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Hypersphere and Antiviral Activity of Three Alkyl Chain Iminocyclitols with D and L Ribitol Stereochemistry

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Abstract: *N*-Alkyl-C_1-dialkyl chains iminocyclitols with D or L-ribitol stereochemistry are synthesized with high diastereoselectivity after Grignard reagents addition to *N*-quaternary pyrrolines salts, and tested for antiviral activity in bovine viral diarrhea virus (BVDV), surrogate for hepatitis C virus (HCV). Dihedral angles are calculated from carbon chemical shift (δ_{Cn}[ppm]) with 3-sphere method without building units. 3-Sphere, a hypersphere in 4D, under Hopf fibration and Lie algebra mathematics theories enable calculation of the dihedral angles from the NMR data (vicinal coupling constant $^3J_{HnHn+1}$[Hz], chemical shift δ_{Cn}[ppm]). Instead of 3D manifold equations on seven sets unit or six sets units are proposed equations between 4D – 2D, in function of the curvature. The relationship between the antiviral activity and the iminocyclitol structure reveals that monoalkyl chain, *N*-n-C_1-dodecyl β-L-ribitol trifloroacetate salt 30 (IC_{50} 1.5 uM) has higher antiviral activity in tangential space, relative to three alkyl chain, *N*-Methyl-C_1-butil, nonyl-L-ribitol. HCl 26 (IC_{50} < 2 uM) with torus and Dupin cyclide coordinate, both with coordinates in 2D. Three alkyl chain isopropylidene protected pyrrolidine 25 has in 4D with all equations for calculation of the dihedral angles, and in protected pyrroline 19b double bond moves the coordinates in 2D.

Keywords: Grignard Addition, Pyrroline, *N*-quaternary Pyrrolines Salts, Pyrrolidine, *N*-Alkyl-C_1-dialkyl Chains Iminocyclitols, Hypersphere, Dihedral Angles, Vicinal Coupling Constants $^3J_{HH}$ [Hz]

1. Introduction

Five membered ring iminocyclitols possessing alkyl substituents are known to be potent antiviral compounds analog to six membered ring [1-4]. Recently we published a facile synthesis of five membered *N*, C_1-dialkyl iminocyclitols. [5] The antiviral activity of C_1 monoalkyl and *N*, C_1 dialkyl analogues was evaluated in the bovine viral diarrhea virus assay (BVDV).

Presence of both, *N*-alkyl group as well as only C_1-alkyl group enhanced antiviral activity. The key step in our synthesis is the rearrangement *exo*-imino to *endo*-iminocyclitol via intramolecular 5-*exo*-*tet* ring opening of the epoxide with inversion of configuration at C_4, where the L-lyxo sugar (A) is converted to the D-ribo 1-*N*-pyrroline (B) [5], usefully synthon for synthesis *N*, C_1 dialkyl or trialkyl analogs (Figure 1). A second advantage, C_1 alkyl chains installed in an earlier stage overcome secondary reaction, *i.e.* dimerization and trimerization of C_1-unsubstituted 1-*N*-pyrrolines. [6]

3-Sphere, a hypersphere in 4 dimensions, enable calculation dihedral angles from vicinal coupling constant [7] and carbon or/and proton chemical shift [8] under unit rule [9, 10] or without unit [11]. The sign of the dihedral angle result certainly from vicinal coupling constant and the stereochemistry from unit build from chemical shift. The relationship between the structure of the iminocyclitols and the antiviral activity can be analyzed with hypersphere equations established for calculation of the dihedral angles without building unit [11]. The main question, the tangential

space or N dimension space indicate higher biological activity along the stereochemistry of iminocyclitol?

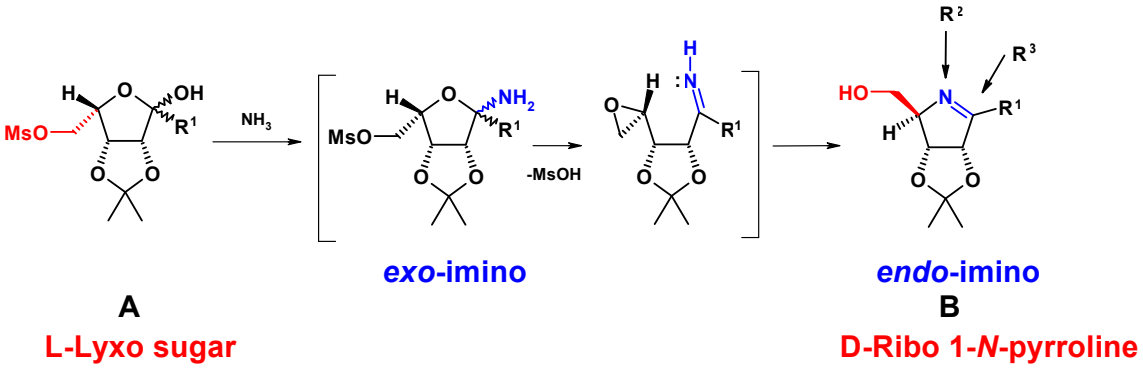


Figure 1. *Basic reaction for rearrangement exo-imino to endo-iminocyclitol.*

2. Method

2.1. Synthesis of N-Alkyl-C$_1$-dialkyl Chains Iminocyclitols with D or L-ribitol Stereochemistry

Melting points were determined using a Fisher Johns apparatus and are uncorrected. ^{1}H NMR spectra are determinates with Bruker spectrometer of 400 MHz or 500 MHz. ^{13}C NMR spectra are recorded with a Bruker spectrometer of 75 MHz. Infrared spectra are recorded on Genesis Services FTIR spectrometers.

D-Ribose and D-xylose were purchased from Sigma-Aldrich. 5-O-Methanesulfonyl-2,3-O-isopropylidene-L-lyxono-1,4-lactone [35] (1a) was prepared from D-ribose. D-Lyxose (D-Lyxopyranose) was converted into D-lyxofuranose-2,3-O-isopropylidene with acetone in the presence of catalytic amount of H_2SO_4. Oxidation of the anomeric hydroxyl group followed by mesylation of the primary alcohol gave 5-O-methanesulfonyl-2,3-O-isopropylidene-D-lyxonolactone (16b). [5] Analytical data for 5-O-metansulfonyl-2,3-isopropylidene-lyxose 2a: 3a, 2c: 3c, 2d: 3d and imines 4a, 4c, 4d are presented in our first communication. [5]

2.1.1. General Procedure for Grignard Addition to 5-O-Mesyloxy-1,4-lactones

The isopropylidene protected 5-O-mesyloxy-1,4-lactone (1 eq) was dissolved in THF anhydrous under Ar, and cooled to – 77°C. Maintaining the temperature between –50°C ~ – 40°C, the Grignard reagent (1.5 eq) was added and stirred over 30 min. The temperature was allowed to warm to 0°C and the solution was stirred 1 - 2 h. After quenching with saturated aqueous NH_4Cl the mixture was extracted with ethyl acetate. The combined extracts were washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, filtered and evaporated under vacuo. The crude product results as a stereoisomeric mixture at the anomeric position.

1-α-Ethyl-5-O-methanesulfonyl-2,3-O-isopropylidene-L-lyxose 2b: 1-β-Ethyl-5-O-methanesulfonyl-2,3-O-isopropylidene-L-lyxose 3b. Colorless crystals (87 %), mp 71 – 74 ^{0}C. Ratio of isomers α:β ~ 14:86. IR: ν_{max}(neat)/cm^{-1} KBr 3488.26, 2981.94, 2941.77, 1460.39, 1352.19, 1265.01, 1211.97, 1171.55, 1083.66

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3b: 4.83 (dd, $J_{3,2}$ = 5.8 Hz, $J_{3,4}$ = 3.7 Hz, 1H, H-3), 4.47 – 4.43 (m, 2H, H-5', H-2), 4.33 - 4.29 (m, 2H, H-4 and H-5), 3.02 (s, 3H, CH_3SO_2), 1.89 – 1.66 (m, 2H, CH_2), 1.41 and 1.26 (2s, 6H, 2CH_3), 0.98 (t, 3H, J = 7.5 Hz, CH_3); 2b: 4.78 (dd, $J_{3,2}$ = 6.0 Hz, $J_{3,4}$ = 4.0 Hz, 1H, H-3), 3.88 (m, 1H, H-4), 3.03 (s, 3H, CH_3SO_2), 1.50, 1.34 (2s, 6H, CH_3-7, CH_3-8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 3b: 112.8 (C-6), 107.6 (C-1), 84.3 (C-2), 80.1 (C-3), 76.4 (C-4), 68.5 (C-5), 37.4 (CH_3SO_2), 28.0 (CH_2), 25.9, 24.6 (CH_3-7, CH_3-8), 7.78 (CH_3); 2b: 113.6 (C-6), 104.8 (C-1), 81.1 (C-2), 79.7 (C-3), 73.8 (C-4), 68.3 (C-5), 37.5 (CH_3SO_2), 14.1 (CH_3).

1-α-Decyl-5-O-methanesulfonyl-2,3-O-isopropylidene-L-lyxose 2e: 1-β-Decyl-5-O-methanesulfonyl-2,3-O-isopropylidene-L-lyxose 3e. Colorless oil (85 %). Ratio of isomers α:β ~ 14:86.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3e: 4.82 (dd, $J_{3,2}$ = 5.8 Hz, $J_{3,4}$ = 3.6 Hz, 1H, H-3), 4.50 – 4.4 (m, 2H, H-5', H-2), 4.40 – 4.33 (m, 2H, H-4, H-5), 3.06 (s, 3H, CH_3SO_2), 1.69 – 1.24 (m, 24H, 9CH_2, CH_3-7, CH_3-8), 0.88 (tl, 3H, CH_3); 3e: 4.78 (dd, $J_{3,2}$ = 6.0 Hz, $J_{3,4}$ = 3.8 Hz, H-3), 3.07 (s, 3H, CH_3SO_2).

1-α-Methyl-5-O-methanesulfonyl-2,3-O-isopropylidene-D-lyxose 17a:1-β-Methyl-5-O-methanesulfonyl-2,3-O-isopropylidene-D-lyxose 18a. Colorless oil (80 %). Ratio of isomers α:β ~ 73:26. $C_{10}H_{18}O_7S$, M = 282.31.

IR: ν_{max}(neat)/cm^{-1} KBr 3470.18, 2985.14, 2939.49, 1458.26, 1355.59, 1211.90, 1172.18, 1075.67

^{1}H-NMR (400 MHz, $CDCl_3$) δ 17a: 4.83 (dd, $J_{3,2}$ = 5.8 Hz, $J_{3,4}$ = 3.7 Hz, 1H, H-3), 4.51 (dd, $J_{5',5}$ = 10.0 Hz, $J_{5',4}$ = 2.9 Hz, 1H, H-5'), 4.48 (d, $J_{2,3}$ = 5.8 Hz, 1H, H-2), 4.41 - 4.32 (m, 2H, H-4 and H-5), 3.06 (s, 3H, CH_3SO_2), 1.54 (s, 3H, CH_3), 1.47, 1.31 (2s, 6H, CH_3-7, CH_3-8); 18a: 4.78 (dd, $J_{3,2}$ = 6.1 Hz, $J_{3,4}$ = 3.9 Hz, 1H, H-3), 4.52 – 4.45 (m, 1H, H-5'), 4.40 – 4.32 (m, 1H, H-2), 4.41 - 4.32 (m, 1H, H-5), 3.92 (m, 1H, H-4), 3.07 (s, 3H, CH_3SO_2), 1.54, 1.36 (2s, 6H, CH_3-7, CH_3-8), 1.41 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 17a: 112.9 (C-6), 107.3 (C-1), 85.2 (C-2), 80.4 (C-3), 76.7 (C-4), 68.1 (C-5), 37.5 (CH_3), 26.0, 25.7 (CH_3-7, CH_3-8), 22.4 (CH_3).

1-α-Butyl-5-O-methanesulfonyl-2,3-O-isopropylidene-D-lyxose 17b:1-β-Butyl-5-O-methanesulfonyl-2,3-O-isopropylidene-D-lyxose 18b. Colorless oil (82 %). Ratio of isomers α:β ~ 69:31. $C_{13}H_{24}O_7S$, M = 324.4. Calcd for $C_{13}H_{24}O_7S$ $(M + Na)^+$ 347.11407, found 347.1143.

IR: ν_{max}(neat)/cm^{-1} KBr 3492.47, 2948.42, 2871.20, 1681.63, 14560.46, 1355.60, 1211.04, 1174.07, 1096.21, 965.98

^{1}H-NMR (400 MHz, $CDCl_3$) δ 17b: 4.83 (dd, $J_{3,2}$ = 5.8 Hz, $J_{3,4}$ = 3.8 Hz, 1H, H-3), 4.53 – 4.32 (m, 4H, H-2, H-4, H-5', H-5), 3.06 (s, 3H, CH_3SO_2), 1.88 – 1.68 (m, 2H, CH_2), 1.46, 1.30 (2s, 6H, CH_3-7, CH_3-8), 1.45 –1.34 (m, 4H, CH_2), 0.91 (m, 3H, CH_3); 18b: 4.77 (dd, $J_{3,2}$ = 5.9 Hz, $J_{3,4}$ = 4.1 Hz, 1H, H-3), 4.53 – 4.32 (m, 3H, H-2, H-5', H-5), 3.93 (m, 1H, H-4), 3.07 (s, 3H, CH_3SO_2), 1.54, 1.36 (2s, 6H, CH_3-7, CH_3-8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 17b: 112.9 (C-6), 107.3 (C-1), 84.6 (C-2), 80.1 (C-3), 76.4 (C-4), 68.4 (C-5), 37.5 (CH_3SO_2), 34.9, 24.8, 22.9 ($3CH_2$), 26.0, 25.4 (CH_3-7, CH_3-8), 14.0 (CH_3); 18b: 113.8 (C-6), 104.8 (C-1), 79.7 (C-3), 73.9 (C-4), 68.4 (C-5), 37.6 (CH_3SO_2), 25.8, 24.6 (CH_3-7, CH_3-8), 13.8 (CH_3).

1-α-Nonyl-5-O-methanesulfonyl-2,3-O-isopropylidene-D-lyxose 17c: 1-β-Nonyl-5-O-methanesulfonyl-2,3-O-isopropylidene-D-lyxose 18c. Colorless oil (86 %). Ratio of isomers α:β ~ 77:33. $C_{18}H_{34}O_7S$, M = 394.5. Calcd for $C_{18}H_{34}O_7S$ $(M + Na)^+$ 417.19232, found 417.1934.

