ELSEVIER

Carbohydrate Research 337 (2002) 2419–2425

CARBOHYDRATE RESEARCH

www.elsevier.com/locate/carres

Synthesis, high-resolution NMR spectroscopic analysis, and single-crystal X-ray diffraction of isoxazoline tetracycles

Mirta L. Fascio,[a] Angel Alvarez-Larena,[b] Norma B. D'Accorso[a,*]

[a]*Centro de Investigaciones de Hidratos de Carbono (CIHIDECAR), Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Pabellón II, 3º Piso, C.P. 1428, Buenos Aires, Argentina*

[b]*Unitat de Cristal.lografía, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain*

Received 24 May 2002; accepted 30 July 2002

Abstract

Three isoxazoline tetracycles were obtained enantiomerically pure by intramolecular 1,3-dipolar cycloaddition. The characterization of the new compounds was performed by high-resolution ^{1}H and ^{13}C NMR spectroscopy. The relative configuration of the new chiral centers was determined by NOESY experiments and confirmed by single-crystal X-ray structural analysis.

Keywords: Isoxazolines; Intramolecular 1,3-dipolar cycloaddition; Stereocontrol, NMR spectroscopy; X-Ray crystallography

1. Introduction

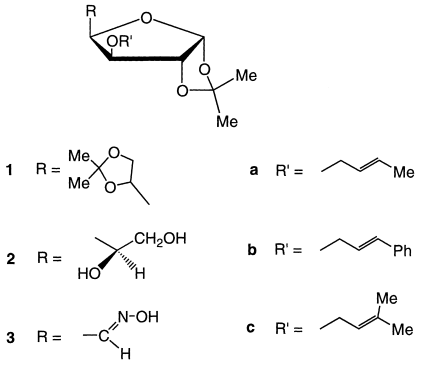
1,3-Dipolar cycloadditions are among the most powerful methods for construction of a variety of five-membered heterocycles in a one-step route.[1] Particularly, intramolecular cycloadditions with regio- and stereocontrol are important tools for efficient assembly of complex molecular structures.[2]

Nitrogen–oxygen heterocycles constitute the largest class of biologically active compounds,[3] and several of these compounds have a chiral isoxazoline ring system.[4,5]

Carbohydrate compounds are a primary source of chirality in organic synthesis and are used as starting material to prepare other chiral compounds. In this field Bhattacharjya and co-workers[6] have reported several isoxazoline syntheses as precursors of natural products with biologycal interest, where the key steps are the synthesis and cleavage of heterocyclic ring.

2. Results and discussion

Synthesis.—In order to study the stereocontrol induced by 1,3-intramolecular dipolar cycloaddition reaction, we synthesized three tetracyclic isoxazolines **4**–**6**, by the technique described in literature[7] for similar compounds. Thus, the hydroxyl group on C-3 of the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[8] was functionalized with the (*E*)-2-butenyl (**a**), the (*E*)-3-phenyl-2-propenyl (**b**) or the 3-methyl-2-butenyl (**c**) group to yield the compounds (**1a**–**1c**). The deprotection of the hydroxyl groups on C-5 and C-6 gave the 1,2-*O*-isopropylidene derivatives (**2a**–**2c**). The dialdose derivatives were obtained by oxidation of the vicinal diols. As these compounds were very unstable, they were directly used for the next step and were characterized only by ^{13}C NMR spectroscopy. The treatment of the dialdose derivatives with hydroxylamine produced the corresponding mono-oxime derivatives (**3a**–**3c**).



* Corresponding author. Tel./fax: +54-11-4576-3346
E-mail address: norma@qo.fcen.uba.ar (N.B. D'Accorso).

