Synthesis of 3-Glycosyl-5-substituted-2-isoxazolines

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The synthesis of eight 3-glycosyl-5-substituted-2-isoxazolines is described. They are obtained by 1,3-dipolar cycloaddition from some 2-deoxy-sugar oximes. A side product was isolated. The physical and spectroscopycal characterization of all compounds are reported.

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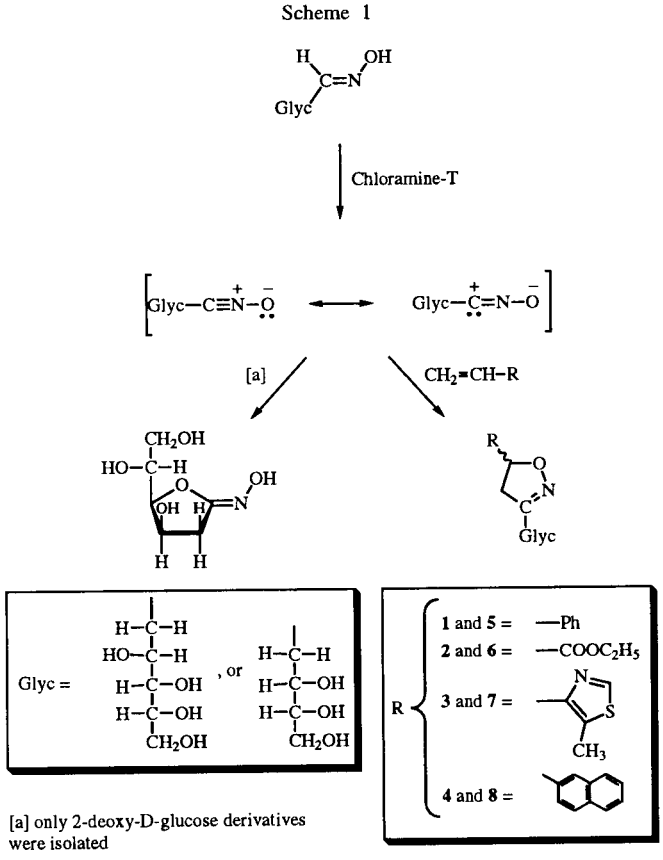
1,3-Dipolar cycloaddition is a general method to synthesize five-membered rings. Particularly, nitrile oxides have been widely used to obtain isoxazoline derivatives [1]. This heterocyclic ring is an interesting intermediate in natural product syntheses. Its interaction with reducing agents can yield: a) γ-amino alcohols; b) β-hydroxyketones and c) β-hydroxynitriles [2].

The application of this cycloaddition in the carbohydrate field not only allows us to obtain nucleoside analogues with possible biological activity, but also, the resulting polyfunctional molecule provides an important tool for further synthetic procedures [3].

In this work, we report the reactions of 2-deoxy-D-glucose oxime and 2-deoxy-D-ribose oxime with Chloramine-T [4] in the presence of some dipolarophiles, as shown in Scheme 1.

Scheme 1



[a] only 2-deoxy-D-glucose derivatives were isolated

As observed, 2-isoxazolines can be obtained in only two steps in moderate yields and without protection of the hydroxyl group. In Figure 1 we show the 2-deoxy-D-glucose oxime derivatives obtained using as dipolarophiles styrene, ethyl acrylate, 4-methyl-5-vinylthiazole and 2-vinylnaphthalene **1-4** and the corresponding 2-deoxy-D-ribose oxime derivatives **5-8** which were obtained using the same olefinic reactives.

