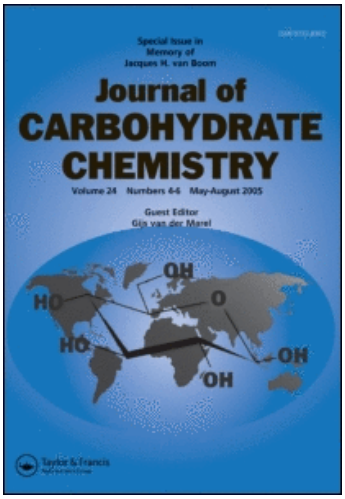

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Spin Labelled *C*-Glycoside Analogs: Derivatives of 1,4-Anhydro-4-deoxy-2,3-*O*-cyclopentylidene-l,4-*N*-hydroxyimino-DL-erythrofuranose

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To cite this Article Tronchet, Jean M. J. , Balkadjian, Mirna , Zosimo-Landolfo, Guido , Barbalat-Rey, Françoise , Lichtle, Patrick , Ricca, Alessandra , Komaromi, Istvan , Bernardinelli, Gérald and Geoffroy, Michel(1995) 'Spin Labelled *C*-Glycoside Analogs: Derivatives of 1,4-Anhydro-4-deoxy-2,3-*O*-cyclopentylidene-l,4-*N*-hydroxyimino-DL-erythrofuranose', Journal of Carbohydrate Chemistry, 14: 1, 17 — 34
To link to this Article: DOI: 10.1080/07328309508006434
URL: http://dx.doi.org/10.1080/07328309508006434

J. CARBOHYDRATE CHEMISTRY, 14(1), 17-34 (1995)

SPIN LABELLED *C*-GLYCOSIDE ANALOGS: DERIVATIVES OF 1,4-ANHYDRO-4-DEOXY-2,3-*O*-CYCLOPENTYLIDENE-1,4-*N*-HYDROXYIMINO-DL-ERYTHROFURANOSE

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Received April 15, 1994 - Final Form August 31, 1994

ABSTRACT

A series of 2,3-*O*-cyclopentylidene *C*-glycoside analogs in which the furanose ring has been replaced with a *N*-hydroxypyrrolidine have been prepared. A structural study of these tricyclic compounds and the aminoxyl radicals thereof has been carried out using variable temperature ^{1}H NMR, X-ray diffraction, molecular dynamics and EPR spectroscopy. Both types of compounds, *N*-hydroxypyrrolidines and pyrrolidine *N*-oxyls, fundamentally prefer - in solutions - N-*endo* conformations over the alternate, N-*exo* forms found by X-ray diffraction studies and computed to be more stable by molecular dynamics.

INTRODUCTION

"Azasugars", sugars in which the ring oxygen has been replaced with a nitrogen atom, constitute useful analogs of natural sugars, *i.e.* anti-HIV glycosidase inhibitors in the case of piperidine derivatives.[1] We have described a number of *N*-hydroxypiperidine[2] and *N*-hydroxymorpholine[3] analogs of sugars or nucleosides and report here on the synthesis and properties of *N*-hydroxypyrrolidine analogs of *C*-glycosides.

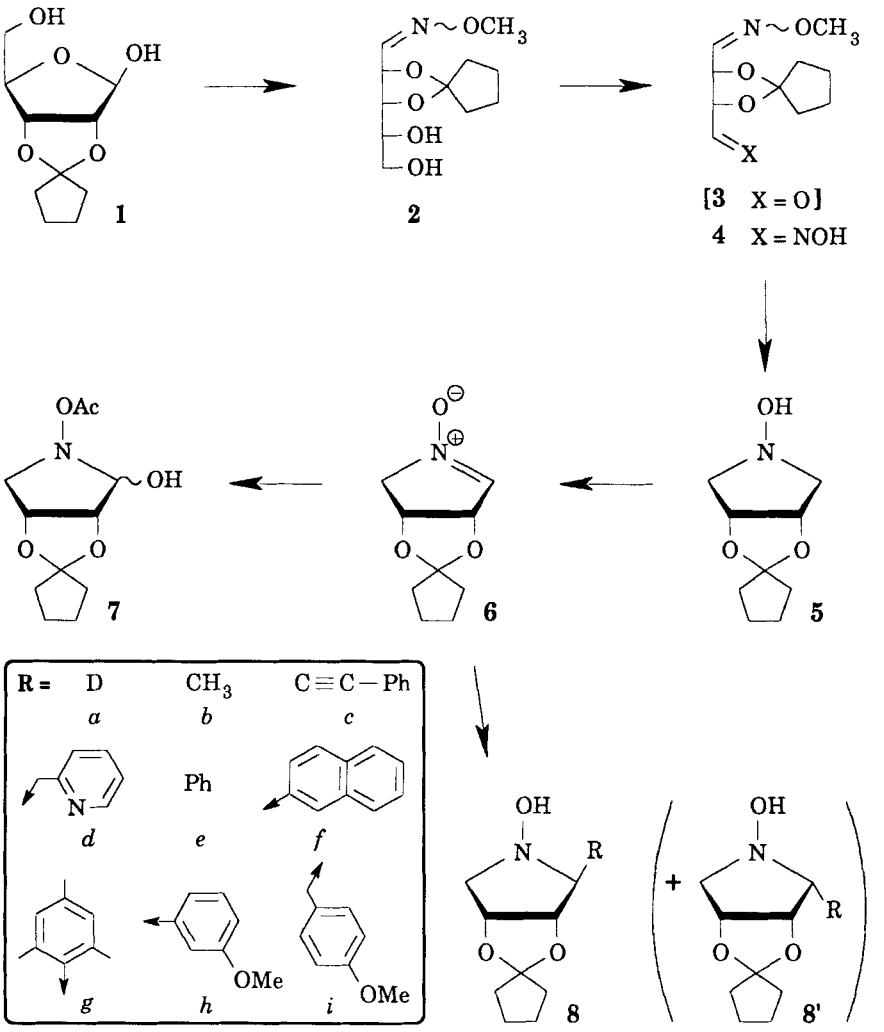
One of the interests of these *N*-hydroxy derivatives, besides the fact that they are close analogs (isosters of the superior homolog) of natural sugars, consists in their easy spontaneous oxidation into aminoxyl radicals which can be studied by EPR spectroscopy.[4] A conformational study of these uncommon, somewhat rigid tricyclic compounds has been carried out. Some of these results have been the subject of a preliminary communication.[5]

RESULTS AND DISCUSSION

Upon *O*-methyloximation, the 2,3-*O*-cyclopentylidene-β-D-ribofuranose[6] **1** gave **2** (77%) as a 6:1 mixture of *E* and *Z* isomers (Scheme 1).