IR: ν_{max}(neat)/cm^{-1} KBr 3490.73, 2925.18, 1694.86, 1460.50, 1357.75, 1172.23, 1097,1, 991.74.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 17c: 4.80 (dd, $J_{3,2}$ = 5.8 Hz, $J_{3,4}$ = 3.6 Hz, 1H, H-3), 4.49 – 4.30 (m, 4H, H-2, H-4, H-5', H-5), 3.04 (s, 3H, CH_3SO_2), 1.99 – 1.64 (m, 2H, CH_2), 1.56 – 1.19 (m, 14H, $7CH_2$), 1.42, 1.28 (2s, 6H, CH_3-7, CH_3-8), 0.86 (m, 3H, CH_3); 18c: 4.76 (dd, 1H, H-3), 4.49 – 4.32 (m, 3H, H-2, H-5', H-5), 3.93 (m, 1H, H-4), 3.05 (s, 3H, CH_3SO_2), 1.53, 1.36 (2s, 6H, CH_3-7, CH_3-8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 17c: 112.9 (C-6), 107.3 (C-1), 84.6 (C-2), 80.1 (C-3), 76.3 (C-4), 68.4 (C-5), 37.4 (CH_3SO_2), 35.3, 35.1, 31.9, 29.8, 29.7, 29.5, 29.3, 23.3, 22.6 ($8CH_2$), 26.0, 24.6 (CH_3-7, CH_3-8), 14.1 (CH_3); 18c: 81.3 (C-2), 79.7 (C-3), 73.9 (C-4), 63.0 (C-5), 37.4 (CH_3SO_2).

2.1.2. General Procedure for Imines Formation

The Grignard product (1.0 mmol) was dissolved in NH_3 (25 ml) and aq EtOH (10 ml). The solution was allowed to stand 2 - 4 days at room temperature in a sealed flask. The solvent was removed under reduced pressure, and the residue was dissolved in ethanol and dried over Na_2SO_4 and filtered. Evaporation of the filtrate under vacuo afforded the crude product which was purified by silica gel column chromatography (solvent ethyl acetate), resulting imines as colorless crystalline products.

1-Ethyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-D-ribitol, ((2S, 3R, 4R)-1-ethyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 4b. Colorless crystals, mp 134°C (39 %). $C_{10}H_{17}NO_3$, M = 199.25; MS m/z 200.2 (M + H); calcd for $C_{10}H_{17}NO_3$ $(M + H)^+$ 200.12812, found 200.12805.

IR: ν_{max}(neat)/cm^{-1} KBr 3174.80, 2976.39, 2933.15, 2848.14, 1644.65, 1452.03, 1374.97

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.95 (d, $J_{2,3}$ = 5.6 Hz, 1H, H-2), 4.55 (d, $J_{3,2}$ = 5.6 Hz, 1H, H-3), 4.20 (bl, 1H, H-4), 3.80 (dd, $J_{5',5}$ = 11.4 Hz, $J_{5',4}$ = 3.4 Hz, 1H, H-5'), 3.72 (dd, $J_{5',5}$ = 11.4 Hz, $J_{5,4}$ = 3.5 Hz, 1H, H-5), 2.58 – 2.35 (m, 2H, CH_2), 1.35 (bs, 6H, CH_3-7, CH_3-8), 1.19 (t, 3H, J = 7.5 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.0 (C-1), 111.6 (C-6), 86.3 (C-2), 80.5 (C-3), 77.6 (C-4), 62.8 (C-5), 25.7 (CH_3-7, CH_3-8), 24.2 (CH_2), 16.9 (CH_3).

1-Decyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-D-ribitol ((2S, 3R, 4R)-1-decyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 4e. Colorless crystals, mp 87 – 88°C (25 %). $C_{18}H_{33}NO_3$, M = 311.46; MS m/z 312.3 (M + H); calcd for $C_{18}H_{33}NO_3$ $(M + H)^+$ 312.2539, found 312.2536.

IR: ν_{max}(neat)/cm^{-1} KBr 3178.71, 2994.34, 2918.56, 2848.94, 1646.72, 1590.03, 1463.52, 1380.01, 1206.84

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.95 (d, $J_{2,3}$ = 5.6 Hz, 1H, H-2), 4.58 (d, $J_{3,2}$ = 5.6 Hz, 1H, H-3), 4.21 (m, 1H, H-4), 3.83 (dd, $J_{5',5}$ = 11.4 Hz, $J_{5',4}$ = 3.4 Hz, 1H, H-5'), 3.78 (dd, $J_{5',5}$ = 11.4 Hz, $J_{5,4}$ = 3.5 Hz, 1H, H-5), 2.48 – 2.42 (m, 2H, CH_2), 1.69 – 1.61 (m, 2H, CH_2), 1.36– 1.26 (m, 14H, $7CH_2$), 1.36, 1.35 (2s, 6H, CH_3-7, CH_3-8), 0.88 (t, J = 7.0 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.5 (C-1), 111.8 (C-6), 86.6 (C-2), 80.7 (C-3), 77.8 (C-4), 63.0 (C-5), 32.1, 31.4, 29.8, 29.6, 29.5, 27.1, 22.9 ($9CH_2$), 26.2, 25.8 (CH_3-7, CH_3-8), 14.3 (CH_3).

1-Methyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol ((2R, 3S, 4S)-1-Methyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 19a. Colorless crystals, mp. 104 - 5°C (33 %). $C_9H_{15}NO_3$, M = 185.22: MS m/z 186.1 (M + H); calcd for $C_9H_{15}NO_3$ $(M + H)^+$ 186.11247, found 186.11242.

IR: ν_{max}(neat)/cm^{-1} KBr 3222.11, 2985.98, 2933.07, 2865.49, 1653.33, 1444.90, 1375.65, 1207.01, 1077.78

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.85 (d, $J_{2,3}$ = 5.3 Hz, 1H, H-2), 4.55 (d, $J_{3,2}$ = 5.3 Hz, 1H, H-3), 4.11 (m, 1H, H-4), 3.80 (dd, $J_{5',5}$ = 11.6 Hz, $J_{5',4}$ = 3.1 Hz, 1H, H-5'), 3.72 (dd, $J_{5',5}$ = 11.6 Hz, $J_{5,4}$ = 3.2 Hz, 1H, H-5), 2.05 (d, 3H, CH_3), 1.31 (bs, 6H, CH_3-7, CH_3-8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.0 (C-1), 111.7 (C-6), 87.2 (C-2), 80.7 (C-3), 77.9 (C-4), 62.2 (C-5), 25.7 (CH_3-7, CH_3-8), 16.9 (CH_3).

1-Butyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol ((2R, 3S, 4S)-1-butyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 19b. Colorless crystals, mp 115 -116°C (34 %). $C_{12}H_{21}NO_3$, M = 227.3: MS m/z 228.3 (M + H); calcd for $C_{12}H_{21}NO_3$ $(M + H)^+$ 228.15942, found 228.15939.

IR: ν_{max}(neat)/cm^{-1} KBr 3183.91, 2987.21, 2935.14, 2863.79, 1648.84, 1457.93, 1378.86, 1213.01, 1078.01.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.94 (d, $J_{2,3}$ = 5.5 Hz, 1H, H-2), 4.58 (d, $J_{3,2}$ = 5.5 Hz, 1H, H-3), 4.17 (m, 1H, H-4), 3.85 (dd, $J_{5',5}$ = 11.4 Hz, $J_{5',4}$ = 3.3 Hz, 1H, H-5'), 3.77 (dd,

$J_{5',5}$ = 11.4 Hz, $J_{5,4}$ = 3.4 Hz, 1H, H-5), 2.49 – 2.42 (m, 2H, CH_2), 1.68 – 1.59 (m, 2H, CH_2), 1.41– 1.30 (m, 2H, CH_2), 1.37 and 1.36 (2s, 6H, CH_3-7, CH_3-8), 0.93 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.1 (C-1), 111.6 (C-6), 86.4 (C-2), 80.4 (C-3), 77.4 (C-4), 62.8 (C-5), 30.8, 28.1, 22.6 ($3CH_2$), 26.8, 25.6 (CH_3-7, CH_3-8), 13.8 (CH_3).

1-Nonyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol ((2R, 3S, 4S)-1-nonyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 19c. Colorless crystals, mp 93 -94°C (29 %). $C_{17}H_{31}NO_3$, M = 297.24.

IR: ν_{max}(neat)/cm^{-1} KBr 3191.70, 2919.54, 2849.88, 1647.47, 1458.88, 1376.67, 1208.82, 1078.34

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.93 (d, $J_{2,3}$ = 5.6 Hz, 1H, H-2), 4.57 (d, $J_{3,2}$ = 5.6 Hz, 1H, H-3), 4.18 (m, 1H, H-4), 3.84 (dd, $J_{5',5}$ = 11.4 Hz, $J_{5',4}$ = 3.4 Hz, 1H, H-5'), 3.76 (dd, $J_{5',5}$ = 11.4 Hz, $J_{5,4}$ = 3.5 Hz, 1H, H-5), 2.48 – 2.38 (m, 2H, CH_2), 1.67 – 1.124 (m, 14H, $7CH_2$), 1.34, 1.33 (2s, 6H, CH_3-7, CH_3-8), 0.86 (t, J = 7.4 Hz, 3H, CH_3).

2.1.3. Synthesis of Iminium Salts

To a solution of imines (1 eq) in CH_2Cl_2 anhydrous was added alkyl halides (2 eq). The mixture was allowed to stand 2 - 4 days at room temperature in a sealed flask. The reaction was monitoring by TLC (EtOAc:EtOH 7:3). After evaporation of the solvent afforded the iminium salts as an oil used directly in the Grignard reaction.

1-Methyl-N-methiodide-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-D-ribitol, ((2S, 3R, 4R)-1-methyl-N-methiodide-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 5a Colorless crystals, mp 185 - 187^{0}C $C_{10}H_{18}NO_3$, M = 200.1; MS m/z 200.2 (M^+); calcd for $C_{10}H_{18}NO_3$ (M^+) 200.12812, found 200.12804.

IR: ν_{max}(neat)/cm^{-1} KBr 3287.04, 2969.31, 2929.16, 2870.31, 1662.92, 1451.58, 1379.51, 1224.46, 1108.75, 1068.08

^{1}H-NMR (400 MHz, DMSO-d_6) 5.39 (d, 1H, $J_{3,2}$ = 5.1 Hz, H-3), 4.84 (d, 1H, $J_{2,3}$ = 5.1 Hz H-2), 4.95 (m, 1H, H-4), 3.84 (sl, 2H, H-5', H-5), 3.55 (s, 3H, N-CH_3), 3.33 (s, 3H, CH_3), 1.34, 1.32 (2s, 6H, CH_3-7, CH_3-8).

^{13}C-NMR (75 MHz, DMSO-d_6) δ 188.3 (C-1), 112.3 (C-6), 84.9 (C-3), 79.7 (C-2), 77.6 (C-4), 57.4 (C-5), 36.7 (N-CH_3), 27.0, 25.6 (CH_3-7, CH_3-8), 15.9 (CH_3).

^{1}H-NMR (400 MHz, CD_3OD) δ 5.43 (d, 1H, $J_{3,2}$ = 5.1 Hz, H-3), 4.93 (d, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 4.52 (m, 1H, H-4), 4.27 (d, 1H, $J_{5',5}$ = 12.6 Hz, $J_{5',4}$ = 2.3 Hz, H-5'), 3.93 (d, 1H, $J_{5,5'}$ = 12.6 Hz, $J_{5,4}$ = 2 Hz, H-5), 3.85 (s, 3H, N-CH_3), 2.77 (s, 3H, CH_3), 1.39, 1.37 (2s, 6H, CH_3-7, CH_3-8).

^{13}C-NMR (75 MHz, CD_3OD) δ 112.7 (C-6), 85.0 (C-3), 80.1 (C-2), 77.6 (C-4), 57.0 (C-5), 35.6 (N-CH_3), 25.6, 23.9 (CH_3-7, CH_3-8), 20.7 (CH_3).

1-Butyl-N-methiodide-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-D-ribitol, ((2S, 3R, 4R)-1-butyl-N-methiodide-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 5c $C_{13}H_{24}NO_3$, M = 242.34; MS m/z 242.3 (M^+); calcd for $C_{13}H_{24}NO_3$ ($M^{+)}$ 242.17507, found 242.17496.

IR: ν_{max}(neat)/cm^{-1} KBr 3278.85, 2958.08, 2933.55, 1670.02, 1462.29, 1381.3, 1214.76, 1070.93

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.47 (d, 1H, $J_{3,2}$ = 5.1 Hz, H-3), 4.95 (d, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 4.71 (m, 1H, H-4), 4.30 (dd, 1H, $J_{5',5}$ = 13.4 Hz, $J_{5',4}$ = 1.5 Hz, H-5'), 3.94 (dd, 1H, $J_{5',5}$ = 13.4 Hz, $J_{5',4}$ = 1.4 Hz, H-5), 3.84 (s, 3H, N-CH_3), 3.01 – 2.81 (m, 2H, CH_2), 1.92 – 1.76 (m, 2H, CH_2), 1.55 - 1.42 (m, 2H, CH_2), 1.40, 1.36 (2s, 6H, CH_3-7, CH_3-8), 0.97 (t, 3H, J = 7.3, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.2 (C-1), 112.7 (C-6), 84.25 (C-3), 80.3 (C-4), 77.1 (C-2), 56.6 (C-5), 38.9 (N-CH_3), 30.3, 27.3 ($2CH_2$), 26.6, 25.0 (CH_3-7, CH_3-8), 22.9 (CH_2), 13.5 (CH_3).

1-Octyl-N-methiodide-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-D-ribitol, ((2S, 3R, 4R)-1-octyl-N-methiodide-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 5d $C_{17}H_{32}NO_3$, M = 298.44; MS m/z 298.3 (M^+); calcd for $C_{17}H_{32}NO_3$, $(M)^+$ 298.23767, found 298.23758.

IR: ν_{max}(neat)/cm^{-1} KBr 3293.54, 2928.92, 2861.46, 1786.86, 1728.21, 1669.63, 1538.67, 1457.73, 1378.80, 1218.26, 1074.02

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.45 (d, 1H, $J_{3,2}$ = 5.1 Hz, H-3), 4.94 (d, 1H, $J_{3,2}$ = 5.1 Hz, H-2), 4.58 (m, 1H, H-4), 4.26 (d, 1H, $J_{5',5}$ = 12.6 Hz, H-5'), 3.94 (d, 1H, $J_{5,5'}$ = 12.6 Hz, H-5), 3.81 (s, 3H, N-CH_3), 2.95 – 2.83 (m, 2H, CH_2), 1.92 – 1.78 (m, 2H, CH_2), 1.63 – 1.25 (m, 12H, $6CH_2$), 1.40, 1.36 (2s, 6H, CH_3-7, CH_3-8), 0,84 (bt, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.2 (C-1), 112.8 (C-6), 84.3 (C-3), 80.3 (C-2), 77.4 (C-4), 56.6 (C-5), 38.8 (N-CH_3), 31.7, 30.5, 29.7, 28.9, 26.6, 25.5, 25.0, 22.5 ($7CH_2$, CH_3-7, CH_3-8), 14.1 (CH_3).