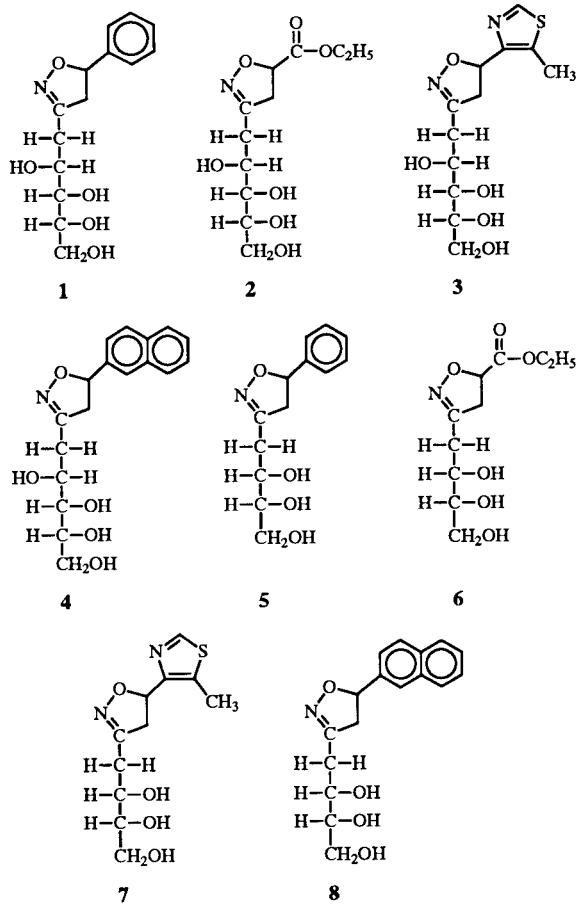


Figure 1.

Oximes were synthesized from the corresponding sugars using hidroxylamine as described in the literature [5].