Periodate oxidation of **2** led to **3** which was not isolated, but directly converted into the dioxime **4** (80% from **2**) obtained as a mixture of the four possible geometrical isomers. Sodium cyanoborohydride reduction of **4** at pH 5 led in good yield (70%) to the *meso*-*N*-hydroxypyrrolidine derivative **5**, oxidation of which (HgO) gave racemic **6** (89%). Upon treatment with acetic anhydride/ sodium acetate **6** led to the sugar analog **7** (82%) obtained as a racemic mixture of α and β anomers. Sugar nitrones readily react with carbon nucleophiles[7] and, treated with a variety of organometallic reagents, **6** gave the expected C-glycoside analogs (Table 1). In every case but one (**8'd**), the reaction proceeded stereospecifically from the *exo* face leading only to the β anomer **8** in yields ranging from poor (**8c**, 20%) to high (**8g**, 82%). With pyrid-2-ylmethyllithium, the major compound formed (25%) was the α anomer **8'd**, the β compound **8d** being obtained in trace amounts. Treated with sodium borodeuteride, **6** led highly stereoselectively to **8a**.

The configurations of compounds **8** and **8'** were established from their ^{1}H NMR data (Tables 2 and 3) and the X-ray structure of **8e** (*vide infra*). For the configurational assignment, a rough conformational study rendered particularly straightforward by the relative rigidity of the tricyclic moiety is sufficient. The value of $J_{2,3}$ (*ca.* 7 Hz) indicates conformations not too far from N-*endo* or N-*exo* envelopes, the value of $J_{3,4endo}$ allowing the discrimination between the N_{endo} ($J_{3,4endo}$ = 0) and the N_{exo} ($J_{3,4endo}$ *ca.* 6 Hz) envelopes. The relative population of the two rough types of conformers is regulated by the nature and the *exo* or *endo* position of the C-1 substituent. Alkyl, aryl or aralkyl substituents tend to adopt an equatorial disposition hence increasing the population of the N-*exo* envelope (time-averaged $J_{3,4endo}$ > 2.5 Hz) for β compounds (**8**) and that of the N-*endo* envelope for α C-glycosides **8'**. Compounds bearing an anomeric hydroxy group are subject to anomeric effect which decreases the $J_{3,4endo}$ value for β anomers

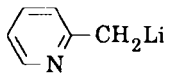
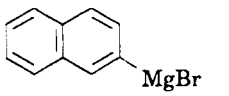
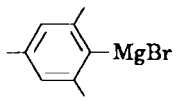
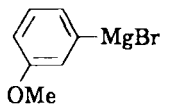
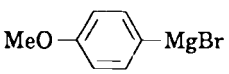


Scheme 1

(β-7 2.5 Hz, β-1 0.5 Hz). For α-7, a $^2T_1$ (R-series) conformation would explain the null value of $J_{3,4endo}$.

Crystalline **8e** was submitted to an X-ray diffraction study. The structure and numbering are reported in Fig. 1. Both pyrrolidine and cyclopentylidene rings adopt a twist conformation with a minimum value of the asymmetry parameter[8] [$\Delta C_2(C(2)) = 0.008(3)$ and $\Delta C_2(C(11')) = 0.005(3)$] associated to quasi ideal C_2 symmetries passing through the C(2) ($^0T_4$ for the D enantiomer) and C(11') atoms

Table 1. Reaction of **6** with Different Nucleophiles

Nucleophile	equiv	solvent	temp °C	time/h	Compd (yield)
$NaBD_4$	4.1	MeOD	25	0.5	**8a** (95%)
MeLi	3.0	Et_2O	0	3	**8b** (72%)
Ph—C≡C—Li	2.5	THF	25	12	**8c** (80.5%)
	3	THF	-15	12	**8'd** (25%) **8d** (traces)
PhMgBr	3	THF	0-25	3	**8e** (70%)
	3	THF	25	12	**8f** (70%)
	3	Et_2O	25	12	**8g** (82%)
	3	Et_2O	25	12	**8h** (36%)
	3	Et_2O	25	12	**8i** (20%)

respectively. The dioxolane ring, *cis*-fused to the pyrrolidine, exhibits an envelope conformation with the O(2) atom out of plane [ΔC_s(O(2)) = 0.010(3)]. The nitrogen atom is pyramidal; its distance to the plane of the three bonded atoms is 0.550(6) Å. The *N*-hydroxy group is equatorial.

In the molecular packing, the molecules are associated by pairs, around a centre of inversion (Fig. 2), with hydrogen bonds involving the hydroxy group and N(4) [(O(4)···$N(4)_{1-x,-y,-z}$ = 2.794(7) Å; O(4)-H(O4)···N(4) = 134.9(3)°].

The simplest example of these *N*-hydroxypyrrolidines, **5**, exhibits coupling constants (Table 2) indicative, as expected of a σ symmetry plane. The large value (7 Hz) of $J_{2,3}$ cannot reliably discriminate between an N-*endo* envelope and a conformational mixture of rapidly interconverting twist forms $^1T_0$(D) and $^4T_0$(D). Even if the X-ray structure of **8e** definitively indicates a twist form with a O(2)-

Table 2. *N*-Hydroxypyrrolidine Ring Interproton Couplings ($CDCl_3$, 200 MHz, 25 °C, *J* in Hz)

Cmpd	$J_{1exo,2}$	$J_{1endo,2}$	$J_{2,3}$	$J_{3,4exo}$	$J_{3,4endo}$	$J_{4endo,4exo}$
1	-	0	6	-	0.5	-
5[a,b]	5	0	7	5	0	-11.5
α-7	5	-	7	5	0	-11
β-7	-	1	7	4	2.5	-11
8a	-	0	7	5	0	-11.5
8b	-	4	7	6	3	-11.5
8c[b,c]	-	2	7	5	2.5	-11
8c-A[c,d]	-	0	7	2.5[e]	2.5[e]	?
8c-B[c,d]	-	7	7	5.2	6	9.8
8d	-	4.5	7	6	4.5	-
8'd	4.5	-	7	5	0	-11
8e	-	6	7	5	6	-10
8f	-	6	7	5	6	-10.5
8g	-	5	7	7	6	-9.5
8h	-	5.8	7	5	6	-10
8i	-	3.5	7	6	4	-12

a. Simulation. b. at 55 °C. c. in $(CD_3)_2CO$. d. At -45 °C. e. Isochronous protons.

C(2)-C(3)-O(3) torsional angle of 18.5° (Table 4), we shall in a first approximation consider only envelope forms. In any case, compounds **8**, independently of the size of the aglycone moiety, retain a σ symmetry as shown by the very close values of $J_{1endo,2}$ and $J_{3,4endo}$ for every compound in these series. Compound **5** exists almost exclusively as an N-*endo* envelope as shown by the null values of $J_{1endo,2}$ and $J_{3,4endo}$. When the probe temperature was decreased from 55 °C to -40 °C, some coalescence was noted at 20 °C, but only one form was observed at -40 °C and the coupling constants were not affected by these temperature changes.