1-Methyl-N-ethiodide-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-L-ribitol, ((2R, 3S, 4S)-1-methyl-N-ethiodide-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline) 20 $C_{11}H_{20}NO_3$, M = 214.28; MS m/z 214.3 (M^+); calcd for $C_{11}H_{20}NO_3$ (M^+) 214.14377, found 214.14371.

IR: ν_{max}(neat)/cm^{-1} KBr 3308.39, 2981.88, 2933.15, 2884.66, 1665.87, 1452.92, 1383.11, 1216.39, 1069.87, 868.51

^{1}H-NMR (400 MHz, CD_3OD) δ 5.46 (d, 1H, $J_{3,2}$ = 5.0 Hz, H-3), 4.95 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-3), 4.79 (m, 1H, H-4), 4.21 – 3.96 (m, 3H, CH_2, H-5', H-5), 1.94 (s, 3H, N-CH_3), 1.40 (m, 9H, CH_3, CH_3-7, CH_3-8).

^{13}C-NMR (75 MHz, CD_3OD) δ 112.5 (C-6), 85.1 (C-3), 77.8 (C-2), 77.6 (C-4), 57.4 (N-CH_2), 44.4 (C-5), 26.0, 24.2 (CH_3-7, CH_3-8), 20.8 (CH_3), 11.0 (CH_3).

1-Methyl-N-benzyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-1-N-dehydro-D-ribitol bromine salt, ((2S, 3R, 4R)-1-methyl-N-benzyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroline bromine salt) **27** $C_{16}H_{21}NO_3$, M = 276.3; MS m/z 276.2 (M^+); calcd for $C_{16}H_{21}NO_3$ (M^+) 276.15942, found 276.15934.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H, Ph), 5.50 – 5.46 (m, 2H, H-3, ACH_2), 5.18 (d, 1H, $J_{A,B}$ = 15.6 Hz, BCH_2), 4.86 (d, 1H, $J_{3,2}$ = 4.9 Hz, H-2), 4.39 (m, 1H, H-4), 4.27 (d, 1H, $J_{5',5}$ = 13.3 Hz, H-5'), 3.84 (d, 1H, $J_{5,5'}$ = 12.3 Hz, H-5), 2.77 (s, 3H, CH_3), 1.33 (2s, 6H, CH_3-7 and CH_3-8).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 189.7 (C-1), 129.9, 129.7, 127.9 (Ph), 112.6 (C-6), 85.4 (C-3), 78.4 (C-2), 77.6 (C-4), 57.3 (N-CH_2), 53.8 (C-5), 26.6, 25.1 (CH_3-7, CH_3-8), 22.6 (CH_3).

Synthesis of N-R^2-1-α-R^1-1-β-R^3-2,3-isopropylidene-1,4-imino-1,4-dideoxy-ribitol:

To a solution of iminium salts (1 eq) in (5 ml) CH_2Cl_2 anhydrous under Ar the Grignard reagent (2 eq) was added at rt carefully. The mixture was stirred at rt 4 - 8 h. After quenching with saturated aqueous NH_4Cl the mixture was extracted with ethyl acetate. The combined extracts were washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, and filtered. Evaporation of the filtrate under vacuo afforded the crude product as an oil.

N-Methyl-1-α-methyl-1-β-vinyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-methyl-1-β-vinyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 6a Colorless oil (24 %). $C_{12}H_{21}NO_3$, M = 227.31; MS m/z 228.2 (M + H$^-$); calcd for $C_{12}H_{21}NO_3$ (M + H)$^+$ 228.15942, found 228.15937.

IR: ν_{max}(neat)/cm^{-1} KBr 3440.4, 2977.6, 2935.1, 2869.6, 1727.9, 1639.2 1461.8, 1376.9, 1261.2, 1207.2, 1153.2, 1068.4, 863.9.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.75 (m, 1H, -CH=CH_2), 5.18 (bs, 1H, -CH=CH_2), 5.15 (d, 1H, J = 9.1 Hz, CH_2=), 4.65 (dd, 1H, $J_{3,2}$ = 7.4 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.19 (d, 1H, $J_{2,3}$ = 7.4 Hz, H-2); 3.75 (dd, 1H, $J_{5',5}$ = 11.3 Hz, $J_{5',4}$ = 2.7 Hz, H-5$^{'}$), 3.70 (d, 1H, $J_{5,5'}$ = 11.3 Hz, H-5), 2.83 (m, 1H, H-4), 2.13 (s, 3H, N-CH_3), 1.51, 1.32 (2s, 6H, CH_3-7, CH_3-8), 1.06 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 115.0 (-CH=CH_2), 113.7 (C-6), 85.3 (C-2), 80.8 (C-3), 67.7 (C-4), 59.3 (C-5), 31.7 (N-CH_3), 24.9, 25.5 (CH_3-7, CH_3-8), 11.47 (CH_3).

N-Methyl-1-α-methyl-1-β-allyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-methyl-1-β-allyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 6b Colorless oil (17 %). $C_{13}H_{23}NO_3$, M = 241.33; MS m/z 242.3 (M + H$^-$); calcd for $C_{13}H_{23}NO_3$ (M + H)$^+$ 242.17507, found 242.17496.

IR: ν_{max}(neat)/cm^{-1} KBr 3443.3, 2978.4, 2930.9, 2874.9, 1635.0 1456.6, 1376.5, 1262.4, 1205.2, 1156.1, 1072.5, 862.0.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.79 (m, 1H, -CH=CH_2), 5.12 (bs, 1H, -CH=CH_2), 5.08 (dd, 1H, J = 3.5 Hz; J = 0.95 Hz, -CH=CH_2), 4.57 (dd, 1H, $J_{3,2}$ = 7.5 Hz, $J_{3,4}$ = 3.8 Hz, H-3), 4.27 (d, 1H, $J_{3,2}$ = 7.5 Hz, H-2), 3.73 (dd, 1H, $J_{5',5}$ = 11.1 Hz, $J_{5',4}$ = 2.9 Hz, H-5$^{'}$), 3.66 (d, 1H, $J_{5,5'}$ = 11.08 Hz, H-5), 2.77 (m, 1H, H-4), 2.31 – 2.16 (m, 1H, CH_2), 2.18 (s, 3H, N-CH_3), 1.49, 1.33 (2s, 6H, CH_3-7, CH_3-8), 0.9 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 133.7 (-CH=CH_2), 118.0 (-CH=CH_2), 113.3 (C-6), 82.7 (C-2), 80.4 (C-3), 67.7 (C-4), 65.3 (C-1), 59.3 (C-5), 43.6 (CH_2), 31.0 (N-CH_3), 24.9, 25.6 (CH_3-7, CH_3-8), 14.65 (CH_3).

N-Methyl-1-dimethyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-dimethyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 6c Colorless oil (50 %). $C_{11}H_{21}NO_3$, M = 215.29.

IR: ν_{max}(neat)/cm^{-1} KBr 3452.7, 2975.54, 2932.86, 2873.77, 2802.75, 1689.41, 1653.66, 1462.72, 1376.37, 1257.33, 1205.67, 1068.69, 865.52

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.58 (dd, 1H, $J_{3,2}$ = 7.5 Hz, $J_{3,4}$ = 3.8 Hz, H-3), 4.08 (d, 1H, $J_{2,3}$ = 7.5 Hz, H-2), 3.71 (dd, 1H, $J_{5',5}$ = 11.1 Hz, $J_{5',4}$ = 2.9 Hz, H-5'), 3.66 (dd, 1H, $J_{5,5'}$ = 11.1 Hz, $J_{4,5}$ = 1.3 Hz, H-5), 2.72 (m, 1H, H-4), 2.14 (s, 3H, CH_3), 1.48, 1.32 (2s, 6H, CH_3-7, CH_3-8), 1.15 (s, 3H, CH_3); 0.93 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 113.4 (C-6), 85.9 (C-2), 80.5 (C-3), 67.8 (C-4), 63.2 (C-1), 59.3 (C-5), 31.1 (N-CH_3), 26.9 (CH_3), 25.6, 24.9 (CH_3-7, CH_3-8), 15.0 (CH_3).

N-Methyl-1-α-butyl-1-β-methyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-methyl-1-β-butyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 6d Colorless oil (18 %). $C_{14}H_{27}NO_3$, M = 257.38: MS m/z 258.3 (M + H$^-$); calcd for $C_{14}H_{27}NO_3$ (M + H)$^+$ 258.20637, found 258.20635.

IR: ν_{max}(neat)/cm^{-1} KBr 3450.04, 2935.14, 2865.71, 2804.00, 1648.84, 1461.78, 1376.93, 1257.36, 1207.22, 1159.01, 1078.01

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.63 (dd, 1H, $J_{3,2}$ = 7.6 Hz, $J_{3,2}$ = 3.8 Hz, H-3), 4.25 (d, 1H, $J_{2,3}$ = 7.6 Hz, H-2), 3.78 (dd, 1H, $J_{5',5}$ = 11.0 Hz, $J_{5',4}$ = 3.0 Hz, H-5'), 3.72 (m, 1H, H-5), 2.82 (m, 1H, H-4), 2.19 (s, 3H, N-CH_3), 1.66-1.28 (m, 6H, 3CH_2), 1.55, 1.39 (2s, 6H, CH_3-7, CH_3-8), 0.99 (s, 6H, 2CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 113.3 (C-6), 83.6 (C-2), 80.5 (C-3), 67.7 (C-4), 65.5 (C-1), 59.3 (C-5), 39.5 (CH_2), 31.2 (N-CH_3), 26.1, 23.4 (2CH_2), 25.6, 24.9 (CH_3-7, CH_3-8), 14.1 (2CH_3).

N-Methyl-1-α-methyl-1-β-nonyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-methyl-1-β-nonyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 6e Colorless oil (19 %). $C_{19}H_{37}NO_3$, M = 327.51; MS m/z 328.28 (M + H$^-$); calcd for $C_{19}H_{37}NO_3$ (M + H)$^+$ 328.28462, found 328.28439.

IR: ν_{max}(neat)/cm^{-1} KBr 3424.68, 2925.45, 2856.04, 1595.45, 1459.59, 1375.79, 1204.08, 1070.91, 864.57

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.56 (dd, 1H, $J_{3,2}$ = 7.6 Hz, $J_{3,4}$ = 3.7 Hz, H-3), 4.17 (d, 1H, $J_{2,3}$ = 7.6 Hz, H-2), 3.71 (dd, 1H, $J_{5',5}$ = 11.1 Hz, $J_{5',4}$ = 2.8 Hz, H-5'), 3.65 (d, 1H, $J_{5,5'}$ = 11.1 Hz, H-5), 2.75 (m, 1H, H-4), 2.13 (s, 3H, N-CH_3), 1.49, 1.32 (2s, 6H, CH_3-7, CH_3-8), 1.58-1.26 (m, 15H, 8CH_2), 0.92 (s, 3H, CH_3), 0.87 (t, 3H, J = 6.4 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 113.3 (C-6), 83.6 (C-2), 80.5 (C-3), 67.7 (C-4), 65.5 (C-1), 59.3 (C-5), 39.8 (CH_2), 31.9 (N-CH_3), 31.2, 30.3, 29.7, 29.6, 29.3, 23.9, 22.7 (8CH_2), 25.7 and 24.9 (CH_3-7 and CH_3-8), 14.1 (2CH_3).

N-Methyl-1-α-methyl-1-β-octyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-methyl-1-β-octyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 6f Colorless oil (18 %). $C_{18}H_{35}NO_3$, M = 313.48; MS m/z 314.4 (M + H$^-$); calcd for $C_{18}H_{35}NO_3$ (M + H)$^+$ 314.26897, found 314.26872

IR: ν_{max}(neat)/cm^{-1} KBr 3468.0, 2927.9, 2855.8, 1647.73 1461.8, 1376.7, 1257.8, 1208.0, 1159.6, 1069.3, 865.6.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.56 (dd, 1H, $J_{3,2}$ = 6.1 Hz,

$J_{3,4}$ = 3.0 Hz, H-3), 4.18 (d, 1H, $J_{2,3}$ = 6.1 Hz, H-2), 3.70 (dd, 1H, $J_{5',5}$ = 11.1 Hz, $J_{5',4}$ = 2.9 Hz, H-5'), 3.64 (m, 1H, H-5), 2.76 (m, 1H, H-4), 2.13 (s, 3H, N-CH_3), 1.49, 1.33 (2s, 6H, CH_3-7, CH_3-8), 1.56-1.27 (m, 14H, 7CH_2), 0.92 (s, 3H, CH_3), 0.89 (t, 3H, J= 6.8 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 113.3 (C-6), 83.6 (C-2), 80.5 (C-3), 67.7 (C-4), 65.5 (C-1), 59.3 (C-5), 39.8 (CH_2), 31.9 (N-CH_3), 31.2, 30.3, 29.5, 29.3, 23.9, 22.6 (7CH_2), 25.7, 24.9 (CH_3-7, CH_3-8), 14.1 (2CH_3).

N-Methyl-1-α-ethyl-1-β-methyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-ethyl-1-β-methyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 8a Colorless oil (38 %). $C_{12}H_{23}NO_3$, M = 229.32; MS m/z 230.2 (M + H^-); calcd for $C_{12}H_{23}NO_3$ (M + $H)^+$ 230.17562, found 230.1757.

IR: ν_{max}(neat)/cm^{-1} KBr 3442.33, 2975.64, 2933.21, 2879.21, 1643.06, 1461.78, 1376.93, 1255.43, 1205.29, 1064.52

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.60 (m, 1H, H-3), 4.30 (m, 1H, H-2), 3.73 – 3.65 (m, 2H, H-5', H-5), 2.87 (m, 1H, H-4), 2.23 (s, 3H, CH_3), 1.64 – 1.42 (m, 2H, CH_2), 1.49 and 1.31 (2s, 6H, 2CH_3), 1.25 (bt, 6H, 2CH_3), 0.95 (bt, 6H, 2CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.9 (C-6), 87.0 (C-2), 80.3 (C-3), 67.8 (C-4), 66.6 (C-1), 59.1 (C-5), 31.2 (CH_3), 25.9, 24.8 (CH_3-7, CH_3-8), 23.6, 21.7 (2CH_2), 14.2 (CH_3), 10.0 (CH_3).

N-Methyl-1-α-ethyl-1-β-butyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-ethyl-1-β-butyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 8b Colorless oil (33 %). $C_{15}H_{29}NO_3$, M = 271.4; MS m/z 272.2 (M + H^-); calcd for $C_{15}H_{29}NO_3$ (M + $H)^+$ 272.22257, found 272.2234.

