



3-Sphere Approach on 9-O-(10,11-di-O-benzyl-12,14-O-benzylidene- α -D-galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol

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Abstract: The conformation of 9-O-(10,11-di-O-benzyl-12,14-O-benzylidene- α -D-galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol 1, phase angles of the pseudorotation of five (C^3) and six (C_1^4) membered rings, was analyzed with dihedral angles θ_{HnHn+1} [deg] calculated only from vicinal coupling constants $^3J_{HH}$ [Hz] with 3-Sphere approach and VISION molecular models. The dimension space around the six and five membered ring are established based on hypersphere equations results from calculation of the dihedral angles from carbon chemical shift. Higher biological activity was observed to date at iminocyclitols having dihedral or vicinal angles calculated in 2D. Tetrahedral angles in close relationships with dihedral angles are calculated from carbon and / or proton chemical shift with manifold equations, conic and rectangle geometries. Equations for calculation of the tetrahedral angles ϕ_{Cn} [deg] only from vicinal coupling constant $^3J_{HnHn+1}$ [deg] or from chemical shift δ_{Cn} [ppm] are analyzed for five and established for six membered ring, resulting general rules for calculation of tetrahedral angles. Conic as manifold in case of six membered ring enable calculation of dihedral angle θ_{HnHn+1} [deg] from tetrahedral angle ϕ_{Cn} [deg] starting with tetrahedral angle on unit, and in case of five membered ring based on opposite relationship between dihedral and tetrahedral (sin versus tan function), unit start with dihedral angles. Rectangle as manifold enable calculation for both the tetrahedral angle from dihedral angle starting with dihedral angle on unit, for six membered ring using two or three units with three sets angles and in case of five membered ring only one unit with seven set angles. The bond distances l_{CnHn+1} [A^0] of five and six membered ring are calculated from 3-Sphere-dihedral angles θ_{HnHn+1} [deg].

Keywords: 3-Sphere-Dihedral Angles, Phase Angle of the Pseudorotation, Tetrahedral Angles, Bond Distances

1. Introduction

Dihedral angles of five and six membered ring θ_{HnHn+1} [deg] can be calculated only from vicinal coupling constant $^3J_{HH}$ [Hz] [1] or with one of the manifold equations [2, 3] from carbon and/or proton chemical shift δ [ppm], resulting dihedral angles with right stereochemistry and sign from torus or invers of torus (Dupin cyclide) equations. From

manifold equations result dihedral angles with values almost equals with angles calculated from vicinal coupling constant $^3J_{HH}$ [Hz] recorded experimentally. The 3-Sphere approach, with its characteristic system of units, enable calculation the tetrahedral angles of five [4] and six [5] membered rings based on relationships between two pairs of angles: dihedral – vicinal and tetrahedral – internal. VISION molecular models ensuring a good simulation of the conformation, phase angle of the pseudorotation P [deg], with dihedral

angles calculated with 3-sphere approach. [6]

Pseudorotation[7] as a degenerate vibrational mode, are in fact a linear combination of degenerated vibrational modes with a phase angle θ , in case of twofold degenerated state, or two phase angles θ, ϕ , in case of three fold degenerated state. [8]

In terms of the puckered coordinates can be define properties (P) as: energy, internal coordinates, dipole moment, charge distribution, frequencies, and magnetic properties, when P is translated in a Fourier series of the pseudorotation phase angle ϕ of a puckered five membered ring under pseudorotation. [8]

$$P(q, \phi) = \sum_{k=0}^{\infty} \{P_k^C(q)\cos(K\phi) + P_k^S(q)\sin(K\phi)\}$$

The DORCO method used the ring pucker coordinates to express any properties U (energy, internal coordinates, dipole moment, charge distribution, frequencies, and magnetic properties) characteristic for puckered five membered ring under pseudorotation. [8]

Origami, the Japanese art of paper folding - The graph theory gives many ways for the representation of five membered ring pucker; to date in literature are known:

A. The pentagon method: Five vectors S_j radiating from the origin to the positions of the carbon atoms are constrained to move in its vertical plane. [9] Under the conformational changes the distances between atoms and the position of the center of mass of the ring remain constant, instead the atoms move along three dimensional curves whose projections on a mean plane of the ring are circular - an ellipse, relatives to an interval in AGB model, and a point in Kilpatrick's model [10].

B. Triangular decomposition method:

Hill – Reilly algorithm used endocyclic dihedral angles calculated from NMR coupling constant to described ring pucker. Six membered ring can be divided into three subtriangular planes, and the puckering is described by the two dihedral angle along the two adjacent subplans. Spherical projection of 38 canonical states in continuous movements in each of N-dimension is known as Cremer-Pople formalism[11] describing the puckered rings. Relative to CP formalism, all coordinates can be calculated using sequential dihedral angles to sequentially place each of atom around the ring. Any three dihedral angles can be translated in a linear combination of three ideal puckered states, and any three of the six endocyclic dihedral angles may be specified. Decomposition of a monocyclic ring into N-2 triangles, with one triangle forming a reference plane, was performed for quantitatively measured the effect of external forces on the ring conformation. [12]

Barnet – Naidoo method calculated the free energy of ring pucker of carbohydrate (furanose, pyranose) using adaptive reaction coordinate (FEARCE) in combination with the Hill-Reilly pucker coordinates. The relationship between the ring pucker and the oxocarbenium ion formation in the transition states of glycosides was established analyzed the free energy surface that can be a function of the motion of the anomeric carbon or the ring

carbon bearing the primary alcohol substituent. The potential of mean forces (W_ξ) has calculated as a function of the puckered coordinate, related to the probability density $P(\xi)$, applied on the triangular decomposition surface (N-3 degree of freedom). For N = 5 there are two puckering coordinates θ_0 and θ_1 between $[-\pi, \pi]$; *i.e.* $\xi_{(\text{ribose})} = (\theta_0, \theta_1)$ and $\xi_{(\text{glucose})} = (\theta_0, \theta_1, \theta_2)$. [13, 14]

$$W(\xi) = -K_B T \ln P(\xi)$$

$$\theta_i = \pi/2 - \cos^{-1}[(q_i \cdot n) \cdot (II q_i II \cdot II u II)^{-1}]$$

Wu method applied on five proline puckering pathways utilizing each endocyclic torsion angle as the reaction coordinates. The triangular decomposition method applied on the five membered ring gives three subtriangular planes, and the puckering is described by the two dihedral angle along the two adjacent subplans. [15] The most stable conformations of puckered ring is analyzed by a comparison of measured and calculated SSCC's (DORCO: determination of ring conformation) as function of $^n J(\phi)$. [16, 8]

C. Vector method: The ring twisting (τ) and ring bending (θ), as well as the atom position can be calculated with vector method.[17] Jang-Laane developed a vector method for kinetic energy (reciprocal reduced mass) for the ring twisting and ring bending vibrations of bicyclic molecules in the tetralin family. [18]

The concept of the circular variate, the Kitamura's model, replaced the usual Euclidean-type variate, because the torsional angle has both directionality and periodicity, and allowed mathematical and statistical treatments of the angular data for the conformational analysis of nucleosides and nucleotides. The method consisting in the calculation of circular correlation coefficients between torsion angles, the estimation of the circular regression lines between torsions, the numerical representation of conformational similarities between nucleotides, a useful method for the classification of various conformers. The movement of one torsion has linearly coupled with that of the other, certain torsion pairs show virtually linear correlations. [19]

$$1/n \sum_{k=1}^n e^{i\theta_k} = \omega e^{i\theta}; \omega = (\alpha^2 + \beta^2)^{1/2}, \theta = \tan^{-1}(\beta/\alpha)$$

$$\alpha = 1/n \sum_{k=1}^n \cos \theta_k = \omega \cos \theta, \beta = 1/n \sum_{k=1}^n \sin \theta_k = \omega \sin \theta$$

2. Method

2.1. Conformational Analysis

3-Sphere approach – dihedral angles calculated from vicinal coupling constant $^3J_{HH}[\text{Hz}]$ applied on VISION molecular models enable conformational analysis, in fact can be simulated the phase angle of the pseudorotation in agreement with Altona map [20] for five membered ring and Stoddart's diagram [21] for six membered ring.

2.2. Relationships Between Biological Activity and Dimension Space

Hypersphere equations are established for five and six

membered rings of **1** for calculation of the dihedral $\theta_{\text{HnHn+1}}[\text{deg}]$ or vicinal angle $\phi[\text{deg}]$ from carbon chemical shift $\delta_{\text{Cn}}[\text{ppm}]$: 2D X_0 , 3D X_1 , 4D X_2 , X_3 . Remarkable biological activity is expected in tangential 2D space.

Hypersphere coordinates:

$$X_0 = r \cos \psi$$

$$X_1 = r \sin \psi \cos \theta$$

$$X_2 = r \sin \psi \sin \theta \cos \phi$$

$$X_3 = r \sin \psi \sin \theta \sin \phi$$

2.3. Hopf Fibration and Lie Algebra for Calculation from NMR Data Dihedral, Tetrahedral and Bond Distance

Dihedral $\theta_{\text{HnHn+1}}[\text{deg}]$, tetrahedral $\varphi_{\text{Cn}}[\text{deg}]$ and bond distance $l_{\text{CnCn+1}}[\text{\AA}]$ are calculated from NMR data, carbon or/and proton chemical shift or vicinal coupling constant, with 3-Sphere approach and conic and rectangle as manifold.