Compounds **8e-h** bearing a large aglycone moiety exist exclusively or almost exclusively in the N-*exo* conformation (both $J_{3,4}$ and $J_{1,2}$ large) corresponding to an equatorial orientation of the aryl group. Compounds **8b-d,i** bearing a medium-sized aglycone exist as a mixture of N-*endo* and N-*exo* forms.

Table 3. Chemical Shifts of the Protons of the *N*-hydroxypyrrolidine Ring ($CDCl_3$, 200 MHz, 25 °C, δ values in ppm)

Cmpd	H_{exo}-1	H_{endo}-1	H-2	H-3	H_{exo}-4	H_{endo}-4
1	-	5.43	4.52	4.77	-	4.43
5[a,b]	2.72	3.50	4.62	4.62	2.72	3.50
α-7	4.48	-	4.42	4.65	2.85	3.67
β-7	-	5.01	~4.50	4.75	3.52	3.45
8a	-	3.48	4.63	4.63	2.74	3.50
8b	-	3.29	4.26	4.62	3.41	3.20
8c[b,c]	-	4.07	4.63	4.69	3.30	3.08
8c-A[c,d]	-	4.20	4.62	4.68	3.13	3.13
8c-B[c,d]	-	3.58	4.45	4.56	3.60	2.78
8d	-	3.48	4.50	4.73	3.51	3.11
8'd	3.05	-	4.50	4.58	2.74	3.60
8e	-	4.00	4.48	4.67	3.18	3.78
8f	-	4.18	4.54	4.60	3.22	3.81
8g	-	4.48	4.58	4.63	3.02	3.79
8h	-	3.99	4.45	4.66	3.18	3.78
8i	-	3.48	4.39	4.67	3.42	3.25

a. Simulation. b. At 55 °C. c. In $(CD_3)_2CO$. d. At -45 °C.

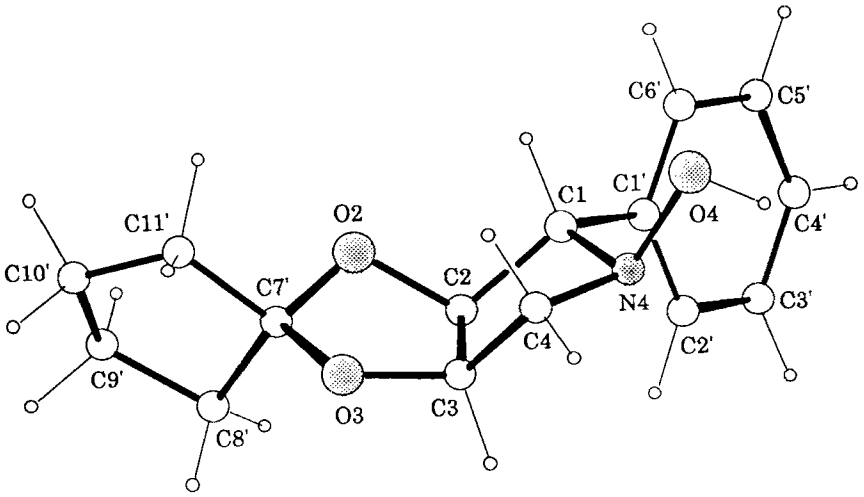


Figure 1 Molecular structure of the compound **8e** showing the atomic numbering.

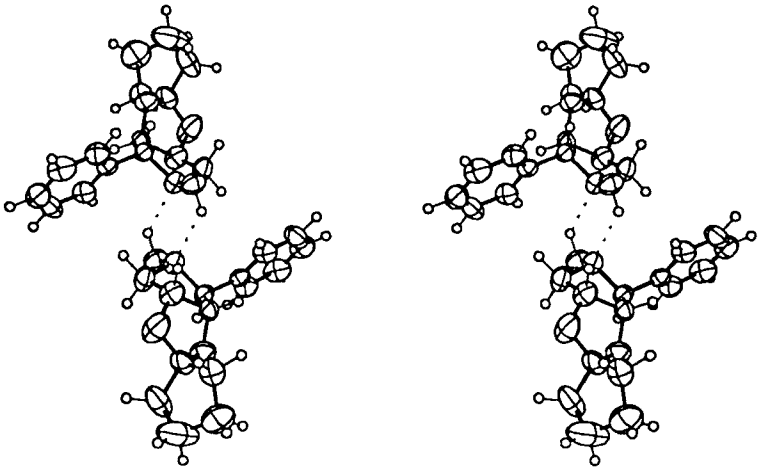


Figure 2 Stereoview of the structure of **8e** showing the hydrogen bonds occurring around a centre of inversion. Ellipsoids are represented with 50% probability.

The assignment of an equatorial or axial orientation to the *N*-hydroxy group can be made on the following bases: a lone pair on the nitrogen atom syn or preferably antiperiplanar to a C-H bond of a vicinal methylene group imparts a small positive increment to the value of $^2J_{CH2}$, thus decreasing its absolute value,[9] whereas in the same conditions, an oxygen atom leads to the opposite result. On the other hand, vicinal protons antiperiplanar to the lone pair on nitrogen are shielded through electron transfer from the lone pair to the antiperiplanar H-C σ^* orbital,[10] whereas an oxygen atom deshields an antiperiplanar proton.

For compounds bearing an encumbering aglycone **8e-h** thus existing in an N-*exo* conformation, there exists no syn or antiperiplanar $O\text{-}C_3\text{-}H\text{-}C_4$ interaction. The value of $^2J_{4endo,4exo}$ exclusively depends on the orientation of the nitrogen lone pair. The small absolute values measured (9.5-10.5 Hz) are in favor of an equatorial position of the *N*-hydroxy group in these cases. For the alternate N-*endo* envelope, the C_3-O bond is nearly antiperiplanar to H_{exo}-C_4, thus increasing the absolute value of $^2J_{4endo,exo}$ in such a way that $^2J_{4endo,4exo}$ values in the range of -11.0 to -11.5 Hz are in accordance with an axial lone pair on the nitrogen, hence also an equatorial *N*-hydroxy group.