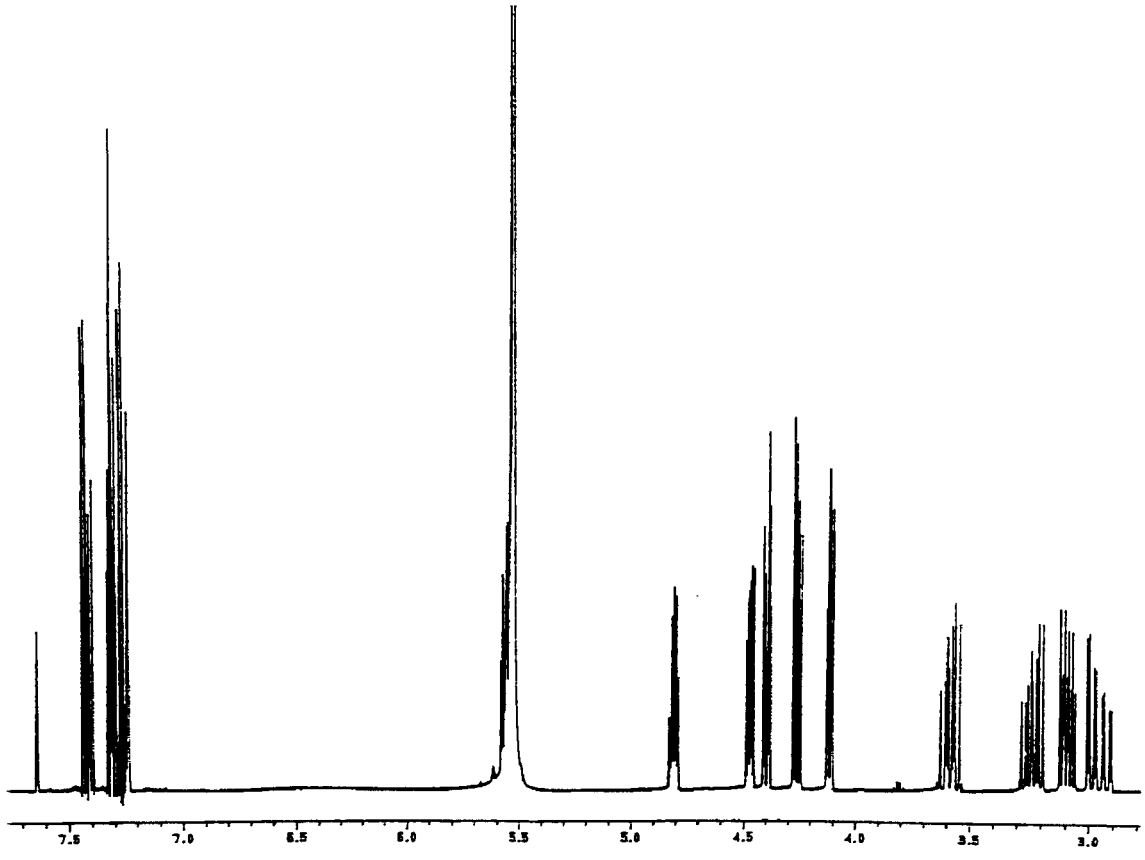


Figure 2.

The oxidation of 2-deoxy-D-glucose oxime with Chloramine-T affords 2-isoxazoline derivatives together with the 1,3-addition product, which was charaterised as 2-deoxy-D-gluconohydroximo-1,4-lactone (**9**). The last compound is the only product when the reaction is realised in organic solvents. The same reaction using 2-deoxy-D-ribose oxime gives isoxazolines in similar yields, but in this case, we could not isolate the analagous 1,3-addition product.

The formation of compound **9** confirms that the oxidation with Chloramine-T takes place *via* a nitrile oxide

Table 1

^{1}H-NMR Chemical Shifts (δ) Multiplicities of compound **1-8**

Compound	H-1'a	H-1'b	H-2'	H-3'	H-4'	H-5'a	H-5'b	H-4a	H-4b	H-5
1	2.99 dd	3.22 dd	4.80 ddd	4.11 dd	4.47 ddd	4.26 dd	4.40 dd	3.10 dd	3.57 dd	5.51 dd
1'	2.93 dd	3.26 dd	4.81 ddd	4.12 dd	4.47 ddd	4.26 dd	4.40 dd	3.09 dd	3.60 dd	5.52 dd
2	2.55 dd	2.70 dd	4.10 ddd	3.40 dd	3.69 ddd	3.59 dd	3.79 dd	3.30 dd	3.48 dd	5.12 dd
3	3.08 dd	3.33 dd	4.94 m	4.22 m	4.58 ddd	4.39 dd	4.53 dd	3.21 dd	3.68 dd	5.93 dd
3'	3.06 dd	3.35 dd	4.94 m	4.22 m	4.58 ddd	4.39 dd	4.53 dd	3.24 dd	3.69 dd	5.94 dd
4	2.92 dd	3.17 dd	4.76 m	4.04 m	4.37 m	4.20 m	4.34 dd	3.15 dd	3.51 dd	5.64 dd
4'	2.90 dd	3.18 dd	4.76 m	4.04 m	4.37 m	4.20 m	4.35 dd	3.15 dd	3.53 dd	5.65 dd
	H-1'a	H-1'b	H-2'	H-3'	H-4'a	H-4'b		H-4a	H-4b	H-5
5	3.14 dd	3.32 dd	4.50 m	4.21 m	4.31 dd	4.41 dd		3.24 dd	3.57 dd	5.64 dd
6	2.96 dd	3.14 dd	4.34 ddd	4.04 ddd	4.14 dd	4.23 dd		3.16 dd	3.44 dd	5.04 dd
6'	2.94 dd	3.14 dd	4.34 ddd	4.04 ddd	4.13 dd	4.22 dd		3.16 dd	3.55 dd	5.07 dd
7	3.15 dd	3.33 dd	4.51 ddd	4.22 ddd	4.32 dd	4.41 dd		3.21 dd	3.72 dd	5.91 dd
7'	3.13 dd	3.34 dd	4.52 ddd	4.22 ddd	4.31 dd	4.40 dd		3.25 dd	3.67 dd	5.94 dd
8	3.02 dd	3.23 dd	4.41 ddd	4.09 ddd	4.18 dd	4.27 dd		3.19 dd	3.60 dd	5.68 dd
8'	3.04 dd	3.21 dd	4.32 ddd	4.09 ddd	4.18 dd	4.27 dd		3.23 dd	3.54 dd	5.69 dd

All the spectra were performed at 500 MHz in pyridine-d_5, except the spectrum of compound **2** which was performed at 200 MHz in deuterium oxide.

