Deoxynojirimycin analogs : 1,5-dideoxy-1,5-(*N*-hydroxyimino)-D-lyxitol derivatives

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1815'046
BSCB 679

J.CHEM.RESEARCH (M), 1994, 0273 — 0281

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The PCSIR Laboratories, Lahore are thanked for some spectral data.

Paper E/3/05096O Received 23rd August 1993

Deoxynojirimycin Analogs: 1,5-Dideoxy-1,5-(*N*-Hydroxyimino)-D-Lyxitol Derivatives

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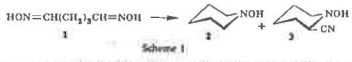
Deoxy *N*-hydroxyamino sugars[1] ("sugar hydroxylamines") spontaneously oxidize in the air to give a very small stationary concentration of the corresponding aminoxyls. This concentration is sufficient to allow the obtention of good ESR spectra but too small to broaden significantly NMR signals. This corresponds to an almost unique situation where both good NMR and ESR spectra are obtainable from the same sample. We have described[2] a number of such sugar analogs in which a hydroxy group has been replaced with a *N*-hydroxyamino group. We report hereunder the extension of these syntheses to anhydroalditol analogs in which the ring oxygen has been replaced with a *N*-hydroxyimino bridge. Six-membered ring compounds of this type are analogs of deoxynojirimycin. Part of these results have been the object of a preliminary communication.[3]

The sodium cyanoborohydride reduction of oximes into hydroxylamines is accompanied by the formation, as a by-product, of *N,N*-disubstituted hydroxylamines,[4]

$$RCH{=}NOH \xrightarrow{NaBH_3CN} RCH_2NHOH + (RCH_2)_2NOH$$

the formation of which was decreased by using a large excess of reducing agent and by lowering the pH.[5] Conversely, at higher pH and with a smaller excess of sodium borohydride, the formation of the *N,N*-disubstituted hydroxylamine should be favored and, starting with an α,ω-dioxime, a ring closure could be expected affording a way to *N*-hydroxypyrrolidines and *N*-hydroxypiperidines. In fact, starting from 1,5-bis(*N*-hydroxyimino)pentane **1**, we obtained the expected 1-hydroxypiperidine[6] **2** (40%) together with its 2-cyano derivative **3** (15%) (Scheme 1).



Scheme 1

This reaction, extended from α,ε-bis(*N*-hydroxyimino)alkanes to α-oxo-ε-*N*-hydroxyimino and α-oxo-ε-*N*-aralkoxyimino compounds, was applied to carbohydrate chemistry.

References: see frame 0287

Di-O-cyclopentylidenation[7] of D-mannose led in high yield to the crystalline compound **4** obtained as the α anomer as shown by its ^{1}H-NMR values (Tables 1 and 2), particularly its small $J_{1,2}$ coupling constant.

TABLE 1. ^{1}H NMR of the Furanose Derivatives. Chemical shifts values (δ in p.p.m.).

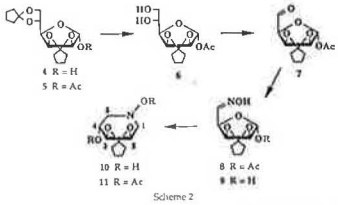
Cmpd	H-1	H-2	H-3	H-4	H-5	H-6
4	5.41	4.57	4.75	4.26	4.39 4.02	3.99
5	6.11	4.65	4.78	4.03	4.36 4.01	3.99
6	6.19	4.67	4.87	4.12	4.02	3.73 3.83
(E)-8	6.22	4.70	4.80	4.65	7.49	
(Z)-8	6.20	4.68	5.07	5.13	6.90	
(E)-9	5.48	4.61	4.79	4.73	7.53	
(Z)-9	5.48	4.59	5.04	5.27	6.92	
(E)-14	6.22	4.77	4.77	4.66	7.50	
(Z)-14	6.22	4.77	5.05	5.12	6.90	
(E)-15	5.48	4.58	4.75	4.66	7.53	
(Z)-15	5.48	4.58	5.00	5.21	6.90	

TABLE 2. ^{1}H NMR of the Furanose Derivatives. Interproton couplings (J in Hz).

Cmpd	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,5'}$
4	<0.5	6.0	4.0	7.0 5.0	7.0
5	<0.5	6.0	4.0	7.8 4.5	6.0
6	<0.5	6.2	4.0	8.0	5.0 3.2
(E)-8	<0.5	6.0	4.0	7.5	
(Z)-8	<0.5	6.0	4.0	3.5	
(E)-9	<0.5	6.0	4.0	7.0	
(Z)-9	<0.5	6.0	4.0	4.0	
(E)-14	<0.5	6.0	4.0	7.0	
(Z)-14	<0.5	6.0	4.0	4.0	
(E)-15	<0.5	6.0	4.0	7.0	

References: see frame 0287

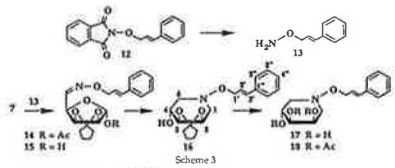
Compound **4** was quantitatively acetylated to **5** which was selectively mono-de-*O*-cyclopentylidenated in high yield to **6**. Periodic oxidation of **6** led to **7** which was not isolated but directly converted to the oxime **8** which, in chloroform solution, existed as a 1:1:1 mixture of *E* and *Z* isomers. De-*O*-acetylation of **8** yielded **9** (3:2 *E/Z* mixture in chloroform). The assignment of the E or Z configuration to the diastereoisomers of **8** and **9** was, as usual, based on ^{1}H-NMR data,[8,9] mainly the $\delta_{H,5'}$, $\delta_{H,4}$ and $J_{4,5}$ values. Reduction of **9** using sodium cyanoborohydride in acidic conditions led to moderate yields of **10** which was di-*O*-acetylated to **11** (Scheme 2).



