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Synthesis, separation and configuration determination of diastereoisomers of (*R*,*S*)-1-methyl-3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides

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Abstract—For synthesizing title compounds, first we carried out the Ferrier's rearrangement involving tri-*O*-acetyl-D-glucal **1** and alcohols **2a**–e using Montmorillonite K-10 as a catalyst. This reaction gave diastereoisomeric mixture of **3a**–e and **4a**–e. Basic hydrolysis of each pair of diastereoisomeric mixture furnished title compounds **5a**–e and **6a**–e, which were separated very carefully over a silica gel column yielding all diastereoisomers in the pure form. One of them **5d** was subjected to a single crystal X-ray analysis to determine the correct configuration at the asymmetric carbon atom of the aglycone. The methyl signals of the diastereoisomers helped to assign the configuration of each diastereoisomer. Molecular orbital calculations of **5d** using the semi-empirical method (AM1) has been performed to compare its results with the crystallographic data. We have also determined the rotational barrier of C(8) and O(9) bond in both (*R*) and (*S*) enantiomers of compounds **5a** and **6a**.

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1. Introduction

The incorporation of heterocyclic moieties in carbohydrates has been gaining impetus.^{1–3} Because of our interest in the synthesis 1,2,4-oxadiazoles and 4,5-dihydro-1,2,4-oxadiazoles, we wished to unite the oxadiazole part with the carbohydrate framework. One of the reasons to undertake such program was that 1,2,4-oxadiazole derivatives manifest a wide range of biological activities^{4–6} including antiinflammatory property.⁷ In 1996, various 4,5-dihydro-1,2,4-oxadiazoles (Δ^2 -1,2,4-oxadiazolines) have been found to possess anti-HIV activity.⁸ Yu and co-workers have reported the preparation, spectroscopic and X-ray diffraction studies of two diastereoisomeric spiroheterocyclic Δ^2 -1,2,4-oxadiazolines having a spiral junction at C-3 of fructopyranose.⁹ The spiroheterocyclic compounds have extensive applications as drugs as well.¹⁰ A literature search revealed that only a few attempts have been made

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to combine an oxadiazole moiety with a sugar framework.^{9,11–14} Further, no work appeared in the literature which describes the synthesis of unsaturated glycosides having an 1,2,4-oxadiazole part as an aglycone. Therefore, this paper gives a detailed account of the preparation, separation and configuration differentiation of the diastereomers of **5a–e** and **6a–e**. Overall, there are 10 new unsaturated glycosides having a stereocenter in the aglycone moiety also. To the best of our knowledge, these have not yet been recorded in the literature.

2. Results and discussion

Racemic 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-2-butanols **2a–e** were used to carry out Ferrier's rearrangement.¹⁵ Reaction of these alcohols individually with tri-*O*-acetyl-D-glucal **1** gave diastereomers **3a–e** and **4a–e**, respectively (Scheme 1). Each diastereomeric pair showed only one spot on a thin-layer chromatogram. However, the ¹H NMR spectrum of each set presented two methyl doublets in the region δ 1.21–1.40 ppm in the ratio of 2:3 indicating the presence of diastereomers. Each methyl doublet has another overlapping doublet of smaller intensity (~40%) suggesting them as a mixture of

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Scheme 1.

conformational isomers. This observation requires some clarifications. Since the reaction has been carried out in methylene chloride, each diastereoisomer formed conformational isomer as shown below for **5d** and **5d'**. The two conformational isomers of each diastereoisomer are visible when the temperature is not higher. There is a small barrier to rotation between C(8) and O(9) which causes this to happen (see the section dealing with M.O. calculations). When the compound is deacetylated, separated and purified, only one conformational isomer is observed for **5a** and **6a**. Apparently, during the work-up rotation along the C(8) and O(9) bond occurred to provide the most stable conformation which shows only one doublet for the methyl group for each diastereoisomer.

crystallized. All of them gave the methyl doublet at δ 1.35 ppm, and the anomeric proton appeared at δ 5.13 ppm. The other set of diastereoisomers (larger quantity) are liquids and it was not possible to crystallize them. All five of them produced a methyl doublet at δ 1.25 ppm, and the anomeric proton absorbed at δ 5.16 ppm. One of the diastereoisomers (either **5d** or **6d**) which had better crystals was subjected to X-ray crystallography. It turned out that it has the configuration (*R*) at the carbon atom containing the methyl group in the aglycone moiety. This diastereoisomer is designated as **5d**. Therefore the other diastereoisomer must possess configuration (*S*) for the same carbon atom (C-8) in **6d**. It is presumed that, all compounds **6a–e** possess configuration (*S*) at the asymmetric carbon atom of the





5d (conformational isomer of higher proportion)

Next, we hydrolyzed the diacetylated sugars using the method of Fraser-Reid and collaborators, ¹⁶ which furnished diols **5a–e** and **6a–e** again as a mixture of diastereoisomers. Thin-layer chromatography displayed two spots of very close R_f values. However, it was possible to separate them by a very careful liquid chromatography over silica gel. The diastereoisomer which is in smaller proportion, in each case,

5d' (conformational isomer of smaller proportion)

aglycone while 5a-e have configuration (*R*) at the same stereocenter.