3-Sphere approach enable calculation of the dihedral angles from NMR data, carbon or proton chemical shift, or only from vicinal coupling constant $^3J_{\text{HnHn+1}}[\text{Hz}]$, having as manifold all geometries of the topological space gives by the cyclide, torus or Dupin cyclide, in continue translation from 4D to 0D, from 3-Sphere (quaternion multiplication) – 2-Sphere (3-dimensional Euclidean space) – 1-Sphere (Abelian Lie group, circle group) to 0-Sphere (pair of points) (Figure 1).

Six dihedral angles with *cis* and *trans* stereochemistry can be drawn on three concentric cons, and translate from 4D in 2D using a system of set bearing six angles on two units $U = C, S$ ($\theta^{\text{CN1}} > 5[\text{deg}]$, $\theta^{\text{SN1}} < 5[\text{deg}]$, $N = A, B, C, D, E, F, G$), in fact four as calculated from sin and tan function. One unit containing seven sets angles, seven circles, with possibility to build another unit through set C. [2]

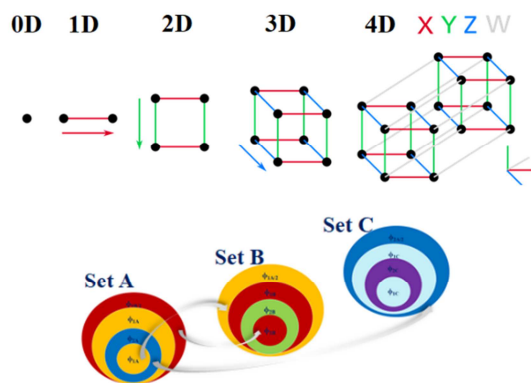


Figure 1. Translation from 4D to 0D analog to cube. Three sets angles.

Trigonometric equations under Hopf coordinates confirmed by Lie algebra are performed for all stereochemistry from NMR data. [2]

Hopf coordinates R^4 , complex C^2 or quaternions:

$$X_0 = \cos \phi \sin \theta, X_1 = \sin \phi \sin \theta$$

$$X_2 = \cos \theta \sin \phi, X_3 = \sin \theta \sin \phi$$

Generalized root system lie group (Figure 2): [22]

$$\sigma_a(\beta) = \alpha - \beta^D$$

$$\sigma_a(\beta) = \alpha - \beta^S$$

$$\text{cis/trans-aa: } \sigma_a(\beta) = \beta - \alpha$$

where: β^D or $\beta^S = \theta^{\text{NN}}$

$$\text{trans-ee}^{1,4}: \sigma_a(\beta) = \alpha + \beta^D$$

where: $\beta^D = \phi_N$

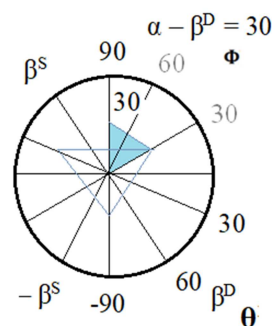


Figure 2. Root system lie group.

3-sphere approach coordinates, R^2 : real fibration $S^0 \rightarrow S^1 \rightarrow S^1$: [2]

$$X_0 = \cos \phi \sin \theta_{\text{HnHn+1}}, X_1 = \sin \phi \sin \theta$$

$$X_0 = \tan \phi \sin \theta_{\text{HnHn+1}}, X_1 = \sin \phi \sin \theta$$

$$X_0 = \sin \phi \tan \theta_{\text{HnHn+1}}, X_1 = \tan \phi \tan \theta$$

where: ϕ – vicinal angle, angle result from vicinal coupling constant $^3J_{\text{HH}}[\text{Hz}]$,

$\theta_{\text{HnHn+1}}$ – dihedral angle [deg].

$$3D: ^3J_{\text{HH}} = [\cos^{-1}(\sin \theta_{\text{HnHn+1}})]^{1/2}/m = \phi^{1/2}/m$$

$$3D: ^3J_{\text{HH}} = [\tan^{-1}(\sin \theta_{\text{HnHn+1}})]^{1/2}/m = \phi^{1/2}/m$$

$$3D: ^3J_{\text{HH}} = [\sin^{-1}(\tan \theta_{\text{HnHn+1}})]^{1/2}/m = \phi^{1/2}/m$$

$$3D: ^3J_{\text{HH}} = [\sin^{-1}(1/\tan \theta_{\text{HnHn+1}})]^{1/2}/m = \phi^{1/2}/m$$

where: vicinal angle: $\phi = f(\phi_2, \phi_{1/2})$;

$$m = 2 \text{ cis, trans-ee; } m = 1 \text{ trans-aa,}$$

For all stereochemistry vicinal angle is a combination of algebraic equation between $\phi_2, \phi_{1/2}$. [2]

3-Sphere equations for calculation of the tetrahedral angles of six membered ring from carbon chemical shift. [4]

$$4D: \sin^{-1} \tan \{-\sin^{-1}[n(1/R_m)]\} = -A$$

$$4D: \tan^{-1} \sin \{-\tan^{-1}[n(1/R_m)]\} = -B$$

$$3D: \cos^{-1} \sin [-B/n] = \varphi_{\text{Cn}}^{\tan}$$

$$3D: \cos^{-1} \sin [-A/n] = \varphi_{\text{Cn}}^{\sin}$$

3-Sphere equations for calculation of the tetrahedral angles of five membered ring from carbon chemical shift. [5]

$$4D: \cos^{-1} \sin\{-\tan^{-1}(1/R_m)/2\} = \phi_{Cn}$$

$$4D: \cos^{-1} \sin\{-\sin^{-1}(1/R_m)/2\} = \phi_{Cn}$$

Bond distance $l_{CnCn+1}[A^0]$ are calculated from dihedral angles. [23]

2.4. NMR Data of 9-O-(10,11-di-O-benzyl-12,14-O-benzylidene- α -D-galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-*N*-dehydro-L-ribitol 1

1H NMR spectra is recorded with Bruker spectrometer of 400MHz and ^{13}C NMR spectra of 75 MHz. Infrared spectra is recorded on Genesis Services FTIR spectrometer. ((2S, 3R, 4R)-1-Methyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline was prepared as previously described[24]. Synthesis of 9-O-(10,11-di-O-benzyl-12,14-O-benzylidene- α -D-Galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-*N*-dehydro-L-ribitol 1 will be presented elsewhere.

9-O-(10,11-di-O-Benzyl-12,14-O-benzylidene- α -D-Galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-*N*-dehydro-L-ribitol (9-O-(10,11-di-O-Benzyl-12,13-O-benzylidene- α -D-galactopyranosyl)-(2R, 3S, 4S)-1-butyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 1.

Colorless oil (15 %). $C_{39}H_{47}NO_8$, M = 657; MS m/z 658.3 (M + H); calcd for $C_{39}H_{47}NO_8$ (M + H)⁺ 658.33744, found 658.33770.

IR: $\nu_{max}(neat)/cm^{-1}$ KBr 3030.41, 2928.21, 2866.45, 2361.92, 2335.18, 1644.58, 1455.66, 1371.67, 1211.90, 1151.98, 1098.14, 1053.32, 1004.96, 741.40, 698.73

1H -NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.31 (m, 15H, 3Ph), 5.49 (s, 1H, H-15), 4.91 (d, 1H, $J_{9,10}$ = 3.4 Hz, H-9), 4.87 (d, 1H, $J_{A,B}$ = 11.7, CH_A Ph), 4.85 (d, 1H, $J_{3,2}$ = 5.3 Hz, H-2), 4.76 (bs, 1H, CH_B Ph), 4.61 (d, 1H, $J_{A,B}$ = 11.7, CH_B Ph), 4.55 (d, 1H, $J_{2,3}$ = 5.3 Hz, H-3), 4.25 (bs, 1H, H-4), 4.17 (d, 1H, $J_{14',14}$ = 12.5 Hz, H-14'), 4.13 (d, 1H, $J_{12,11}$ = 3.3 Hz, H-12), 4.04 (dd, 1H, $J_{10,11}$ = 10.0 Hz, $J_{10,11}$ = 3.4 Hz, H-10), 3.98 – 3.93 (m, 2H, H-11, H-5'), 3.70 – 3.64 (m, 1H, H-11), 3.53 (dd, $J_{5,5'}$

= 9.73 Hz, $J_{5,4}$ = 2.57 Hz, H-5), 3.43 (bs, 1H, H-13), 2.38 – 2.04 (m, 2H, CH_2), 1.57 – 1.29 (m, 4H, 2 CH_2), 1.35 and 1.29 (2s, 6H, 7- CH_3 , 8- CH_3), 0.91 (t, 3H, J = 7.2 Hz, CH_3).