0008-6215/02/$ - see front matter
PII: S0008-6215(02)00258-6

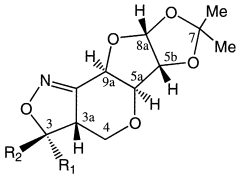
Table 1
^{1}H NMR chemical shifts (δ, ppm) for compounds **1**–**3**, performed in $CDCl_3$

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	H-1′a	H-1′b	H-2′	H-3′	H-4′a	H-4′b	Aromatic protons
1a[a]	5.87	4.52	3.92	4.12	4.29	3.98	4.08	4.01–4.08		5.55	5.73	1.72	–	–
1b[a]	5.89	4.56	4.01	4.12	4.35	4.01	4.10	4.24	4.31	6.24	6.61	–	–	7.21–7.38
1c[a]	5.87	4.53	3.91	4.10	4.30	3.98	4.08	4.07–4.11		5.32	-	1.69	1.75	–
2a[a]	5.92	4.56	4.03	4.14	4.00	3.72	3.83	3.96	4.12	5.56	5.77	1.72	–	–
2b[b]	5.93	4.61	4.10	4.15	4.04	3.74	3.84	4.22	4.35	6.26	6.63	–	–	7.20–7.41
2c[a]	5.90	4.57	4.01	4.11	3.98	3.70	3.81	4.06	4.16	5.34	–	1.69	1.76	–
3a[a] (*syn*)	5.96	4.57	3.97	4.73	7.48	–	–	3.91	3.98	5.48	5.70	1.71	–	–
(*anti*)	5.97	4.59	4.29	5.21	6.93			3.94	4.03	5.51	5.71	1.70		
3b[b] (*syn*)	5.99	4.61	4.04	4.77	7.54	–	–	4.12	4.25	6.16	6.56	–	–	7.17–7.39
(*anti*)	6.00	4.64	4.37	5.24	6.96			4.13	4.26	6.18	6.58			
3c[a] (*syn*)	5.96	4.58	3.94	4.72	7.47	–	–	3.98	4.05	5.27	–	1.65	1.72	–
(*anti*)	5.97	4.60	4.26	5.21	6.92			3.99	4.07			1.66	1.74	

[a] Performed at 500 MHz.
[b] Performed at 200 MHz.

Compounds **1**–**3** were characterized by their NMR spectra (1D and 2D homonuclear experiments). The chemical shifts and coupling constants are listed in Tables 1 and 2, respectively. The assignment of the ^{13}C NMR spectra was performed using 2D heteronuclear experiment (HETCOR), see Table 3.

The cycloaddition reaction from compounds **3a**–**3c** using Chloramine-T yielded the tetracyclic isoxazolines **4**–**6**. We characterized these new compounds spectroscopically using 2D NMR techniques for unequivocal assignation.



4 $R_1 = H$; $R_2 = CH_3$

5 $R_1 = H$; $R_2 = Ph$

6 $R_1 = CH_3$; $R_2 = CH_3$

Although during the cyclization two new stereogenic centers (compounds **4** and **5)** or one new chiral center (compound **6**) were generated, the spectroscopical analysis showed the presence of only one diasteromer in each case. The chemical shifts for ^1H NMR, coupling constants and ^{13}C NMR assigments are shown in Tables 4–6, respectively. The stereochemistry at C-3a and C-3 were determined by the combined analysis of the NOESY spectrum and molecular modeling (AM1) of all the epimers.

In the NOESY spectrum of compound **4** the correlation observed for the pairs H-4/H-5a let us to discard the 3*S*, 3a*R* and the 3*R*, 3a*S* stereoisomers, because these diasteromers do not present this correlation. So both, the 3*S*, 3a*S* or the 3*R*, 3a*R* stereoisomers, are possible. The single-crystal X-ray crystallographic data concluded that the configuration of new chiral centers of compound **4** are 3*R*, 3a*R* (Fig. 1).