Pure **5a** and **6a** were reacetylated individually and their spectra recorded. This was done just to make correct assignments of their chemical shifts in the ¹H NMR spectra, which are give in Section 4.



Figure 1. Ortep diagram of compound 1-(R)-methy-[3-(p-tolyl)-1,2,4-oxadiazol-5-yl]lpropryl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside 5d.

2.1. Structure, configuration and conformation of 5d

The crystallographic data provided the precise information regarding the configuration (at C-8) and also about the molecular conformation of **5d**. As expected, the configurations at C(10), C(12) and C(13) are (*S*), (*R*) and (*S*), respectively. It is interesting to know that the C(8)–H bond is found approximately parallel to those on C(10) and C(13), and antiparallel to the one on C(12). The ortep diagram is shown in Figure 1.

There is another feature which needs comment. This concerns the hydrogen bonding between the molecules. Each hydroxyl oxygen atom, O(25) and O(26), is involved in two hydrogen bonds, one as a donor and one as acceptor. O(25) donates a hydrogen bond to O(26) of a parallel molecular in an adjacent cell, O(26) donates a hydrogen bond to O(25) of a molecule generated by a two-fold screw rotation in the [010] direction. The result is that molecules are linked into slabs normal to the [010] direction; the two slabs that pass through one unit cell are not linked together. The other oxygen and nitrogen atoms are not involved in hydrogen bond (see Figs. 2 and 3).

2.2. Semi-empirical molecular orbital calculations of compounds 5d and 6d

The semi-empirical calculations (AM1) showed that compound **5d** has a torsion angle H(15)–C(15)–C(10)– H(10) of -43.2° which clearly shows that the anomeric proton is disposed equatorially. The ring oxygen atom is a little above the plane of C(10)-C(15)-C(14)-C(13). The C(12) atom is slightly below the plane just described. The enthalpy of formation of this compounds is -112.04 kcal/

mol. A comparison of some selected dihedral angles of **5d** with its crystallographic data are given in Table 1, which shows that the experimental and calculated values are somewhat closer. The calculations further demonstrate that the *p*-tolyl ring and the 1,2,4-oxadiazole rings are coplanar (torsion angle N(2)–C(3)–C(16)–C(17) = 10.61°). The bond distances between C(13)–C(12) and C(12)–O(11) are 1.54 Å and 1.43 Å, respectively.

Figure 4 depicts the most stable conformation of **5d** obtained by the AM1 level of calculation.

Next, we examined the stable conformation of **6d** using the same method as described for **5d**. The dihedral angle H(15)-C(15)-C(10)-H(10) is -46.20° which clearly indicates the disposition of H-10 equatorially. The other interesting feature is that C(23)-C(8)-C(7) and C(6) form an angle of -165.9° . The heterocyclic and the *p*-tolyl rings are at the lower level of the pyranose ring as exhibited in Figure 5. In this case also, the *p*-tolyl ring and 1,2,4oxadiazole ring are almost coplanar. Selected bond lengths, bond angles and torsion angles of **5d** and **6d** are given in Table 2.

In order to determine the rotational barrier of the C(8) and O(9) bond, diastereoisomers **5a** and **6a** were chosen.

The rotational impediment along the C(8) and O(9) bond in **5a** is approximately 4.0 kcal/mol, whereas in **6a** it approximates about 8.0 kcal/mol. Although the semiempirical method is less sophisticated, the barrier seems reasonable. Figure 6 represents the structures of **5a** and **6a**. The numbering of the atoms of these molecules here has been slightly modified.



Figure 2. Compound 1-(*R*)-methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]propryl 2,3-dideoxy- α -D-*erythro*-hex-2-enopyranoside **5d** showing the hydrogen bonds between O(25A) and H-26, H(25B) and O(26), O(26A) and H(25), and O(25) and H(26B).



Figure 3. Unit cell depicting the packing of 1-(*R*)-methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]propryl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside 5d molecules in the crystal.