Compound **8c** which exists as a conformational mixture, was submitted to a variable temperature ^{1}H NMR experiment. At -45 °C, a 5:1 mixture of **A** and **B**

Table 4. Selected Bond Lengths (Å), Bond Angles and Torsional Angles (°) for **8e**

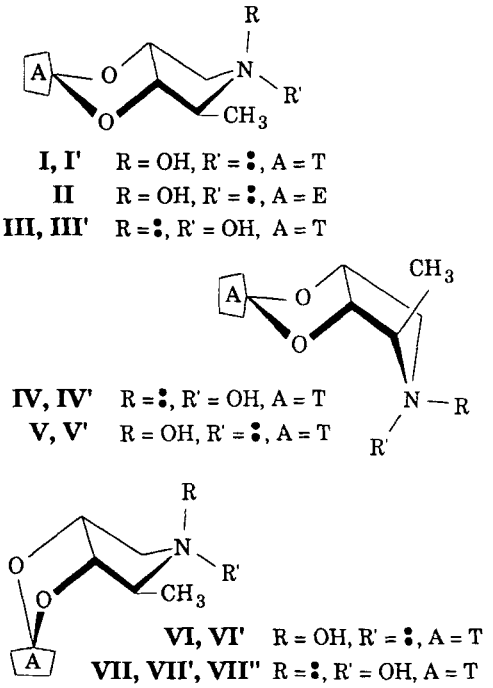
O(2)-C(2)	1.416(8)	N(4)-C(4)	1.472(8)
O(2)-C(7')	1.419(8)	C(1)-C(2)	1.523(9)
O(3)-C(3)	1.417(8)	C(1)-C(1')	1.521(8)
O(3)-C(7')	1.410(9)	C(2)-C(3)	1.533(9)
O(4)-N(4)	1.444(7)	C(3)-C(4)	1.50(1)
N(4)-C(1)	1.488(8)		
O(4)-N(4)-C(1)	106.4(4)	O(2)-C(2)-C(3)	102.7(5)
O(4)-N(4)-C(4)	108.5(4)	C(1)-C(2)-C(3)	105.2(5)
C(1)-N(4)-C(4)	105.5(5)	O(3)-C(3)-C(2)	105.1(5)
N(4)-C(1)-C(2)	102.4(5)	O(3)-C(3)-C(4)	113.2(6)
N(4)-C(1)-C(1')	110.6(5)	C(2)-C(3)-C(4)	105.3(5)
C(2)-C(1)-C(1')	117.3(5)	N(4)-C(4)-C(3)	99.8(5)
O(2)-C(2)-C(1)	109.8(5)		
C(4)-N(4)-C(1)-C(2)	-39.2(6)	O(2)-C(2)-C(3)-O(3)	18.5(7)
N(4)-C(1)-C(2)-C(3)	14.7(6)	C(7')-O(2)-C(2)-C(3)	-32.0(6)
C(1)-C(2)-C(3)-C(4)	13.6(7)	C(2)-O(2)-C(7')-O(3)	34.5(7)
C(2)-C(3)-C(4)-N(4)	-36.5(6)	O(2)-C(7')-O(3)-C(3)	-21.8(8)
C(1)-N(4)-C(4)-C(3)	47.4(6)	C(7')-O(3)-C(3)-C(2)	1.9(7)
C(11')-C(7')-C(8')-C(9')	27.4(7)	N(4)-C(1)-C(1')-C(2')	72.6(8)
C(7')-C(8')-C(9')-C(10')	-33.6(8)	N(4)-C(1)-C(1')-C(6')	-105.2(7)
C(8')-C(9')-C(10')-C(11')	28.(1)	C(2)-C(1)-C(1')-C(2')	-44.3(9)
C(9')-C(10')-C(11')-C(7')	-10.(1)	C(2)-C(1)-C(1')-C(6')	137.9(7)
C(8')-C(7')-C(11')-C(10')	-11.1(9)		

invertomers was observed. Using the Gutowski's approximation,[11] a free energy of activation of 52.3 kJ.mol^{-1} was estimated for the nitrogen inversion. The major invertomer (**A**) corresponds to an N-*endo* envelope ($J_{1,2} = 0$) with the phenethynyl group in axial position. The moderate shielding of H_{exo}-4 indicate an equatorial position of the *N*-hydroxy group and thus an *N*-hydroxy *exo* configuration of the asymmetric nitrogen atom. Invertomer **B** adopts a conformation close to an N-*exo* envelope ($^{0}T_{1(D)}$). The small absolute value of $^{2}J_{4endo,4exo}$ and the shielding of

H_{endo}-4 and H-1 indicate an equatorial disposition of the *N*-hydroxy group in accordance with the *N*-hydroxy *endo* configuration of this second invertomer.

In these series, a "slow" configurational change of the asymmetric nitrogen atom induces a fast conformational change of the pyrrolidine ring. This situation is opposite to that previously studied[3] of *N*-hydroxymorpholines, where both "slowly" interconverting invertomers existed in the same chair conformation. Compound **8c** was submitted to a conformational study using the MacroModel 3.5 software[11] in which were introduced the MM2 parameters developed[12] from ab initio studies for the N(sp^3)-O(sp^3) bond. In order to establish conditions as close as possible to those of the ^{1}H NMR experiments, a continuum solvation model[13] with chloroform parameters was used. As the MM2 force field treats explicitly the lone pairs and thus does not allow nitrogen inversion, each invertomer was subjected to a 25 ps high temperature (1500 K) molecular dynamics simulation.

We resorted to this short dynamics exploration of the conformational hypersurface, in order to avoid the short-comings of Monte Carlo simulations applied to five-membered ring with this software. For each of the invertomers, 200 structures were saved during the simulation time and each of them reminimized. This reminimization led to only seven conformers for each invertomer. For these fourteen conformers **I-VII"** (Scheme 2), the Boltzmann distribution and the time-averaged $^3J_{H,H}$ coupling constants were calculated using a modified[14] Karplus equation. The results, computed from the MacroModel output files using a slightly modified QCPE program[15] are collected in Table 5. The molecular dynamics results enlighten another aspect of the conformation of these compounds, the general shape of the tricyclic system. Both pyrrolidine and dioxolane rings are found in envelope forms. The cyclopentylidene ring is found to exist either as a twist form (Scheme 2), A = T) or an envelope (A = E), the former being more favorable. Of the three possible double-envelope conformations of the dioxolano-pyrrolidine bicycle, the N-*exo*,C-*exo*



Scheme 2. Computed conformations of **8c**

Table 5. Computed Interproton Ring Coupling Constants for Conformers I-VII" of 8b