Table 2

Vicinal Proton-Proton Coupling Constants (Hz) of Compound **1-8**

Compound	$J_{1'a,2'}$	$J_{1'b,2'}$	$J_{1'a,1'b}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{4a,5}$	$J_{4b,5}$	$J_{4a,4b}$
1	4.5	9.4	14.6	2.0	8.4	5.7	3.7	11.2	8.6	10.8	17.3
1'	4.2	9.4	14.6	2.6	8.4	5.7	3.8	11.2	8.4	10.9	17.2
2	4.7	9.0	15.2	1.9	8.1	5.6	2.5	10.8	6.6	11.4	17.9
3	4.6	9.5	14.5			5.6	4.0	10.9	8.6	10.6	17.1
3'	4.3	9.9	14.5			5.6	4.0	10.9	8.3	10.6	17.2
4	4.3	9.7	14.5			5.4	3.3	11.0	8.4	10.8	17.1
4'	4.4	8.7	14.5			5.4	3.3	11.0	8.4	10.9	17.1
	$J_{1'a,2'}$	$J_{1'b,2'}$	$J_{1'a,1'b}$	$J_{2',3'}$	$J_{3',4'a}$	$J_{3',4'b}$	$J_{4'a,4'b}$		$J_{4a,5}$	$J_{4b,5}$	$J_{4a,4b}$
5	9.5	2.8	14.6	5.7	5.8	3.9	10.9		8.3	10.9	17.1
6	8.7	3.1	14.7	10.5	6.0	4.2	10.9		6.9	11.6	17.4
6'	8.5	3.1	14.7	10.5	5.8	4.1	11.0		6.9	7.0	17.4
7	9.4	3.2	14.7	6.0	5.9	4.3	11.0		8.4	10.5	17.2
7'	9.3	3.3	14.7	6.0	5.8	4.2	11.0		8.5	10.5	17.1
8	9.4	3.2	14.5	6.3	5.9	4.2	10.9		8.1	10.8	17.2
8'	9.5	3.2	14.5	6.3	5.9	4.2	10.9		8.4	10.8	17.2

All the spectra were performed at 500 MHz in pyridine-d_5, except spectrum of compound **2** which is performed at 200 MHz in deuterium oxide.

intermediate. The cycloaddition of this dipole to monosubstituted alkenes is regioselective but not stereoselective. In most of the cases, we obtained the diastereoisomeric pair as a 1:1 unresolved mixture of epimers.

In Figure 2 we show the spectrum of compound **1** at 500 MHz in pyridine-d_5, where we observe the duplication of signals.

The analysis of the ^{1}H-mnr spectra of compounds **1-8** allow us to observe the duplication of the signals near the new chiral centre (C-5), in most of the cases. The chemical shifts and the coupling constants are listed in Tables 1 and 2.

The epimeric pair was also observed in the ^{13}C-nmr spectrum. Several signals appear duplicated (Table 3).

The total assignment of the ^{13}C-nmr spectra may be performed by a 2D-heteronuclear spectrum. As the model compound we chose **2**, as this compound was obtained as only one epimer.

The mass spectra of all the compounds were analyzed. The molecular ion peak was found to be present in all of them with low intensities.