Table 2
^1H NMR coupling constants (Hz) for compounds **1**–**3**

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{1'a,2'}$	$J_{1'b,2'}$	$J_{1'a,1'b}$	$J_{2',3'}$	$J_{3',4'}$
1a	3.6	~0	2.9	7.5	5.8	6.2	8.5		6.4	12.3	15.3	6.5
1b	3.7	~0	3.1	7.9	5.5	6.2	8.6	6.0	5.9	12.9	16.0	–
1c	3.6	~0	2.9		5.9	6.2	8.5	6.8	6.8		–	–
2a	3.9	~0	3.4	7.4	5.7	3.6	11.5	6.6	6.2	11.8	15.3	6.4
2b	3.8	~0	3.1	7.8	5.0	3.3	11.4	6.2	5.8	12.7	15.9	–
2c	3.8	~0	3.2	8.0	5.5	3.3	11.5	7.3	6.8	11.7	–	–
3a (*syn*)	3.7	~0	3.2	7.5	–	–	–	6.4	6.1	12.0	15.2	6.8
(*anti*)	3.7	~0	3.4	4.1				6.4	6.1	12.0	15.2	6.8
3b (*syn*)	3.6	~0	3.3	7.4	–	–	–	6.1	6.4	12.9	15.9	–
(*anti*)	4.0	~0	3.4	4.4				6.1	6.4	12.8	15.9	
3c (*syn*)	3.6	~0	3.2	7.5	–	–	–	6.1	7.1	11.5	–	–
(*anti*)	3.7	~0	3.2	4.1	–			6.2	7.1	11.5		

Table 3
^{13}C NMR chemical shifts (δ, ppm) for compounds **1–3**, performed in $CDCl_3$

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	$\underline{C}(CH_3)_2$	Aromatic carbons
1a[a]	105.2	82.9	81.0	81.2	72.5	67.2	71.1	127.0	129.7	17.6	108.8; 111.6	–
1b[a]	105.3	82.9	81.2	81.2	72.5	67.4	70.9	125.4	132.6	–	109.0; 111.8	126.5–136.6
1c[a]	105.2	83.0	80.9	81.3	72.5	67.3	67.0	120.6	133.6	17.9; 25.7	108.8; 111.6	–
2a[a]	104.9	82.2	81.4	79.7	69.1	64.2	70.8	126.5	130.5	17.6	111.6	–
2b[b]	105.0	82.3	81.9	79.9	69.1	64.2	70.8	124.8	133.2	–	111.7	126.5–136.3
2c[a]	105.0	82.3	81.7	79.8	69.4	64.3	66.5	120.0	138.3	18.0; 25.6	111.6	–
3a[a] (*syn*)	105.3	83.2	83.0	77.8	147.7	–	71.2	126.7	130.3	17.6	111.9	–
(anti)	104.8	82.8	81.8	75.5	149.4		71.3	126.4	130.5		112.0	
3b[b] (*syn*)	104.8	83.1	83.5	77.9	147.8	–	71.0	124.6	133.0	–	112.0	126.5; 136.5
(anti)	105.3	82.8	82.1	75.6	149.6		71.1	125.0	133.2		112.1	
3c[a] (*syn*)	105.3	83.3	83.2	77.9	148.1	–	67.2	120.0	138.3	18.0; 25.7	112.0	–
(*anti*)	104.8	82.9	82.0	75.5	149.7		67.0	120.2	138.0	18.1; 25.7	111.9	

[a] Performed at 125 MHz.
[b] Performed at 50 MHz.

Table 4
^{1}H NMR chemical shifts (δ, ppm) for compounds **4–6** performed at 500 MHz in $CDCl_3$

Compound	H-3	H-3a	H-4	H-4′	H-5a	H-5b	H-8a	H-9a	H-10	CH_3	Aromatic protons
4	4.29	3.17	3.31	4.15	3.97	4.57	5.97	4.93	1.45	1.33; 1.53	–
5	5.11	3.57	3.47	4.27	4.05	4.59	5.95	5.01	–	1.34; 1.55	7.31–7.41
6	–	3.16	3.40	4.05	3.94	4.57	5.97	4.94	1.25; 1.45	1.33; 1.53	–

Table 5
^{1}H NMR coupling constants (Hz) for compounds **4–6**

Compound	$J_{3,3a}$	$J_{3,10}$	$J_{3a,4}$	$J_{3a,4'}$	$J_{4,4'}$	$J_{5a,9a}$	$J_{5a,5b}$	$J_{5b,8a}$
4	8.6	6.2	11.3	5.5	9.9	2.2	~0	3.7
5	9.1	–	11.2	6.2	10.3	1.8	~0	3.5
6	–	–	11.7	5.9	10.5	2.0	~0	3.6