Conformer	Rel. Energy kJ.mol^{-1}	Population %	$\varphi_{1,2}$	$J_{1,2}$	$\varphi_{2,3}$	$J_{2,3}$	$\varphi_{3,4exo}$	$J_{3,4exo}$	$\varphi_{3,4endo}$	$J_{3,4endo}$
I	0	39.6	150.2	7.0	-2.8	6.3	-21.7	6.4	-143.0	5.9
I'	0.06	38.6	147.3	6.4	1.7	6.4	-24.6	6.4	-146.0	6.4
II	3.08	11.4	150.6	7.1	-3.3	6.3	-21.4	6.4	-142.7	5.8
III	5.91	3.6	150.0	6.0	-4.1	6.2	-18.7	6.5	-141.2	4.9
III'	6.09	3.4	146.4	5.4	1.2	6.3	-22.5	6.5	-145.2	5.4
IV	7.88	1.6	92.7	0.4	3.4	6.1	28.5	2.3	-92.6	1.5
IV'	8.02	1.6	95.4	0.5	-0.7	6.1	31.3	1.9	-89.9	1.4
V	15.62	0.07	92.3	0.5	2.5	6.2	27.7	3.01	-91.2	1.6
V'	15.71	0.07	94.2	0.6	-0.5	6.2	29.6	2.7	-90.0	1.5
VI	16.86	0.04	145.1	6.1	5.0	6.5	-27.7	6.6	-149.0	6.8
VI'	16.94	0.04	152.7	7.4	-5.1	6.5	-20.5	6.7	-141.0	5.6
VII	20.79	0.01	151.6	6.3	-5.6	6.4	-18.0	6.8	-140.0	4.9
VII'	21.36	0.01	152.1	6.4	-6.3	6.4	-17.6	6.8	-139.6	4.8
VII"	21.47	0.01	143.2	5.1	5.4	6.4	-26.1	6.7	-150.0	6.0
Weighted Average				6.5		6.3		6.2		5.9

(I-III') is preferred over N-*endo*,C-*exo* (IV-V') itself more favorable than the C-*endo*,N-*exo* (VI-VII") even if the methyl group is axial in conformers IV-V' and equatorial in conformers VI-VII".

From these molecular dynamics results, it appears that the favorable conformational factors should be, in decreasing order: 1) the general shape of the tricycle, 2) the equatorial orientation of the methyl group, 3) the axial orientation of the *N*-hydroxy group. This differs significantly from the experimental results which indicate a preference for an N-*endo* conformation and an equatorial *N*-hydroxy group.

N-Hydroxypyrrolidines spontaneously oxidize in the air to give the corresponding pyrrolidine *N*-oxyl free radicals. EPR spectra of some of these paramagnetic species are collected in Table 6. Contrarily to most organic functional groups, the aminoxyl group has no well-defined geometry being either planar or bent. However, when its nitrogen atom is included in a five-membered ring, the aminoxyl group is planar or almost planar as shown in particular from X-ray diffraction studies.[16] In these conditions, one can use the one-term equation

$$a_H = B_2\cos^2\theta$$

where θ represents the torsional angle between the C-H bond and the p orbital on the nitrogen atom and B_2 a constant computed[17] to be 23.8 G or estimated to 25 ± 1 G from experimental measurements.[18]

In an envelope conformation the hyperfine coupling constants of the axial protons should be close to 24 G, those of the equatorial ones close to 6 G. The values measured for **5** could be roughly explained by a conformational equilibrium between two envelopes (N-*endo* and N-*exo*), one being largely preponderant. As upon deuteriation to **8a**, from the *exo* face, one large coupling disappears, it is clear that the preferred conformation is close to an N-*endo* envelope. When going from a deuterium atom to larger groups as in **8b**, **8e** and **8h**, no significant change was noted in the relative population of conformers, neither upon a configurational change to **8'd**. This indicates that these pyrrolidine *N*-oxyl radicals prefer N-*endo* conformations and are almost insensitive to changes in the size of the C-1 substituent, situation fundamentally different from that of their *N*-hydroxypyrrolidine precursors.

EXPERIMENTAL

General Methods. See ref. 19.

Crystallography. Single crystals were grown at room temperature from 99:1 hexane/acetone solutions. The diffracted intensities were measured at room

Table 6. EPR Data of Aminoxyl Radicals from N-Hydroxypyrrolidine Sugar Analogs (a and Γ values in G)

Cmpd	Solvent	Temp	g	Γ	a_N	a_H					
5	diglyme	25 °C	2.0062	0.5	14.8	22.5	22.5	15.3	15.3	0.4	0.4
8a[a]	diglyme	75 °C	2.0051	0.4	15.3	22.4	18.5	11.5	0.5	0.5	
8b	diglyme	75 °C	2.0062	0.5	14.8	20.6	17.1	17.1	0.6	0.6	
8e	CCl_4	75 °C	2.0060	0.7	13.9	20.9	15.9	15.9			
8e	diglyme	76 °C	2.0060	0.6	14.2	22.0	16.3	15.8			
8e	diglyme	90 °C	2.0060	0.6	14.1	21.2	15.5	15.5			
8h	diglyme	100 °C	2.0060	1.0	14.0	21.7	15.75	15.75			
8'd[b]	diglyme	125 °C	2.0060	1.0	15.0	22.6	21.0	13.5			

a. a_D 3.15 G. b. A second radical (a_H 21.6, 16.1, 16.1 G) was present in minute concentration.

temperature on a Philips PW1100 diffractometer with monochromated MoKα radiation (λ = 0.71069 Å). Corrections for Lorentz-polarization were applied but not for absorption. The structure was solved by direct methods (MULTAN 87)[20] and refined by full-matrix least-squares with XTAL program.[21] Atomic scattering factors and anomalous dispersion terms were taken from ref. 22. All coordinates of the H atoms were calculated except for the hydroxyl group where the H atom was observed. A summary of crystal data, intensity measurement and structure refinement is given in Table 7. Final positional parameters are reported in Table 8.

Crystallographic data have been deposited with the *Cambridge Crystallographic Data Center*, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, England.

2,3-*O*-Cyclopentylidene-1-deoxy-1(*N*-methoxyimino)-D-ribitol (2). To a solution of **1** (15.5 g, 71.7 mmol) in dry pyridine (200 mL) *O*-methylhydroxylamine hydrochloride (15 g, 179.5 mmol) was added and the mixture stirred at room temperature for 24 h. After codistillation of the solvent with toluene (3x100 mL), the residue was extracted with $CHCl_3$ (200 mL) and the organic phase washed with water (2x100 mL). Column chromatography (2:1 AcOEt/hexane) yielded a 6:1 mixture of the *E* and *Z* isomers (13.5 g, 77%) of **2**: mp 53-61.5 °C; R_F 0.26 (2:1 AcOEt/hexane). ^{1}H NMR: *E isomer*: δ 1.70 and 1.90 (2 *m*, 6 and 2 H, cyclopentylidene), 2.06 (*t*, 1 H, $J_{5,OH}$ = 5 Hz, HO-C_5), 2.80 (*d*,

Table 7. Summary of Crystal Data, Intensity Measurements and Structure Refinement for **8e**