The characteristic fragmentation patterns are:

- The retro 1,3-cycloaddition with formation of the ion-radical of the dipolarophile and the products of it.
- The succesive loss of 30 u.m.a. from the molecular ion, due to the fragmentation of the polyhydroxyl chain.
- The hydrogen rearrangement with loss of the hydroxyl

Table 3

^{13}C-NMR Chemical Shifts (δ) of Compounds **1-8**

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-3	C-4	C-5	Solvent
1	32.1	67.7	73.1	71.6	63.9	157.9	45.1	80.7	DMSO-d_6
1'	32.2	67.8	73.1	71.6	63.9	157.9	45.2	80.6	
2	31.9	68.0	73.4	71.8	63.9	160.4	42.3	77.6	deuterium oxide
3	32.3	68.2	73.5	72.0	64.0	161.3	45.8	75.7	deuterium oxide
3'	32.3	68.0	73.5	72.0	64.0	161.3	45.8	75.7	
4	33.1	69.1	74.5	73.0	65.0	158.0	45.7	81.6	pyridine-d_5
4'	33.0	69.3	74.5	73.0	65.0	158.0	45.9	81.5	
5	32.6	71.1	75.9	64.7		158.2	46.1	81.5	pyridine-d_5
5'	32.6	70.9	75.9	64.7		158.2	46.1	81.5	
6	32.1	70.8	75.7	64.6		158.1	41.9	77.6	pyridine-d_5
6'	32.1	71.0	75.7	64.6		158.1	42.2	77.6	
7	31.6	69.8	75.3	63.3		161.3	45.8	75.7	deuterium oxide
7'	31.6	69.8	75.3	63.3		161.3	45.8	75.7	
8	32.5	71.0	75.8	64.6		158.1	46.1	81.4	pyridine-d_5
8'	32.5	71.0	75.8	64.6		158.1	45.9	81.4	

Compound **1** and **5** - Aromatic carbons: 126.2-142.5, Compound **2** - Carbonilic carbon: 173.5; methyl group: 14.1; methylene group: 63.9, Compound **6** - Carbonilic carbon: 170.4; methyl group: 21.3; methylene group: 69.0, Compound **3** - Thiazolic carbons: 154.5, 151.3, 131.9; Methyl group: 14.8, Compound **7** - Thiazolic carbons: 154.4, 151.2, 131.8; Methyl group: 14.8, Compound **4** and **8** - Aromatic Carbons: 122.7-139.7.

chain with formation of 3-methyl-5-substituted-2-isoxazolines as the ion radical.

The principal ions for each compound are listed in the Experimental.

EXPERIMENTAL

General Methods.

Melting points were measured on a Unimelt apparatus and are uncorrected. Optical rotations were determined at 20° with a Perkin-Elmer 141 Polarimeter. The ^{1}H-nmr spectra were recorded with a Bruker EM 360A instrument at 200 or 500 MHz and the ^{13}C-nmr spectra were recorded at 50 MHz for solutions in perdeuteriopyridine or deuterium oxide with TMS as the internal standard. Mass spectra were performed by electron impact ionization. Analysis (tlc) was performed on plates coated with Silica Gel G (Merck, Darmstadt) with toluene-ethanol (1:1) as the eluent and potasium permanganate-sodium periodate [1:4] for detection.

General Procedure I.

3-(2'-Deoxy-D-*gluco*-pentitol-1'yl)-5-substituted-2-isoxazoline.

To a solution of 2-deoxy-D-glucose oxime (1.00 g, 5.58 mmoles) in water at 0°, a solution of dipolarophile in ethanol was added (it is very important that only one phase is formed). Finally, 2.00 g (7.1 mmoles) of Chloramine-T was added slowly. The reaction was followed by thin layer chromatography with toluene-ethanol (1:1) as the eluent. If not all the oxime reacted, a second portion of Chloramine-T can be added until no more oxime could be observed. The reaction mixture was evaporated and *p*-toluenesulfonamide was extracted with dichloromethane. The aqueous phase was evaporated and purified.