IR: ν_{max}(neat)/cm^{-1} KBr 3450.04, 2937.07, 2869.57, 2804.00, 1652.70, 1459.85, 1376.93, 1257.36, 1207.22, 1159.01, 1068.37

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.59 (dd, 1H, $J_{3,2}$ = 7.3 Hz, $J_{3,4}$ = 4.5 Hz, H-3), 4.30 (d, 1H, $J_{2,3}$ = 7.3 Hz, H-2), 3.76 (dd, 1H, $J_{5',5}$ = 11.0 Hz, $J_{5',4}$ = 3.0 Hz, H-5'), 3.68 (dd, 1H, $J_{5',5}$ = 11.0 Hz, H-5), 2.91 (m, 1H, H-4), 2.24 (s, 3H, N-CH_3), 1.77 – 1.23 (m, 8H, 4CH_2), 1.54, 1.37 (2s, 6H, CH_3-7, CH_3-8), 1.01 (t, 3H, J = 7.5 Hz, CH_3), 0.96 (t, 3H, J = 7.2 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.9 (C-6), 84.1 (C-2), 80.0 (C-3), 67.8 (C-4), 66.6 (C-1), 59.2 (C-5), 35.4 (CH_2), 31.9 (N-CH_3), 26.1, 23.4, 21.8 (3CH_2), 25.5, 24.8 (CH_3-7, CH_3-8), 14.1 (CH_3), 9.7 (CH_3).

N-Methyl-1-α-ethyl-1-β-nonyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-ethyl-1-β-nonyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 8c Colorless oil (32 %). $C_{20}H_{39}NO_3$, M = 341.54; MS m/z 342.3 (M + H^-); calcd for $C_{20}H_{39}NO_3$ (M + $H)^+$ 342.30027, found 342.30019.

IR: ν_{max}(neat)/cm^{-1} KBr 3421.12, 2925.50, 2856.07, 1641.13, 1461.78, 1376.93, 1205.29, 1060.66

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.57 (dd, 1H, $J_{3,2}$ = 7.2 Hz, $J_{3,4}$ = 4.6 Hz, H-3), 4.28 (d, 1H, $J_{2,3}$ = 7.2 Hz, H-2), 3.70 – 3.61 (m, 2H, H-5', H-5), 2.90 (m, 1H, H-4), 2.22 (s, 3H, N-CH_3), 1.72 – 1.29 (m, 8H, 4CH_2), 1.55, 1.36 (2s, 6H, CH_3-7, CH_3-8), 0.99 (t, 3H, J = 7.2 Hz, CH_3), 0.90 (t, 3H, J = 7.2 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.9 (C-6), 84.1 (C-2), 80.0 (C-3), 68.0 (C-4), 66.7 (C-1), 59.2 (C-5), 35.4, 32.8 (2CH_2), 31.9 (N-CH_3), 30.3, 29.6, 29.5, 29.3, 23.3, 22.6, 21.8 (7CH_2), 25.5, 24.9 (CH_3-7, CH_3-8), 14.1 (CH_3), 9.7 (CH_3).

N-Methyl-1-dibutyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-dibutyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 10a Colorless oil (15 %). $C_{17}H_{33}NO_3$, M = 299.46; MS m/z 300.2 (M + H^-); calcd for $C_{17}H_{33}NO_3$ (M + $H)^+$ 300.25332, found 300.25327.

IR: ν_{max}(neat)/cm^{-1} KBr 3433.12, 2954.24, 2933.66, 2866.55, 1650.88, 1461.3, 1376.48, 1207.68, 1071.98

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.58 (dd, 1H, $J_{3,2}$ = 7.4 Hz, $J_{3,4}$ = 4.6 Hz, H-3), 4.30 (d, 1H, $J_{2,3}$ = 7.4 Hz, H-2), 3.76 (dd, 1H, $J_{5',5}$ = 11.0 Hz, $J_{5',4}$ = 3.0 Hz, H-5'), 3.69 (dd, 1H, $J_{5',5}$ = 11.0 Hz, H-5), 2.91 (m, 1H, H-4), 2.23 (s, 3H, N-CH_3), 1.671 – 1.22 (m, 12H, 6CH_2), 1.54, 1.37 (2s, 6H, CH_3-7, CH_3-8), 0.95 (bt, 6H, 2CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.9 (C-6), 84.0 (C-2), 80.0 (C-3), 67.8 (C-4), 66.6 (C-1), 59.2 (C-5), 36.1 (CH_2), 31.8 (N-CH_3), 29.4, 27.0, 26.0, 23.9, 23.3, (5CH_2), 25.5, 24.8 (CH_3-7, CH_3-8), 14.1 (2CH_3).

N-Methyl-1-α-buthyl-1-β-nonyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-butyl-1-β-nonyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 10b Colorless oil (17 %). $C_{22}H_{43}NO_3$, M = 369.58; MS m/z 370.3 (M + H^-); calcd for $C_{22}H_{43}NO_3$ (M + $H)^+$ 370.33212, found 370.3311.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.58 (dd, 1H, $J_{3,2}$ = 7.4 Hz, $J_{3,4}$ = 4.6 Hz, H-3), 4.29 (d, 1H, $J_{2,3}$ = 7.4 Hz, H-2), 3.76 (dd, 1H, $J_{5',5}$ = 11.0 Hz, $J_{5',4}$ = 3.0 Hz, H-5'), 3.69 (dd, 1H, $J_{5',5}$ = 11.0 Hz, H-5), 2.90 (m, 1H, H-4), 2.23 (s, 3H, N-CH_3), 1.70 – 1.24 (m, 22H, 11CH_2), 1.53, 1.36 (2s, 6H, CH_3-7, CH_3-8), 0.93 (m, 6H, 2CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ112.9 (C-6), 84.0 (C-2), 80.0 (C-3), 67.8 (C-4), 66.6 (C-1), 59.2 (C-5), 36.4 (CH_2), 31.9 (N-CH_3), 30.3, 29.7, 29.6, 29.5, 29.4, 29.3, 27.0, 23.9, 23.3, 22.7 (10CH_2), 26.0, 24.8 (CH_3-7, CH_3-8), 14.1 (CH_3), 14.0 (CH_3).

N-Methyl-1-α-buthyl-1-β-decyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-butyl-1-β-decyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 10c Colorless oil (7 %). $C_{23}H_{45}NO_3$, M = 383.62.

IR: ν_{max}(neat)/cm^{-1} KBr 3378.7, 2952.5, 2925.5, 2856.07, 1693.2, 1652.7, 1461.8, 1375.0, 1247.7, 1213.01, 1160.9, 1064.5, 873.6.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.60 (t, 1H, $J_{3,2}$ = 6.1 Hz, H-3), 4.39 (d, 1H, $J_{2,3}$ = 6.1 Hz, H-2), 3.77 (dd, 1H, $J_{5',5}$ = 11.4 Hz, $J_{5',4}$ = 3.1 Hz, H-5'), 3.73 (dd, 1H, $J_{5,5'}$ = 11.4 Hz, $J_{5,4}$ = 1.9 Hz, H-5), 2.76 – 2.74 (m, 1H, H-4), 2.31 (s, 3H, N-CH_3), 1.62 – 1.29 (m, 24H, 12CH_2), 1.47, 1.29 (2s, 6H, CH_3-7, CH_3-8), 0.93 (t, 3H, J= 7.1 Hz, CH_3), 0.88 (t, 3H, J= 6.5 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 110.9 (C-6), 85.4 (C-2),

78.9 (C-3), 72.5 (C-4), 70.6 (C-1), 60.0 (C-5), 35.1, 33.7 ($2CH_2$), 31.9 (N-CH_3), 30.5, 29.6, 29.6, 29.4, 29.2, 28.2, 27.9, 25.7, 24.2 22.7, 19.6 ($10CH_2$), 14.1 ($2CH_3$).

N-Methyl-1-α-buthyl-1-β-tetradecyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-butyl-1-β-tetradecyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 10d Colorless oil (32 %). $C_{27}H_{53}NO_3$, M = 439.72; MS m/z 440.5 (M + H^-); calcd for $C_{27}H_{53}NO_3$ (M + H)$^+$ 440.41037, found 440.4087.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.52 (dd, 1H, $J_{3,2}$ = 7.2 Hz, $J_{3,4}$ = 4.5 Hz, H-3), 4.39 (d, 1H, $J_{2,3}$ = 7.2 Hz, H-2), 3.77 (dd, 1H, $J_{5',5}$ = 11.0 Hz, $J_{5',4}$ = 3.3 Hz, H-5'), 3.73 (d, 1H, $J_{5,5'}$ = 11.0 Hz, H-5), 2.84 (m, 1H, H-4), 2.16 (s, 3H, N-CH_3), 1.61 – 1.24 (m, 32H, $16CH_2$), 1.48, 1.31 (2s, 6H, CH_3-7, CH_3-8), 0.88 (m, 6H, $2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ112.9 (C-6), 84.0 (C-2), 80.0 (C-3), 67.8 (C-4), 66.7 (C-1), 59.1 (C-5), 36.4, 32.8 ($2CH_2$), 31.9 (N-CH_3), 31.8, 30.3, 29.6, 29.4, 29.3, 26.9, 26.0, 23.9, 23.3, 22.7 ($14CH_2$), 25.7, 24.8 (CH_3-7, CH_3-8), 14.1 ($2CH_3$).

N-Methyl-1-α-octyl-1-β-nonyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-octyl-1-β-nonyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 12a Colorless oil (16 %). $C_{26}H_{51}NO_3$, M = 425.69; MS m/z 426.3 (M + H^-); calcd for $C_{25}H_{51}NO_3$ (M + H)$^+$ 426.39417, found 426.39396.

IR: ν_{max}(neat)/cm^{-1} KBr 3381.24, 2955.45, 2926.15, 2854.89, 166.57, 1590.19, 1463.28, 1375.46, 1208.9, 1156.9, 1073.59

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.52 (m, 1H, H-3), 4.23 (d, 1H, $J_{2,3}$ = 7.3 Hz, H-2), 3.71 – 3.62 (m, 2H, H-5', H-5), 2.85 (m, 1H, H-4), 2.17 (s, 3H, N-CH_3), 1.61 – 1.18 (m, 32H, $16CH_2$), 1.48, 1.31 (2s, 6H, CH_3-7, CH_3-8), 0.87 (m, 6H, $2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 84.0 (C-2), 80.0 (C-3), 59.1 (C-4), 43.9 (C-5), 31.9 (N-CH_3), 30.2, 29.6, 29.5, 29.3, 29.2, 24.3, 23.3, 22.6 ($15CH_2$), 26.1, 24.7 (CH_3-7, CH_3-8), 14.1 ($2CH_3$).

N-Methyl-1-α-octyl-1-β-vinyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-octyl-1-β-vinyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 12b Colorless oil (20 %). $C_{19}H_{35}NO_3$, M = 325.49; MS m/z 326.3 (M + H^-); calcd for $C_{19}H_{35}NO_3$ (M + H)$^+$ 326.26897, found 326.26879.

IR: ν_{max}(neat)/cm^{-1} KBr 3394.10, 2923.29, 2852.91, 1747.11, 1665.70, 1588.98, 1459.6, 1375.38, 1207.85, 1068.86

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88 (bs, 1H, -CH=CH_2), 5.14 (bd, 1H, -CH=CH_2), 4.54 (dd, 1H, $J_{3,2}$ = 6.8 Hz, $J_{3,4}$ = 4.1 Hz, H-3), 4.38 (bs, 1H, H-2), 3.71 (m, 2H, H-5', H-5), 2.87 (m, 1H, H-4), 2.29 (s, 3H, N-CH_3), 1.52, 1.32 (2s, 6H, CH_3-7, CH_3-8), 1.56 – 1.26 (m, H, CH_2), 0.88 (t, 3H, J = 6.4 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 113.02 (C-6), 31.84, 29.5, 29.3, 24.8, 22.6 (CH_2), 14.1 (CH_3).

N-Methyl-1-α-decyl-1-β-nonyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-methyl-1-α-decyl-1-β-nonyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 14 Colorless oil (36 %). $C_{28}H_{55}NO_3$, M = 453.75; MS m/z 454.5 (M + H^-); calcd for $C_{28}H_{55}NO_3$ (M + H)$^+$ 454.42547, found 454.42516

IR: ν_{max}(neat)/cm^{-1} KBr 3415.17, 3354.38, 2923.49, 2853.12, 1665.91, 1629.27, 1604.41, 1461.75, 1375.59, 1207.18, 1068.53

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.52 (dd, 1H, $J_{3,4}$ = 4.6 Hz, $J_{3,2}$ = 7.4 Hz, H-3), 4.23 (d, 1H, $J_{2,3}$ = 7.4 Hz, H-2), 3.70 (dd, 1H, $J_{5',4}$ = 3 Hz, $J_{5',5}$ = 10.9 Hz, H-5'), 3.64 – 3.53 (d, 1H, $J_{5,5'}$ = 10.9 Hz, H-5), 2.84 (m, 1H, H-4), 2.17 (s, 3H, N-CH_3), 1.61 – 1.25 (m, 34H, $17CH_2$), 1.48, 1.32 (2s, 6H, CH_3-7, CH_3-8), 0.87 (m, 6H, $2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.9 (C-6), 84.0 (C-2), 80.0 (C-3), 67.8 (C-4), 66.7 (C-1), 63.1 (C-5), 59.1, 36.4, 32.8 (CH_2), 31.8 (N-CH_3), 30.9, 29.6, 29.5, 29.4, 29.3, 29.2, 25.7, 24.7, 23.3, 22.6 ($14CH_2$) 25.7, 24.7 (CH_3-7, CH_3-8), 14.1 ($2CH_3$).

N-Ethyl-1-α-nonyl-1-β-methyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-L-ribitol, ((2R, 3S, 4S)-N-ethyl-1-α-nonyl-1-β-methyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 21 Colorless oil (39 %). $C_{20}H_{39}NO_3$, M = 341.54; MS m/z 342.5 (M + H^-); calcd for $C_{20}H_{39}NO_3$ (M + H)$^+$ 342.30027, found 342.29998.

IR: ν_{max}(neat)/cm^{-1} KBr 3394.65, 2925,92, 2854.89, 1462.53, 1376.4, 1255.1, 1207.58, 1157.85, 1074.06, 867.34

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.53 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{3,2}$ = 7.4 Hz, H-3), 4.13 (d, 1H, $J_{2,3}$ = 7.4 Hz, H-2), 3.69 – 3.60 (m, 2H, H-5', H-5, CH_2), 2.95 (m, 1H, H-4), 2.79 – 2.29 (m, 2H, N-CH_2), 1.58 – 1.25 (m, 16H, $8CH_2$), 1.48, 1.312 (2s, 6H, CH_3-7, CH_3-8), 1.02 (t, 3H, J = 7.2 Hz, N-CH_2-CH_3), 0.94 (s, 3H, CH_3), 0.87 (t, 6H, J = 6.6 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 113.0, 83.9 (C-2), 80.9 (C-3), 67.5 (C-4), 66.4 (C-1), 63.0 (H-5), 60.8 (CH_2), 41.1 (CH_2), 40.5 (CH_2), 32.8, 31.9, 30.4, 29.6, 29.5, 29.4, 29.3, 29.2 (CH_2), 25.7, 25.6 (CH_3-7, CH_3-8), 25.0, 24.1, 22.7 (CH_2), 16.6 (N-CH_2-CH_3), 15.5 (CH_3), 14.1 (CH_2-CH_3).