Formula	$C_{15}H_{19}NO_3$	$((\sin\theta)/\lambda)_{max}$ (Å^{-1})	0.53
Mol. wt.	261.3	Temperature (K)	298
Crystal system	Monoclinic	No. measured reflc.	1775
Space Group	$P\,2_1/c$	No. observed reflc.	1075
a (Å)	12.502(4)	Criterion for observed	$\|Fo\| > 4\sigma(Fo)$
b (Å)	5.842(1)	Refinement (on F)	Full-matrix
c (Å)	19.423(3)	No. parameters	172
β (°)	99.01(2)	Weighting scheme	$\omega = 1/\sigma^2(Fo)$
V (Å^3)	1401.1(6)	Max. and average Δ/σ	0.032 , 0.003
Z	4	Max. and min. $\Delta\rho$ (e.Å^{-3})	0.37 , -0.51
F(000)	560	S	2.91
Dc gr.cm^{-3}	1.24	R , ωR	0.078 , 0.052
μ(MoKα) mm^{-1}	0.080		

TABLE 8. Atomic Coordinates and Equivalent Isotropic Displacement Parameters (Å^2) with e.s.d.'s in Parenthesis for 8e. U_{eq} is the Average of Eigenvalues of *U*

	x/a	y/b	z/c	U_{eq}
O(2)	0.2125(3)	0.2215(8)	0.1303(2)	0.062(2)
O(3)	0.1345(3)	0.283(1)	0.0190(2)	0.099(3)
O(4)	0.4316(3)	-0.1966(7)	0.0306(2)	0.060(2)
N(4)	0.3945(4)	0.0375(9)	0.0305(3)	0.050(2)
C(1)	0.3843(5)	0.093(1)	0.1040(3)	0.047(3)
C(2)	0.2994(5)	0.282(1)	0.0952(3)	0.049(3)
C(3)	0.2475(5)	0.273(1)	0.0184(3)	0.063(3)
C(4)	0.2837(5)	0.048(1)	-0.0083(3)	0.062(3)
C(1')	0.4945(5)	0.150(1)	0.1456(3)	0.044(3)
C(2')	0.5449(6)	0.356(1)	0.1347(3)	0.056(3)
C(3')	0.6459(6)	0.404(1)	0.1716(4)	0.069(4)
C(4')	0.6978(5)	0.251(2)	0.2193(4)	0.078(4)
C(5')	0.6481(6)	0.046(2)	0.2293(4)	0.071(4)
C(6')	0.5456(5)	-0.007(1)	0.1925(3)	0.058(3)
C(7')	0.1170(5)	0.305(1)	0.0887(4)	0.062(3)
C(8')	0.0907(5)	0.550(1)	0.1059(4)	0.068(3)
C(9')	0.0166(7)	0.524(2)	0.1596(5)	0.110(5)
C(10')	-0.0435(7)	0.315(2)	0.1386(6)	0.140(6)
C(11')	0.0208(6)	0.170(1)	0.1028(5)	0.090(4)

1 H, $J_{4,OH}$ = 5 Hz, HO-C_4), 3.75 (*m*, 3 H, H-C_4, H_2-C_5), 3.49 (*s*, 3 H, NOMe), 4.10 (*dd*, 1 H, $J_{2,3}$ = 6 Hz, $J_{3,4}$ = 8 Hz, H-C_3), 4.72 (*dd*, 1 H, $J_{1,2}$ = 7 Hz, H-C_2), 7.45 (*d*, 1 H, H-C_1); *Z isomer*: δ 1.70 and 1.90 (2 *m*, 6 and 2 H, cyclopentylidene), 2.15 (*t*, 1 H, $J_{5,OH}$ = 5 Hz, HO-C_5), 3.01 (*d*, 1 H, $J_{4,OH}$ = 5 Hz, HO-C_4), 3.75 (*m*, 3 H, H-C_4, H_2-C_5), 4.10 (*s*, 3 H, NOMe), 4.19 (*t*, 1 H, $J_{2,3}$ = 6.2 Hz, $J_{3,4}$ = 6.5 Hz, H-C_3), 5.19 (*t*, 1 H, $J_{1,2}$ = 5.8 Hz, H-C_2), and 6.88 (*d*, 1 H, H-C_1)].

Anal. Calcd for $C_{11}H_{19}NO_5$ (245.28): C, 53.87; H, 7.81; N, 5.71. Found: C, 54.00; H, 7.97; N, 5.56.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1-(*N*-hydroxyimino)-4-(*N*-methoxyimino)-L-erythritol (4). A solution of **2** (13.45 g, 54.8 mmol) and $NaHCO_3$ (4.61 g, 54.8 mmol) in water (300 mL) was oxidized by $NaIO_4$ (11.7 g, 54.7 mmol) for 2 h, then extracted with Et_2O (3x100 mL). The ether solution dried (Na_2SO_4), concentrated gave **3** (14.45 g) which was dissolved in pyridine (250 mL) and NH_2OH, HCl (14.07 g, 202.4 mmol) was added. After 12 h at room temperature, the solvent was coevaporated with toluene (3x100 mL), the residue extracted with $CHCl_3$ (200 mL), and the organic phase washed with water (3x100 mL), dried (Na_2SO_4), then concentrated to give 10 g (80% from **2**) of **4** as a 8:7:5:1 mixture of the four geometrical isomers *(1Z,4E)*, *(1E,4E)*, *(1E,4Z)*, and *(1Z,4Z)*: syrup, R_F 0.55 (2:1 AcOEt/hexane); λ_{max}^{EtOH} 206 nm (ε 8810). ^1H NMR: δ 1.75 and 2.0 (2 *m*, 6 and 2 H, cyclopentylidene), 3.88, 3.90, 3.92, and 2.93 (4 *s*, 4x3 H, OMe, *(1E,4E)*, *(1Z,4Z)*, *(1Z,4E)*, *(1E,4Z)*), 3.73 (*m*, 2 H, H-C_2, H-C_3, *(1E,4E)*), 3.84 (*dd*, 1 H, $J_{1,2}$ = 8 Hz, $J_{2,3}$ = 6.7 Hz, H-C_2, *(1E,4Z)*), 4.87 (*dd*, 1 H $J_{2,3}$ = 6.7 Hz, $J_{3,4}$ = 8 Hz, H-C_3, *(1Z,4E)*), 5.14 (*dd*, 1 H, $J_{3,4}$ = 4.5 Hz, H-C_3, *(1E,4Z)*), 5.23 (*dd*, 1 H, $J_{1,2}$ = 4.5 Hz, H-C_2, *(1Z,4E)*), 6.72 (*d*, 1 H, $J_{1,2}$ = 4.5 Hz, H-C_1, *(1Z,4Z)*), 6.72 (*d*, 1 H, $J_{3,4}$ = 4.5 Hz, H-C_4, *(1Z,4Z)*), 6.83 (*d*, 1 H, H-C_4, *(1E,4Z)*), 6.89 (*d*, 1 H, H-C_1, *(1Z,4E)*), 7.20 (*d*, 1 H, H-C_4, *(1Z,4E)*), 7.20 (*d*, 1 H, H-C_1, *(1E,4Z)*), 7.29 and 7.33 (2 *m*, 2x1 H, H-C_4 and H-C_1, *(1E,4E)*), 8.12, 8.23, 8.39, and 8.53 (4 *s*, 4x1 H, NOH, *(1E,4Z)*, *(1Z,4E)*, *(1Z,4Z)*, *(1E,4E)*). MS: *m/z* (%) 55 (100), 84 (38), 149 (26), 169 (12), 199 (14), and 228 (1, $M^{\cdot+}$).