Table 1. Comparison of the calculated and experimental torsion angles of 5d

Torsion angle (°C)	X-ray	AM1 method
C(10)=O(11)=C(12)=C(13)	67.70	62.07
C(10)-C(12)-C(13) C(10)-C(15)-C(14)-C(13)	2.10	1.48
C(15)-C(14)-C(13)-C(12)	19.0	10.25
C(14)-C(13)-C(12)-O(11)	-52.1	-40.16
C(10)-O(11)-C(12)-C(24)	-170.3	-177.67
O(26)-C(13)-C(14)-C(15)	140.7	128.64
O(9)-C(10)-O(11)-C(12)	77.3	71.62
O(9)-C(10)-C(15)-C(14)	-115.6	-97.12

Point Apparatus, series IA-9100, Electrothermal Ltd., England. IR spectra were recorded as KBr films on a Brucker IFFS66 series Fourier transform spectrophotometer. The 300 MHz ¹H NMR spectra were recorded with a Varian Unity Plus spectrophotometer or a Brucker DRX 300 using CDCl₃ as solvent and TMS as an internal standard. Elemental analyses were performed in the Department of Fundamental Chemistry, Federal University of Pernambuco, Recife (Brazil). Thin-layer chromatography (TLC) was carried out on plates coated with silica gel 60



Figure 4. Stable conformation of (1R)-1-methyl-3-[(*p*-tolyl)-1,2-4-oxadiazol-5-yl]propyl 2,3-didesoxy- α -D-*erythro*-hex-2-enopyranoside 5d obtained by the AM1 method.



Figure 5. Stable conformation of (1S)-1-methyl-3-[(*p*-tolyl)-1,2-4-oxadiazol-5-yl]propyl 2,3-didesoxy- α -D-*erythro*-hex-2-enopyranoside 6d obtained by the AM1 method.

3. Conclusion

In summary, the glycosides 5a-e and 6a-e have been synthesized and diastereoisomers have been separated by chromatography. Also the configuration of compound 5dwas proved by X-ray crystallography.

4. Experimental

Melting points were determined with a Digital Melting

followed by the exposure of the plates in a chamber containing iodine vapors, which revealed the spots. The solvent system for running the TLC plates was a mixture of 0.5:9.5 ethyl acetate–dichlromethane. For compounds **5e** and **6e**, the solvent system for the development of the plate was CHCl₃/AcOEt/MeOH, 8.5:1.0:0.5. Optical rotaions were measured with a Prkin–Elmer 141 and 241 polarimeters at the Université Claude Bernard Lyon 1, Villeurbanne (France), and at the University of São Carlos, São Carlos, São Paulo (Brazil), respectively.

Table 2. Selected bond lengths, bond angles and torsion angles of 5d and 6d obtained by AM1 calculations

Atoms	AM1	
Configuration at C(8) (<i>R</i>)	Configuration at C(8) (<i>S</i>)	
Bond length (Å)		
C(10)–O(9) 1.42	1.42	
C(10)–O(11) 1.41	1.42	
C(10)–O(15) 1.50	1.50	
C(14)–O(15) 1.33	1.33	
O(9)–C(8) 1.43	1.43	
C(5)–C(6) 1.48	1.48	
C(5)–N(4) 1.33	1.33	
C(5)–O(1) 1.43	1.43	
N(2)–C(3) 1.36	1.36	
O(1)–C(2) 1.31	1.31	
C(3)–C(16) 1.46	1.46	
Bond angle $(^{\circ})$		
H(15)–C(15)–C(10) 115.8	115.3	
C(10)–O(11)–C(12) 113.7	114.4	
H(10)–C(10)–O(11) 105.4	104.7	
O(9)–C(10)–H(10) 111.1	113.4	
C(10)–O(9)–C(8) 115.6	117.0	
O(9)–C(8)–C(23) 106.8	113.5	
C(23)–C(8)–C(7) 112.3	111.2	
C(6)–C(5)–N(4) 134.1	133.6	
C(6)–C(5)–O(1) 116.4	116.9	
Torsion angle (°)		
O(9)-C(10)-O(11)-C(12) 71.6	71.2	
C(10)-O(11)-C(12)-C(13) 62.1	60.6	
C(10)-O(9)-C(8)-C(23) - 131.8	-44.5	
C(23)-C(8)-C(7)-C(6) -75.3	-165.9	
H(10)-C(10)-C(15)-H(15) -43.2	-46.2	
С(10)–О(9)–С(8)–С(7) 106.4	81.3	





Figure 6. Structures of 5a and 6a.

AM1 method: Semi-empirical molecular orbital calculations were carried out employing the AM1 method.¹⁷ The MOPAC 93 program^{18,19} was used for the calculations. Geometry optimization could be achieved in all cases, the gradient norm being ≤ 0.2 .

4.1. General procedure for the preparation of 4-[3-aryl-1,2,4-oxadiazol-5-yl]-2-butanol 2a-e

Sodium borhydride (7.66 mmol) was added to a solution of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-2-butanones²¹ (16.15 mmol) dissolved in methanol (57 mL) under stirring at room temperature. After an hour of agitation, thin layer chromatography showed the disappearance of the starting material and the formation of a new product. Later, most of the solvent was evaporated and the residue was treated with a saturated aqueous sodium chloride solution and extracted with ethyl acetate (3×30 mL). Drying (Na₂SO₄) and solvent evaporation afforded of the crude product. Liquid

chromatography over silica gel using hexane–ethyl acetate (9:1) gave chromatographically pure $2a-e^{.22}$

4.2. General procedure for the preparation of (*R* e S)-1methyl-3-[3-(aryl)-1,2,4-oxadiazol-5-yl]propyl 4,6-di-*O*acetyl-2,3-dideoxy-α-*D*-*erythro*-hex-2-enopyranosides 3a–e and 4a–e

The reaction of 2a-e with compound 1 were conducted according to the method of Toshima et al.²⁰ The details are given below.