Scheme 2

The *N*-(*E*)-phenylprop-2-enyl derivative of *gluco*-deoxynojirimycin having shown interesting anti-HIV activity,[10] we planned to attach a (*E*)-phenylprop-2-en-1-yloxy group (an oxa derivative of the superior homolog of a phenylprop-2-enyl group) to the nitrogen atom of trihydroxypiperidines, analogs of deoxynojirimycin. The phthalimide derivative **12** and the *O*-substituted hydroxylamine **13** were prepared using classical methods and the oxime **14**, was obtained in good yield by reacting **7** with **13**. Deacetylation of **14** gave **15**. In chloroform, both **14** and **15** existed in *ca* 3:2 *E/Z* mixtures. Acidic cyanoborohydride reduction of **15** led to a mixture of **16** (38%) and **17** (35%). Compound **17** was quantitatively acetylated to **18** (Scheme 3). At room temperature, the ^{1}H-NMR spectra of the piperidine derivatives **10**, **11**, **16**-**18** were poorly resolved whereas good spectra were obtained either at 50-60 °C (time-averaged) or at -40 to -50 °C (two frozen species) (Tables 3 and 4). The ratio of the concentrations of the more (A) to the less abundant (B) forms and the values of the energy barriers obtained using the Gutowski's approximation[11] are collected in Table 5.

References: see frame 0287



Scheme 3

TABLE 3. ^{1}H NMR of Piperidine Derivatives. Chemical Shifts of the Ring Protons.

Cmpd	Solvent t/°C	δpro-R)-H-1	δPro-S)-H-1	H-2	H-3	H-4	δpro-R)-H-5	δpro-S)-H-5
10	$CDCl_3$ +60°	3.10	3.10	4.33	3.91	4.03	3.12	2.89
10A	$CDCl_3$ -40°	2.89	3.53	4.26	3.89	3.89	3.27	2.58
10B	$CDCl_3$ -40°	3.18	2.89	4.26	3.98	4.37	2.58	3.30
11	$CDCl_3$ +22°	3.31	3.20	4.40	4.00	5.30	3.25	3.10
11A	$CDCl_3$ -50°	3.45	3.02	4.46	3.98	5.34	3.12	3.19
11B	$CDCl_3$ -50°	2.97	3.83	4.31	4.07	5.12	3.53	2.62
16	$CDCl_3$ +60°	3.30	2.91	4.38	3.99	4.07	3.10	3.10
17	C_5D_5N +110°	3.27	3.59	4.53	4.02	4.38	3.68	3.19
18	$CDCl_3$ +55°	3.1	3.30	5.37	5.04	5.21	3.39	2.92
18A	$CDCl_3$ -40°	2.71	3.47	5.39	4.85	5.26	3.72	2.46
18B	$CDCl_3$ -40°	3.41	2.77	5.19	5.12	4.96	2.79	3.41

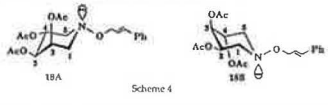
TABLE 4. ^{1}H NMR of Piperidine Derivatives Interproton Couplings in the Ring.

Cmpd	Solvent t/°C	$^3J_{1,1}$	$^3J_{1pro-R,2}$	$^3J_{1pro-S,2}$	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5pro-R}$	$^3J_{5,pro-S}$	$^3J_{5,5}$
10	$CDCl_3$ +60°	?	4.5	4.5	5.0	5.0	4.0	6.8	11.5
10A	$CDCl_3$ -40°	13.0	~7	~2	?	?	~7	9.0	9.0
10B	$CDCl_3$ -40°	11.0	?	~2	?	?	?	?	?
11	$CDCl_3$ +22°	12.0	5.5	6.0	5.0	5.0	4.0	6.0	12.0
11A	$CDCl_3$ -50°	11.5	5.5	7.0	4.8	3.8	3.0[a]	5.3[a]	12.5
11B	$CDCl_3$ -50°	13.0	2.0[a]	3.0[a]	5.5	7.0	4.0	10.0	10.0
16	$CDCl_3$ +60°	11.7	6.0	7.5	5.0	4.0	4.0	4.0	12.0
17	C_5D_5N +110°	11.0	3.5	7.0	3.5	7.0	4.0	7.0	11.0
18	$CDCl_3$ +55°	11.5	3.0	6.5	3.5	7.5	3.5	7.0	11.0
18A	$CDCl_3$ -40°	11.5	1.0	2.0	3.5	10.5	4.5	11.0	9.5
18B	$CDCl_3$ -40°	11.0	4.0	11.5	2.5	2.5	2.0	2.0	12.0
10A calcd			2.6	2.9	5.1	7.1	5.5	10.7	
10B calcd			7.0	9.5	4.7	2.9	2.3	3.0	

TABLE 5. Inversion Isomerism of Piperidine Derivatives.