^{13}C -NMR (75 MHz, $CDCl_3$) δ 178.5, 138.8, 138.4, 137.7, 128.9 – 126.3 (3Ph), 111.4 (C-15), 101.1 (C-6), 98.2 (C-9), 86.7 (C-2), 80.7 (C-3), 75.7 (C-10), 75.2 and 75.1 (C-4, C-11), 74.4 (C-12), 73.4 (CH_2 Ph), 71.5 (CH_2 Ph), 69.4 (C-14), 67.7 (C-5), 62.6 (C-13), 30.4, 28.2, 22.6 (3 CH_2), 27.0 and 25.6 (7- CH_3 , 8- CH_3), 13.9 (CH_3).

3. Results

The phase angle of the pseudorotation was established with 3-Sphere dihedral angles $\theta_{HnHn+1}[deg]$ calculated only from vicinal coupling constant $[1] \ ^3J_{HnHn+1}[Hz]$ on VISION molecular models for 6-O-(7,8-di-O-Benzyl-9,11-O-benzylidene- α -D-galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-*N*-dehydro-L-ribitol 1 (Table 1, Figure 3). Torsional angles of *trans-ee*, *trans-aa* stereochemistry are calculated as already established using the rule of 3-sphere,[22] relationships between two sets angles in agreement with corresponding trigonometric equations between vicinal and dihedral angles.

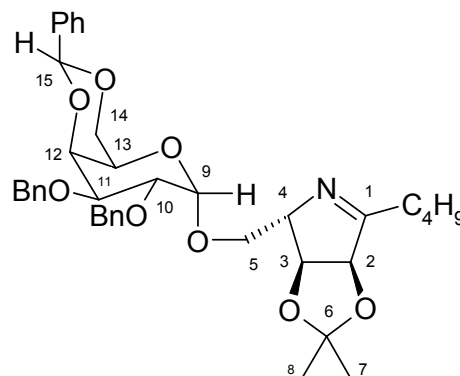


Figure 3. 9-O-(10,11-di-O-Benzyl-12,14-O-benzylidene- α -D-Galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-*N*-dehydro-L-ribitol 1.

Table 1. Phase angle of the pseudorotation $P[deg]$ and 3-Sphere dihedral angles $\theta_{HnHn+1}[deg]$ calculated from vicinal coupling constant $^3J_{HnHn+1}[Hz]$ for α -D-Galactosyl-iminocyclitols 1.

| Entry | $\delta_{Hn}[ppm]^a$ | $\delta_{Cn}[ppm]^a$ | $^3J_{HnHn+1}[Hz]$ | $\phi[deg]$ | $\theta_{HnHn+1}[deg]$ | $P[deg]$ |
|-------|----------------------|----------------------|--|-------------|--|--|
| 1. | Bu-6 ring | | | | | |
| 2. | H-9: 4.91 | C-9: 98.2 | <i>cis</i> H ₉ H ₁₀ : 3.4 | 46.24 | 1. 43.76 3. -35.83 | P: C ₁ ⁴ |
| 3. | H-10: 4.04 | C-10: 75.7 | <i>trans</i> H ₁₀ H ₁₁ : 10 | 100 | 1. -170.0 3. -135.43 4. 169.984 | θ_{HnHn+1} H ₉ H ₁₀ : 43.76 H ₁₀ H ₁₁ : -170.0 |
| 4. | H-11: 3.7 – 3.64 | C-11: 75.1 | <i>cis</i> H ₁₁ H ₁₂ : 3.3 | 43.56 | 1. 46.44 3. -34.57 | H ₁₁ H ₁₂ : 46.44 H ₁₂ H ₁₃ : 89.36 |
| 5. | H-12: 4.13 | C-12: 74.4 | <i>trans-ee</i> H ₁₂ H ₁₃ : bs ^b | 0.64 | 1. 89.36 2. 90.64 3. -89.36 4. -89.36 | θ_{nn+1} H ₉ H ₁₀ : 43.76 H ₁₀ H ₁₁ : -10 H ₁₁ H ₁₂ : 46.44 H ₁₂ H ₁₃ : 30.64 |
| 6. | H-13: 3.43 | C-13: 62.6 | - | - | - | - |
| 7. | Bu-5 ring | | | | | |

| Entry | $\delta_{\text{Hn}}[\text{ppm}]^a$ | $\delta_{\text{Cn}}[\text{ppm}]^a$ | $^3J_{\text{HnHn+1}}[\text{Hz}]$ | $\phi[\text{deg}]$ | $\theta_{\text{HnHn+1}}[\text{deg}]$ | P[deg] |
|-------|------------------------------------|------------------------------------|--|--------------------|--|---|
| 8. | H-2: 4.85 | C-2: 86.7 | <i>cis</i> H ₂ H ₃ : 5.3 | 112.36 | 1.-22.36 2.-42.73 3. 24.28 | P: C ³ $\theta_{\text{HnHn+1}}$ H ₂ H ₃ : 24.28 H ₃ H ₄ : 89.36 |
| 9. | H-3: 4.55 | C-3: 80.7 | <i>trans-ee</i> H ₃ H ₄ : bs | 0.64 | 1. 89.36 2. 90.64 3.-89.36 4.-89.36 | $\theta_{\text{nn+1}}$ H ₂ H ₃ : 24.28 H ₃ H ₄ : 30.64 |
| 10. | H-4: 4.25 | C-4: 75.2 | | | | |

[a] ¹H-NMR (400 MHz, CDCl₃) ¹³C-NMR (75 MHz, CDCl₃), [b] bs ~ ³J_{HnHn+1} 0.4[Hz].

Dihedral angles $\theta_{\text{HnHn+1}}[\text{deg}]$ of five and six membered ring[1] are calculated with eq. 1-5, torus (eq. 1-2) and torus inversion to Dupin cyclide (eq. 3-5), from vicinal coupling constant with eq. 6 between 0 - 6.1[Hz] for *cis* and *trans-ee* stereochemistry, and with eq. 7 between 5.5 – 13.4[Hz] for *trans-aa* stereochemistry. In case of *cis* stereochemistry with higher values of vicinal constant coupling will be used eq. 8 and at smaller value of the *trans* stereochemistry eq. 9.

$$\text{cis, trans-ee: } \sin^{-1}\cos\phi = \theta_{\text{HnHn+1}} \quad (1)$$

$$\text{trans-aa: } \cos^{-1}\sin(-\phi) = \theta_{\text{HnHn+1}} \quad (2)$$

$$\text{cis, trans-ee: } \tan^{-1}\sin(-\phi) = Y \quad (3)$$

$$\text{cis, trans-ee: } \tan^{-1}(1/\sin\phi) = Y \quad (4)$$

$$\text{cis, trans-ee: } \sin^{-1}\tan(-\phi) = Y \quad (5)$$

where: $Y = \theta_{\text{HnHn+1}}$ with *cis* or *trans-ee* stereochemistry, *cis* can be transformed in *trans-aa* or *trans-ee* under 3-Sphere rule [22].

$$\text{trans } \phi = (^3J_{\text{HH}})^2 \quad (6)$$

$$\text{cis } \phi = (2 \times ^3J_{\text{HH}})^2 \quad (7)$$

$$\text{trans } ^3J_{\text{HH}} = (\phi)^{1/2} \quad (8)$$

$$\text{cis } ^3J_{\text{HH}} = (\phi)^{1/2} \quad (9)$$

Dihedral angles $\theta_{\text{HnHn+1}}[\text{deg}]$ of α -D-Galactosyl-iminocyclitols 1 calculated from carbon chemical shift $\delta_{\text{Cn}}[\text{ppm}]$, comparable with dihedral angles $\theta_{\text{HnHn+1}}[\text{deg}]$ calculated from vicinal coupling constants $^3J_{\text{HnHn+1}}[\text{Hz}]$, are presented in table 2 along the corresponding N dimensional 3-Sphere equations and the corresponding dimension space. As reported recently [23, 24], correlation between the biological activity and the shape of the iminocyclitols [25] was performed based on the dimensional number space N of the equations for calculation of the dihedral $\theta_{\text{HnHn+1}}[\text{deg}]$ or/and vicinal angles $\phi[\text{deg}]$. The most active iminocyclitols on bovine viral diarrhea virus (BVDV), surrogate for hepatitis C virus (HCV) have the equations for calculation of the dihedral or the vicinal angles in 2-D, with tan or sin/cos trigonometric equations (Figure 4): *i.e.* *monoalkyl chain* [24, 25]: *N*-n-C₁-dodecyl- β -L-ribitol trifluoroacetate salt 2 (IC₅₀ 1.5 μ M); 2D, C₁₋₄ = f(tan), *dialkyl chain*: *N*-nonyl-C₁-nonyl-L-ribitol 3 (IC₅₀ 8.2 μ M), *N*-nonyl-C₁-nonyl-D-ribitol 4 (IC₅₀ 4.6 μ M), 2D, C_{1,4} θ_{HH} = f(sin), C_{2,3} θ_{HH} = f(tan), 4D, ϕ ; *trialkyl chain* [23]: *N*-methyl-C₁-butyl, nonyl-L-ribitol.HCl 5 (IC₅₀ < 2 μ M); 2D, C_{2,3} θ_{HH} = f(sin), 2D, C_{3,4} θ_{HH} = f(tan). All dihedral angles $\theta_{\text{HnHn+1}}[\text{deg}]$ or corresponding vicinal angles $\phi[\text{deg}]$ are calculated in 2D for both, six and five membered ring of 1 (Table 2).

