, 2935; doi.org/10.1021/jo3027438.

[16] R. Caputo, H. Kunz, D. Mastroianni, G. Palumbo, S. Pedatella, F. Solla, *Eur. J. Chem.* 1999, 3147; doi.org/10.1002/(SICI)1099-0690.

[17] A. J. Hoog, Carbon-13 nuclear magnetic resonance spectra of some 2-substitute tetrahydropyrans, *Organic Magnetic Resonance*, 1974, 6, 233; doi.org/10.1002/mrc.1270060410.

[18] R. J. Andersen, R. M. Dixon, B. T. Golding, Alkylcobalamins: formation by enantioselective alkylation of cob(I)alamin, 1H NMR spectra, and conformational analysis of the alkyl group, *J. Organomet. Chem.* 1992, 437, 227; doi.org/10.1016/0022-328x(92)83446-O.

[19] M. J. Han, K. S. Yoo, Y. H. Kim, J. Y. Chang, The catalytic activity of ribose containing polymers for the hydrolysi of phosphordiester and cleavage of nucleic acid, *Tetrahedron Lett*, 2002, 43 (32), 5597; doi.org/10.1016/50040-4039(02)01123-1.

[20] B. G. Roy, A. Roy, B. Achari, S. B. Mandal, A simple one-pot entry to cyclic ethers of varied ring sizes from diols via phosphonium ion induced iodination and base catalyzed Williamson etherification, *Tetrahedron Lett.* 2006, *47*, 7783; doi.org/10.1016/j.tetlet.2006.08.090.

[21] B. Classon, Z. Liu, New halogenation reagent systems useful for the mild one-step conversion of alcohols into iodides or bromides, *J. Org. Chem.* 1988, *53*, 6126; doi.org/10.1021/jo00261a032.

[22] N. K. Kochetkov, A. I. Usov, The reaction of carbohydrates with triphenyl phosphite methiodide and related compounds, *Tetrahedron* 1963, *19*, 973-983; doi.org/10.1016/50040-4020/01799352.

[23] C.-I. Mitan, E. Bartha, P. Filip, C. Draghici, M. T. Caproiu, R. M. Moriarty, Two isomers with *trans-aa*^{5,2} stereochemistry are calculated with 3-sphere trigonometric equations approach at circle inversion motion from NMR data. ACS National Meeting in Chicago, IL, August 21- 25, 2022, CARB 3717658, 22 august 2022, doi.org/10.1021/scimeetings.2c00523.

[24] E. Bartha, C.-I. Mitan, C. Draghici, M. T. Caproiu, P. Filip, R. Moriarty, Program for prediction dihedral angle from vicinal coupling constant with 3-sphere approach, *Rev. Roum. Chim.* 2021, 66, 178-183; DOI: 10.33224/rrch.2021.66.2.08 (Eng).

[25] C.-I. Mitan, E. Bartha, C. Draghici, M. T. Caproiu, P. Filip, R. M. Moriarty, Hopf fibration on relationship between dihedral angle θ_{HnHn+1}[deg] and vicinal angle ϕ[deg], angles calculated from NMR data with 3-sphere approach and Java Script, *SciencePG* 2022, 10, 21; DOI: 10.11648/j.sjc.20221001.13 (Eng).

[26] P. C. Kline, A. S. Seriani, 13C-Enriched ribonucleosides: synthesis and applications of ^{13}C-^1H and ^{13}C-^{13}C spin coupling constants to assess furanose and N-glycoside bond conformations, *J. Am. Chem. Soc.* 1990, *112*, 7373; doi.org./10 1021/ja001760043.