Table 6
^{13}C NMR chemical shifts (δ, ppm) for compounds **4–6** performed at 125 MHz in $CDCl_3$

Compound	C-3	C-3a	C-4	C-5a	C-5b	C-7	C-8a	C-9a	C-9b	C-10	$C(\underline{CH_3})_2$	Aromatic carbons
4	79.1	50.0	70.2	82.4	83.3	112.4	106.1	71.5	154.5	19.7	26.2; 26.7	–
5	84.6	51.0	70.6	82.4	83.3	112.6	106.1	71.6	154.3	–	26.3; 26.8	126.1–138.8
6	85.0	51.3	67.5	82.2	83.4	112.4	106.1	72.2	154.0	21.7; 28.4	26.2; 26.8	–

In the NOESY spectrum of compound **5** the correlation observed between H-4/H-5a showed that the 3*S*,3a*S* or 3*R*,3a*R* configurations are the only possibles. As there was a correlation for the pairs H-4/H-aromatic (only possible for 3*R*,3a*R* stereoisomer) and no correlation between H-3a/H-9a, which should be present in the 3*S*,3a*S* stereoisomer, we could discard the latter one. Thus the new chiral centers are of the R configuration (Fig. 2). It should be noted that the configurations at C-3 and C-3a are coincident with that of compound **4**.

The NOESY spectrum of compound **6** showed a correlation for the pair H-4/H-5a that is only possible if C-3a has the R configuration.

In conclusion, we obtained three compounds enantiomerically pure by intramolecular 1,3-dipolar cycloaddition reaction. In our cases, the steroechemistry of the reaccion happened to be independently of the sustituents on the dipolarophile moiety.

X-Ray crystallographic data.—Suitable crystals of **4** were obtained by cristalization from hexane. Data were collected on an Enraf–Nonius CAD4 diffractometer using Mo K_α radiation. Crystal data and structure determination details are shown in Table 7. The structure was solved by direct methods (SHELXS-86)[9] and refined by least-squares on F^2 for all reflections (SHELXL-97).[10] Atomic coordinates are included in Table 8. Non-hydrogen atoms were refined anisotropically. Hydrogen were placed in calculated positions with isotropic displacement parameters 1.5 (methyl H) or 1.2 (the rest) times the U_{eq} values of corresponding carbons. The weighting scheme was $w = [\sigma^2(F_0^2) + (0.0743P)^2 + 0.0565P]^{-1}$ where $P = [\max(F_0^2, 0) + 2F_c^2]/3$.

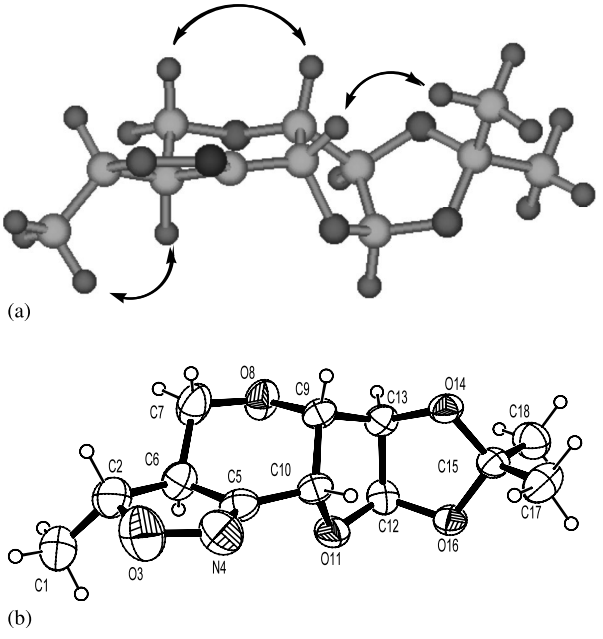


Fig. 1. (a) NOESY correlations for compound **4**. (b) ORTEP structure for compound **4**.