Compd	[A]/[B] (K)	$\Delta G^{\ddagger}$ /kJ.mol^{-1} (K)
10	1.8 (223)	52.9 (263)
11	4.5 (223)	52.3 (253)
16	1.3 (223)	54.4 (293)
17	1.0 (233)	57.7 (283)
18	2.7 (233)	55.1 (295)

As variable temperature ^{1}H-NMR (400 MHz) of **18** could be fully interpreted, it was chosen as a model compound for structure assignments. The interproton coupling values of **18A** and **18B** (Table 4) indicate a $^4C_1$ chair for A and a $^1C_4$ chair for B. A reliable way to establish the orientation (axial or equatorial) of the phenylpropenyloxy group borne by the nitrogen atom consists in the examination of the effect of vicinal groups[12] on the absolute value of geminal coupling constants (*i.e.* $^2J_{1,1}$ and $^2J_{5,5}$). An axial lone pair decreases this value by 3-4 Hz whereas an axial electron-withdrawing (*i.e.* acetoxy) group increases it by 1-2 Hz. In the absence of either an axial lone pair or an electron-withdrawing group, the expected absolute value of these geminal coupling constants should amount to 14.0-14.5 Hz.[13] For **18A**, the very low value (9.5 Hz) of $^2J_{5,5}$ is explained by the presence of a vicinal axial lone pair and no axial acetoxy group whereas the intermediate value (11.5 Hz) of $^2J_{1,1}$ corresponds to the partial cancellation of the effect of the lone pair by that of an axial acetoxy group, thus indicating an equatorial disposition of the *N*-phenylpropenyloxy group (Scheme 4).



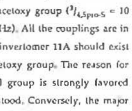
Scheme 4

For **18B**, $^2J_{1,1}$ and $^2J_{5,5}$ are both smaller than it would be expected for an axial *N*-phenylpropenyloxy group, $^2J_{5,5}$ being lightly increased by the vicinal axial acetoxy group. The most probable structure of **18B** thus corresponds also to an equatorial *N*-phenylpropenyloxy group. In these conditions, **18A** and **18B** are invertomers and the transformation observed by variable temperature NMR is a slow (at the NMR time scale) nitrogen inversion followed by a rapid chair inver-

References: see frame 0287

sion. The $\Delta G^{\ddagger}$ values measured are close (somewhat smaller) to those found for nitrogen inversion without chair interconversion in *N*-acetoxymorpholine derivatives.[13]

The conformation of compounds **10**-**11** is more difficult to ascertain owing to the fact that the presence of a 2,3-*O*-cyclopentylidene group prohibits their existence as genuine chair forms. An X-ray diffraction study[14] of the L-*gulo* analog of **10** (Scheme 5) showed this compound to exist in a $^1C_4$ flattened chair ($F_{4,0}$)[15] form with the *N*-phenylpropenyloxy group in equatorial position. Interproton coupling constants of **11B** (Table 4) indicate an equatorial position of the 4-acetoxy group ($^3J_{4,5pro-S}$ = 10 Hz) and a close to axial disposition of 2-OR ($^3J_{1,2}$ = 13 Hz). All the couplings are in accordance with a flattened $^4C_1$ form ($F_{1,2}$). The major invertomer **11A** should exist in a flattened $^1C_4$ ($F_{4,0}$) form with an equatorial *N*-acetoxy group. The reason for which the conformer **11A** bearing an axial 4-*O*-acetyl group is strongly favored over its equatorial counterpart **11B**, is not well understood. Conversely, the major conformer of **10** corresponds to a $^4C_1$ form with both hydroxy groups in equatorial position as appears from its incomplete set of NMR data (Tables 3 and 4). A Monte Carlo conformational search was performed on **10** using the MacroModel 3.5 software[16] in which were introduced the MM2 parameters developed[17] from ab initio studies for the N(sp^3)-O(sp^3) bond. The search was conducted using the chloroform solvation option and the solvent accessible surface area was analytically recomputed at each optimization step. Two hundred conformers were generated and minimized for each invertomer. Starting from the (*Ns*) invertomer, the most stable form found was a $^4C_1$ flattened chair ($F_{1,2}$) corresponding to **10A** (same conformation as **11B**) whereas from the (*Nr*) invertomer a $^1C_4$ flattened chair ($F_{4,0}$) was obtained corresponding to **10B** (same conformation as **11A**). The two forms were almost isoenergetic (**10A** more stable than **10B** by 0.6 kJ/mol). The coupling constants calculated for **10A** using the Altona's equation[18] included in the MacroModel software (Table 4) are in good accordance with the experimental values measured for **11B**. The agreement is somewhat less satisfactory between computed **10B** and **11A**.



Scheme 5

In any case, these observations indicate that in this series, the nitrogen inversion provokes a chair inversion whereas in a previously studied[13] morpholine series,

References: see frames 0287 and 0288

the energy difference between the two chairs was much larger so we could observe both invertomers in the same chair conformation.