Anal. Calcd for $C_{10}H_{16}N_2O_4$ (228.25): C, 52.62; H, 7.07; N, 12.27. Found: C, 52.58; H, 7.00; N, 12.21.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)erythritol (5). To a solution of **4** (4.7 g, 20.6 mmol) in MeOH (150 mL), $NaBH_3CN$ (6.47 g, 103.07 mmol) was added and the pH of the reaction mixture kept at 5 by addition of N HCl. After 12 h, the pH was brought to 7 (saturated aqueous $NaHCO_3$) and the reaction mixture extracted with $CHCl_3$ (3x100 mL). The organic phase was dried (Na_2SO_4), concentrated to a solid residue which was recrystallized (hexane) to give 2.66 g (70%) of **5**: mp 180.5-180.6 °C; R_F 0.4 (2:1 AcOEt/hexane); λ_{max}^{EtOH} 203 nm

(ε 2160) and 240 (260); ν_{max}^{KBr} 3260 (νOH) cm^{-1}. MS: *m/z* (%) 54 (14), 55 (71), 56 (40), 57 (52), 67 (33), 72 (16), 84 (100), 85 (36), 156 (47), and 187 (12, $M^{\cdot+}$).

Anal. Calcd for $C_9H_{15}NO_3$ (185.22): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.09; H, 8.03; N, 7.68.

2,3-*O*-Cyclopentylidene-DL-*erythro*-1-pyrroline-3,4-diol *N*-oxide (6). To a solution of **5** (170 mg, 0.92 mmol) in CH_2Cl_2 (20 mL), yellow HgO (198.8 mg, 0.92 mmol) was added. After 12 h at room temperature, the mixture was filtered on celite and the filtrate concentrated, then crystallized (heptane) to give 150 mg (89%) of **6**: mp 135.2-135.3 °C; R_F 0.08 (6:1 AcOEt/hexane); λ_{max}^{EtOH} 235 nm (ε 10900); ν_{max}^{KBr} 3058 and 2964 (νC-H), 1575 (νC=N), 1454, 1334, 1279, 1107, 1001, and 648 cm^{-1}. MS: *m/z* (%) 54 (33), 83 (100), 101 (14), 138 (11), and 149 (8), and 183 (10, $M^{\cdot+}$).

Anal. Calcd for $C_9H_{13}NO_3$ (183.21): C, 59.00; H, 7.15; N, 7.65. Found: C, 59.24; H, 6.93; N, 7.92.

4-Acetoxy-2,3-*O*-cyclopentylidene-4-deoxy-(α + β)-DL-erythrofuranose (7). To a solution of **6** (101.5 mg, 0.55 mmol) in acetic anhydride (5 mL), anhydrous NaOAc (273 mg, 3.32 mmol) was added). After 24 h stirring at 20 °C, the excess Ac_2O was codistilled with toluene (4x25 mL) and the residue submitted to a column chromatography (7:3 CH_2Cl_2/Et_2O) to give **7** (110 mg, 82%) as a *ca.* 8:3 syrupy mixture of α and β anomers: R_F 0.22 (8:3 CH_2Cl_2/Et_2O); λ_{max}^{EtOH} 202 nm (ε 4700), and 236 (7600); ν_{max}^{film} 3250 (OH), and 1755 (CO) cm^{-1}. MS: *m/z* (%) 55 (100), 67 (19), 83 (59), 100 (32), 138 (6), 154 (8), 172 (10), 184 (42, $M^{\cdot+}$ - AcO), 226 (23, $M^{\cdot+}$ - OH), and 243 (0.3, $M^{\cdot+}$).

Anal. Calcd for $C_{11}H_{17}NO_5$ (243.26): C, 54.31; H, 7.04; N, 5.76. Found: C, 54.04, H, 6.87; N, 5.76.

Reaction of 6 with a series of nucleophiles. The conditions of these reactions are collected in Table 1.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)-β-DL-[1-^{2}H]erythritol (8a). The reaction was conducted on 30 mg (0.16 mmol) of **6** to give 29 mg of **8a**: MS: *m/z* (%) 55 (71), 57 (60), 85 (100), 157 (24), and 186 (7, $M^{\cdot+}$).

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)-1-*C*-methyl-β-DL-erythritol (8b). A solution of **6** (102 mg, 0.56 mmol) in Et_2O (15 mL) is treated with methyllithium as reported in Table 1, then submitted to column chromatography (6:1 AcOEt/hexane) to give **8b** as a syrup: R_F 0.25 (6:1 AcOEt/hexane); λ_{max}^{EtOH} 201 nm (ε 128), and 234 (213); ν_{max}^{film} 3250 (OH) cm^{-1}. MS: *m/z* (%) 56 (100), 67 (32), 85 (65), 98 (88), 115 (32), 170 (58), 182 (5), and 199 (36, $M^{\cdot+}$).

Anal. Calcd for $C_{10}H_{17}NO_3$ (199.25): C, 60.28; H, 8.60; N, 7.03. Found: C, 60.34; H, 8.55; N, 7.07.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)-1-*C*-phenylethynyl-β-DL-erythritol (8c). **6** (175.5 mg, 0.96 mmol) was treated as reported in Table 1 with 2.5 mL of a M solution of sodium phenylethynide then submitted to a column chromatography (1:4 AcOEt/petroleum ether) to give **8c**: mp 163.1-163.7 °C; R_F 0.15 (1:4 AcOEt/petroleum ether); λ_{max}^{EtOH} 206 nm (ε 20500), 240 (20400), and 251 (17500); ν_{max}^{KBr} 3300 (OH) and 2190 (C≡C) cm^{-1}. MS: *m/z* (%) 51 (17), 55 (100), 77 (36), 97 (18), 105 (29), 115 (80), 128 (56), 142 (75), 155 (38), 171 (15), 184 (20, $M^{\cdot+}$ - $PhC_2^{\cdot}$), 268 (14, $M^{\cdot+}$ - ·OH), and 285 (0.5, $M^{\cdot+}$).