3-(2'-Deoxy-D-*gluco*-pentitol-1'-yl)-5-phenyl-2-isoxazoline (**1**)

The general procedure I was applied using styrene (in excess) as the dipolarophile to obtain **1**. This compound was purified by flash chromatography with toluene-ethanol (8:2) and recrystallized from ethanol/water to give **1** (0.65 g, 42%); mp 154-156°; $[\alpha]_D$ -29.8 (c 1, methanol:water 4:1); ms: 281 ($M^{+\bullet}$), 250 ($M^{+\bullet}$ -$HOCH_2\bullet$), 249 ($M^{+\bullet}$ -CH_3OH), 220 ($M^{+\bullet}$-$C_2H_5O_2\bullet$), 190 ($M^{+\bullet}$ -$C_3H_7O_3\bullet$), 161 ($C_{10}H_{11}NO^{+\bullet}$, base peak), 104 ($C_8H_8^{+\bullet}$). The ^{1}H and ^{13}C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.79; H, 6.76; N, 4.98. Found: C, 60.08; H, 7.05; N, 4.78.

3-(2'-Deoxy-D-*gluco*-pentitol-1'-yl)-5-carboxyethyl-2-isoxazoline (**2**).

The general procedure I was applied using ethyl acrylate (in excess) as the dipolarophile to obtain **2**. This compound was recrystallized from ethanol:water to give **2** (0.43 g, yield 28%), mp 160-161°; $[\alpha]_D$ -86.0 (c 1, water); ms: 277 ($M^{+\bullet}$), 246 ($M^{+\bullet}$ -$HOCH_2\bullet$), 216 ($M^{+\bullet}$ -$C_2H_5O_2\bullet$), 186 ($M^{+\bullet}$ -$C_3H_7O_3\bullet$), 157 ($C_7H_{11}NO_3^{+\bullet}$), 112 ($C_7H_{11}NO_3^{+\bullet}$-$C_2H_5O\bullet$), 84 ($C_7H_{11}NO_3^{+\bullet}$-$C_2H_5O\bullet$-CO; base peak). The ^{1}H and ^{13}C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for $C_{11}H_{19}NO_7$: C, 47.65; H, 6.86; N, 5.06. Found: C, 47.96; H, 6.80; N, 5.30.

3-(2'-Deoxy-D-*gluco*-pentitol-1'-yl)-5-(5-(4-methyl-thiazole))-2-isoxazoline (**3**).

The general procedure I was applied using 4-methyl-5-vinylthiazole (in excess) as the dipolarophile to obtain **3**. This compound was purified by flash chromatography RP-18 and recrystallized from dioxane-water to give **3** (0.67 g, yield 40%), mp 160-163°; $[\alpha]_D$ +63.1 (c 1, methanol); ms: 302 ($M^{+\bullet}$), 271 ($M^{+\bullet}$ -$HOCH_2\bullet$), 270 ($M^{+\bullet}$ -CH_3OH), 241 ($M^{+\bullet}$ -$C_2H_5O_2\bullet$), 211 ($M^{+\bullet}$ -$C_3H_7O_3\bullet$), 182 ($C_8H_{10}N_2O_3S^{+\bullet}$), 125 ($C_6H_7NS^{+\bullet}$), 61 ($C_2H_5O_2^+$; base peak). The ^{1}H and ^{13}C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for $C_{12}H_{18}N_2O_5S$: C, 47.68; H, 5.96; N, 9.27; S, 10.60. Found: C, 47.94; H, 6.25; N, 8.99; S, 10.47.

3-(2'-Deoxy-D-*gluco*-pentitol-1'-yl)-5-naphtyl-2-isoxazoline (**4**).

To a solution of 2-deoxy-D-glucose oxime (1.00 g, 5.58 mmoles) in water at 0° a solution of 2-vinylnaphthalene in ethanol was added (it is very important that only one phase is formed). Finally, 2.00 g (7.1 mmoles) of Chloramine-T was added slowly. The reaction was followed by thin layer chromatography with toluene-ethanol (1:1) as the eluent. If not all the oxime reacted a second portion of Chloramine-T can be added until no more oxime could be observed. The reaction mixture was evaporated and extracted with ethyl acetate. The solution was kept at 0° and compound **4** precipitated. It was recrystallized from water to give 0.55 g (yield 30%), mp 181-183°; $[\alpha]_D$ +9.8 (c 1, pyridine); ms: (FAB) 332 ($MH^{+\bullet}$).