Upon spontaneous oxidation in the air, **10** gave the corresponding aminoxyl radical **10'**, EPR spectrum of which was measured in diglyme at 50 °C (Fig. 1). Besides the hyperfine coupling with nitrogen, four unequal couplings with the H_2C-1 and H_2C-5 vicinal protons were observed, this excluding a conformation having a σ plane of symmetry perpendicular to the mean plane of the ring and passing through the nitrogen atom and C-3. A recent ab initio study of model aminoxyls[19] showed that the angular dependence of vicinal a_H^{β} couplings upon the θ rotational angle between the C-H bond and an axis perpendicular to the C-N-C plane and passing through the nitrogen atom could be expressed by the classical equation:[20]

$$a_H^{\beta} = B_0 + B_2\cos^2\theta$$

only if using specific values of B_0 and B_2 depending on the out-of-plane deformation of the aminoxyl group (α) and on whether the C-H bond is on the same side of the molecule as aminoxyl oxygen or on the opposite side.[19] On the other hand, the a_N value depends on the α angle. In the case of **10'**, the experimental value of a_N (14.4 G) corresponds to an α angle of about 15° which gives B_0 and B_2 values of *ca* 1.4 and 19.3 respectively.

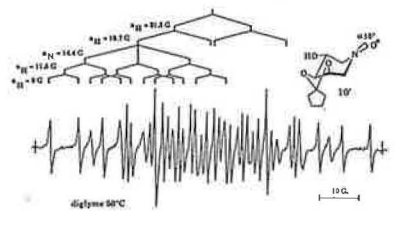
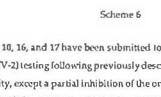


Figure 1. EPR spectrum of **10'**.

References: see frame 0288

From this, the following assignments were made (Scheme 6) θ_{H5eq} 55° (exp. a_H 8 G, calcd a_H 7.8 G), θ_{H5ax} 175° (exp. a_H 21.3 G, calcd a_H 20.6 G), θ_{H1eq} 45° (exp. a_H 11.1 G, calcd a_H 11.4 G), θ_{H1ax} 165° (exp. a_H 19.7 G, calcd a_H 19.4 G). These angular values correspond well to those expected from a flattened $^1C_4$ chair ($F_{1,2}$).



Scheme 6

Compounds **10**, **16**, and **17** have been submitted to antibacterial and antiviral (including HIV-1 and HIV-2) testing following previously described procedures.[21] None showed any notable activity, except a partial inhibition of the onco-virus SV_{40} by **16** at a concentration of 105 μM, half the minimum cytotoxic concentration. No inhibition of either α-D-mannosidase or α-D-glucosidase was exhibited by compounds **16** and **17**. Compound **17** constitutes an analog of *manno*-deoxynojirimycin missing its terminal hydroxymethyl group. It is probable that the presence of this group is a prerequisite to anti-HIV activity.

ACKNOWLEDGMENTS

The authors thank Prof. A. Buchs and Dr F. Gulaçar for the MS, Prof. M. Geoffroy for the EPR spectra, and M. A. Pinto for the 400 MHz NMR spectra. This work was generously supported by the Swiss National Science Foundation (Grant # 20-31259.91).

EXPERIMENTAL

General methods. See ref. 22. 400 MHz ^{1}H-NMR spectra were measured using a Bruker AMX400 spectrometer.

Sodium cyanobrohydride **reduction of 1,5-bis(*N*-hydroxyimino)pentane (1)**. To a solution of **1** (6.5 g, 0.05 mol) in water (300 mL, 80 °C) $NaBH_3CN$ (6 g, 0.1 mol) was added and the pH kept at 4-5 by dropwise addition of aqueous 1 M HCl. After completion of the reaction (TLC), the pH was brought to 7 (saturated aqueous $NaHCO_3$) and the organic products were extracted (AcOEt, 3x100 mL). The collected organic fractions were dried (Na_2SO_4), concentrated and submitted to a column chromatography (4:1 AcOEt/hexane) yielding **2**[6] (2 g, 40%) and **3** (0.9 g, 15%).

References: see frame 0288

2-Cyano-1-hydroxypiperidine (3). Obtained as described hereupon: mp 96.7-100.6 °C; ν_{max}^{KBr} 3255 (OH), 2946 and 2849 (CH), and 2218 (CN) cm^{-1}. MS: *m/z* (%) 99 (100), 59 (70), 54 (64), 69 (54), 67 (47), 109 (47, M^+ - OH), 53 (32), 126 (32, M^+), and 100 (25, M^+ - CN). *Anal.* Calcd for $C_6H_{10}N_2O$ (126.16): C, 57.12; H, 7.99; N, 22.20. Found: C, 57.14; H, 7.94; N, 22.19.

2,3:5,6-Di-*O*-cyclopentylidene-α-D-mannofuranose (4). To a solution of D-mannose (15 g, 83.26 mmol) in freshly distilled cyclopentanone (400 mL), dried $CuSO_4$ (20 g, 94 mmol) and concentrated H_2SO_4 (1 mL) were added. After 36 h, the solution was filtered, neutralized ($NaHCO_3$, 15 g, 0.18 mmol) for 1 h, then concentrated and extracted with ether (250 mL). The organic phase was washed with water (3x200 mL), dried (Na_2SO_4), then concentrated. Crystallization (heptane) gave **4** (21.48 g, 82.6%): mp 118.4 °C; R_F 0.2 (1:4 AcOEt/hexane); $[\alpha]_D^{21}$ +16.3° (*c* 1.2); ν_{max}^{KBr} 3420 (OH) cm^{-1}. MS: *m/z* (%) 55 (100), 56 (22), 57 (24), 67 (13), 69 (19), 81 (12), 83 (11), 85 (27), 127 (26), and 312 (0.4, M^+).