N-Ethyl-1-dinonyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-L-ribitol, ((2R, 3S, 4S)-N-ethyl-1-dinonyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) **23** Colorless oil (22 %). $C_{28}H_{55}NO_3$, M = 453.75; MS m/z 454.6 (M + H^-); calcd for $C_{28}H_{55}NO_3$ (M + H)$^+$ 454.42602, found 454.4258.

IR: ν_{max}(neat)/cm^{-1} KBr 3326.62, 2923.57, 2852.22, 2362.38, 2335.38, 1698.99, 1650.77, 1558.21, 1538.92, 1513.85, 1457.93, 1371.14.

N-Methyl-1-α-nonyl-1-β-butyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-L-ribitol, ((2R, 3S, 4S)-N-methyl-1-α-nonyl-1-β-butyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 25 Colorless oil (26 %). $C_{22}H_{43}NO_3$, M = 369.59; MS m/z 370.3 (M + H^-); calcd for $C_{22}H_{43}NO_3$ (M + H)$^+$ 370.33212, found 370.3339.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.52 (dd, 1H, $J_{3,4}$ = 4.5 Hz, $J_{3,2}$ = 7.3 Hz, H-3), 4.23 (d, 1H, $J_{2,3}$ = 7.3 Hz, H-2), 3.70 (dd, 1H, $J_{5',4}$ = 2.9 Hz, $J_{5',5}$ = 11.1 Hz, H-5'), 3.63 (d, 1H, $J_{5,5'}$ = 11.1 Hz, H-5), 2.85 (m, 1H, H-4), 2.17 (s, 3H, N-CH_3), 1.61 – 1.25 (m, 22H, $11CH_2$), 1.48, 1.39 (2s, 6H, CH_3-7, CH_3-8), 0.87 (m, 6H, $2CH_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 112.9 (C-6), 84.0 (C-2), 80.0 (C-3), 67.8 (C-4), 66.7 (C-1), 63.1 (C-5), 59.1, 36.4, 32.8 (CH_2), 31.9 (N-CH_3), 30.3, 29.6, 29.4, 29.3, 26.9, 26.0, 23.9, 23.3, 22.7 (8CH_2), 25.7, 24.8 (CH_3-7, CH_3-8), 14.1 (2CH_3).

N-Benzyl-1-α-methyl-1-β-octyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)-N-benzyl-1-α-methyl-1-β-octyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 28 Colorless oil (16 %). $C_{24}H_{39}NO_3$, M = 389.58; MS m/z 390.3 (M + H$^-$); calcd for $C_{24}H_{39}NO_3$ (M + H)$^+$ 390.30027, found 390.30012.

IR: ν_{max}(neat)/cm^{-1} KBr 3484.76, 2926.5, 2856.1, 1731.77, 1646.92, 1457.93, 1376.93, 1257.36, 1207.22, 1157.08, 1076.09

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.41 - 7.22 (m, 5H, Ph), 4.56 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,2}$ = 7.6 Hz, H-3), 4.22 (d, 1H, $J_{2,3}$ = 7.6 Hz, H-2), 4.01 (d, 1H, J = 14.8 Hz, N-CH_2), 3.41 (bd, 1H, $J_{5',5}$ = 11.7 Hz, H-5$'$), 3.28 (d, 1H, J = 14.8 Hz, N-CH_2), 3.63 (d, 1H, $J_{5,4}$ = 2.9 Hz, $J_{5,5'}$ = 11.7 Hz, H-5), 2.97 (m, 1H, H-4), 1.63 – 1.14 (m, 14H, 7CH_2), 1.52, 1.34 (2s, 6H, CH_3-7, CH_3-8), 1.08 (s, 3H, CH_3), 0.87 (bt, 3H, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.5 Ph, 128.7 Ph, 127.5 Ph, 127.2 Ph, 113.2 (C-6), 84.2 (C-2), 80.5 (C-3), 69.8 (C-4), 66.9 (C-1), 60.8 (C-5), 52.4 (CH_2Ph), 41.5, 31.9, 30.5, 29.7, 29.5, 29.4 (5CH_2), 25.7 and 25.0 (CH_3-7, CH_3-8), 24.4, 22.7 (2CH_2), 14.8 (CH_3), 14.1 (CH_3).

2.1.4. Cleavage of the Protecting Groups

(i). Cleavage of the Benzyl Group

A solution of N-benzyl-1-α-methyl-1-β-octyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol (25 mg) in acetic acid (2 ml) was shaken for 6 h under hydrogen in the presence of 10 % palladium-carbon (50 mg) using 48 psi pressures. The catalyst was removed by filtration through a celite pad and washed with acetic acid. Concentration in vacuo and purification of the residue by column chromatography (silica gel, elute with ethyl acetate) afforded 1-α-methyl-1-β-octyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol as an oil product.

1-α-Methyl-1-β-octyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-D-ribitol, ((2S, 3R, 4R)- 1-α-methyl-1-β-octyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrroldine) 29 Colorless oil (95 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.50 (dd, 1H, $J_{3,4}$ = 3.5, $J_{3,2}$ = 6.6, H-3), 4.23 (d, 1H, $J_{2,3}$ = 6.6, H-2), 3.64 (bd, 1H, $J_{5',4}$ = 4.6 Hz, $J_{5',5}$ = 10.6 Hz, H-5$'$), 3.50 (d, 1H, $J_{5,4}$ = 6.4, $J_{5,5'}$ = 10.6, H-5), 3.38 (m, 1H, H-4), 1.42 – 1.26 (m, H, CH_2), 1.50, 1.32 (2s, 6H, CH_3-7, CH_3-8), 1.17 (s, 3H, CH_3), 0.87 (t, 3H, J = 7 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.5 Ph, 128.7 Ph, 127.5 Ph, 127.2 Ph, 113.2 (C-6), 84.2 (C-2), 80.5 (C-3), 69.8 (C-4), 60.8 (C-5), 52.4 (CH_2Ph), 41.5, 31.9, 30.5, 29.7, 29.5, 29.4 (5CH_2), 25.7, 25.0 (CH_3-7, CH_3-8), 24.4, 22.7 (2CH_2), 14.8 (CH_3), 14.1 (CH_3).

(ii). Cleavage of the Isopropylidene Groups

The protected pyrrolidine was dissolved in ethanol (3 ml)/HCl (0.04 ml) at room temperature. The mixture was allowed to stand at room temperature 3 h and then evaporated to dryness, affording the crud products as a colorless oil almost quantitatively.

N-Methyl-1-α-methyl-1-β-vinyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-α-methyl-1-β-vinyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 7a $C_9H_{18}ClNO_3$, M = 223.7; MS m/z 188.1 (M + H$^-$); calcd for $C_9H_{17}NO_3$ (M + H)$^+$ 188.12812, found 188.12808.

IR: ν_{max}(neat)/cm^{-1} KBr 3407.25, 3370.90, 2960.57, 2919.63, 2849.18, 1726.19, 1662.51, 1639.15, 1482.51, 1271.54, 1144.57, 1082.83, 1029.65

^{1}H-NMR (400 MHz, CD_3OD) δ 6.05 (dd, 1H, CH=), 5.57 (m, 2H, CH_2=), 4.19 (dd, 1H, $J_{3,2}$ = 4.7 Hz, $J_{3,4}$ = 5.9 Hz, H-3), 3.98 (dd, 1H, $J_{5',4}$ = 3.2 Hz, $J_{5',5}$ = 12.5 Hz, H-5$'$), 3.93 – 3.89 (m, 2H, H-2, H-5), 3.51 (m, 1H, H-4), 2.83 (s, 3H, N-CH_3), 1.51 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, CD_3OD) δ 135.6 (CH=), 120.6 (=CH_2), 75.3 (C-2), 74.8 (C-4), 73.6 (C-1), 69.4 (C-3), 57.4 (C-5), 34.9 (N-CH_3), 10.9 (CH_3).

N-Methyl-1-α-methyl-1-β-allyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-α-methyl-1-β-allyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 7b $C_{10}H_{20}ClNO_3$, M = 237.73; MS m/z 202.2 (M + H$^-$); calcd for $C_{10}H_{19}NO_3$ (M + H)$^+$ 202.14377, found 202.14371.

IR: ν_{max}(neat)/cm^{-1} KBr 3349.56, 2946.79, 1637.48, 1460.1, 1387.15, 1085.64.

^{1}H-NMR (400 MHz, CD_3OD) δ 5.95 – 5.88 (m, 1H, CH=), 5.30 – 5.24 (m, 2H, CH_2=), 4.24 (t, $J_{3,2}$ = 5.9 Hz, H-3), 3.96 (dd, 1H, $J_{5',4}$ = 3.0 Hz, $J_{5',5}$ = 12.5 Hz, H-5$'$), 3.93 – 3.89 (m, 2H, H-2, H-5), 3.44 (m, 1H, H-4), 2.90 (s, 3H, N-CH_3), 2.57 (d, 2H, J = 7.4 Hz, CH_2), 1.43 (s, 3H, CH_3).

^{13}C-NMR (75 MHz, CD_3OD) δ 130.6 (CH=), 119.9 (=CH_2), 74.6 (C-2), 74.3 (C-4), 73.6 (C-1), 68.8 (C-3), 56.5 (C-5), 40.9 (CH_2), 36.6 (N-CH_3), 13.4 (CH_3).

N-Methyl-1-dimethyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-dimethyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 7c $C_8H_{18}ClNO_3$, M = 211.69; MS m/z 176.2 (M + H$^-$); calcd for $C_8H_{17}NO_3$ (M + H)$^+$ 176.12812, found 176.12812.

^{1}H-NMR (400 MHz, CD_3OD) δ 4.21 (t, 1H, $J_{3,2}$ = 5.6 Hz, H-3), 3.97 (dd, $J_{5',5}$ = 12.6 Hz, $J_{5',4}$ = 3 Hz, H-5$'$), 3.91 (dd, 1H, $J_{5,5'}$ = 12.6 Hz, $J_{5,4}$ = 4.5 Hz, H-5), 3.75 (d, 1H, $J_{2,3}$ = 5.6 Hz, H-2), 3.43 (m, 1H, H-4), 2.88 (s, 3H, N-CH_3), 1.44, 1.39 (2CH_3).

^{13}C-NMR (75 MHz, CD_3OD) δ 76.0 (C-2), 74.9 (C-4), 71.3 (C-1), 69.5 (C-3), 57.1 (C-5), 35.6 (N-CH_3), 22.0 (CH_3), 15.3 (CH_3).

N-Methyl-1-α-methyl-1-β-butyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-α-methyl-1-β-butyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 7d $C_{11}H_{24}ClNO_3$, M = 253.77; MS m/z 218.2 (M + H$^-$); calcd for $C_{11}H_{23}NO_3$ (M + H)$^+$ 218.17507, found 218.17506.

IR: ν_{max}(neat)/cm^{-1} KBr 3334.3, 2950.6, 2869.6, 1648.8, 1423.2, 1461.8, 1390.43, 1128.16, 1089.6

^{1}H-NMR (400 MHz, CD_3OD) δ 4.19 (t, 1H, $J_{3,2}$ = 5.9 Hz, H-3), 3.98 (dd, $J_{5',4}$ = 2.9 Hz, $J_{5',5}$ = 12.4 Hz, H-5'), 3.91-3.87

(m, 1H, H-2, H-5), 3.41 (m, 1H, H-4), 2.87 (s, 3H, N-CH_3), 1.84 -1.24 (m, 6H, 3CH_2), 1.41 (s, 3H, CH_3), 0.94 (t, J = 3.7 Hz, 3H, CH_3).

^{13}C-NMR (75 MHz, CD_3OD) δ 74.6 (C-2), 74.5 (C-1), 74.3 (C-4), 68.9 (C-3), 56.7 (C-5), 36.9 (N-CH_3), 36.2, 25.5, 22.8 (3CH_2), 13.1 (CH_3), 12.7 (CH_3).

N-Methyl-1-α-methyl-1-β-nonyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-α-methyl-1-β-nonyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 7e $C_{16}H_{34}ClNO_3$, M = 323.91; MS m/z 288 (M + H^-); calcd for $C_{16}H_{33}NO_3$ (M + H)$^+$ 288.25332, found 288.25315.

^{1}H-NMR (400 MHz, CD_3OD) δ 4.18 (t, 1H, $J_{3,2}$ = 5.8 Hz, H-3), 3.95 (dd, $J_{5',5}$ = 12.4 Hz, $J_{5',4}$ = 2.9 Hz, H-5,), 3.88 (m, 2H, H-2, H-5), 3.40 (m, 1H, H-4), 2.87 (s, 3H, N-CH_3), 1.82 -1.29 (m, 16H, 8CH_2, 2CH_3). 0.90 (t, 3H, J = 6.5 Hz, CH_3).

^{13}C-NMR (75 MHz, CD_3OD) δ 74.6 (C-2), 74.2 (C-4), 68.9 (C-3), 56.7 (C-5), 37.2 (N-CH_3), 36.2, 31.6, 29.7, 29.2, 29.1, 29.0, 23.4, 22.3 (8CH_2), 13.1 and 13.0 (2CH_3).

N-Methyl-1-α-ethyl-1-β-butyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-α-ethyl-1-β-butyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 9b $C_{12}H_{26}ClNO_3$, M = 267.8; MS m/z 232.3 (M + H^-); calcd for $C_{12}H_{25}NO_3$ (M + H)$^+$ 232.19072, found 232.19070.

IR: ν_{max}(neat)/cm^{-1} KBr 3342.05, 2956.35, 2867.64, 1643.06, 1459.85, 1388.50, 1108.87, 1078.01

^{1}H-NMR (400 MHz, CD_3OD) δ 4.4 (dd, 1H, $J_{3,2}$ = 4.0 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 4.0 (dd, 1H, $J_{5',5}$ = 12.5 Hz, $J_{5',4}$ = 2.7 Hz, H-5,), 3.94 (d, 1H, $J_{2,3}$ = 4.0 Hz, H-2), 3.85 (m, 1H, $J_{5',5}$ = 12.5 Hz, $J_{5',4}$ = 3.1 Hz, H-5), 3.35 (dt, 1H, $J_{4,5'}$ = 2.7 Hz, $J_{4,5}$ = 3.1 Hz, $J_{4,3}$ = 9.2 Hz, H-4), 2.81 (s, 3H, N-CH_3), 2.13 -1.34 (m, 6H, 3CH_2), 1.02 (t, 3H, J = 7.5 Hz, CH_3), 0.96 (t, 6H, J = 6.9 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 78.2 (C-1), 75.1 (C-2), 74.7 (C-4), 68.6 (C-3), 55.5 (C-5), 39.9 (N-CH_3), 31.6, 24.6, 22.5, 19.7 (4CH_2), 12.7 and 7.4 (2CH_3).

N-Methyl-1-α-ethyl-1-β-nonyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-α-ethyl-1-β-nonyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 9c $C_{17}H_{36}ClNO_3$, M = 337.93; MS m/z 302.3 (M + H^-); calcd for $C_{17}H_{35}NO_3$ (M + H)$^+$ 302.26897, found 302.26891.