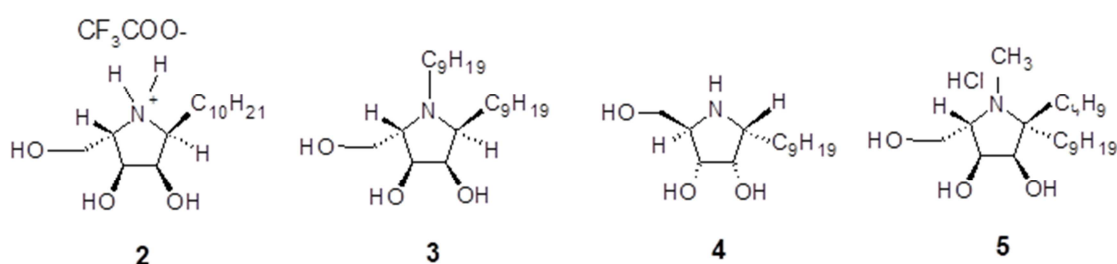


Figure 4. Mono-, di-, trialkyl chain iminocyclitols.

Table 2. N -Dimension and corresponding hypersphere equations on calculation of the dihedral angles from carbon chemical shift $\delta_{\text{Cn}}[\text{ppm}]$ for α -D-Galactosyl-iminocyclitols 1.

| Entry | $\delta_{\text{Cn}}[\text{ppm}]^a$ | R_m^b [gauss] | $^3J_{\text{HnHn+1}}^{\text{exp}}$ [Hz] | N -D equations | $\theta_{\text{HnHn+1}}$ or $\phi[\text{deg}]$ | $^3J_{\text{HnHn+1}}^{\text{calc}}$ [Hz] |
|-------|------------------------------------|--------------------|--|--|---|---|
| 1. | Bu-6 ring | | | | | |
| 2. | C-9: 98.2 | 2.7507 | <i>cis</i> H ₉ H ₁₀ : 3.4 | 2D: $\theta_{\text{H9H10}} = 2x\sin^{-1}(1/R_m)$ 4D: $\phi = \sin^{-1}\cos[2x\sin^{-1}(1/R_m)]$ | 42.635 47.364 | 3.44 |
| 3. | C-10: 75.7 | 2.1204 | <i>trans-aa</i> H ₁₀ H ₁₁ : 10 | 2D: $\phi = 2x\tan^{-1}(1/R_m)$ 4D: $\theta_{\text{H10H11}} = -180 - \sin^{-1}\cos[4x\tan^{-1}(1/R_m)]$ | 100.75 -169.005 | 10.03 |
| 4. | C-11: 75.1 | 2.1036 | <i>cis</i> H ₁₁ H ₁₂ : 3.3 | 2D: $\phi = \tan[1/(R_m/2)]$ 3D: $\theta_{\text{H11H12}} = \cos^{-1}\sin\phi$ | 43.553 46.44 | 3.29 |

| Entry | δ_{Cn} [ppm] ^a | R_m^b [gauss] | $^3J_{HnHn+1}^{exp}$ [Hz] | N-D equations | θ_{HnHn+1} or ϕ [deg] | $^3J_{HnHn+1}^{calc}$ [Hz] |
|----------|----------------------------------|--------------------|--|---|--|-------------------------------|
| 5. | C-12: 74.4 | 2.0840 | <i>trans-ee</i> H ₁₂ H ₁₃ : bs | 2D: $\phi = 60 - \cos^{-1}(1/R_m)$ 3D: $\theta_{H12H13} = \cos^{-1}\sin\phi$ 4D: $\theta_{H12H13} = 2\tan^{-1}\cos[(\sin^{-1}1/R_m)/2]$ 4D: $\theta_{H12H13} = 2\tan^{-1}\cos[(\tan^{-1}1/R_m)/2]$ | 1.324 88.676 88.187 88.554 | 0.575 0.673 0.601 |
| 6. 7. | C-13: 62.6 <i>Bu-5 ring</i> | 1.7535 | - | | | |
| 8. | C-2: 86.7 | 2.4285 | <i>cis</i> H ₂ H ₃ : 5.3 | 2D: $\phi = 180 - \cos^{-1}(1/R_m)$ 3D: $\theta_{H2H3} = \sin^{-1}\cos\phi$ 2D: $\phi = 180 - \tan^{-1}(R_m)$ 2D: $\theta_{H2H3} = -\tan^{-1}(1/R_m)$ | 114.315 -24.315 112.380 -22.380 | 5.34 5.30 |
| 9. | C-3: 80.7 | 2.2605 | <i>trans-ee</i> H ₃ H ₄ : bs | 2D: $\phi = 60 - \cos^{-1}(1/R_m)$ 3D: $\theta_{H3H4} = \cos^{-1}\sin\phi$ | 3.744 86.255 | 0.967 |
| 10. | C-4: 75.2 | 2.8085 | | 4D: $\theta_{H3H4} = 2\tan^{-1}\cos[(\sin^{-1}1/R_m)/2]$ 4D: $\theta_{H3H4} = 2\tan^{-1}\cos[(\tan^{-1}1/R_m)/2]$ | 88.482 88.748 | 0.615 0.559 |

[a] ¹H-NMR (400 MHz, CDCl₃) ¹³C-NMR (75 MHz, CDCl₃), [b] $R_m = \delta_{Cn}\omega_C/4\pi \times 10^{-3}/10.71$ [gaussx10], where δ_{Cn} – chemical shift [ppm], ω_C – carbon Larmor frequencies [MHz], γ – gyromagnetic ratio (C: 10.71).

Tetrahedral angles of 1 are calculated in Table 3 from carbon chemical shift δ_{Cn} [ppm] with generalized equations 10 – 16 for six membered ring and equations 17 – 19 for five membered ring.

Generalized equations of six membered ring:

$$\sin^{-1}1/R_m = X^S \quad (10)$$

$$\tan^{-1}1/R_m = X^{IT} \quad (11)$$

$$\tan^{-1}R_m = X^T \quad (12)$$

$$\sin^{-1}\tan(-X^S n_a) = -\phi_2^F, n_a, n_b = 1/2, 1, 2 \quad (13)$$

a. if $\phi_2^F = \theta^{C3}/2 < 59.9$ [deg], $\phi_2^F = \theta^{C2}/2 = (120 - \theta^{C3})/2$, $\cos^{-1}\sin(120 - \theta^{C3})/2 = \cos^{-1}\sin(\theta^{B1}) = \phi_{Cn}^{A4}$,

where: Two pairs of sets angles D, E or F, G bearing dihedral and vicinal angles, algebraic angle $\phi_2^{F \text{ or } D}$

b. $\phi_2^B = \theta^{C1} < 29.9$ [deg], $\cos^{-1}\sin(\theta^{E1})/2 = \phi_{Cn}^{D4}$
where: Two sets angles A, B bearing dihedral and vicinal angles, algebraic angle ϕ_2^B

$$\tan^{-1}\sin(-X^{IT} n_a) = -\phi_2^F, n_a, n_b = 1/2, 1, 2 \quad (14)$$

if $\phi_{Cn} = \phi_{Cn}^{A5}$ and $\phi_2^G = \theta^{B2} < 29.9$ [deg], $\phi_2^F = \theta^{C2}/2$, $\cos^{-1}\sin(\phi_2^F) = \phi_{Cn}^{A4}$

$$180 - \phi_{Cn}^{A5} = \theta^{A2}, 60 + \theta^{A2} = \phi_{Cn}^{A4}$$

$$\tan^{-1}\sin(-X^T n_a) = -\phi_2^F, n_a, n_b = 1/2, 1, 2 \quad (15)$$

$$\cos^{-1}\sin(-\phi_2^F n_b) = \phi_{Cn} \quad (16)$$

Generalized equations of five membered ring:

$$\sin^{-1}1/R_m = -\phi_2^{F,S} \quad (17)$$

$$\tan^{-1}1/R_m = -\phi_2^{F,IT} \quad (18)$$

$$\cos^{-1}\sin(-\phi_2^{F,X}/2) = \phi_{Cn} \quad (19)$$

where: $\phi_2^{F,X}$ – algebraic angle of set F, X = unit build from sin function (S) or tan function (IT).

Dihedral angles and tetrahedral angles are in close relationships on unit build from tetrahedral angles, or from $\phi_2^{F,X}$ in case of five membered ring. Dihedral angle θ_{HnHn+1} [deg] of five membered ring result in opposite with tetrahedral angle ϕ_{Cn} [deg], one on unit build from *sin* function and one on unit build from *tan* function. In case of *six* membered ring are preferred unit results from tetrahedral angle in close relationship with dihedral angle through the algebraic angles ϕ_2 of sets angle corresponding to vicinal angle.