Anal. Calcd for $C_{18}H_{24}O_6$ (312.37): C, 61.52; H, 7.74. Found: C, 61.49; H, 7.56.

1-*O*-Acetyl-2,3:5,6-di-*O*-cyclopentylidene-α-D-mannofuranose (5). A solution of **4** (21 g, 67.2 mmol) in a mixture of pyridine (30 mL) and Ac_2O (30 mL) was kept 12 h at room temperature, then extracted as usual. Column chromatography (1:2 AcOEt/hexane) gave **5** (23.5 g, 98.6%): syrup, R_F 0.4 (1:4 AcOEt/hexane); $[\alpha]_D^{20}$ +27° (*c* 0.5); ν_{max}^{film} 1750 (CO) cm^{-1}. MS: *m/z* (%) 55 (100), 56 (25), 57 (18), 67 (11), 69 (23), 81 (12), 84 (19), 85 (24), 127 (52), and 354 (0.5, M^+).

Anal. Calcd for $C_{18}H_{26}O_7$ (354.40): C, 61.00; H, 7.39. Found: C, 60.88; H, 7.31.

1-*O*-Acetyl-2,3-*O*-cyclopentylidene-α-D-mannofuranose (6). A solution of **5** (22.62 g, 63.83 mmol) in MeOH (250 mL) and 1M HCl (5 mL) was kept 3 h (TLC) at room temperature then neutralized (saturated aqueous $NaHCO_3$), diluted with water (200 mL), and extracted with $CHCl_3$ (3x200 mL). The organic phase was dried (Na_2SO_4), then concentrated. Crystallization (toluene) gave **6** (13 g, 71%): mp 151.1-151.3 °C; R_F 0.5 (6:1 AcOEt/hexane); $[\alpha]_D^{21}$ +52° (*c* 0.9); ν_{max}^{KBr} 3400 and 3180 (OH), and 1746 (CO) cm^{-1}. MS: *m/z* (%) 55 (94), 56 (28), 57 (24), 61 (17), 69 (20), 71 (18), 84 (25), 85 (100), 127 (26), and 288 (1, M^+).

Anal. Calcd for $C_{13}H_{20}O_7$ (288.30): C, 54.16; H, 6.99. Found: C, 54.42; H, 7.06.

1-*O*-Acetyl-2,3-*O*-cyclopentylidene-5-deoxy-5-hydroxyimino-α-D-lyxofuranose (8). To a solution of **6** (11.4 g, 39.5 mmol) in water (200 mL), $NaIO_4$ (8.45 g, 39.5 mmol) and $NaHCO_3$ (3.32 g, 39.5 mmol) were added. After 45 min at room temperature, the mixture was extracted with $CHCl_3$ (3x100 mL), the organic phase dried (Na_2SO_4) and concentrated to give **7** (10 g) which was not further purified but dissolved in pyridine (100 mL), then hydroxylamine hydrochloride (8.14 g, 117.1 mmol) was added. After 12 h at room temperature, the solvent was coevaporated with toluene (2x100 mL) and the residue extracted with AcOEt (200 mL). The organic phase was washed with water (3x100 mL), dried (Na_2SO_4) and concentrated. Column chromatography (1:1 AcOEt/hexane) gave **8** (5.54 g, 52% from **6**): mp 130.7-130.8 °C; R_F: 0.4 and 0.5 (1:1 AcOEt/hexane); λ_{max}^{EtOH} 204 nm (ε 2400); ν_{max}^{KBr} 3233 (OH) and 1754 (CO) cm^{-1}. MS: *m/z* (%) 55 (100), 56 (24), 57 (13), 67 (13), 84 (11), 85 (27), 86 (16), 128 (22), 242 (13), and 271 (2, M^+).

Anal. Calcd for $C_{13}H_{19}NO_6$ (271.27): C, 53.13; H, 6.32; N, 5.16. Found: C, 52.99; H, 6.18; N, 5.41.

2,3-*O*-Cyclopentylidene-5-deoxy-5-hydroxyimino-α-D-lyxofuranose (9). A solution of **8** (4.78 g, 17.63 mmol) and NaOMe (925 mg, 17.6 mmol) in MeOH (75 mL) was kept at room temperature for 30 min, then concentrated and the residue extracted with EtOAc (100 mL). The organic phase was washed with water (3x50 mL), dried (Na_2SO_4), and concentrated. Column chromatography (1:1 AcOEt/hexane) gave **9** (2.5 g, 62%): mp 109.7-109.8 °C; R_F: 0.2 and 0.3 (1:1 AcOEt/hexane); λ_{max}^{EtOH} 204 nm (ε 3200); ν_{max}^{KBr} 3370 (OH) cm^{-1}. MS: *m/z* (%) 52 (16), 55 (100), 56 (29), 57 (19), 67 (19), 69 (11), 75 (11), 85 (20), 200 (23), and 229 (1, M^+).

Anal. Calcd for $C_{10}H_{15}NO_5$ (229.23): C, 52.40; H, 6.60; N, 6.11. Found: C, 52.53; H, 6.66; N, 5.99.