IR: ν_{max}(neat)/cm^{-1} KBr 3340.12, 2925.50, 2852.22, 1650.77, 1560.13, 1538.92, 1456.00, 1120.44

^{1}H-NMR (400 MHz, CD_3OD) δ 4.39 (dd, 1H, $J_{3,2}$ = 4.0 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 3.97 (dd, 1H, $J_{5',5}$ = 12.5 Hz, $J_{5',4}$ = 2.7 Hz, H-5,), 3.95 (d, 1H, $J_{2,3}$ = 4.0 Hz, H-2), 3.85 (m, 1H, $J_{5',5}$ = 12.5 Hz, $J_{5',4}$ = 3.1 Hz, H-5), 3.36 (dt, 1H, $J_{4,5'}$ = 2.7 Hz, $J_{4,5}$ = 3.1 Hz, $J_{4,3}$ = 9.3 Hz, H-4), 2.89 (s, 3H, N-CH_3), 2.15 -1.29 (m, 18H, 9CH_2), 1.01 (t, 3H, J = 7.5 Hz, CH_3), 0.89 (t, 6H, J = 6.9 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 78.2 (C-1), 75.1 (C-2), 74.7 (C-4), 68.6 (C-3), 55.5 (C-5), 39.9 (N-CH_3), 32.2, 31.8, 31.6, 29.2, 28.9, 25.5, 22.5, 22.3, 19.7 (9CH_2), 13.0 and 7.4 (2CH_3).

N-Methyl-1-dibutyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-dibutyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 11a $C_{14}H_{30}ClNO_3$, M = 295.85; MS m/z 260.2 (M + H^-); calcd for $C_{14}H_{29}NO_3$ (M + H)$^+$ 260.22202, found 260.22197.

^{1}H-NMR (400 MHz, CD_3OD) δ 4.49 (t, 1H, $J_{3,2}$ = 5.0 Hz, H-3), 3.98 (dd, 1H, $J_{5',5}$ = 12.5 Hz, $J_{5',4}$ = 2.6 Hz, H-5,), 3.93 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 3.88 (m, 1H, $J_{5',5}$ = 12.5 Hz, $J_{5',4}$ = 2.6 Hz, H-5), 3.35 (m, 1H, H-4), 2.89 (s, 3H, N-CH_3), 2.0 - 1.35 (m, 12H, 6CH_2, 2CH_3), 0.90 (t, 6H, 2CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 77.8 (C-2), 75.0 (C-1), 74.9 (C-4), 68.6 (C-3), 55.5 (C-5), 39.9 (N-CH_3), 32.2, 26.7, 25.8, 24.7, 22.7, 22.5, (6CH_2), 12.8 and 12.7 (2CH_3).

N-Methyl-1-α-buthyl-1-β-decyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-α-butyl-1-β-decyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 11c $C_{20}H_{42}ClNO_3$, M = 380.01.

IR: ν_{max}(neat)/cm^{-1} KBr 3364.97, 2954.04, 2924.37, 2854.8, 1728.73, 1665.7, 1461.65, 1376.68, 1148.74, 1090.45.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.30 (dd, 1H, $J_{3,2}$ = 5.0, $J_{3,4}$ = 8.8, H-3), 3.83 (d, 1H, $J_{2,3}$ = 5.0, H-2), 3.76 – 3.68 (m, 2H, H-5,, H-5), 3.50 (d, 1H, J = 10.5, CH_2), 2.66 (d, 1H, $J_{4,3}$ = 8.8, H-4), 2.30 (s, 3H, N-CH_3), 1.84 (m, 2H, CH_2), 1.60 – 1.13 (m, 16H, 8CH_2), 0.92 (t, 3H, J = 7.1, CH_3), 0.88 (t, 3H, J = 6.7, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 76.3 (C-2), 74.8 (C-4), 71.1 (C-1), 69.6 (C-3), 58.6 (C-5), 34.7 (N-CH_3), 33.8, 31.9, 30.7, 29.7, 29.6, 29.5, 29.3, 24.9, 22.7, 19.4 (12CH_2), 14.1 (CH_3), 14.0 (CH_3).

N-Methyl-1-α-octyl-1-β-vinyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-α-octyl-1-β-vinyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 13b $C_{16}H_{32}ClNO_3$, M = 321.8909; MS m/z 286.3 (M + H^-); calcd for $C_{16}H_{31}NO_3$ (M + H)$^+$ 286.23767, found 286.23754.

IR: ν_{max}(neat)/cm^{-1} KBr 3448.85, 2955.07, 2923.23, 2850.15, 1639.86, 1457.09, 1393.96, 1316.93, 1178.81, 1078.9

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, 1H, J = 10.8 Hz, J = 17.4 Hz, CH=), 5.15 (dd, 2H, CH_2=), 4.11 (m, 1H, H-3), 3.80 (d, $J_{2,3}$ = 4.9 Hz, 1H, H-2), 3.74-3.63 (m, 2H, H-5,, H-5), 2.88 (m, 1H, H-4), 2.36 (s, 3H, N-CH_3), 1.85 – 1.77 (m, 2H, CH_2), 1.56 – 1.50 (m, 2H, CH_2), 1.37 – 1.26 (m, 10H, 5CH_2), 0.87 (t, 3H, J = 6.4 Hz, CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 133.1 (CH=), 113.9 (=CH_2), 77.3 (C-2), 71.5 (C-4), 70, 6 (C-3), 59.1 (C-5), 31.9 (N-CH_3), 30.9, 29.7, 29.5, 29.3, 25.6, 22.6 (7CH_2), 14.1 (CH_3).

N-Methyl-1-α-decyl-1-β-nonyl-1,4-imino-1,4-dideoxy-D-ribitol HCl, ((2S, 3R, 4R)-N-methyl-1-α-decyl-1-β-nonyl-2,3-diol-4-hydroxymethyl-1-pyrrolidine HCl) 15 $C_{25}H_{52}ClNO_3$, M = 450.14; MS m/z 414.3 (M + H^-); calcd for $C_{25}H_{51}NO_3$ (M + H)$^+$ 414.39417, found 414.39386.

IR: ν_{max}(neat)/cm^{-1} KBr 3364.74, 2926.3, 2850.27, 1696.55, 1650.6, 1558.12, 1513.7, 1459.5.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.16 (t, 1H, $J_{3,2}$ = 5.8, H-3), 3.73 – 3.70 (m, 2H, H-2, H-5,), 3.61 (d, 1H, $J_{5',5}$ = 11.0, H-5), 3.49 (s, 2H, CH_2), 2.80 (m, 1H, H-4), 2.29 (s, 3H, N-CH_3), 1.67 – 1.26 (m, 32H, 16CH_2), 0.87 (t, 3H, J = 6.5, CH_3).

N-Ethyl-1-α-nonyl-1-β-methyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-L-ribitol, ((2R, 3S, 4S)-N-ethyl-1-α-nonyl-1-β-methyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) **22** $C_{17}H_{36}ClNO_3$, M = 337.91; MS m/z 302.3 (M + H^-); calcd for $C_{17}H_{35}NO_3$ (M + H)$^+$

302.26897, found 302.26877.

IR: ν_{max}(neat)/cm^{-1} KBr 3381.15, 2925.33, 2857.64, 1689.12, 1550.24, 1462.67, 1061.57

^{1}H-NMR (400 MHz, CD_3OD) δ 3.92 (m, 1H, H-3), 3.66 - 3.61 (m, 3H, H-5', H-2, H-5), 3.45 (m, 1H, H-4), 2.82-2.49 (m, 3H, N-CH_2), 1.54-1.29 (m, 16H, 8CH_2), 0.98 (m, 6H, 2CH_3), 0.89 (t, 3H, J = 6.5 Hz, CH_3).

^{13}C-NMR (75 MHz, CD_3OD) δ 74.0 (C-2), 72.4 (C-3), 71.4 (C-4), 55.5 (C-5), 39.4, 31.7, 30.2, 29.3, 29.0, 23.1, 22.3 (9CH_2), 14.4 (2CH_3), 13.0 (CH_3).

N-Ethyl-1-dinonyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-L-ribitol, ((2R, 3S, 4S)-N-ethyl-1-dinonyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 24 $C_{26}H_{51}ClNO_3$, M = 450.18; MS m/z 414.4 (M + H$^-$); calcd for $C_{28}H_{55}NO_3$ (M + H)$^+$ 414.39472, found 414.3935.

IR: ν_{max}(neat)/cm^{-1} KBr 3293.84, 2925.50, 2854.14, 2383.60, 2346.95, 2304.53, 1602.56, 1461.78, 1380.79, 1085.73

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.60 (m, 1H, H_3), 4.11 (d, 1H, $J_{5',5}$ = 10.0 Hz, H-5'), 3.96 (m, 2H, H-2, H-5), 3.39 (m, 1H, H-4), 3.30 (m, 2H, N-CH_2), 1.99 – 1.26 (m, 32H, 16CH_2), 1.50 (t, 3H, J = 5.6 Hz, N-CH_2-CH_3), 0.89 (m, 6H, 2CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 75.1 (C-2), 72.5 (C-3), 69.6 (C-4), 57.8 (C-5), 31.9, 31.8, 30.0, 29.8, 29.6, 29.4, 29.3, 29.3, 27.4, 24.0, 23.7, 22.7 (17CH_2), 14.1 (2CH_3), 11.5 (CH_3).

N-Methyl-1-α-nonyl-1-β-butyl-2,3-isopropylidene-1,4-imino-1,4-dideoxy-L-ribitol, ((2R, 3S, 4S)-N-methyl-1-α-nonyl-1-β-butyl-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine) 26 $C_{17}H_{36}ClNO_3$, M = 337.91; MS m/z 302.3 (M + H$^-$); calcd for $C_{17}H_{35}NO_3$ (M + H)$^+$ 302.26897, found 302.26877.

IR: ν_{max}(neat)/cm^{-1} KBr 3311.19, 2923.57, 2854.14, 1697.06, 1558.21, 1459.85, 1376.93, 1079.94

^{1}H-NMR (400 MHz, CD_3OD) δ 4.39 (dd, 1H, $J_{3,2}$ = 3.9 Hz, $J_{3,4}$ = 9.1 Hz, H-3), 3.98 (dd, 1H, $J_{5',5}$ = 12.5 Hz, $J_{5',4}$ = 2.6 Hz, H-5'), 3.93 (d, 1H, $J_{2,3}$ = 3.9 Hz, H-2), 3.85 (m, 1H, $J_{5',5}$ = 12.5 Hz, $J_{5,4}$ = 3.0 Hz, H-5), 3.35 (dt, 1H, $J_{4,5'}$ = 2.6 Hz, $J_{4,5}$ = 3.0 Hz, $J_{4,3}$ = 9.1 Hz, H-4), 2.89 (s, 3H, N-CH_3), 2.11-1.29 (m, 22H, 11CH_2), 0.98 (t, 3H, J = 6.8 Hz, CH_3), 0.89 (t, 3H, J = 6.4 Hz, CH_3).

^{13}C-NMR (75 MHz, CD_3OD) δ 77.9 (C-1), 75.0 (C-2), 74.9 (C-4), 68.8 (C-3), 55.5 (C-5), 39.9, 32.4 (CH_2), 31.6 (N-CH_3), 29.4, 29.2, 28.9, 26.7, 25.9, 25.5, 22.7, 22.6, 22.3 (9CH_2), 13.0 (CH_3), 12.8 (CH_3).

2.2. Hypersphere Approach for Calculation of Dihedral Angles from Carbon Chemical Shift

3-Sphere, a hypersphere in 4D, enable calculation of the dihedral angle θ_{HnHn+1}[deg] from vicinal angle ϕ[deg], angle result from vicinal coupling constants $^{3}J_{HnHn+1}$[Hz], based on two mathematics theories Hopf fibration and Lie algebra, both working well on the wave character of NMR data. Dihedral angles are calculated from vicinal coupling constant or from chemical shift with 3D coordinate (eq. 1, 2) building units [8-10].

$$3D: \sin^{-1}\cos\phi = \theta_{HnHn+1} \quad (1)$$

$$3D: \tan^{-1}\sin\phi = \theta_{HnHn+1} \quad (2)$$

In this paper we proposed the calculation of the dihedral angles θ_{HnHn+1}[deg] from carbon chemical shift δ_{Cn}[ppm] without building units [11], in attempt to found 1. the best hypersphere equation for every curvature around the iminocyclitol ring with biological activity, 2. to analyzed the implication of the N dimension space on antiviral activity, and 3. the change on shape in function of the structure of the iminocyclitols analyzed. Since in first case the units contain all the manifold circles, in this case are found trigonometric equations between the 4D and 2D (eq. 3, 4, 5, Table 1).

$$4D: \sin^{-1}\cos[(\tan^{-1}R_m)/2] \quad (3)$$

$$2D: \theta = -\cos^{-1}[1/(R_m)]/2 \quad (4)$$

$$2D: \phi = \tan^{-1}(1/R_m) \quad (5)$$

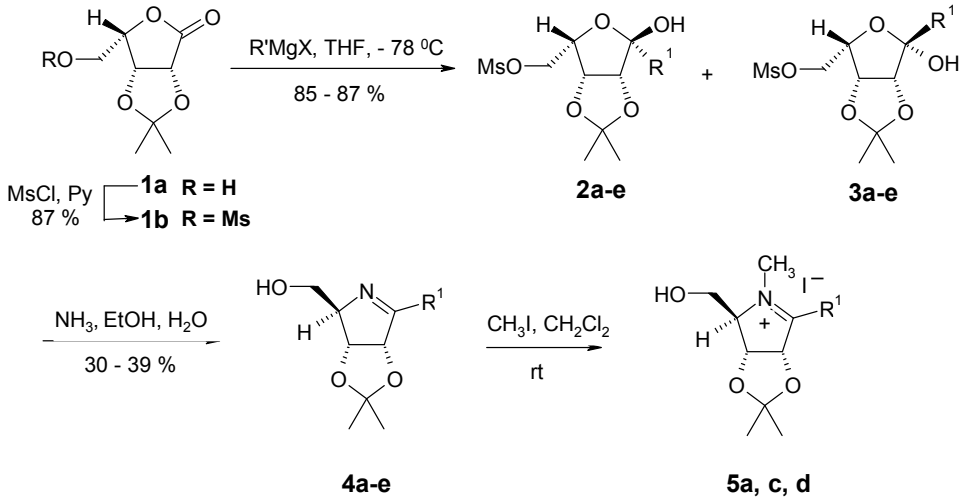
3. Results and Discussion

The imino double bond is a site for nucleophilic additions of organometalic reagents, severely limited by the low electrophilicity [12-14] of azometin carbon or by competition between α-deprotonation (enamine or azaallyl anion formation) or intramolecular addition of hydroxyl group to the imine group [15]. The electrophilicity of the imine carbon C=N can be increased by: *N*-alkylation, *N*-oxidation, *N*-acylation, *N*-sulfonylation to give, respectively, reactive iminium salts, reactive nitrones, acylimines, and sulfonimines. [12] For example phenyl magnesium bromide addition to benzyl protected nitrone with D-xylose stereochemistry has high stereoselectivity through a Felkin-Anh transition state model, resulting after deprotection the natural product *N*-hydroxylpyrrolidine, namely Radicanine B. [16] The standard methods for activation at the imine carbon involve coordination of a Lewis acid with the nitrogen lone pair [17] or by addition of external promoters. Additions to polyhydroxylated cyclic imines with C_1 unsubstituted have been reported. [18-21] Allylmagnesium reagent has lower diastereoselectivity relative to other Grignard reagents. [22] Grignard reagents are prepared in dry organic solvents and inert atmosphere [23], or in air using ball milling technique [24].