4.2.1. (*R* e *S*)-1-Methyl-3-[3-(phenyl)-1,2,4-oxadiazol-5yl] propyl-4,6-di-*O*-acetyl-2,3-dideoxy- α -D-*eryhtro*-hex-2-enopyranoside 3a and 4a. Yield 68%, R_f =0.58 (dichromethane–ethyl acetate, 9:1); IR ν_{max} (KBr): 1743, 1368, 1231, 1034, 722 cm⁻¹; ¹H NMR (CDCl₃): δ 8.12–8.02 (m, 2H, H-17 and H-21), 7.54–7.42 (m, 3H, H-18, H-19 and H-20), 6.00–5.72 (m, 2H, H-14 and H-15), 5.23 (dd, 1H,

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J=9.6 Hz, 3.0 Hz, H-13), 5.16 and 5.13 (2bs, each 1H, H-10), 4.30–4.16 (m, 2H, H-23 and H-23'), 4.16–3.84 (m, 2H, H-12 and H-8), 3.20–3.00 (m, 2H, H-6 and H-6'), 2.18–2.02 (m, 2H, H-7 and H-7'), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 1.36 and 1.34 (2d, each 3H, J=6.3 Hz, H-22), 1.25 and 1.24 (2d, each 3H, J=6.0 Hz, H-22).

4.2.2. 1-(*R* and *S*)-Methyl-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy- α -D-*erythro*-hex-**2-enopyranoside (3b and 4b).** Yield 53%; IR ν_{max} (KBr): 1743, 1370, 1223, 1053, 741 cm⁻¹; ¹H NMR (CDCl₃): δ 7.94–7.80 (m, 1H, H-21), 7.38–7.15 (m, 3H, H-18, H-19 and H-20), 5.86–5.60 (m, 2H, H-14 and H-15'), 5.25 (dd, 1H, *J*=9.6 and 2.7 Hz, H-13), 5.15 and 5.12 (2s, each 1H, H-10), 4.24 (m, 2H, H-24 and H-24'), 4.10–3.78 (m, 2H, H-12 and H-8), 3.18–3.01 (m, 2H, H-6 and H-6'), 2.60 (s, 3H, Ar-CH₃), 2.09–2.04 (m, 2H, H-7 and H-7'), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.38 (2d, each 3H, *J*=6.3 Hz, H-23), 1.24 (2d, each 3H, *J*=6.0 Hz, H-23).

4.2.3. 1-(*R* and *S*)-Methyl-[3-(*m*-tolyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy- α -D-*erythro*-hex-**2-enopyranoside** (3c and 4c). Yield 83%; IR ν_{max} (KBr): 1744, 1575, 1369, 1034, 738 cm⁻¹; ¹H NMR (CDCl₃): δ 3.00–7.81 (m, 2H, H-17 and H-21), 7.41–7.24 (m, 2H, H-19 and H-20), 6.00–5.78 (m, 2H, H-14 and H-15), 5.36–5.20 (m, 1H, H-13), 5.16 and 5.12 (2d, each 1H, H-10), 4.36–4.18 (m, 2H, H-24 and H-24'), 4.18–4.10 (m, 1H, H-12), 4.06–3.80 (m, 1H, H-8), 3.22–2.90 (m, 2H, H-6 and H-6'), 2.42 (bs, 3H, Ar-CH₃), 2.15–2.02 (m, 2H, H-7 and H-7'), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.35 (d, 3H, *J*=6.3 Hz, H-23), 1.25 (d, 3H, *J*=6.3 Hz, H-23).

4.2.4. 1-(*R* and *S*)-Methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy- α -D-*erythro*-hex-2-enopyranoside (3d and 4d). Yield 92%; IR ν_{max} (KBr): 1744, 1370, 1034, 756 cm⁻¹; ¹H NMR (CDCl₃): δ 7.97 and 7.94 (2d, each 2H, J=8.4 Hz, H-17 and H-21), 7.29 and 7.28 (2d, each 2H, J=8.4 Hz, H-18 and H-20), 6.00–5.54 (m, 2H, H-14 and H-15), 5.28 and 5.25 (2bd, each 1H, J=9.9 and 9.0 Hz, H-13), 5.16 and 5.13 (2bs, each 1H, H-10), 4.40–4.20 (m, 2H, H-24 and H-24'), 4.20–3.85 (m, 2H, H-12 and H-8), 3.28–2.95 (m, 2H, H-6 and H-6'), 2.41 (s, 3H, Ar-CH₃), 2.22–2.02 (m, 2H, H-7 and H-7'), 2.08 and 2.07 (2s, 3H, OAc), 1.35 (d, 3H, J=6.0 Hz, H-23), 1.23 (d, 3H, J=6.0 Hz, H-23).