2,3-*O*-Cyclopentylidene-1,5-dideoxy-1,5-(*N*-hydroxyimino)-D-lyxitol (10). To a solution of **9** (2.27 g, 9.9 mmol) in MeOH (250 mL), $NaBH_3CN$ (3.13 g, 49.8 mmol) was added and the pH was kept at 2 by dropwise addition of 1 M HCl. After 30 min, the mixture was brought to pH 8 (saturated aqueous $NaHCO_3$), diluted with water (200 mL) then extracted with $CHCl_3$ (3x200 mL). The organic phases were dried (Na_2SO_4) then concentrated, and after column chromatography (2:1 AcOEt/hexane) gave **10** (300 mg, 38%): syrup, R_F: 0.15 (1:1 AcOEt/hexane); $[\alpha]_D^{20}$ -13.5° (*c* 0.8); λ_{max}^{EtOH} 204 nm (ε 570), 240 (200), and 290 (90); ν_{max}^{film} 3400 (OH) cm^{-1}. MS: *m/z* (%) 45 (70), 48 (26), 55 (57), 64 (28), 67 (25), 77 (36), 79 (28), 91 (100), 105 (23), and 215 (1, M^+).

Anal. Calcd for $C_{10}H_{17}NO_4$ (215.25): C, 55.80; H, 7.96; N, 6.51. Found: C, 55.66; H, 8.06; N, 6.51.

4-*O*-Acetyl-2,3-*O*-cyclopentylidene-1,5-dideoxy-1,5-(*N*-acetyloxyimino)-D-lyxitol (11). To a solution of **10** (45 mg, 0.209 mmol) in Py (3 mL) Ac_2O (0.5 mL, 5 mmol) was added. After 5 h stirring at room temp, the solvent was coevaporated with toluene (5x10 mL), and the residue, extracted with column chromatography (15:1 AcOEt/hexane), gave **11** (60 mg, 96%): syrup, R_F 0.6 (15:1 AcOEt/hexane); $[\alpha]_D^{22}$ -3.78° (*c* 0.9); λ_{max}^{EtOH} 204 nm (ε 1023); ν_{max}^{KBr} 2950 (νCH sat.), 1750 and 1730 (νC=O) cm^{-1}. MS: *m/z* (%) 55 (86), 68 (53), 84 (58), 85 (46), 113 (61), 173 (100), 240 (27), and 299 (1.33 M^+).

Anal. Calcd for $C_{14}H_{21}NO_6$ (299.33): C, 56.18; H, 7.07; N, 4.68. Found: C, 55.93; H, 7.11; N, 4.60.

(*E*)-*N*-(3-Phenylprop-2-enyloxy)phthalimide (12). To a solution of (*E*)-3-phenylprop-2-enol (10 g, 74.5 mmol) in THF (500 mL), *N*-hydroxyphthalimide (13.24 g, 74.5 mmol), triphyenylphosphine (21.5 g, 74.5 mmol) and then dropwise, diethyl azodicarboxylate (12.74 mL, 74.5 mmol) were added at 0 °C. After 4 days at room temperature, the reaction mixture was concentrated, and the residue purified by crystallization (EtOH) gave **12** (16 g, 81%): mp 128.6-130.1 °C; λ_{max}^{EtOH} 210 nm (ε 45200), 216 (45500), and 241 (26300); ν_{max}^{KBr} 1767, 1727 (CO), 1580, 1464, and 1453 (Ar) cm^{-1}. ^1H NMR: δ 4.89 (*dd*, 2 H, $J_{1,2}$ 7 Hz, $J_{1,3}$ 1.1Hz, H_2C-1), 6.48 (*dt*, 1 H, $J_{2,3}$ 16 Hz, 1IC-2), 6.70 (*dt*, 1 H, HC-3), 7.39 (*m*, 5 H, Ar), and 7.80 (*m*, 4 H, Ar). MS: *m/z* (%) 117 (100), 91 (9), 147 (5), and 223 (0.5).

Anal. Calcd for $C_{17}H_{13}NO_3$ (279.30): C, 73.11; H, 4.69; N, 5.01. Found: C, 72.95; H, 4.65; N, 5.10.

(*E*)-*O*-3-Phenylprop-2-enylhydroxylamine (13). To a solution of **12** (16 g, 60.7 mmol) in EtOH (300 mL), hydrazine hydrate (8.8 mL, 182.1 mmol) was added. After 5 min stirring at room temperature, the reaction mixture filtered and concentrated was submitted to column chromatography (1:1 AcOEt/hexane) to give **13** (6.4 g, 79%): syrup; R_F 0.5 (1:1 AcOEt/hexane); λ_{max}^{EtOH} 205 nm (ε 20300), and 250 (16400); ν_{max}^{KBr} 3314, 3240 (NH), 1598, 1580, 1495, and 1450 (Ar) cm^{-1}. ^1H NMR: δ 4.35 (*dd*, 2 H, $J_{1,2}$ 6 Hz, $J_{1,3}$ 1 Hz, H_2C-1), 4.45 (*bs*, 2 H, ONH_2), 6.35 (*dt*, 1 H, $J_{2,3}$ 16 Hz, HC-2), 6.68 (*dt*, 1 H, HC-3), and 7.35 (*m*, 5 H, Ar). MS: *m/z* (%) 117 (100, M^+ - NH_2O), 91 (19), 77 (10), 51 (8), 103 (3), and 149 (2, M^+).

Anal. Calcd for $C_9H_{11}NO$ (149.19): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.42; H, 7.58; N, 9.16.