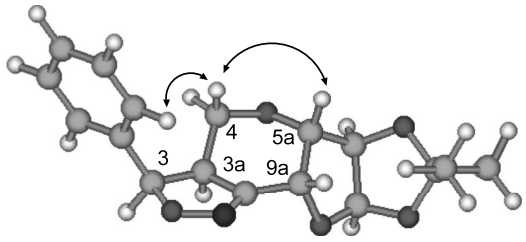


Fig. 2. NOESY correlations for compound **5**.

Table 7
Crystal data and structure refinement for compound **4**

Empirical formula	$C_{12}H_{17}NO_5$
Formula weight	255.27
Temperature (K)	293(2)
Wavelength (Å)	0.71069
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	5.261(3)
b (Å)	10.491(2)
c (Å)	23.566(4)
α (°)	90
β (°)	90
γ (°)	90
V (Å^3)	1300.7(8)
Z	4
Density (calculated) (Mg m^{-3})	1.304
Absorption coefficient (mm^{-1})	0.102
F(000)	544
Crystal size (mm^3)	$0.72\times0.50\times0.36$
Theta range for data collection (°)	1.73–24.95
Index ranges	$0\le h\le6$, $0\le k\le12$, $0\le l\le27$
Independent reflections	1141
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1141/0/163
Goodness-of-fit on F^2	1.040
Final R indices [$I>2\sigma$ (I)]	$R(F)=0.0388$, $R_w(F^2)=0.1070$
R indices (all data)	$R(F)=0.0506$, $R_w(F^2)=0.1109$
Largest diff. peak and hole (e Å^{-3})	0.140 and −0.122

3. Experimental

General methods.—^{1}H and ^{13}C NMR spectra were recorded at 200 or 500 MHz and 50 or 125 MHz, respectively, in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were performed with a Shimadzu QP-5000 instrument by electron impact ionization. Optical rotations were recorded at 20 °C, and the melting points are uncorrected. AM1 calculations were performed with HyperChem™. Elemental analyses were performed at the UMYMFOR, Facultad de Ciencias Exactas y Naturales, University of Buenos Aires, Buenos Aires, Argentina.

*General procedure I. Synthesis of 3-*O*-alkenyl-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose* (**1**).—1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (3.00 g, 11.5 mmol)[8] was dissolved in dry *N*,*N*-dimethylformamide (DMF 10 mL), and 0.3 g of solid NaH was added. The mixture was maintained under a nitrogen atmosphere at 0 °C. When the bubbling stopped, 12 mmol of the appropriate alkenyl clhoride was added. The reaction mixture was stirred for 1 h at room temperature, and then MeOH was added to destroy the excess NaH. The mixture was concentrated at diminished pressure, and the product was extracted with CH_2Cl_2, dried with anhyd Na_2SO_4, and the solvent was evaporated under reduced pressure. The colourless syrup was purified by column chromatography on aluminium oxide (90 active, neutral, 70–230 mesh ASTM) using 9:1 cyclohexane–EtOAc as the eluent. The products were characterized as follows:

*(2′*E*)-3-*O*-(2′-Butenyl)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose* (**1a**). Yield: 3.10 g (86%); $[\alpha]_D^{20}$ −25.2° (*c* 0.8, $CHCl_3$); ^{1}H NMR see Tables 1 and 2; ^{13}C NMR see Table 3; EIMS *m*/*z* (relative intensity) 299 (M − CH_3, 4), 101 (33), 55 (100). Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.15; H, 8.28. Found: C, 60.79; H, 8.10.