Table 3. 3-Sphere dihedral angles and tetrahedral angles calculated from carbon chemical shift δ_{Cn} [ppm] with conic section as manifold and eq. 10 - 19.

| Entry | δ_{Cn} [ppm] | R_m [gauss] | $^3J_{HnHn+1}$ [Hz] | ϕ_{Cn} [deg] $n = 1/2, 1, 2$ | θ_{HnHn+1} [deg] | $^3J_{HnHn+1}^{calc}$ [Hz] | ϕ_{Cn} [deg] |
|-------|---------------------|------------------|---|--|--|---|----------------------|
| 1. | <i>Bu-6 ring</i> | | | | | | |
| 2. | C-9: 98.2 | 2.7507 | <i>cis</i> H ₉ H ₁₀ : 3.4 | 13. 112.969, n_a, n_b : 1 116.485, n_a, n_b : 2, 1/2 14. 122.709, n_a, n_b : 2, 1 117.291 15. 119.844, n_a, n_b : 1/2, 1 111.611, n_a, n_b : 1, 1/2 | θ_{H9H10} 41.484 θ_{H9H10} 43.242 θ_{H9H10} 43.645 θ_{H9H10} 44.922 θ_{H9H10} 40.805 | 3.48 3.41 3.40 3.37 3.50 | 117.291° |
| 3. | C-10: 75.7 | 2.1204 | <i>Trans-aa</i> H ₁₀ H ₁₁ : 10 | 13. 110.936, n_a, n_b : 2, 1/2 14. 127.653, n_a, n_b : 2, 1/2 112.347 15. 118.167, n_a, n_b : 1129.407 110.592, n_a, n_b : 1 | θ_{H9H10} 40.468 θ_{H10H11} -169.53 θ_{H9H10} 41.173 θ_{H10H11} -168.51 θ_{H9H10} 44.083 θ_{H10H11} -165.916 θ_{H9H10} 40.296 θ_{H10H11} -169.704 | 3.51 10.02 3.49 10.07 3.38 10.2 3.52 10.01 | 110.936 110.592 |

| Entry | δ_{Cn} [ppm] | R_m [gauss] | $^3J_{HnHn+1}$ [Hz] | φ_{Cn} [deg] $n = 1/2, 1, 2$ | θ_{HnHn+1} [deg] | $^3J_{HnHn+1}^{calc}$ [Hz] | φ_{Cn} [deg] |
|-------|---------------------|------------------|--|--|--|---|-------------------------|
| 4. | C-11: 75.1 | 2.1036 | <i>cis</i> $H_{11}H_{12}$: 3.3 | 13. 117.293, n_a, n_b : 1 14. 113.235, n_a, n_b : 1 15. 118.109, n_a, n_b : 1/2, 1 114.940, n_a, n_b : 1/2, 1 13. 123.156, n_a, n_b : 1 116.843 | θ_{H11H12} 46.353 θ_{H11H12} 48.382 θ_{H11H12} 47.529 θ_{H11H12} 47.529 θ_{H11H12} 46.578 θ_{H12H13} 88.421 | 3.30 3.22 3.31 3.25 3.29 0.628 | 117.293 ^c |
| 5. | C-12: 74.4 | 2.0840 | <i>trans-ee</i> $H_{12}H_{13}$: bs | 14. 113.394, n_a, n_b : 1 15. 118.040, n_a, n_b : 1/2, 1 115.016, n_a, n_b : 1/2, 1 13. 111.983, n_a, n_b : 1, 1/2 114.048 ^{UtoS} | θ_{H12H13} 86.843 θ_{H12H13} 88.040 θ_{H12H13} 87.508 θ_{H12H13} 85.991 θ_{H12H13} 87.024 | 0.908 0.699 ⁸² 0.789 1.00 0.85 | 116.843 |
| 6. | C-13: 62.6 | 1.7535 | - | 14. 116.353, n_a, n_b : 1, 1 110.358, n_a, n_b : 2, 1/2 15. 116.459, n_a, n_b : 1/2, 1 | θ_{H12H13} 88.176 θ_{H12H13} 85.179 θ_{H12H13} 88.229 | 0.67 1.09 0.665 | 116.459 |
| 7. | <i>Bu-5 ring</i> | | | | | | |
| 8. | C-2: 86.7 | 2.4285 | <i>cis</i> H_2H_3 : 5.3 | 101.190 ^T 101.931 | θ_{H2H3} 24.315 ^S θ_{H3H4} 86.13 | 5.3 0.98 | 101.190 |
| 9. | C-3: 80.7 | 2.2605 | <i>trans-ee</i> H_3H_4 : bs | 103.127 104.0634 ^{SG} 101.797 ^b | θ_{H3H4} 83.86 θ_{H3H4} 88.12 | 1.238 0.684 | 101.931 101.797 |
| 10. | C-4: 75.2 | 2.10644 | | 107.302 | θ_{H3H4} 88.342 | 0.643 | 107.302 |

[a] $R_m = vx4\pi x 10^{-3}/\gamma$ [gaussx10] = $\delta_{Cn}x7.0028x4\pi x 10^{-3}$ [Tx10⁻³], ν – frequency [Hz], $\nu = \delta_{Cn}x\omega_L$: ω_L – Larmor frequency [¹³C: 75MHz], δ_{Cn} – chemical shifts [ppm], γ – gyromagnetic ratio: ¹³C: $\gamma = 10.71$ [MHzxT⁻¹] = 6.7 [10⁷radxT⁻¹xs⁻¹]; [b] $2x\tan^{-1}\{2x\sin[(180 - 104.064)/2]\} = 100.797$ [deg]; [c] 110.28[deg], 110.092[deg] under polyhedron eq. $\tan\phi/2 = X/2 = 2\sin\theta$; eq. 13, 14, 16: entry 2: $\sin^{-1}\tan[-\sin^{-1}(1/2.7507)] = -22.969$ [deg], $\cos^{-1}\sin(-22.969) = 112.969$ [deg]; $\sin^{-1}\tan[-2x\sin^{-1}(1/2.7507)] = -67.029$ [deg], $\cos^{-1}\sin(-52.970) = 116.843$ [deg]; $\tan^{-1}\sin[2x(\tan^{-1}1/2.7507)] = -32.709$ [deg], $\cos^{-1}\sin(-32.709) = 122.709$ [deg], 117.291[deg]; eq. 13, 14, 15, 16: entry 5: $\sin^{-1}\tan[-\sin^{-1}(1/2.0840)] = -33.1563$, $\cos^{-1}\sin(-33.1563) = 123.1562$ [deg], 116.843[deg]; $\tan^{-1}\sin[-(\tan^{-1}2.0840)/2] = -23.3942$ [deg], $\cos^{-1}\sin(-23.3942) = 113.3942$ [deg]; $\tan^{-1}\sin[-(\tan^{-1}2.0840)/2] = -28.0409$ [deg], $\cos^{-1}\sin(-28.04093) = 118.0409$ [deg].

For a vicinal constant coupling of 3.4[Hz] (Table 3, entry 1) results angle θ^{C3} of 67.029[deg] (eq. 13, $n = 2$) and an angle of 123.514[deg] (eq. 16 with $n = 1/2$), angles calculated from carbon chemical shift of C_9 , $R_m = 2.7507$ [gaussx10]. Using θ^{C2} of 52.9703[deg] instead of θ^{C3} 67.029[deg] in eq. 13 results tetrahedral angle of 116.485[deg] with dihedral angle of 43.242[deg] and a vicinal coupling constant of 3.41[Hz].

In case of eq. 13 with $n = 1$ results an angle of 112.969[deg] with a vicinal coupling constant of 3.48[Hz]. From eq. 14 with $n = 2$ results an angle θ^5 of 122.709[deg] having on same set θ^4 of 117.291[deg] with a vicinal coupling constant of 3.4[Hz] calculated from vicinal angle found on set F of ϕ 46.35[deg]. As observation, until now the values of the calculated vicinal coupling constant can be almost equal with the recorded one, thus two possible tetrahedral angles 116.485 and 117.291[deg] results from eq. 13 and 16, but both involve some modification on corresponding equations. In case of eq. 15 for $n = 2$ and $n = 1$ results angles of 119.844 and 111.611[deg] with vicinal coupling constant of 3.37 and 3.5[Hz] (Table 3, entry 2).

In case of *trans-ee* stereochemistry ϕ_2 of sets containing dihedral and vicinal angles are $\theta^{A1} = \phi_2^D$, $\theta^{A2} = \phi_2^E$, instead of θ^{B1} , θ^{B2} , sometimes resulting the angle θ^{A5} 123.156[deg] instead of θ^{A4} 116.843[deg] (Table 3, entry 5 analog with entry 2 eq. 14).

In case of C_{10} with a vicinal coupling constant *trans-aa* $^3J_{H10H11}$ of 10[Hz], the preferred tetrahedral angle φ_{C10} 110.93[deg] has the calculated dihedral angles θ_{H10H11} - 169.53[deg] with vicinal coupling constant almost equals with recorded vicinal coupling constant 10.02[Hz] (Table 3,

entry 3), in same set with a possible dihedral angle θ_{H9H10} 40.46[deg], but with a vicinal coupling constant of 3.51[Hz] instead of 3.4[Hz].

Tetrahedral angles φ_{C11} 117.293[deg] have vicinal coupling constant of 3.30[Hz] and dihedral angle θ_{H11H12} 46.353[deg] (Table 3, entry 4). Between tetrahedral angles φ_{C12} 113.394, 116.843[deg] with vicinal coupling constants of 0.9, 0.628[Hz] will be chosen 116.84[deg], as well as φ_{C13} 116.459[deg] with vicinal coupling constants of 0.665[Hz] for *trans-ee*^{3,2} θ_{H12H13} (88.42 and 88.22[deg]) (Table 3 entry 5 and 6).