(5*E* and 5*Z*)-1-*O*-Acetyl-2,3-*O*-cyclopentylidene-5-deoxy-5-[(2'*E*)-3'-phenylprop-2'-enyloxyimino]-α-D-lyxofuranose (14). To a solution of **7** (2.47 g, 9.61 mmol) in EtOH (100 mL), **13** (1.5 g, 10.05 mmol) was added and the mixture stirred for 12 h at room temperature. The reaction mixture, concentrated, was submitted to column chromatography (1:1 AcOEt/hexane) to give **14** (3 g, 80.6%): syrup; R_F 0.71 (1:1 AcOEt/hexane); $[\alpha]_D^{25}$ -59° (*c* 0.6); λ_{max}^{EtOH} 206 nm (ε 17600) and 250 (12400); ν_{max}^{film} 2950 (CH), and 1751 (CO) cm^{-1}. ^1H NMR (2:3 5*E*/5*Z*): δ 1.70 (*m*, 6 H, (*E* + *Z*) cyclopentylidene), 1.92 (*m*, 2 H, (*E* + *Z*) cyclopentylidene), 2.09 (*s*, 3 H, (*E* + *Z*) OAc), 4.66 (*dd*, 1 H, $J_{3,4}$ 4 Hz, $J_{4,5}$ 7.5 Hz, (*Z*) HC-4), 4.77 (*m*, (*E* + *Z*) H_2C-1', (*E* + *Z*) HC-2, (*Z*) HC-3), 5.05 (*dd*, 1 H, $J_{2,3}$ 6 Hz, $J_{3,4}$ 4 Hz, (*E*) HC-3), 5.12 (*t*, 1 H, $J_{4,5}$ 4 Hz, (*E*) HC-4), 6.22 (*s*, 1 H, (*E* + *Z*) HC-1), 6.36 and 6.38 (2 *dt*, 1 H, $J_{1',2'}$ 6.5 Hz, $J_{2',3'}$ 16 Hz, (*E* + *Z*) HC-2'), 6.64 (*bd*, 1 H, $J_{1',2'}$ 1 Hz, (*E* + *Z*) HC-3'), 6.90 (*d*, 1 H, (*E*) H-C5), 7.35 (*m*, 5 H, (*E* + *Z*) Ar), and 7.50 (*d*, 1 H, (*Z*) HC-5). MS: *m/z* (%) 117 (100), 55 (15), 91 (10), 24 (1), 325 (0.6), and 387 (0.2, M^+).

Anal. Calcd for $C_{13}H_{25}NO_6$ (387.44): C, 65.10; H, 6.50; N, 3.62. Found: C, 65.01; H, 6.53; N, 3.74.

(5*E* and 5*Z*)-2,3-*O*-Cyclopentylidene-5-deoxy-5-[(2'*E*)-3'-phenylprop-2-enyloxyimino]-α-D-lyxofuranose (15). To a solution of **14** (2.37 g, 6.11 mmol) in EtOH (70 mL), NaOMe (0.33 g, 6.11 mmol) was added. After 1 h at room temperature, water (150 mL) was added and the reaction mixture extracted with $CHCl_3$ (3x100 mL). The collected organic phases, dried (Na_2SO_4) and concentrated, were submitted to column chromatography (1:1 AcOEt/hexane) to give **15** (2 g, 94.7%): mp 68.0-73.4 °C; R_F 0.6 (1:1 AcOEt/hexane); $[\alpha]_D^{25}$ -61.6° (*c* 1); λ_{max}^{EtOH} 205 nm (ε 26300), 210 (25000), 216 (16000), and 250 (19000); ν_{max}^{KBr} 3360 (OH), 1635 (C=N), 1690, 1670, 1490, and 1445 (C=C and Ar) cm^{-1}. ^1H NMR (Z/E = 1.6): δ 1.19 (*m*, 6 H, (*Z* + *E*) cyclopentylidene), 1.90 (*m*, 2 H, (*Z* + *E*) cyclopentylidene), 2.53 (*d*, 1 H, $J_{1,OH}$ 2.5 Hz, (*E*) HOC-1), 2.62 (*d*, 1 H, $J_{1,OH}$ 2.5 Hz (*Z*) HOC-1), 2.58 (*d*, 1 H, $J_{2,3}$ 6 Hz, (*E*) HC-2), 2.56 (*d*, 1 H, $J_{2,3}$ 6 Hz, (*Z*) HC-2), 4.75 (*m*, 4 H, (*E* + *Z*) H_2C-1', (*Z*) HC-3 and (*Z*) HC-4), 5.00 (*dd*, 1 H, $J_{3,4}$ 4 Hz, (*E*) HC-3), 5.48 (*d*, 1 H, (*E* + *Z*) HC-1), 6.35 (*dt*, 1 H, $J_{1',2'}$ 6 Hz, $J_{2',3'}$ 16 Hz, (*E* + *Z*) HC-2'), 6.66 (*d*, 1 H, (*E* + *Z*) HC-3'), 6.90 (*d*, 1 H, (*E*) HC-5), 7.35 (*m*, 5 H, (*E* + *Z*) Ph), and 7.53 (*d*, 1 H, (*Z*) HC-5). MS: *m/z* (%) 117 (100), 55 (36), 91 (30), 77 (20), 199 (1), and 345 (0.2, M^+).