Table 8
Atomic coordinates ($\times10^4$) and equivalent isotropic displacement parameters (Å$^2\times10^3$) for compound **4**

	x	y	z	U_{eq}
C(1)	−777(13)	−2208(5)	6644(2)	131(2)
C(2)	1391(10)	−2277(5)	7062(2)	102(1)
O(3)	3016(8)	−1131(4)	6987(1)	129(1)
N(4)	3417(7)	−523(3)	7503(2)	102(1)
C(5)	2082(7)	−1095(3)	7882(1)	74(1)
C(6)	647(9)	−2239(4)	7688(2)	84(1)
C(7)	1491(11)	−3336(4)	8057(2)	99(1)
O(8)	1084(6)	−3018(2)	8641(1)	89(1)
C(9)	2636(7)	−2015(3)	8839(1)	61(1)
C(10)	2242(7)	−804(3)	8497(1)	64(1)
O(11)	−183(5)	−349(3)	8689(1)	78(1)
C(12)	−326(6)	−592(3)	9272(1)	67(1)
C(13)	1609(6)	−1633(3)	9410(1)	64(1)
O(14)	3519(4)	−1000(2)	9726(1)	67(1)
C(15)	2403(6)	117(3)	9967(1)	62(1)
O(16)	449(4)	471(2)	9589(1)	68(1)
C(17)	4362(6)	1157(4)	9976(2)	90(1)
C(18)	1302(8)	−161(4)	10548(2)	94(1)

U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

*(2′*E*)-3-*O*-(3′-Phenyl-2′-propenyl)-1,2;5,6-di-*O*-isopropylidene-α-*D*-glucofuranose* (**1b**). Yield: 3.40 g (78%); $[\alpha]_D^{25}$ −34.9° (*c* 1.3, $CHCl_3$); ^{1}H NMR see Tables 1 and 2; ^{13}C NMR see Table 3; EIMS *m*/*z* (relative intensity) 376 (M, 1), 361 (M − CH_3, 2), 117 (100), 101 (39), 43 (99). Anal. Calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.04; H, 7.37.

*3-*O*-(3′-Methyl-2′-butenyl)-1,2;5,6-di-*O*-isopropylidene-α-*D*-glucofuranose* (**1c**). Yield: 2.65 g (70%); $[\alpha]_D^{25}$ −19.4° (*c* 0.8, $CHCl_3$); ^{1}H NMR see Tables 1 and 2; ^{13}C NMR see Table 3; EIMS *m*/*z* (relative intensity) 328 (M, 1), 313 (M − CH_3, 1), 101 (44), 69 (100), 43 (90). Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.20; H, 8.54. Found: C, 61.85; H, 8.33.

*General procedure II. Synthesis of 3-*O*-alkenyl-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**2**).—3-Alkenyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) (7.96 mmol) was dissolved in MeOH (10 mL), and 0.8% sulfuric acid (10 mL) was added. The reaction mixture was allowed to stand at room temperature until the starting material disappeared, checked by TLC. The solution was neutralized with barium carbonate, boiled, and filtered. The filtrate was evaporated under reduced pressure. The colourless syrup was purified by chromatography on aluminium oxide (90 active, neutral 70–230 mesh ASTM) using 3:2 toluene–EtOAc as the eluent. The products were characterized as follows:

*(2′*E*)-3-*O*-(2′-Butenyl)-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**2a**). Yield: 1.60 g, 5.85 mmol (74%); $[\alpha]_D^{25}$ −43.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR see Tables 1 and 2; ^{13}C NMR see Table 3; EIMS *m*/*z* (relative intensity) 275 (M + 1, 5), 259 (M − CH_3, 1), 61 (33), 55 (100). Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.93; H, 8.03. Found: C, 57.20; H, 8.30.

*(2′*E*)-3-*O*-(3′-Phenyl-2′-propenyl)-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**2b**). Yield: 2.15 g, 6.39 mmol (80%); $[\alpha]_D^{25}$ −34.4° (*c* 2.5, $CHCl_3$); ^{1}H NMR see Tables 1 and 2; ^{13}C NMR see Table 3; EIMS *m*/*z* (relative intensity) 335 (M − 1, 7), 321 (M − CH_3, 1), 131 (87), 117 (100). Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.29; H, 7.14. Found: C, 64.41; H, 7.34

*3-*O*-(3′-Methyl-2′-butenyl)-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**2c**). Yield: 1.72 g, 5.99 mmol (75%); $[\alpha]_D^{25}$ −22.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR see Tables 1 and 2; ^{13}C NMR see Table 3; EIMS *m*/*z* (relative intensity) 289 (M + 1, 1), 273 (M − CH_3, 1), 221 (9), 69 (100), 41 (45). Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.25; H, 8.51.