Tetrahedral angles of five membered ring φ_{C2} 101.19, φ_{C3} 101.93, φ_{C4} 107.302[deg] are calculated in opposite [4] with dihedral angles θ_{H2H3} 24.315, θ_{H3H4} 86.25[deg], 88.343[deg] (Table 3, entry 8 – 10). Considering dihedral angle θ_{H3H4} 88.12 [deg], an angle of sets F and G calculated from $\sin^{-1}1/R_m = 26.255$ [deg], after building its seven sets angles was calculated an angle of 101.797[deg] from 104.063[deg] with eq. 26 published in Science Journal of Chemistry 2023 [26]. In this case the vicinal coupling constant is 0.684[Hz]. The calculated vicinal coupling constant for *trans-ee* stereochemistry from carbon chemical shift have values of 0.665 or 0.595[Hz] as calculated with eq. 9d, 9e published in Rev. Roum. Chim. 2023 [4]. Three tetrahedral angles result from units builds from dihedral angle *cis* $\theta_{H9H10} = 43.76$ [deg] with a vicinal constant coupling of 3.4[Hz], respectively φ_{C9} 113.12, 111.88, 117.51[deg] (Table 4). Algebraic angles ϕ_2 [deg] of dihedral and vicinal angles: ϕ_2^{U1A} 27.51 and ϕ_2^{U1B} 32.48[deg] in accord with general rule of six membered ring indicate angle θ^{S2B4} 117.15[deg] as tetrahedral angle φ_{C9} [deg].

Table 4. Tetrahedral angle φ_{C9} 117.51[deg] predicted for a dihedral angle $cis\ \theta_{H9H10} = 43.76[deg]$ with a vicinal constant coupling of 3.4[Hz].

| Entry | Unit | θ^n, ϕ_n [deg] | A | B | C | D | E | F | G |
|-------|----------------|--------------------------|--------|---------|--------|--------|--------|--------|--------|
| 1. | U ₁ | θ^1 | 13.75 | 16.24 | 27.51 | 6.87 | 23.12 | 8.12 | 21.87 |
| | | θ^2 | 46.24 | 43.75 | 32.48 | 53.12 | 36.87 | 51.87 | 38.12 |
| | | θ^3 | 73.75 | 76.24 | 87.51 | 66.88 | 83.12 | 68.12 | 81.88 |
| | | θ^4 | 106.24 | 103.75 | 92.48 | 113.12 | 96.88 | 111.88 | 98.12 |
| | | θ^5 | 133.76 | 136.24 | 147.51 | 126.88 | 143.12 | 128.12 | 141.88 |
| | | θ^6 | 166.24 | 163.76 | 152.48 | 173.12 | 156.88 | 171.88 | 158.12 |
| | | ϕ_2 | 27.51 | 32.48 | 55.03 | 13.75 | 46.24 | 16.24 | 43.75 |
| | | $\phi_{1/2}$ | 16.24 | 13.75 | 2.48 | 23.12 | 6.879 | 21.87 | 8.12 |
| | | θ^1 | 27.51 | 2.48 | 4.96 | 13.75 | 16.24 | 12.40 | 28.75 |
| | | θ^2 | 32.48 | 57.51 | 55.03 | 46.24 | 43.75 | 58.75 | 31.24 |
| 2. | S ₂ | θ^3 | 87.51 | 62.48 | 64.96 | 73.75 | 76.24 | 61.24 | 88.75 |
| | | θ^4 | 92.48 | 117.51 | 115.03 | 106.24 | 103.75 | 118.75 | 91.24 |
| | | θ^5 | 147.51 | 122.48 | 124.96 | 133.76 | 136.24 | 121.24 | 148.75 |
| | | θ^6 | 152.48 | 177.519 | 175.03 | 166.24 | 163.76 | 178.75 | 151.24 |
| | | ϕ_2 | 55.03 | 4.96 | 9.923 | 27.51 | 32.48 | 2.48 | 57.51 |
| | | $\phi_{1/2}$ | 2.48 | 27.51 | 25.038 | 16.24 | 13.75 | 28.75 | 1.24 |

Tetrahedral angles of five membered ring can be calculated only from θ^{S4} with eq. 20 - 23.

$$\cos^{-1}\sin Z/2 = \varphi_{Cn} \quad (20)$$

$$Z = [60 - (\theta^{S4} - 90)]/1.5 \quad (21)$$

with: $\theta^{4A} > \theta^{4B} \rightarrow \varphi_{C2}, \varphi_{C3}$

$\theta^{4A} < \theta^{4B} \rightarrow \varphi_{C1}, \varphi_{C4}$

$$trans-aa^{6,1}, trans-ee: Z = \theta^{S4} - 60 \quad (22)$$

$$cis^{5,2}: \cos^{-1}\sin(-2\theta^{B1}) = \varphi_{C1} \quad (23)$$

from $2\theta^{B1}: \theta^{A2} = \phi, \theta^{B2} = \theta_{HH}$

Tetrahedral angles can be calculated only from vicinal coupling constant, in fact from vicinal angle ϕ [deg] with eq. 20, 24 - 29, but also from carbon chemical shift δ_{Cn} [deg]. From vicinal coupling constant result tetrahedral angles φ_{C2} and φ_{C3} [deg] with same value.

Five membered ring [4]:

$$cis^{5,2}: Z = \phi_{2B} \quad (24)$$

with $\phi_{1A}/2 = \phi_{2B}/2 = \theta^{B1}, \theta^{B2} = \theta_{HnHn+1}$

$trans-aa^{5,2}: \theta^{2A} = \theta^{5B} - 90$

$$cis^{6,1}: Z = (\phi - X)/n \quad (25)$$

where $X = 30, 60$ for/or $\theta^3, \theta^4, n = 4$ for $\phi > 90[deg]$, negative angles

$$\tan^{-1}\sin \phi = A, A + 60 = \varphi_{C2} \text{ or } \varphi_{C3} \quad (26)$$

$$Z/2 = \phi/4 \quad (27)$$

$$trans-aa^{6,1}: Z/2 = \phi - 60 \quad (28)$$

with $Z/2 = \theta^{1B} = \theta^{6A} - 150$

$$trans-ee: \cos^{-1}\sin \phi = \theta_{HnHn+1} \quad (29)$$

Six membered ring:

$$Z/2 = \phi_2^F \quad (30)$$

with $cis^{5,2}: \phi_2^F = \theta^{B1}, \theta^{A4} = \varphi_{Cn}, \theta^{F2} = \phi$
 $trans-aa^{6,1}: \phi_2^F = \theta^{B1}, \theta^{A4} = \varphi_{Cn}, \theta^{F6} = \theta_{HnHn+1}$
 $trans-ee: \phi_{1/2}^A = \theta^{B1}, \theta^{A4} = \varphi_{Cn}, \theta^{E3} = \theta_{HnHn+1}, \theta^{D1} = \phi, \phi_2^D = \theta^{A1}$

The calculation of the tetrahedral angles only from vicinal coupling constant can be take in consideration as a prediction approach, tetrahedral angles calculated in table 5 from carbon and proton chemical shift under rectangle geometries as manifold are comparable with angles calculated from carbon chemical shift in table 3. In attempt to obtain the dihedral and vicinal angles on sets A and B of the unit, was chose rectangle as manifold [3], in case of *trans-aa* and *-ee* stereochemistry resulting the corresponding torsional angles in accord with 3-sphere approach [22]. Dihedral angles θ_{H12H13} with *trans-ee* stereochemistry and the corresponding vicinal angle results in sets A, B from middle line of antiparallelogram (eq. 34) has a vicinal coupling constant of 1.11[Hz] and a tetrahedral angle of φ_{C12} 110.139[deg]. In same unit on sets D, E are found vicinal and dihedral angles 2.464, 87.535[deg] with vicinal coupling constant $^3J_{H12H13}$ 0.784[Hz] and tetrahedral angle φ_{C12} 115.07[deg] (Table 5, entry 5).

Skew circles [3]:

$$\theta^{An} = nx[(\Delta\delta_{HnHn+1} \times \Delta\delta_{CnCn+1})/2]^{1/2} \times 90: cis-ea, ae, trans-ee \quad (31)$$

$n = 2, cis-ea, -ae, trans-ee$

$$\theta^{An} = nx[(\Delta\delta_{HnHn+1} \times \Delta\delta_{CnCn+1})/2]^{1/2} \times 90: trans-aa^{6,1} \quad (32)$$

$n = 1, trans-aa^{6,1}$

Middle circles: *cis-ea, -ae, trans-aa*

$$\theta^{An} = nx[90x(\Delta\delta_{HnHn+1} + \Delta\delta_{CnCn+1})/2]^{1/2} \quad (33)$$

$n = 2, cis-ea, -ae, trans-ee$

$$\theta^{An} = nx[90x(\Delta\delta_{HnHn+1} - \Delta\delta_{CnCn+1})/2]^{1/2} \quad (34)$$

$n = 1, trans-aa^{6,1}$

where: θ^{An} – an angle of set A from unit U or S, $\Delta\delta_{HnHn+1}$, $\Delta\delta_{CnCn+1}$ – the differences between two consecutive protons

and two atoms of carbon [ppm].