Anal. Calcd for $C_{19}H_{23}NO_5$ (345.40): C, 66.07; H, 6.71; N, 4.06. Found: C, 65.94; H, 6.72; N, 4.10.

(*E*)-2,3-*O*-Cyclopentylidene-1,5-dideoxy-1,5-[*N*-(3'-phenylprop-2'-enyloxy)imino]-D-lyxitol (16). To a solution of **15** (2.21 g, 6.4 mmol) in EtOH (150 mL), $NaBH_3CN$ (1.2 g, 19.1 mmol) was added at room temperature and the pH kept at 1 by dropwise addition of 1 M HCl. After 18 h, water (200 mL) was added and the reaction mixture extracted with $CHCl_3$ (4x100 mL). The organic phases, dried (Na_2SO_4) were concentrated and submitted to column chromatography to afford **16** (810 mg, 38.2%) and **17** (600 mg, 35.4%). Properties of **16**: syrup; R_F 0.52 (1:1 AcOEt/hexane); $[\alpha]_D^{25}$ +14.1° (*c* 0.9); λ_{max}^{EtOH} 205 nm (ε 35000), 210 (32000), 216 (20000), and 250 (28500); ν_{max}^{film} 3450 (OH) cm^{-1}. MS: *m/z* (%) 117 (100, phenylpropenyl), 55 (16), 91 (8), 130 (7), 77 (4), 68 (3), 214 (0.4), and 332 (0.1, M^+ + H).

Anal. Calcd for $C_{19}H_{25}NO_4$ (331.42): C, 68.86; H, 7.60; N, 4.23. Found: C, 68.73; H, 7.71; N, 4.19.

(*E*)-1,5-Dideoxy-1,5-[*N*-(3'-phenylprop-2'-enyloxy)imino]-D-lyxitol (17). Obtained as described for **15**: mp 138.0-140.6 °C; R_F 0.1 (9:1 AcOEt/hexane); $[\alpha]_D^{24}$ -5.4° (*c* 0.7); λ_{max}^{EtOH} 205 nm (ε 19000), 210 (17000), 216 (10000), and 250 (15000); ν_{max}^{KBr} 3350 (OH) cm^{-1}. MS: *m/z* (%) 117 (100, phenylpropenyl), 91 (10), 103 (5), 77 (8), 235 (1), 194 (0.9), 180 (0.5), 259 (0.5), 222 (0.4), and 249 (0.3).

Anal. Calcd for $C_{14}H_{19}NO_4$ (265.31): C, 63.38; H, 7.22; N, 5.28. Found: C, 63.24; H, 7.15; N, 5.38.

(*E*)-2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-[*N*-(3'-phenylprop-2'-enyloxy)imino]-D-lyxitol (18). To a solution of **17** (95 mg, 0.358 mmol) in pyridine (10 mL), acetic anhydride (1 mL, 10.6 mmol) was added and the mixture stirred for 12 h at room temperature. After codistillation of the pyridine with toluene (4x20 mL), the residue was submitted to a column chromatography (1:1 AcOEt/hexane) to give **18** (136 mg, 97%), syrup; R_F 0.8 (1:1 AcOEt/hexane); $[\alpha]_D^{25}$ -19.9° (*c* 0.8); λ_{max}^{EtOH} 206 nm (ε 21900), and 252 (17900); ν_{max}^{film} 1745 (CO) cm^{-1}. ^{13}C NMR (100.6 MHz, $CDCl_3$) 55 °C: 169.61 (CO), 136.92 (C1''), 133.70 (C3'), 128.56 (C3''), 127.78 (C4''), 126.56 (C2''), 125.27 (C2'), 73.68 (C1'), 69.82 (C3), 67.91 and 67.21 (C2 and C4), 56.04 and 55.68 (C1 and C5), 20.69, 20.66, and 20.53 (CH_3); -40 °C a 3:1 mixture of 18A and 18B: 18A, 170.80, 170.80, and 170.49 (3 *s*, 3xCO), 135.60 (*s*, C1''), 134.66 (*d*, C3'), 128.41 (*d*, C3''), 127.89 (*d*, C4''), 126.31 (*d*, C2''), 122.99 (*d*, C2'), 73.12 (*t*, C1'), 70.77 (*d*, C3), 66.35 (2 *d*, C2 and C4) 57.00 and 56.91 (2 *dd*, C5 and C1), 21.20, 21.15 and 21.06 (3 *q*, 3xMe); 18B, 170.40, 170.17, and 169.84 (3 *s*, 3xCO), 135.90 (*s*, C1''), 134.40 (*d*, C3'), 128.41 (*d*, C3''), 127.89 (*d*, C4''), 126.31 (*d*, C2''), 123.28 (*d*, C2'), 72.98 (*t*, C1'), 67.88 (*d*, C4), 66.07 (*d*, C2), 65.25 (*d*, C3), 53.86 and 53.02 (2 *dd*, C1 and C5), 21.20, 21.15, and 21.06 (3 *q*, 3xMe). MS: *m/z* (%) 117 (100, phenylpropenyl), 91 (10), 57 (9), 342 (9, M^+ - AcO), and 220 (5).

Anal. Calcd for $C_{20}H_{25}NO_7$ (391.42): C, 61.37; H, 6.44; N, 3.58. Found: C, 61.33; H, 6.57; N, 3.45.

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