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.26; H, 6.34. Found: C, 65.02; H, 6.53.

General Procedure II.

3-(2'-Deoxy-D-*ribo*-tetritol-1'-yl)-5-substituted-2-isoxazoline.

To a solution of 2-deoxy-D-ribose (1.00 g, 7.46 mmoles) in water, a solution of hydroxylamine in ethanol was added (this solution was obtained by adding 0.6 g of hydroxylamine hydrochloride in water (2 ml) to a solution of 0.18 g of sodium in ethanol (10 ml)). The solution was stirred at room temperature for 1 hour. A solution of dipolarophile in ethanol and finally, 2.1 g of Chloramine-T was added. The reaction mixture was evaporated and *p*-toluenesulfonamide was extracted with dichloromethane. The aqueous phase was evaporated and purified.

3-(2'-Deoxy-D-*ribo*-tetritol-1'-yl)-5-phenyl-2-isoxazoline (**5**).

The general procedure II was applied using styrene (in excess) as the dipolarophile to obtain **5**. This compound was purified by flash chromatography with toluene-ethanol (9:1) and recrystallized from 2-propanol to give **5** (0.90 g, yield 51%), mp 100-102°; $[\alpha]_D$ +157.2 (c 1, methanol); ms: 251 ($M^{+\bullet}$), 220 ($M^{+\bullet}$ -$HOCH_2\bullet$), 219 ($M^{+\bullet}$ -CH_3OH), 190 ($M^{+\bullet}$ -$C_2H_5O_2\bullet$), 161 ($C_{10}H_{11}NO^{+\bullet}$), 104 ($C_8H_8^{+\bullet}$), 61 ($C_2H_5O^+$), 43 ($C_2H_5O^+$-$H_2O$, base peak). The ^{1}H and ^{13}C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.77. Found: C, 61.89; H, 6.76.

3-(2'-Deoxy-D-*ribo*-tetritol-1'-yl)-5-carboxyethyl-2-isoxazoline (**6**).

The general procedure II was applied using ethyl acrylate (in excess) as the dipolarophile to obtain **6**, which was purified by flash chromatography (toluene:ethanol 9:1 as eluent) to give 0.49 g as a syrup (yield 28%), $[\alpha]_D$ -17.2 (c 1, methanol); ms: 247 ($M^{+\bullet}$), 216 ($M^{+\bullet}$ -$HOCH_2\bullet$), 186 ($M^{+\bullet}$ -$C_2H_5O_2\bullet$), 157 ($C_7H_{11}NO_3^{+\bullet}$), 112 ($C_7H_{11}NO_3^{+\bullet}$-$C_2H_5O\bullet$), 84 ($C_7H_{11}NO_3^{+\bullet}$-$C_2H_5O\bullet$-CO), 61 ($C_2H_5O^+$), 43 ($C_2H_5O^+$-H_2O, base peak). The ^{1}H and ^{13}C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for $C_{10}H_{17}NO_6$: C, 48.58; H, 6.87. Found: C, 48.44; H, 6.90.

3-(2'-Deoxy-D-*ribo*-tetritol-1'-yl)-5-(5-(4-methylthiazole))-2-isoxazoline (**7**).

The general procedure II was applied using 4-methyl-5-vinylthiazole (in excess) to obtain **7** which was purified by flash chromatography RP-18 to give 0.51 g of **7** as a syrup (yield 25%); $[\alpha]_D$ -20.3 (c 2, methanol); ms: 272 ($M^{+\bullet}$), 241 ($M^{+\bullet}$ -$HOCH_2\bullet$), 240 ($M^{+\bullet}$ -CH_3OH), 211 ($M^{+\bullet}$ -$C_2H_5O_2\bullet$), 182 ($C_8H_{10}N_2O_3S^{+\bullet}$), 125 ($C_6H_7NS^{+\bullet}$), 61 ($C_2H_5O_2^+$), 43 ($C_2H_5O^+$-$H_2O$, base peak). The ^1H and ^{13}C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for $C_{11}H_{16}N_2O_4S$: C, 48.53; H, 5.88. Found: C, 48.80; H, 6.00.