*General procedure III. Synthesis of 3-*O*-alkenyl-1,2-*O*-isopropylidene-α-*D*-xylo-pentodialdo-1,4-furanose oxime* (**3**).—3-*O*-Alkenyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**2**) (5.48 mmol) was treated according to the technique described in literature,[11] and 3-*O*-alkenyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose was obtained as an unstable syrup, which was identified by its ^{13}C NMR spectrum. The syrup was dissolved in MeOH (10 mL), and a solution of 0.48 g (6.3 mmol) of hydroxylamine hydrochloride in water (2 mL) and 0.14 g (6.0 mmol) of Na in MeOH (5 mL) was added. The mixture was allowed to stand at room temperature until the starting material disappeared as determined by TLC. The syrup was purified by column chromatography on aluminium oxide (90 active, neutral, 70–230 mesh ASTM) using 9:1 toluene–EtOAc as the eluent.

*(2′*E*)-3-*O*-(2′-Butenyl)-1,2-*O*-isopropylidene-α-*D*-xylo-pentodialdo-1,4-furanose oxime* (**3a**). Yield: 1.12 g, 4.37 mmol (80%); $[\alpha]_D^{25}$ −92.0° (*c* 0.9, $CHCl_3$); ^{1}H NMR see Tables 1 and 2; ^{13}C NMR see Table 3; EIMS *m*/*z* (relative intensity) 258 (M + 1, 3), 242 (M − CH_3, 2), 129 (27), 59 (28), 55 (100). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.10; H, 7.59; N, 5.14.

*(2′*E*)-3-*O*-(3′-Phenyl-2′-propenyl)-1,2-*O*-isopropylidene-α-*D*-xylo-pentodialdo-1,4-furanose oxime* (**3b**). Yield: 1.47 g, 4.60 mmol (84%); $[\alpha]_D^{25}$ −98.6° (*c* 1.3, $CHCl_3$); ^{1}H NMR see Tables 1 and 2; ^{13}C NMR see Table 3; EIMS *m*/*z* (relative intensity) 319 (M, 1), 304 (M − CH_3, 2), 129 (28), 117 (100), 91 (25), 59 (23), 55 (45), 43 (70). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.58; N, 4.39. Found: C, 63.93; H, 6.87; N, 4.17.

*3-*O*-(3′-Methyl-2′-butenyl)-1,2-*O*-isopropylidene-α-*D*-xylo-pentodialdo-1,4-furanose oxime* (**3c**). Yield: 1.04 g, 3.83 mmol (70%); $[\alpha]_D^{25}$ −94.6° (*c* 1.7, $CHCl_3$); ^{1}H NMR see Tables 1 and 2; ^{13}C NMR see Table 3; EIMS *m*/*z* (relative intensity) 272 (M + 1, 2), 256 (M − CH_3, 2), 143 (19), 69 (100). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 58.04; H, 8.13; N, 4.84.

General procedure IV. Synthesis of isoxazoline tetracyclic.—3-*O*-Alkenyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose oxime (**3**, 3.89 mmol) was dissolved in 4:1 MeOH–water (10 mL), and Chloramine-T (1.32 g, 4.67 mmol) was added. The reaction was stirred at room temperature until the starting material disappeared as determined by TLC. The reaction product was purified by flash chromatography on Silica Gel G, using 95:5 cyclohexane–EtOAc as the eluent. The products were characterized as follows:

*(3*R*,3a*R*,5a*S*,5b*R*,8a*R*,9a*R*)-3,7,7-Trimethyl-3a,4,5a,5b,8a,9a-hexahydro-3*H*-[1,3]dioxolo[4″,5″:4′,5′]-oxolo[2′,3′:5,6]oxino[4,3-*c*]isoxazole* (**4**). Yield: 0.77 g, 3.04 mmol (78%); mp 115–117 °C; $[\alpha]_D^{25}$ +182.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR see Tables 4 and 5; ^{13}C NMR see Table 6; EIMS *m*/*z* (relative intensity) 255 (M, 2), 240 (M − CH_3, 24), 55 (27), 43 (100). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.47; H, 6.67; N, 5.49. Found: C, 56.74; H, 6.95; N, 5.46.