4.2.5. 1-(*R* and *S*)-Methyl-[3-(*p*-chlorophenyl)-1,2,4-oxadiazol-5-yl] propyl 4,6-di-*O*-acetyl-2,3-dideoxy- α -*Derythro*-hex-2-enopyranoside (3e and 4e). Yield 58%; IR ν_{max} (KBr): 1744, 1475, 1035, 748 cm⁻¹; ¹H NMR (CDCl₃): δ 8.00–7.99 (2d, each 2H, *J*=8.7 Hz, H-17 and H-21), 7.45–7.44 (2d, each 2H, *J*=8.7 Hz, H-18 and H-20), 5.97–5.73 (m, 2H, H-14 and H-15), 5.28 and 5.21 (2ddd, each 1H, *J*=9.5 Hz, 3.3 Hz, 1.5 Hz, H-13), 5.15 and 5.11 (2bs, each 1H, H-10), 4.25–4.16 (m, 2H, H-24 and H-24'), 4.15–3.82 (m, 2H, H-12 and H-8), 3.20–3.10 (m, 2H, H-6 and H-6'), 2.10–2.02 (m, 2H, H-7 and H-7'), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.35 (d, 3H, *J*=6.3 Hz, H-23), 1.23 (d, 3H, *J*=6.0 Hz, H-23). 4.3. General procedure for the preparation of (*R* and *S*)-1-methyl-3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propyl2,3dideoxy-α-D-*erythro*-hex-2-enopyranosíde 5a–e and 6a–e

The hydrolysis of **3a–e** and **4a–e** were conducted according to the method of Fraser-Reid et al.¹⁶ The products were purified by chromatography using dichlromethane–ethyl acetate (9.5:0.5) to give **5a–e** as a crystalline solids and **6a–e** as a syrup.

4.3.1. 1-(*R*)-Methyl-[3-(phenyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy- α -D-*erythro*-hex-2-enopyranoside (5a). $R_{\rm f}$ =0.12, yield 45%; mp 105.3–106.5 °C; $[\alpha]_{\rm D}^{27}$ = +10±1° (*c*=1.5, CH₂Cl₂); IR $\nu_{\rm max}$ (KBr): 3407, 1594, 1025 cm⁻¹; ¹H NMR (CDCl₃): ¹H NMR (300 MHz, CDCl₃): δ 8.10– 8.04 (ddd, 2H, *J*=1.8, 5.4, 10.2 Hz, H-17 and H-21), 7.48 (dd, 3H, *J*=1.8, 10.2 Hz, H-18, H-19 and H-20), 5.94 (d, 1H, *J*=10.5 Hz, H-14), 5.74 (ddd, 1H, *J*=10.5, 2.4, 2.1 Hz, H-15), 5.08 (s, 1H, H-10), 4.22 (dd, 1H, *J*=3.6, 7.5 Hz, H-13), 3.91–3.71 (m, 4H, H-12, H-23, H-23' and H-8), 3.04 (m, 2H, H-6 and H-6'), 2.10–2.02 (m, 2H, H-7 and H-7'), 1.97 (s, 1H, OH), 1.90 (s, 1H, OH), 1.32 (d, 3H, *J*=6.3 Hz, H-22). Anal. Calcd for (C₁₈H₂₂O₅N₂·3/4H₂O): C, 60.07; H, 6.58; N, 7.78. Found: C, 60.32; H, 6.39; N, 7.46.

4.3.2. 1-(S)-Methyl-[3-(phenyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy- α -*D*-*erythro*-hex-2-enopyranoside (6a). $R_{\rm f}$ =0.15, colorless thick liq., yield 53%; $[\alpha]_D^{27}$ = +57±1° (*c*=1.5, CH₂Cl₂); IR $\nu_{\rm max}$ (KBr): 3353, 1594, 1025 cm⁻¹; ¹H NMR (CDCl₃): ¹H NMR (300 MHz, CDCl₃): δ 8.10–8.04 (ddd, 2H, *J*=1.8, 5.1, 10.2 Hz, H-17 and H-21), 7.51–7.46 (dd, 3H, *J*=1.8, 10.2 Hz, H-18, H-19 and H-20), 5.95 (dd, 1H, *J*=1.5, 10.2 Hz, H-14), 5.70 (ddd, 1H, *J*=10.2, 2.1, 1.5 Hz, H-15), 5.04 (d, 1H, *J*=1.5 Hz, H-10), 4.10 (d, 1H, *J*=7.2 Hz, H-13), 3.94–3.74 (m, 4H, H-12, H-23, H-23' and H-8), 3.31–3.01 (m, 2H, H-6 and H-6'), 2.58 (s, 1H, OH), 2.12–2.04 (m, 2H, H-7 and H-7'), 1.97 (s, 1H, OH), 1.20 (d, 3H, *J*=6.0 Hz, H-22). Anal. Calcd for (C₁₈H₂₂O₅N₂·3/4H₂O): C, 60.07; H, 6.58; N, 7.78. Found: C, 60.32; H, 6.39; N, 7.46.