3-(2'-Deoxy-D-*ribo*-tetritol-1'-yl)-5-naphtyl-2-isoxazoline (**8**).

To a solution of 2-deoxy-D-ribose (1.00 g, 7.46 mmoles) in water, a solution of hydroxylamine in ethanol was added (this solution was obtained to added 0.6 g of hydroxylamine hydrochloride in water (2 ml) to a solution of 0.18 g of sodium in ethanol (10 ml)). The solution was stirred at room temperature for 1 hour. A solution of 2-vinylnaphthalene in ethanol and finally, 2.1 g of Chloramine-T was added. The reaction mixture was evaporated and was extracted with ethyl acetate. The solution was kept at 0° and compound **8** precipitated and it was recrystallized from ethyl acetate to give 0.81 g (yield 35%), mp 152-154°; $[\alpha]_D$ -98.3 (c 1, methanol); ms: 301 ($M^{+\bullet}$), 270 ($M^{+\bullet}$ -$HOCH_2\bullet$), 269 ($M^{+\bullet}$ -CH_3OH), 240 ($M^{+\bullet}$ -$C_2H_5O_2\bullet$), 211 ($C_{14}H_{13}NO^{+\bullet}$), 154 ($C_{12}H_{10}^{+\bullet}$, base peak), 61 ($C_2H_5O^+$), 43 ($C_2H_5O^+$-$H_2O$). The ^1H and ^{13}C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.78; H, 6.31. Found: C, 67.99; H, 6.66.

2-Deoxy-D-gluconohydroximo-1,4-lactone (**9**).

To a solution of 2-deoxy-D-glucose oxime (1.00 g, 5.58 mmoles) in ethanol, 2.00 g (7.1 mmoles) of chloramine-T was added slowly. The reaction was followed by thin layer chromatography with toluene-ethanol (1:1) as the eluent. The reaction mixture was evaporated and *p*-toluenesulfonamide was extracted with dichloromethane. The aqueous phase was evaporated and the solid obtained was recrystallized from water, compound **9** was obtained (0.62 g, yield 67%). mp 180-181°; $[\alpha]_D$+19.8 (c 1, methanol); ms: 177 ($M^{+\bullet}$), 146 ($M^{+\bullet}$ -$HOCH_2\bullet$), 117 ($M^{+\bullet}$ -$C_2H_4O_2$), 116 ($M^{+\bullet}$ -$C_2H_5O_2\bullet$), 99 ($M^{+\bullet}$ -$C_2H_4O_2$-H_2O, base peak), 57 ($C_3H_5O^+$). ^1H nmr (200 MHz, deuterium oxide): H-2a 2.60 (d, $J_{2a,3} < 1$), H-2b 3.01 (dd, $J_{2b,3}$ 4.9), H-3 4.65 (dd, $J_{2a,2b}$ 17.1), H-4 4.41 (dd, $J_{3,4}$ 3.1), H-5 4.00 (m, $J_{4,5}$ 9.2), H-6a 3.73 (dd, $J_{5,6a}$ 2.7), H-6b 3.88 (dd, $J_{5,6b}$ 5.4, $J_{6a,6b}$ 12.2); ^{13}C nmr (50 MHz, deuterium oxide): C-1 161.8, C-2 36.8, C-3 C-5 69.2, C-4 86.5, C-6 64.8.

Anal. Calcd. for $C_6H_{11}NO_5$: C, 40.68; H, 6.21; N, 7.91. Found: C, 40.88; H, 5.99; N, 8.23.

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