Table 5. 3-Sphere dihedral angles $\theta_{\text{HnHn+1}}[\text{deg}]$ and corresponding tetrahedral angles $\varphi_{\text{Cn}}[\text{deg}]$ calculated from chemical shift $\delta_{\text{x}}[\text{ppm}]$ ($X = {}^{13}\text{C}$, ${}^1\text{H}$ -RMN) using rectangle as manifold.

| Entry | $\delta_{\text{Hn}}[\text{ppm}]$ | $\delta_{\text{Cn}}[\text{ppm}]$ | ${}^3J_{\text{HnHn+1}}[\text{Hz}]$ | Rectangle $\theta_{\text{HnHn+1}}[\text{deg}]$ | Manifold equations | n | $\varphi_{\text{Cn}}[\text{deg}]$ |
|-------|----------------------------------|----------------------------------|--|---|---|--------|-----------------------------------|
| 1. | Bu-6 ring | | | | | | |
| 2. | H-9: 4.91 | C-9: 98.2 | <i>cis</i> H ₉ H ₁₀ : 3.4 | 44.12 | $\Delta\delta_{\text{CnCn+1}} - 1/\Delta\delta_{\text{HnHn+1}}$ | 1 | 118.24 116.479 ^c |
| 3. | H-10: 4.04 | C-10: 75.7 | <i>trans</i> H ₁₀ H ₁₁ : 10 | -169.91 ^a -169.08 ^a | $\Delta\delta_{\text{CnCn+1}} \times 1/\Delta\delta_{\text{HnHn+1}}$ $\Delta\delta_{\text{CnCn+1}} - 1/\Delta\delta_{\text{HnHn+1}}$ | 2 1 | 110.18 |
| 4. | H-11: 3.7 – 3.64 | C-11: 75.1 | <i>cis</i> H ₁₁ H ₁₂ : 3.3 | 47.06 | $\Delta\delta_{\text{CnCn+1}} + 1/\Delta\delta_{\text{HnHn+1}}$ | 1 | 115.87 |
| 5. | H-12: 4.13 | C-12: 74.4 | <i>trans-ee</i> H ₁₂ H ₁₃ : bs | 85.07 ^b 87.53 ^b | $1/\Delta\delta_{\text{CnCn+1}} - 1/\Delta\delta_{\text{HnHn+1}}$ | 1 | 110.139 115.07 |
| 6. | H-13: 3.43 | C-13: 62.6 | | 88.823 | $\Delta\delta_{\text{CnCn+1}} - 1/\Delta\delta_{\text{HnHn+1}}$ | 1 | 117.64 115.29 ^d |
| 7. | Bu-5 ring | | | | | | |
| 8. | H-2: 4.85 | C-2: 86.7 | <i>cis</i> H ₂ H ₃ : 5.3 | 23.811 | $\Delta\delta_{\text{CnCn+1}} + 1/\Delta\delta_{\text{HnHn+1}}$ | 1 | 101.905 103.824 |
| 9. | H-3: 4.55 | C-3: 80.7 | <i>trans-ee</i> H ₃ H ₄ : bs | 32.31 ^e | $\Delta\delta_{\text{CnCn+1}} + 1/\Delta\delta_{\text{HnHn+1}}$ | 2 | 104.705 101.392 ^f |
| 10. | H-4: 4.25 | C-4: 75.2 | | 30.59 ^e | $\Delta\delta_{\text{CnCn+1}} - 1/\Delta\delta_{\text{HnHn+1}}$ | 2 | 106.155 109.889 ^g |

[a] $\phi_{1/2}$ 10.099[deg], 10.927[deg]; [b] $\phi_{1/2}$ 4.929[deg], ${}^3J_{\text{H12H13}}$ 1.11[Hz], φ_{C12} 110.139[deg]; sets D, E θ^1 : 2.464, 87.535[deg], ${}^3J_{\text{H12H13}}$ 0.784[Hz], φ_{C12} 115.07[deg]; [c] set S₂C, $\phi_{1/2}^{\text{S2A}} = \theta^{\text{S3B}} = 26.479$, eq.16: φ_{C12} 116.47[deg]; [d] set S₂C, $\phi_{1/2}^{\text{S2A}} = \theta^{\text{S3B}} = 25.292$, eq.16: φ_{C12} 115.29[deg]; [e] $\phi_{1/2}$ 32.31[deg], 30.59[deg] – torsional angles: $120 - \theta^{\text{cis}} = \theta^{\text{trans-ee}}$; [f] $2\text{x}\tan^{-1}\{2\text{x}\sin[(180 - 104.705)/2]\} = 101.392[\text{deg}][23]$; [g] $2\text{x}\sin^{-1}\{(1/\sin[(180 - 104.705)/2])/2\} = 109.889[\text{deg}][26]$.

The bond distance $l_{\text{CnCn+1}}[\text{\AA}]$ can be calculated from dihedral angles (eq. 35) as reported recently [23], with results comparable with eq. 36 reported by Maksic and Randic [27]. In table 6 are calculated bond distances of six and five membered rings on 6-O-(7,8-di-O-Benzyl-9,11-O-benzylidene- α -D-galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol 1.

$$l_{\text{CnCn+1}} = (l^0 \text{xr})^{1/2} [\text{\AA}] \quad (35)$$

where l^0 – theoretic bond distance of C_nC_{n+1} : $1.54[\text{\AA}]$

$$r = 1.57 \cos^{1/2}(\theta_{\text{HnHn+1}}/m) [\text{rad}]$$

cis^{6,1}- $\theta_{\text{HnHn+1}}$: m = 1, *cis*^{5,2}- $\theta_{\text{HnHn+1}}$: m = 2; *trans-aa* and *trans-ee* are transformed in *cis* conform with 3-sphere rule [22].

alternatively: θ_{H3H4} *trans-ee*^{3,2}: $r = 1.57 \cos^{1/2}(\phi)$ or m = 4

$$l_{\text{CC}}[\text{\AA}] = -1.166\delta_{\text{CC}} + 2.298 \quad (36)$$

where $\delta_{\text{CC}} = 1/r$, r = bond distance [rad]

Table 6. Bond distances $l_{\text{CnCn+1}}[\text{\AA}]$ of six and five membered rings on 6-O-(7,8-di-O-Benzyl-9,11-O-benzylidene- α -D-galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol 1.

| Entry | $\delta_{\text{Cn}}[\text{ppm}]$ | $R_{\text{m}}[\text{gauss}]$ | ${}^3J_{\text{HnHn+1}}[\text{Hz}]$ | $\theta_{\text{HnHn+1}}[\text{deg}]$ | r[deg] | $l_{\text{CnCn+1}}[\text{\AA}]$ Eq. 35 | $l_{\text{CnCn+1}}[\text{\AA}]$ Eq. 36 |
|-------|----------------------------------|------------------------------|--|---|--------------------|---|---|
| 1. | Bu-6 ring | | | | | | |
| 2. | C-9: 98.2 | 2.7507 | <i>cis</i> H ₉ H ₁₀ : 3.4 | θ_{H9H10} 43.76 | 1.51239 | 1.52613 | 1.527034 |
| 3. | C-10: 75.7 | 2.1204 | <i>Trans-aa</i> H ₁₀ H ₁₁ : 10 | θ_{H10H11} -170.0 | 1.55687 | 1.54841 | 1.549061 |
| 4. | C-11: 75.1 | 2.1036 | <i>cis</i> H ₁₁ H ₁₂ : 3.3 | θ_{H11H12} 46.44 | 1.50507 | 1.52243 | 1.523285 |
| 5. | C-12: 74.4 | 2.0840 | <i>trans-ee</i> H ₁₂ H ₁₃ : bs | θ_{H12H13} 89.36 ϕ 0.64 | 1.54185 1.56998 | 1.54185 1.554921 | 1.541765 |
| 6. | C-13: 62.6 | 1.7535 | - | | | | |
| 7. | Bu-5 ring | | | | | | |
| 8. | C-2: 86.7 | 2.4285 | <i>cis</i> H ₂ H ₃ : 5.3 | θ_{H2H3} 24.28 | 1.498956 | 1.519339 | 1.520125 |
| 9. | C-3: 80.7 | 2.2605 | <i>trans-ee</i> H ₃ H ₄ : bs | θ_{H3H4} 89.36 ϕ 0.64 | 1.54185 1.56998 | 1.54185 1.554921 | 1.541765 |
| 10. | C-4: 75.2 | 2.10644 | | | | | |

4. Discussions

The conformation of 6-O-(7,8-di-O-Benzyl-9,11-O-benzylidene- α -D-galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol

1 as simulated with VISION molecular models from 3-Sphere dihedral angles calculated only from vicinal constant coupling are C_1^4 for six and C^3 ($\text{P} = 18[\text{deg}]$) for five membered rings (Table 1, Figure 5). The shape of the six and five membered ring in 2D with sin and tan trigonometric functions (Table 2) predicted a higher biological activity.