4.3.3. 1-(*R*)-Methyl-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy- α -*D*-*erythro*-hex-2-enopyranoside (5b). $R_{\rm f}$ =0.08, yield 33%; mp 124.3–125 °C; $[\alpha]_{\rm D}^{28}$ = +19.8° (*c*=0.5, CHCl₃); IR $\nu_{\rm max}$ (KBr): 3400, 1595, 1365, 1059, 738 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.96–7.93 (d, 1H, *J*=7.5 Hz, H-21), 7.41–7.27 (dd, 3H, *J*=1.8, 7.8 Hz, H-18, H-19 and H-20), 5.97 (dd, 1H, *J*=10.5, 1.8 Hz H-14), 5.68 (tt, 1H, *J*=10.5, 1.8, 2.1 Hz, H-15), 5.25 (td, 1H, *J*=1.8 Hz, H-13), 5.08 (bs, 1H, H-10), 4.22–3.72 (m, 4H, H-12, H-24, H-24' and H-8), 3.07 (m, 2H, H-6 and H-6'), 2.61 (s, 3H. ArCH₃), 2.12–2.04 (m, 2H, H-7 and H-7'), 1.98 (s, 2H, OH), 1.33 (d, 3H, *J*=6.3 Hz, H-23). Anal. Calcd for (C₁₉H₂₄O₅N₂): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.93; H, 6.71; N, 7.40.

4.3.4. 1-(*S*)-Methyl-[3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy- α -*D*-*erythro*-hex-2-enopyranoside (**6b**). $R_{\rm f}$ =0.08, colorless syrup, yield 33%; $[\alpha]_{\rm D}^{27}$ = +18° (*c*=0.4, CHCl₃); IR $\nu_{\rm max}$ (KBr): 3350, 1594, 1026, 1370, 738 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.96–7.93 (d, 1H, *J*=7.2 Hz, H-21), 7.41–7.30 (m, 3H, H-18, H-19 and H-20), 5.96 (d, 1H, *J*=10.2 Hz, H-14), 5.68 (tt, 1H, *J*= 10.2, 1.5 Hz, H-15), 5.18 (td, 1H, J=3.0 Hz, H-13), 5.06 (s, 1H, H-10), 4.10–3.75 (m, 4H, H-12, H-24, H-24' and H-8), 3.07 (m, 2H, H-6 and H-6'), 2.61 (s, 3H. ArCH₃), 2.23 (s, 2H, OH), 2.10–1.97 (m, 2H, H-7 and H-7'), 1.23 (d, 3H, J= 6.0 Hz, H-23). Anal. Calcd for (C₁₉H₂₄O₅N₂): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.95; H, 6.65; N, 7.43.

4.3.5. 1-(*R*)-Methyl-[3-(*m*-tolyl)-1,2,4-oxadiazol-5yl]propyl **2,3-dideoxy-** α -D-*erythro*-hex-2-enopyranoside (**5c**). $R_f = 0.09$, yield 43%; mp 127.3–128.9 °C; $[\alpha]_{27}^{27} = +17.6^{\circ}$ (c=0.8, CHCl₃); IR ν_{max} (KBr): 3352 (OH), 1574, 1351, 1027, 738 cm⁻¹; H NMR (300 MHz, CDCl₃) δ : 7.88–7.84 (dd, 2H, J=1.5, 9.6 Hz, H-17 and H-21), 7.39–7.30 (d, 2H, J=7.8 Hz, H-19 and H-20), 5.95 (d, 1H, J=9.9 Hz, H-14), 5.75 (ddd, 1H, J=9.9, 3.0, 1.2 Hz, H-15), 5.08 (s, 1H, H-10), 4.23 (sl, 1H, H-13), 4.01–3.77 (m, 4H, H-12, H-24, H-24'and H-8), 3.01–3.10 (m, 2H, H-6 and H-6'), 2.62 (s, 1H, OH), 2.42 (s, 3H, Ar-CH₃), 2.10–2.02 (m, 2H, H-7 and H-7'), 1.32 (d, 3H, J=6.0 Hz, H-10). Anal. Calcd for (C₁₉H₂₄O₅N₂): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.98; H, 6.77; N, 7.48.