*(3*R*,3a*R*,5a*S*,5b*R*,8a*R*,9a*R*)-7,7-Dimethyl-3-phenyl-3a,4,5a,5b,8a,9a-hexahydro-3*H*-[1,3]dioxolo[4″,5″:4′,5′]-oxolo[2′,3′:5,6]oxino[4,3-*c*]isoxazole* (**5**). Yield: 0.88 g, 2.77 mmol (71%); mp 119–121 °C; $[\alpha]_D^{25}$ +252.8° (*c* 1.0,

$CHCl_3$); ^1H NMR see Tables 4 and 5; ^{13}C NMR see Table 6; EIMS m/z (relative intensity) 317 (M, 8), 302 ($M - CH_3$, 14), 105(14), 91 (23), 59 (28), 55 (20), 43 (100). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03. Found: C, 64.02; H, 6.44.

*(3a*R,*5a*S,*5b*R,*8a*R,*9a*R*) - 3,3,7,7 - Tetramethyl - 3a,4,5a,5b,8a,9a - hexahydro - [1,3]dioxolo[4″,5″:4′,5′]oxolo-[2′,3′:5,6]oxino[4,3-c]isoxazole* (**6**). Yield: 0.80 g, 2.98 mmol (77%); mp 129–131 °C; $[\alpha]_D^{25}$ +122.6° (*c* 1.0, $CHCl_3$); ^1H NMR see Tables 4 and 5; ^{13}C NMR see Table 6; EIMS m/z (relative intensity) 269 (M, 2), 254 ($M - CH_3$, 25), 43 (100). Anal. Calcd for $C_{12}H_{17}NO_5$: C, 57.99; H, 7.06; N, 5.20. Found: C, 58.29; H, 7.34; N, 5.14.

4. Supplementary material

Full crystallographic details, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre. These data (CCDC 189789) may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Tel. + 44 1223 336408, Fax + 44 1223 336033, E-mail deposit@ccdc.cam.ac.uk

Acknowledgements

The authors thank the Consejo Nacional de Investigaciones Científicas y Técnicas and the Universidad de Buenos Aires for financial support. Dr. N. B. D'Accorso is research member of CONICET. They are also very grateful to UMYMFOR (CONICET-FCEyN UBA) for the recording of the ^1H and ^{13}C NMR, as well as for the microanalyses and mass spectra.

References

1. Padwa, A. 1,3-*Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vol. 1 and references cited therein.
2. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.
3. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677–1716.
4. Kwon, T.; Heiman, A. S.; Oriaku, E. T.; Yoon, K.; Lee, H. J. *J. Med. Chem.* **1995**, *38*, 1048–1051.
5. Gordaliza, M.; Faircloth, G. T.; Castro, M. A.; Miguel del Corral, J. M.; Lopez-Vazquez, M. L.; San Feliciano, A. *J. Med. Chem.* **1996**, *39*, 2865–2868.
6. Saha, A.; Bhattacharjya, A. *Chem. Commun. (Cambridge)* **1997**, 495–496.
7. Mukhopadhyay, R.; Datta, S.; Chattopadhyay, P.; Bhattacharjya, A. *Indian J. Chem. Sect. B* **1996**, *35*, 1190–1193.
8. Wolfrom, M. L.; Thomas, G. H. S. *Methods Carbohydr. Chem.* **1963**, *2*, 320–322.
9. Sheldrick, G. M. In *Crystallographic Computing* 3; Sheldrick, G. M.; Kruger, C.; Goddard, R., Eds.; Oxford University Press: Oxford, 1985; pp 175–189.
10. Sheldrick, G. M. SHELX97. *Program for Crystal Structure Analysis (Release 97-2).* University of Göttingen, Germany, **1997**.
11. Sowden, J. C. *J. Am. Chem. Soc.* **1951**, *73*, 5496–5497.