Low diastereoselectivity of Grignard addition to anomeric position of isopropylidene protected 5-*O*-mesyloxy-1,4-lactone 1b can be explained (Scheme 1) in case of α anomer 2 with Cram chelation model or for β anomer 3 with Felkin-Anh model with preferred *si* attach. The chelating effect of the oxygen atom is increased by the presence of isopropylidene group. The isopropylidene group is likely to enforce a rigid butterfly conformation that favors nucleophile approach from the convex face.

The α, β anomeric mixture of hemiacetals 2, 3 upon treatment with NH_3 in aq EtOH yielded imines 4. Methansulfonyl chloride react by a direct displacement mechanism so is expected solvent nucleophilicity to have the major effect. The isopropylidene group forces the molecule into a rigid *cis*-bicyclo[3.3.0] ring system which may be

optimal for the intramolecular cyclization (Thoape-Ingold effect). Wasserman et al claim that δ,ε epoxyimines undergo intramolecular cyclization, in consequence 6,7-epoxy-2-heptanone upon treatment with benzylamine yielded *N*-benzyl-6-oxa-8-azabicyclo[3.2.1]octane. In contrast to imine formation (Figure 1), in the epoxy heptanone system, intramolecular addition of the hydroxymethyl groups to imino double bond yield oxatropane [25-27].



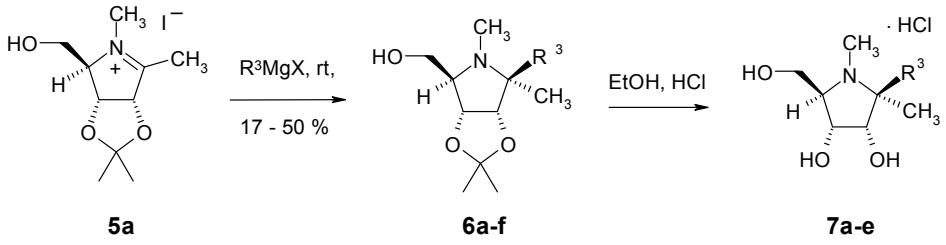
a) $R^1 = CH_3$; b) $R^1 = C_2H_5$; c) $R^1 = C_4H_9$; d) $R^1 = C_8H_{17}$; e) $R^1 = C_{10}H_{21}$

Figure 2. *Synthesis of (2S, 3R, 4R)-1-R^1-N- methiodides -2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolines.*

The highly diastereoselectivity of the Grignard reagents additions the imino double bond (Figure 1) can be understood on the base of the nonchelation control (Cram selectivity) supported by the Yamamoto [28] model. The addition is governed by steric effect, the isopropylidene group reduces the degree of freedom of a molecule and that favors nucleophile approach from the less-hindered β-face of the C=N bond. [12] Metal coordination to oxygen enhanced the steric effect. [29]

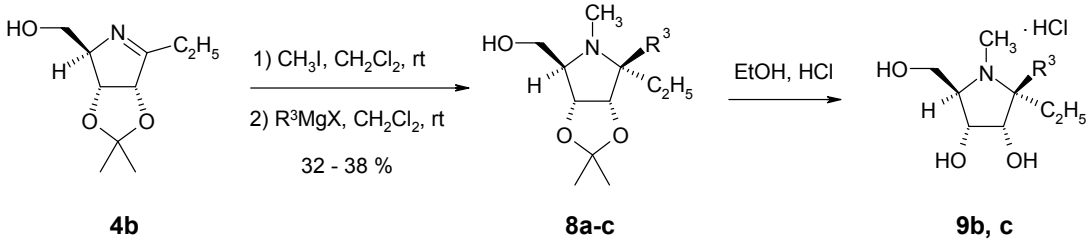
The reactivity of the C=N was increased by addition of Grignard reagent to the *N*-quaternary salts 5, synthetized with iodomethane in methylen chloride. The presence of the $C=N^+X^-$ bond was confirmed by characteristic ^{13}C NMR (C_1 ~ 191 - 185 ppm) relative to imines C=N bond C_1 ~ 179 ppm.

The nucleophilic addition of organometallic reagent to the *N*-quaternary salts (Figure 3) was performed in ether, THF, toluene, or preferably methylene chloride. The ^{13}C NMR signal considerable shifted (191 - 185 ppm → 66.5 ppm) at C_1 confirming the disappearance of the C=N bond. The crude ^1H NMR showed only one diastereomer resulting from β-face attack.



a) R^3 = ; b) R^3 =

c) $R^3 = CH_3$; d) $R^3 = C_4H_9$; e) $R^3 = C_9H_{19}$; f) $R^3 = C_8H_{17}$



a) $R^3 = CH_3$; b) $R^3 = C_4H_9$; c) $R^3 = C_9H_{19}$

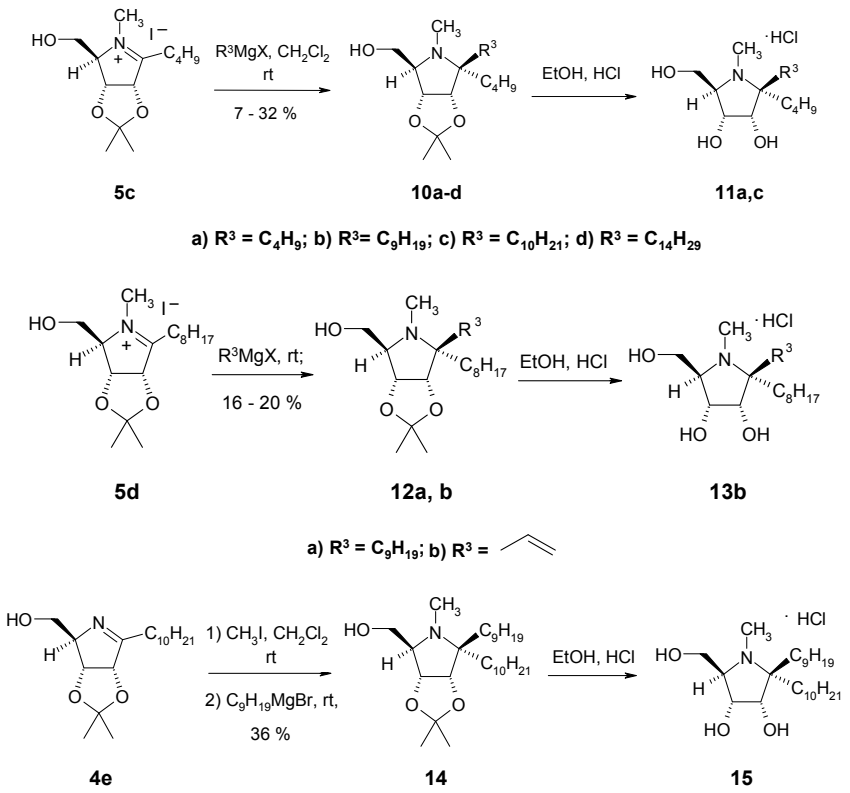


Figure 3. *Synthesis of (2S, 3R, 4R)-N-methyl-1-α-R[1]-1-β-R[3]-2,3-diol-4-hydroxymethyl-1-pyrrolidines.HCl.*

The pyrrolidine (6) ring system is conformationally more flexible than the pyrroline (4, 5) ring system, NMR data assigned based on COSY and HMQC show a switch between H_2 and H_3 in imine 4 relative to *N*-quaternary salts 5: H_2 4.95[ppm], H_3 4.58[ppm] ($J_{3,2}$ = 5.6 Hz. $J_{3,4}$ = 0[Hz]) (4), H_3 5.45[ppm], H_2 4.94[ppm] ($J_{3,2}$ = 5.1 Hz, $J_{3,4}$ = 0[Hz]) (5).

Isopropylidene protecting group and dialkyl chain of pyrrolidines 6 forces the ring to adopt a conformation with vicinal coupling constant *trans* $^3J_{H3H4}$ 3.0 - 4.7[Hz] from shorter alkyl chain to longer alkyl chain, and *cis* $^3J_{H3H2}$ 6.1 - 7.6[Hz], both vicinal coupling constant unexpecting, with values too smaller and two higher for *trans* and *cis* stereochemistry, nan of them under 3-sphere rule, but under ax and eq. rule (J_{AB}^{eq} 5.5[Hz] > J_{AB}^{ax} 2.5[Hz]) [30].

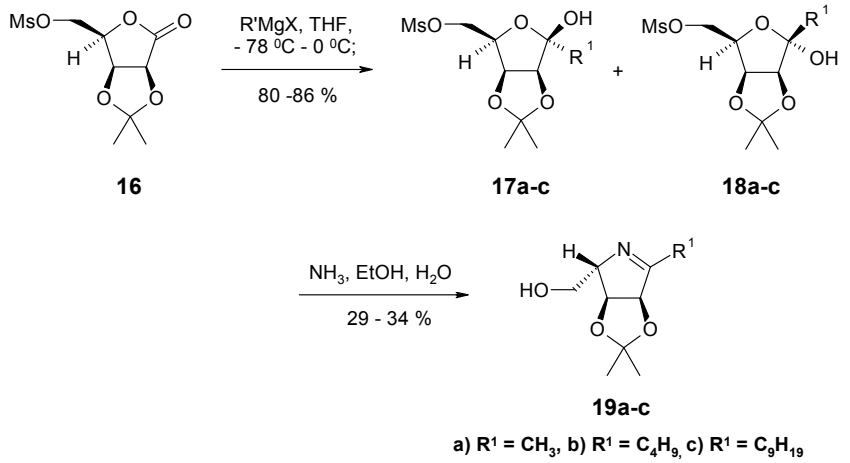


Figure 4. *Synthesis of (2R, 3S, 4S)-1-R[1]-2,3-isopropylidenedioxy-4-hydroxymethyl-1-pyrrolines.*

The vicinal coupling constant $^3J_{H3H2}$ 7.3[Hz] of isopropylidene pyrrolidine 25 with *cis* stereochemistry, as result from 3D COSY NMR spectra, gives a vicinal angle of ϕ = 213.16[deg] under *cis, trans-ee* Rule II (Table 1), instead of *trans-aa* Rule I [7-9] gives a negative dihedral angle *cis*[5,2] θ_{H3H2} -56.84[deg]. In case of *trans* vicinal coupling constant $^3J_{H3H2}$ 4.5[Hz] results a vicinal angle of 81[deg] from *trans*-vicinal equation Rule II and a vicinal angle of 20.25[deg] from *cis*-vicinal equation Rule II (Table 1). Dihedral angles with positive sign in accord with L-ribitol stereochemistry are *trans-aa*[6,1] 171[deg] or *trans-ee*[3,2] 69.7[deg]. In first case result a *cis* torsional angle transformed in *trans-aa*[6,1] dihedral

angle, in second case result a *trans-ee*[3,2] dihedral angles calculated from algebraic equation characteristics for *trans-aa* stereochemistry, respectively Rule II (Table 1), slightly unexpected. Isopropylidene deprotection decreased steric bulkiness and the vicinal coupling constants becomes: 7a $^3J_{H3H4}$ of 5.9[Hz] and $^3J_{H3H2}$ of 4.7[Hz], 9b,c $^3J_{H3H4}$ of 9.2[Hz] and $^3J_{H3H2}$ of 4.0[Hz], 11c $^3J_{H3H4}$ of 8.8[Hz] and $^3J_{H3H2}$ of 5.0[Hz].

Members of the enantiomeric series of compounds have been made in the D-lyxo sugar → L-ribo iminocyclitol series (Figure 4, 5). In the *N*-benzyl series (Figure 6), removal of the benzyl protecting group by hydrogenolysis provided the desired *N*-unprotected iminosugar that could be *N*-alkylated with a long alkyl chain. The *N*-quaternary salts 28 could be a site for cycloaddition reaction *via* ylids.

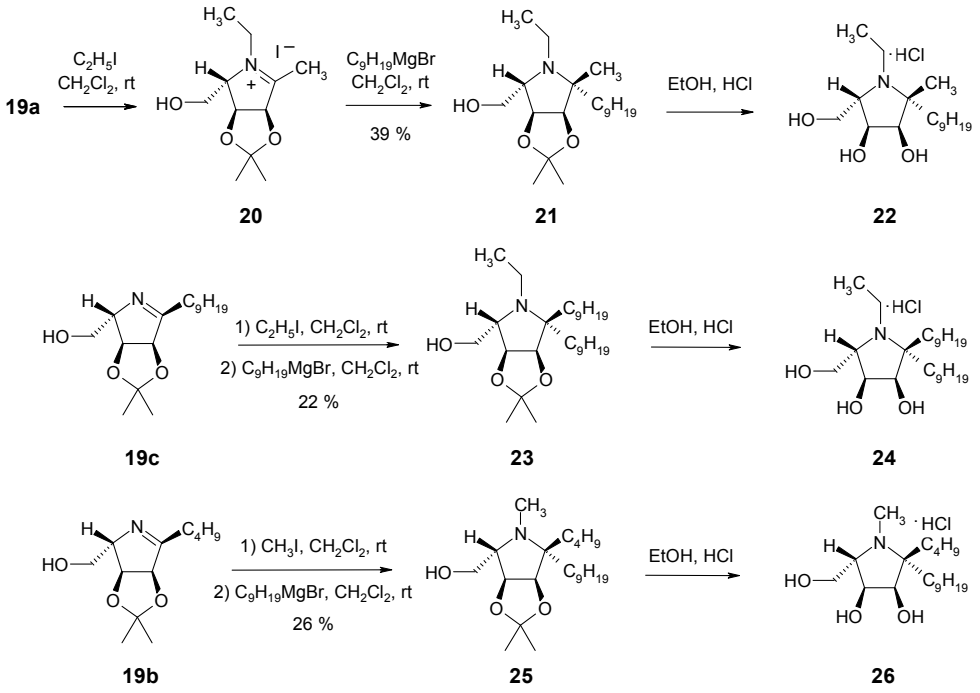


Figure 5. *Synthesis of (2R, 3S, 4S)-N-R^2-1-α-R^3-1-β-R^1-2,3-diol-4-hydroxymethyl-1-pyrrolidines.HCl.*

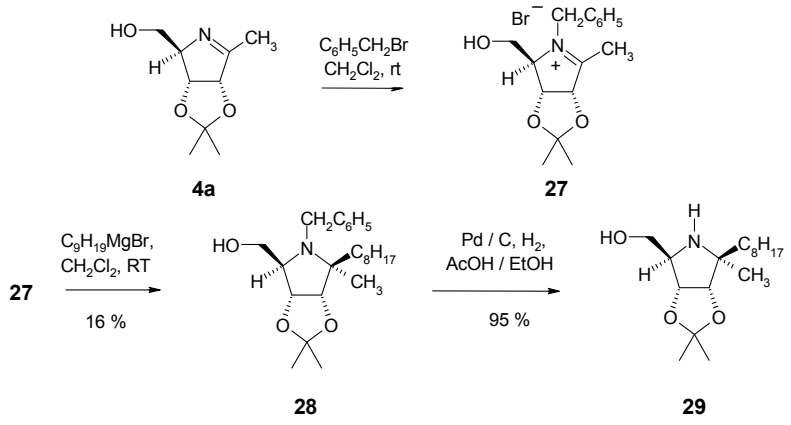


Figure 6. *Synthesis of (2S, 3R, 4R)-1-α-methyl-1-β-octyl-2,3- isopropylidenedioxy-4-hydroxymethyl-1-pyrrolidine.*

The antiviral activity of selected C_1 dialkyl and *N*-alkyl iminocyclitols (7d, 11a, 15, 22, 26) was evaluated in bovine viral diarrhoea virus yield reduction assay (BVDV) [5, 31]. The iminocyclitol 26 *N*-methyl-C_1-butil-nonyl-L-ribitol reduced BVDV virus yield by 50% at less than 2 uM (IC_{50} < 2 uM), while its cytotoxicity concentration to reduce cell viability (MTT assay) is over 100 uM (Figure 7). Therefore, The *N*-alkyl analogue 26 can be considered a lead compound, relative to N-alkyl-monoalkyl-C_1 iminocyclitols, *i.e.* N-nonyl-C_1-nonyl D or L-ribitol (IC_{50} = 4.6 – 8.2 uM) [5], analog to *N*-n-C_1-dodecyl β-L-ribitol trifloroacetate salt 30 (IC_{50} 1.5 uM).