4.3.6. 1-(*S*)-Methyl-[3-(*m*-tolyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy- α -*D*-*erythro*-hex-2-enopyranoside (6c). Colorless syrup, $R_f=0.14$, yield 48%; $[\alpha]_D^{27}=$ +18.5° (c=1.2, CHCl₃); IR ν_{max} (KBr): 3406 (OH), 1596, 1366, 1059, 738 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ : 7.92–7.84 (dd, 2H, J=4.5, 10.8 Hz, H-17 and H-21), 7.40– 7.30 (d, 3H, J=7.8 Hz, H-19 and H-20), 5.95 (d, 1H, J=10.2 Hz, H-15), 5.69 (dd, 1H, J=10.2, 2.7 Hz, H-14), 5.05 (s, 1H, H-10), 4.11 (sl, 1H, H-14), 3.93–3.80 (m, 4H, H-12, H-24, H-24'and H-8), 3.00–3.16 (m, 2H, H-6 and H-6'), 2.85 (s, 1H, OH), 2.42 (s, 3H, Ar-CH₃), 2.18–1.97 (m, 2H, H-7 and H-7'), 1.24 (d, 3H, J=6.0 Hz, H-23). Anal. Calcd for (C₁₉H₂₄O₅N₂): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.94; H, 6.88; N, 7.45.

4.3.7. 1-(*R*)-Methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]propyl **2,3-dideoxy-α-***D*-*erythro*-hex-2-enopyranoside (5d). $R_{\rm f}$ =0.19, yield 42%; mp 128.9–129.5 °C; $[\alpha]_{\rm D}^{27}$ = +14±1° (*c*=0.7, CH₂Cl₂); IR $\nu_{\rm max}$ (KBr): 3335 (OH), 1588, 1365, 1026, 744 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.95 (d, 2H, *J*=8.1 Hz, H-17 and H-21), 7.30 (dd, 2H, *J*= 8.7 Hz, H-18 and H-20), 5.92 (d, 1H, *J*=10.2 Hz, H-14), 5.72 (ddd, 1H, *J*=10, 2 Hz, e *J*=2, 7, 2.1 Hz, H-15), 5.22 (d, 1H, *J*=7.5 Hz, H-13), 5.07 (s, 1H, H-10), 3.96–3.71 (m, 4H, H-12, H-24, H-24' and H-8), 3.03 (m, 2H, H-6 and H-6') 2.41 (s, 3H, Ar-CH₃), 2.09–2.02 (m, 2H, H-7 and H-7'), 1.32 (d, 3H, *J*=6.3 Hz, H-23). Anal. Calcd for (C₁₉H₂₄O₅N₂): C, 63.31; H, 6.71; N, 7.77. Found: C, 62.89; H, 6.68; N, 7.71.

4.3.8. 1-(*S*)-Methyl-[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy- α -D-*erythro*-hex-2-enopyranoside (6d). $R_{\rm f}$ =0.22, colorless syrup, yield 30%; $[\alpha]_{\rm D}^{25}$ = +79° (*c*=0.7, CH₂Cl₂); IR $\nu_{\rm max}$ (KBr): 3414 (OH), 1590, 1365, 1026, 757 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.95–7.92 (d, 2H, *J*=8.4 Hz, H-2″ and H-21), 7.29–7.26 (dd, 2H, *J*= 7.8, 2.1 Hz, H-18″ and H-20″), 5.95 (dd, 1H, *J*=10.2, 1.8 Hz, H-14), 5.68 (dd, 1H, *J*=10, 2 Hz, e *J*=2, 7 Hz, H-15), 5.05 (s, 1H, H-10), 4.10 (d, 1H, *J*=9.3 Hz, H-13), 3.92–3.73 (m, 4H, H-12, H-24, H-24′and H-8), 3.20–3.00 (m, 2H, H-6 and H-6′), 2.96 (s, 2H, OH), 2.41 (s, 3H, Ar CH_3), 2.12–2.04 (m, 2H, H-7 and H-7'), 1.22 (d, 3H, J = 6.0 Hz, H-23). Anal. Calcd for ($C_{19}H_{24}O_5N_2$): C, 63.31; H, 6.71; N, 7.77. Found: C, 63.89; H, 7.24; N, 7.56.

4.3.9. 1-(*R*)-Methyl-[3-(*p*-chlorophenyl)-1,2,4-oxadiazol-**5**-yl]propyl **2,3-dideoxy-\alpha-D**-*erythro*-hex-2-enopyranoside (**5e**). $R_{\rm f}$ =0.27, yield 30%; mp 132.7–133.8 °C; $[\alpha]_D^{25}$ =+13.14° (*c*=0.7, CHCl₃); IR $\nu_{\rm max}$ (KBr): 3404 (OH), 1589, 1474, 1449 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.02–7.99 (dd, 2H, *J*=8.4, 3.0 Hz, H-17 and H-21), 7.47–7.44 (dd, 2H, *J*=7.8, 1.2 Hz, H-18 and H-20), 5.90 (d, 1H, *J*=10.5 Hz, H-14), 5.74 (ddd, 1H, *J*=10, 5 Hz, e *J*=1.8, 1.5 Hz, H-15), 5.07 (s, 1H, H-10), 4.22 (d, 1H, *J*= 7.5 Hz, H-13), 3.95–3.67 (m, 4H, H-12, H-24, H-24'and H-8), 3.09–3.01 (m, 2H, H-6 and H-6'), 2.09–2.02 (m, 2H, H-7 and H-7'), 1.70 (bs, 2H, OH), 1.32 (d, 3H, *J*=6.3 Hz, H-23). Anal. Calcd for (C₁₈H₂₄O₅N₂Cl): C, 56.77; H, 5.56; N, 7.36. Found: C, 56.88; H, 5.78; N, 7.14.