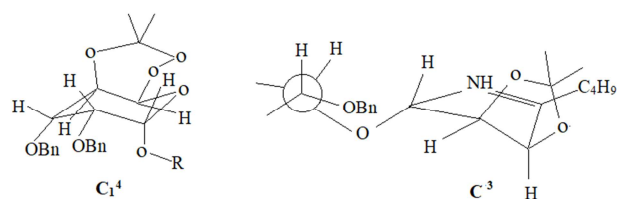


Figure 5. Conformation of 6-O-(7,8-di-O-Benzyl-9,11-O-benzylidene- α -D-galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol 1 simulated with VISION molecular models.

3-Sphere dihedral angles and tetrahedral angles calculated from carbon chemical shift δ_{Cn} [ppm] with Euler - Conic approach (Table 3, entry 2, 5 and Table 7): *As a general rule:* The vicinal coupling constant $^3J_{HH}$ [Hz] established at list the position of ϕ_2 and implicit the values of the tetrahedral angle: *i.e.* if in first two sets angles A and B are placed the tetrahedral angle $\varphi_{Cn} = \theta^{A4}$, internal angle $\gamma_{Cn} = \theta^{A3}$ and angles $\phi_2^N = \theta^{B1}$, θ^{B2} or θ^{A1} , θ^{A2} , with N = D, E or F, G, the dihedral angle θ_{HnHn+1} [deg] and the corresponding vicinal angle ϕ [deg] will be found in D, E or F, G (Table 7, entry 1). Alternatively, dihedral and vicinal angles in sets A or B and

corresponding tetrahedral angle in close relationship with corresponding ϕ_2 . *Trans-ee* stereochemistry has three angles on same set, *i.e.* $\theta^{A1} = \phi_2^D$, $\theta^{A2} = \phi_2^E$, θ_{HnHn+1} [deg] and corresponding tetrahedral angle φ_{Cn} [deg] in set E (Table 7, entry 11).

3-Sphere dihedral angles θ_{HnHn+1} [deg] and corresponding tetrahedral angles φ_{Cn} [deg] calculated from chemical shift δ_X [ppm] (X = ^{13}C , ^1H -RMN) using rectangle as manifold: Two main observation results from Table 5, entry 2 and Table 7: A. in case of six membered ring the relationship between tetrahedral angles and dihedral angle place on first set has at base one or two other unit increased through the $\phi_{1/2}^{U1C}$, $\phi_{1/2}^{U2C}$, with U = C (values of first angle higher as 5[deg]) or U = S (values of first angle smaller as 5[deg]) (Table 7, entry 20); B. in case of five membered ring on seven sets angles with dihedral angle placed in first set (set A), ϕ_2 of set bearing the tetrahedral angle is equal with first or second angle of set A. The unit is build based on calculated dihedral angle, therefore is not build with sin and tan function, but can be transforming the dihedral angle in R_m [radien].

Table 7. Tetrahedral angles φ_{Cn} [deg] calculated with conic and rectangle manifold under unit rule.

| Entry | A | B | C | D | E | F | G |
|-------|-------------------------------|----------------------|------------------------|-----------------------|--------------------------|------------------------|--------------------------|
| 1. | 6 ring - Conic | | | | | | |
| 2. | φ_{C9} [deg] | | | | | | |
| 3. | 2.709 | θ^{B1} 27.290 | 5.418 | 1.354 | 28.645 | 13.645 | 16.354 |
| 4. | 57.291 | θ^{B2} 32.709 | 54.581 | 58.645 | 31.354 | ϕ 46.359 | θ_{HnHn+1} 43.645 |
| 5. | 62.709 | 87.291 | 65.418 | 61.354 | 88.645 | 73.645 | 76.354 |
| 6. | φ_{C9} 117.291 | 92.709 | 114.582 | 118.645 | 91.354 | 106.354 | 103.645 |
| 7. | 122.709 | 147.291 | 125.418 | 121.354 | 148.645 | 133.645 | 136.354 |
| 8. | 177.291 | 152.709 | 174.582 | 178.645 | 151.354 | 166.354 | 163.645 |
| 9. | 5.418 | 54.581 | 10.836 | 2.709 | 57.291 | ϕ_2 27.290 | ϕ_2 32.709 |
| 10. | 27.2903 | 2.709 | 24.581 | 28.645 | 1.374 | 16.354 | 13.645 |
| 11. | φ_{C12} [deg] | | | | | | |
| 12. | 3.156 | θ^{B1} 26.843 | 6.313 | ϕ 1.578 | 28.421 | 13.421 | 16.578 |
| 13. | 56.843 | θ^{B2} 33.157 | 53.686 | 58.421 | 31.578 | 46.578 | 43.421 |
| 14. | 63.157 | 86.843 | 66.314 | 61.576 | θ_{HnHn+1} 88.421 | 73.421 | 76.578 |
| 15. | φ_{C12} 116.843 | 93.157 | 113.686 | 118.421 | 91.578 | 106.578 | 103.421 |
| 16. | 123.157 | 146.843 | 126.311 | 121.578 | 148.421 | 133.421 | 136.578 |
| 17. | 176.843 | 153.156 | 173.686 | 178.421 | 151.578 | 166.578 | 163.421 |
| 18. | 6.313 | 53.686 | 12.629 | 3.156 | 56.843 | ϕ_2 26.843 | ϕ_2 33.156 |
| 19. | 26.843 | 3.156 | 23.686 | 28.421 | 1.578 | 16.572 | 13.421 |
| 20. | Rectangle | | | | | | |
| 21. | 6 ring - φ_{C9} [deg] | | | | | | |
| 22. | 15.879 | 14.12 | θ^{C1C1} 28.24 | θ^{C2B1} 1.76 | | θ^{U2C1} 3.52 | θ^{C3B1} 26.479 |
| 23. | θ_{HnHn+1} 44.12 | ϕ 45.87 | θ^{C1C2} 31.759 | 58.23 | | 56.47 | 33.52 |
| 24. | 75.88 | 74.12 | 88.24 | 61.76 | | 63.52 | 86.47 |
| 25. | 104.12 | 105.88 | 91.759 | φ_{C9} 118.24 | | φ_{C9} 116.479 | 93.52 |
| 26. | 135.88 | 134.12 | 148.24 | 121.76 | | 123.52 | 146.48 |
| 27. | 164.12 | 165.88 | 151.76 | 178.24 | | 176.48 | 153.52 |
| 28. | ϕ_2 31.75 | ϕ_2 28.24 | 56.48 | 3.52 | | 7.04 | 52.954 |
| 29. | 14.12 | 15.87 | 1.758 | 28.23 | | $\phi_{1/2}$ 26.47 | 3.520 |

Tetrahedral angles φ_{Cn} [deg] calculated with conic and rectangle as manifold, from carbon in first case and carbon and proton chemical shift in second case, for C_1^4 and C^3 conformations of six and five membered rings are presented in Table 8. With both methods result in case of tetrahedral angle of C-9 values around 117.29 – 116.479[deg]. The

transformation of φ_{C9} with polyhedron equation (Table 3) from 117.29 to 110.28[deg] in case of conic or from 118.24 to 113.461[deg] in case of rectangle as manifolds gives values of 110.28 and 113.461[deg], but without any correlation between tetrahedral angle φ_{Cn} [deg] and dihedral angle θ_{HnHn+1} [deg].

Table 8. Tetrahedral angles φ_{Cn} [deg] of 1 calculated with conic and rectangle as manifold.

| Entry | Method | φ_{C-9} C_1^4 | φ_{C-10} | φ_{C-11} | φ_{C-12} | φ_{C-13} | φ_{C-2} C_3 | φ_{C-3} |
|-------|-----------|--------------------------------|------------------|----------------------|--------------------|--------------------|--------------------------|-------------------|
| 1. | Conic | 117.291 ^a | 110.592 | 117.293 ^c | 116.843 115.016 | 116.459 114.048 | 101.931 | 107.302 |
| 2. | Rectangle | 118.24 ^b 116.479 | 110.18 | 115.87 | 110.139 115.07 | 117.64 115.29 | 101.392 | 106.155 109.88 |

Polyhedron eq. $\tan\phi/2 = X/2 = 2\sin\theta$: [a] 110.28[deg], [b] 113.461, [c] 110.092[deg].

5. Conclusions

The conformational analysis, the phase angle of the pseudorotation P [deg], was analyzed using 3-Sphere torsional angles and VISION molecular models for 6-O-(7,8-di-O-Benzyl-9,11-O-benzylidene- α -D-galactopyranosyl)-1-butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-*N*-dehydro-L-ribitol 1. Dihedral angles of 1 calculated from carbon chemical shift shown trigonometric equations in 2D under tan and sin function. Iminocyclitol 2 has higher biological activity on 2D under tan functions.

General rules are established for calculation of dihedral and tetrahedral angles from carbon and proton chemical shift or only from vicinal coupling constant with conic or rectangle as manifold. Bond distances of six and five membered rings on 1 are calculated from 3-Sphere-dihedral angles. The wave character of NMR data under 3-Sphere approach giving information about physics properties of five and six membered rings.

Abbreviations

NMR: Nuclear Magnetic Resonance

ND: N Dimension

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Conflicts of Interest

The authors declare no conflicts of interest.

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