These results demonstrate the potential of these compounds as antivirals for flaviviruses [32]. The missing inhibitory activity of pyrolines with D-ribose stereochemistry without substituent at C_1, as result from QASAR study [33], increased once the alkyl chain are introduced at C_1.

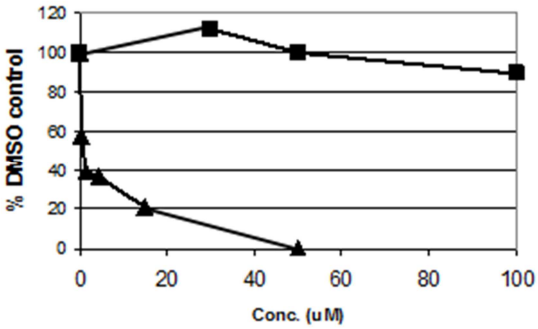


Figure 7. *Activity and toxicity of 26 in MDBK cells against BVDV. Square: Cytotoxicity measurement as % of DMSO control. Triangle: Virus yield as % of DMSO control treatment.*

Hypersphere in 4-D with (n+1) Euclidean coordinates, *N*-manifold with hypersphere, sphere, torus, Hopf coordinates, or from other point of view with points, line, circles a huge mathematics equations which fit well with wave character of NMR data (vicinal coupling constant $^3J_{HH}$[Hz], chemical shift δ_{Cn}[ppm]) for calculation of the physical constant, dihedral angles – tetrahedral angles [9], hypersphere S^3 of quaternion in 4D space and the unit sphere S^2 in 3D space [9, 6]. In table 1 are calculated dihedral angles from carbon chemical shift, in fact are established the best equation on Euclidean space for pyroline 19b, isopropylidene protected pyrrolidine 25 and deprotected pyrrolidine 26. The sign of the dihedral angles results only from the vicinal angle ϕ and its trigonometric equations.

Table 1. *Dihedral angles of 19b, 25, 26, 30 calculated with Hypersphere equations from carbon chemical shift δ_{Cn}[ppm].*

Entry	δ_{Cn}[a] [ppm]	R_m [π][a]	$^3J_{HH}^{exp}$[Hz] ϕ^J, $\theta_{HnHn+1}{}^J$ [deg][f]	$\theta_{HnHn+1}{}^{calc}$ [deg]	ϕ^{calc} [deg]	$^3J_{HH}^{calc}$ [Hz]	3-Sphere equations
1.	19b-C_2: 86.4	2.4201	H_3H_2: 5.5[b]	H_3H_2:-32.79 H_3H_2:-33.77	122.79 123.77	5.54 5.56	H_3H_2-2D: $\theta = -\cos^{-1}[1/(R_m)]/2$ H_3H_2-4D: $\phi = 180 - \sin^{-1}\cos[(\tan^{-1}R_m)/2]$
2.	19b-C_3: 80.4	2.2521	121[b], -31 H_4H_3: bs[b]	H_3H_2: -31.81 H_3H_2: -33.02	121.81 123.02	5.51 5.54	H_3H_2-2D: $\theta = -\cos^{-1}[1/(R_m)]/2$ H_3H_2-4D: $\phi = 180 - \sin^{-1}\cos[(\tan^{-1}R_m)/2]$
3.	19b-C_4: 77.4	2.1680	-	H_4H_3: 88.33 H_4H_3: 87.83	1.66 2.168	0.64 0.73	H_4H_3-4D: $\theta = 2x\tan^{-1}\cos\{[\sin^{-1}(1/R_m)]/2\}$[g] H_4H_3-3D: $\theta = \cos^{-1}\tan R_m$
4.	25-C_1: 66.7	1.8683		H_3H_2: -59.07	210.92	7.26	H_3H_2-4D: $\theta = -\sin^{-1}\cos[(\tan^{-1}R_m)/2]$ H_3H_2-4D: $\phi = 180 + \{\sin^{-1}\cos[\tan^{-1}(1/R_m)]\}/2$
5.	25-C_2: 84.0	2.3529		H_3H_2: -56.51	213.48	7.30	H_3H_2-4D: $\theta = -\sin^{-1}\cos[(\tan^{-1}R_m)/2]$ H_3H_2-4D: $\phi = 180 + \{\sin^{-1}\cos[\tan^{-1}(1/Rm)]\}/2$
6.	25-C_3: 80.0	2.2408	H_3H_2: 7.3[c] 213.16[b], -56.84 H_4H_3: 4.5[c] 20.25[c], 69.75 81[b], 171	H_3H_2: -57.02 Trans-aa[c]: H_4H_3: 171.56 H_4H_3: 173.83 Trans-ee[c]: H_4H_3: 65.95 H_4H_3: 69.04	212.97 81.56 83.82 24.04 20.95	7.29 4.51 4.57 4.903 4.57	H_3H_2-4D: $\theta = -\sin^{-1}\cos[(\tan^{-1}R_m)/2]$ H_3H_2-4D: $\phi = 180 + \{\sin^{-1}\cos[\tan^{-1}(1/R_m)]\}/2$ H_4H_3-2D: $\theta = 180 - \{\tan^{-1}[1/(R_m{}^{1/2})]\}/4$ $\phi = 2x\sin^{-1}[1/(R_m{}^{1/2})]$ $\theta = 180 - \sin^{-1}\cos\phi$ H_4H_3-2D: $\phi = \tan^{-1}(1/R_m)$ H_4H_3-4D: $\theta = \sin^{-1}\cos[\tan^{-1}(1/R_m)]$ H_4H_3-2D: $\phi = [\sin^{-1}1/(R_m{}^{1/2})]/2$ H_4H_3-2D: $\theta = 180 - \{\tan^{1}[1/(R_m{}^{1/2})]\}/4$
7.	25-C_4: 67.8	1.8991		Trans-aa[c]: H_4H_3: 171.01 H_4H_3: 176.95 Trans-ee[c]: H_4H_3: 62.23 H_4H_3: 68.26	81.01 86.95 27.76 21.73	4.50 4.66 4.90 4.66	H_4H_3-2D: $\phi = 2x\cos^{-1}[1/(R_m{}^{1/2})]$ $\theta = 180 - \sin^{-1}\cos\phi$ H_4H_3-2D: $\phi = \tan^{-1}[1/(R_m)]$ H_4H_3-4D: $\theta = \sin^{-1}\cos[\tan^{-1}(1/Rm)]$ H_4H_3-2D: $\phi = \{\cos^{1}[1/(R_m{}^{1/2})]\}/2$
8.	26-C_1: 77.9	2.1820		H_3H_2: 27.27	62.72	3.95	H_3H_2-2D: $\theta = \sin^{-1}(1/R_m)$ H_3H_2-2D: $\phi = \cos^{-1}(1/R_m)$
9.	26-C_2: 75.0	2.1008	H_3H_2: 3.9[c]	H_3H_2: 28.42	61.57	3.92	H_3H_2-2D: $\theta = \sin^{-1}(1/R_m)$ H_3H_2-2D: $\phi = \cos^{-1}(1/R_m)$
10.	26-C_3: 68.8	1.9271	60.84, 29.16 H_4H_3: 9.1[c] 82.81, 172.81	H_3H_2: 29.37 H_3H_2: 27.48	60.62 62.51	3.89 3.95	H_3H_2-2D: $\theta = [\cos^{-1}(1/R_m)]/2$ H_3H_2-2D: $\phi = 2x[\sin^{-1}(1/R_m)]$
11.	26-C_4: 74.9	2.0980		H_4H_3: 171.34 H_4H_3: 172.63	81.34 82.63	9.01 9.09	H_4H_3-2D: $\theta = 180 + \tan^{-1}(-1/R_m{}^{1/2})/4$ H_4H_3-4D: $\phi = 2x\tan^{-1}\cos[\sin^{-1}(1/R_m)]$ $\theta = 180 - \sin^{-1}\cos\phi$
12.[d]	30-C_1: 63.3[e]	1.773		H_1H_2: 58.84 H_1H_2: 59.71	31.15 30.28	2.79 2.75	H_1H_2-2D: $\theta = 2x\tan^{-1}(1/R_m)$ H_1H_2-2D: $\phi = [\tan^{-1}(R_m)]/2$
13.[d]	30-C_2: 72.1[e]	2.019	H_1H_2: 2.8[b,d] 31.36, 58.64	H_2H_3: 37.31 H_2H_3: 38.41	52.69 51.59	3.62 3.59	H_2H_3-2D: $\phi = 2x\tan^{-1}(1/R_m)$ H_4H_3-4D: $\theta = \{\sin^{-1}\cos[\tan^{-1}(1/R_m)]/2\}/2$
14.[d]	30-C_3: 73.4[e]	2.056	H_2H_3: 3.6 [b,d] 51.84, 38.16	H_2H_3: 38.12 H_2H_3: 38.12	51.87 51.48	3.60 3.58	H_2H_3-2D: $\phi = 2x\tan^{-1}(1/R_m)$ H_4H_3-4D: $\theta = \{\sin^{-1}\cos[\tan^{-1}(1/R_m)]/2\}/2$
15.[d]	30-C_4: 63.9[e]	1.789	H_3H_4: 8.8 [b,d] 77.44, 167.44	H_3H_4: 166.6 H_3H_4: 167.9	76.6 77.9	8.75 8.82	H_3H_4-2D: $\theta = \tan^{-1}(-1/R_m{}^{1/2})/4$ $\phi = \sin^{-1}[1/(R_m{}^{1/2})]/4$ $\theta = 180 - \sin^{-1}\cos\phi$

[a] δ[ppm], ^{1}H-NMR 400MHz, ^{13}C-NMR 75MHz, 19b, 25 $CDCl_3$, 26, 30 CD_3OD; $R_m = (\delta_C x \omega_C x 4x10^{-3})/10.71$[gauss]; [b] Rule I: *cis, trans-ee*: $^3J_{HH} = \phi^{1/2}/2$, *trans-aa*: $^3J_{HH} = \phi^{1/2}$; [c] Rule II: *cis*, *trans-ee*: $^3J_{HH} = \phi^{1/2}$, *trans-aa*: $^3J_{HH} = \phi^{1/2}/2$; [d] compound 8b in reference 5; [e] NMR data from supporting information reference 5; [f] reference 7; [g] reference 11.

Higher antiviral activity of trifluoroacetate salt β-L-ribitol with dodecyl chain at C_1 (IC_{50} 1.5 uM) was explained by the tangential space, all the equations are under Dupin cyclide equations [11]. In case of iminocyclitol with trialkyl chain (19a, 25, 26) results coordinates between 4D to 2D without higher symmetry as observed in case of mono- and dialkyl chain [11]. (2R, 3S, 4S)-*N*-Methyl-1-α-nonyl-1-β-butyl-2,3-diol-4-hydroxymethyl-1-pyrrolidines.HCl 26 with IC_{50} << 2uM with dihedral angle *trans-aa*^{6,1} θ_{H4H3} result from *tan* function (Table 1, entry 11) and θ_{H3H2} with *cis* stereochemistry from cos function (Table 1, entry 8-10), invers of circle *versus* circle equations, Dupin cyclide *versus* torus equations, excepting the dihedral angle θ_{H3H2} calculated from C_3 in tangential space (Table 1, entry 10, Figure 8). Unsubstituted nitrogen atom [5] or shorter alkyl chain (*i.e.* methyl 26) have also higher antiviral activity, potential mimics of glycofuranosyl cation [3, 4, 34] The values of R_m (2.0-2.4) are around icosahedron (2.56) or borderline (1.8 – 1.9) with dodecahedron (1.6) (Table 1).

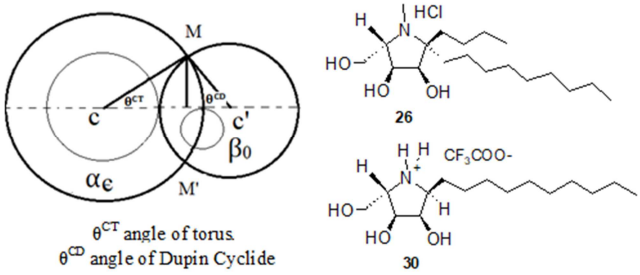


Figure 8. *Torus and Dupin cyclide circles. N-Methyl-C_1-butil, nonyl-L-ribitol.HCl 26 and N-n-C_1-dodecyl β-L-ribitol trifloroacetate salt 30.*

4. Conclusion

Iminocyclitols bearing three alkyl chains synthesized by Grignard reagents addition to *N*-quaternary pyrrolines salts with high diastereoselectivity are evaluated in bovine viral diarrhea virus assay (BVDV) surrogate for hepatitis C. Dihedral angles are calculated from carbon chemical shift without building unit with 3-sphere theory for pyroline 19b, isopropylidene protected pyrrolidine 25 and deprotected pyrrolidine 26. The sign of the dihedral angles results only from the vicinal angle ϕ and its trigonometric equations. Attempts to found explication between antiviral activity and structure of iminocyclitols based on tangential space or 2D coordinate of torus – Dupin ciclide.

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