Anal. Calcd for $C_{17}H_{19}NO_3$ (285.35): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.32; H, 6.72; N, 4.93.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)-1-*C*-pyrid-2-ylmethyl-α-DL-erythritol (8'd). A solution of **6** (240 mg, 1.31 mmol) in THF (3 mL) was treated with a mixture of 2-methylpiperidine and butylithium as reported in Table 1 then submitted to a column chromatography (9:1 AcOEt/hexane) to give an impure fraction (6 mg) consisting in a 9:2 mixture of **8d** and **8'd** and 98 mg of pure **8'd**: mp 120.7-123.4 °C; R_F 0.16 (9:1 AcOEt/hexane); λ_{max}^{EtOH} 205 nm (ε 6300), 256 (3500), 262 (3900), and 268 (2800); ν_{max}^{KBr} 3250 (OH), 1476 and 1590 (Ar) cm^{-1}. MS: *m/z* (%) 55 (10), 93 (100), 118 (10), 159 (48), 175 (20), 229 (15), 259 (2, $M^{\cdot+}$ - ·OH), and 276 (3, $M^{\cdot+}$).

Anal. Calcd for $C_{15}H_{20}N_2O_3$ (276.34): C, 65.20; H, 7.30; N, 10.14. Found: C, 65.22; H, 7.10; N, 10.38.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)-1-*C*-phenyl-β-DL-erythritol (8e). A solution of **6** (161.3 mg, 0.88 mmol) in THF (6 mL) was treated with phenylmagnesium bromide as reported in Table 1 then submitted to a column chromatography (1:4 AcOEt/hexane) to obtain 160 mg of **8e**: mp 101.4-107.9 °C; R_F 0.2 (1:4 AcOEt/hexane); λ_{max}^{EtOH} 208 nm (ε 8500); ν_{max}^{KBr} 3300 (OH), and 1455 (Ar) cm^{-1}. MS: *m/z* (%) 55 (85), 77 (43), 104 (53), 130 (100), 159 (70), 214 (43), 243 (15, $M^{\cdot+}$ - H_2O), 244 (8, $M^{\cdot+}$ - OH), 261 (5, $M^{\cdot+}$).

Anal. Calcd for $C_{15}H_{19}NO_3$ (261.32): C, 68.94; H, 7.33; N, 5.36. Found: C, 68.82; H, 7.26; N, 5.51.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)-1-*C*-(naphth-2-yl)-β-DL-erythritol (8f). A solution of **6** (208 mg, 1.13 mmol) in THF (2 mL) was treated with naphth-2-ylmagnesium bromide as reported in Table 1 then submitted to a column chromatography (1:1 Et_2O/hexane) to give 250 mg of **8f**: mp 130.9-133.3 °C; R_F 0.35 (1:1 Et_2O/hexane); λ_{max}^{EtOH} 205 nm (ε 113000); ν_{max}^{KBr} 3260 (OH) cm^{-1}. MS: *m/z* (%) 55 (34), 84 (10), 97 (15), 128 (30), 153 (73), 180 (100), 209 (63), 237 (13), 264 (43), 294 (45, $M^{\cdot+}$ - OH), and 311 (25, $M^{\cdot+}$).

Anal. Calcd for $C_{19}H_{21}NO_3$ (311.38): C, 73.29; H, 6.80; N, 4.50. Found: C, 73.02; H, 6.85; N, 4.61.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)-1-*C*-(2,4,6-trimethylphenyl)-β-DL-erythritol (8g). A solution of **6** (176.5 mg, 0.96 mg) in THF (2 mL) was treated with mesitylmagnesium bromide as reported in Table 1 then submitted to a column chromatography (1:4 AcOEt/petroleum ether) to give 240 mg of **8g**: mp 64.8-70.9 °C; R_F 0.4 (1:4 AcOEt/petroleum ether); λ_{max}^{EtOH} 207 nm (ε 13500), and 220 (7100); ν_{max}^{KBr} 3380 (OH) cm^{-1}. MS: *m/z* (%) 55 (49), 83 (12), 91 (15), 120 (28), 133 (23), 148 (25), 160 (67, $M^{\cdot+}$ - mesityl), 184 (100), 204 (9), 220 (2), 286 (3, $M^{\cdot+}$ - OH), 288 (6), 303 (2, $M^{\cdot+}$).

Anal. Calcd for $C_{18}H_{25}NO_3$ (303.40): C, 71.26; H, 8.31; N, 4.62. Found: C, 70.98; H, 8.30; N, 4.45.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)-1-*C*-(3-methoxyphenyl)-β-DL-erythritol (8h). A solution of **6** (120.5 mg, 0.66 mmol) in THF (2 mL) was treated with 3-methoxyphenyl magnesium bromide as reported in Table 1 then submitted to a column chromatography (6:1 AcOEt/hexane) to give 68 mg of **8h**: mp 82.9-84.6 °C; R_F 0.6 (6:1 AcOEt/hexane); λ_{max}^{EtOH} 202 nm (ε 5500); ν_{max}^{KBr} 3250 (OH), and 1586 (Ar) cm^{-1}. MS: *m/z* (%) 51 (14), 55 (100), 77 (29), 121 (25), 148 (56) 190 (14), 274 (11, $M^{\cdot+}$ - OH), and 291 (1, $M^{\cdot+}$).

Anal. Calcd for $C_{16}H_{21}NO_4$ (291.35): C, 65.96; H, 7.27; N, 4.81. Found: C, 65.77; H, 7.01, N, 5.06.

2,3-*O*-Cyclopentylidene-1,4-dideoxy-1,4-(*N*-hydroxyimino)-1-*C*-(4-methoxybenzyl)-β-DL-erythritol (8i). A solution of **6** (150 mg, 0.82 mmol) in ether (5 mL) was treated with *p*-methoxybenzylmagnesium chloride as reported in Table 1 then submitted to a column chromatography (6:1 AcOEt/hexane) to give 50 mg of **8i**: mp 102.0-107.6 °C; R_F 0.6 (6:1 AcOEt/hexane); λ_{max}^{EtOH} 202 nm (ε 1100), 225 (12700), 277 (1950), and 284 (1600); ν_{max}^{KBr} 3200 (OH), and 1513 (Ar) cm^{-1}. MS: *m/z* (%) 55 (20), 68 (5), 84 (14), 121 (100), 138 (20), 168 (50), 184 (19), 258 (17, $M^{\cdot+}$ - ·OH), and 305 (2, $M^{\cdot+}$).

Anal. Calcd for $C_{17}H_{23}NO_4$ (305.38): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.95; H, 7.31; N, 4.68.

ACKNOWLEDGEMENTS

The authors thanks Profs A. Buchs and F. Gulaçar for the MS, Dr H. Eder for the elementary analyses, Mr G. Moret for the drawings and Mrs C. Gratiot for the formatting of the document. This work was generously supported by the Swiss

National Research Foundation (grants No 20.31259-91, 20.37626-93 and 3139-037156).

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