4.3.10. 1-(*S*)-Methyl-3-(*p*-chlorophenyl)-1,2,4-oxadiazol-5-yl]propyl 2,3-dideoxy- α -D-*erythro*-hex-2-enopyranoside (6e). $R_{\rm f}$ =0.40, colorless syrup, yield 35%; $[\alpha]_{\rm D}^{25}$ = + 33.7° (*c*=0.6, CHCl₃); IR $\nu_{\rm max}$ (KBr): 3404 (OH), 1589, 1564, 1474, 1449 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.02–7.98 (dd, 2H, *J*=1.5, 8.1 Hz, H-17 and H-21), 7.47– 7.38 (dd, 2H, *J*=8.4, 2.1 Hz, H-18 and H-20), 6.34 (dd, 1H, *J*=9.8, 1.8 Hz, H-14), 5.90 (dd, 1H, *J*=9.8 Hz, e *J*= 3.3 Hz, H-15), 5.06 (s, 1H, H-10), 4.12 (d, 1H, *J*=6.9 Hz, H-13), 3.98–3.65 (m, 4H, H-12, H-24, H-24'and H-8), 3.13– 303 (m, 2H, H-6 and H-6'), 2.96 (s, 2H, OH), 2.10–1.92 (m, 2H, H-7 and H-7'), 1.28 (d, 3H, *J*=6.0 Hz, H-23). Anal. Calcd for (C₁₈H₂₄O₅N₂Cl): C, 56.77; H, 5.56; N, 7.36. Found: C, 56.31; H, 5.70; N, 6.96.

4.4. General procedure for the acetylation of (*R*) and (*S*)-1-methyl-3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propyl-2,3dideoxy-α-D-*erythro*-hex-2-enopyranoside (5a and 6a)

To the pure dihydroxy compounds **5a** or **6a** (0.07 g, 0.21 mmol) in dry pyridine (2.0 mL), in a 10 mL roundbottom flask and cooled to 0 °C was added Ac₂O (1.0 mL). Stirring at rt overnight gave mixture of 4,6-di-*O*-acetyl-2,3dideoxy- α -D-*erythro*-hex-2-enopyranosides **3a** and **4a**. Purification was achieved by column chromatography over silica gel. Elution with 1:9 EtOAc–*n*-hexane gave **5a** or **6a** in pure forms.

4.4.1. 1-(*R*)-Methyl-[3-(phenyl)-1,2,4-oxadiazol-5-yl]propyl 4,6-di-*O*-acetyl-2,3-dideoxy- α -D-*erythro*-hex-2enopyranoside (3a). $R_f = 0.61$, liq., yield 90%; $[\alpha]_D^{25} = 43^\circ$ (c = 0.49, CHCl₃); IR ν_{max} (KBr): 1743, 1571, 1368, 1231, 1034, 722 cm⁻¹; ¹H NMR (CDCl₃): δ 8.09–8.06 (dd, 2H, J=3.3, 9.6 Hz, H-17 and H-21), 7.53–7.49 (m, 3H, H-18, H-19 and H-20), 5.80 (d, 1H, J = 10.2 Hz, H-14), 5.85 (ddd, 1H, J=10.2, 2.7, 2.0 Hz, H-15), 5.31 (dd, 1H, J=9.6, 1.5 Hz, H-13) 5.14 (bs, 1H, H-10), 4.60–4.40 (m, 2H, H-23 or H-23'), 4.35 (m, 1H, H-8), 3.82 (dd, 1H, J=9.7, 5.4 Hz, H-12), 3.06 (t, 2H, J=7.5 Hz, H-6 and H-6'), 2.15–2.00 (m, 2H, H-7 and H-7'), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 1.36 (d, 3H, J=6.3 Hz, H-22). Anal. Calcd for (C₂₂H₂₆O₇N₂): C, 61.39 H, 6.09 N, 6.51. Found: C, 61.37 H, 6.07 N, 6.28. 4.4.2. 1-(S)-Methyl-[3-(phenyl)-1,2,4-oxadiazol-5-yl]propyl 4,6-di-O-acetyl-2,3-dideoxy-a-D-erythro-hex-2enopyranoside (4a). $R_f = 0.65$, mp 63.6 °C (from *n*-hexane–ether), 96%; $[\alpha]_D^{25} = 69^\circ$ (*c*=0.91, CHCl₃); IR $\nu_{\rm max}$ (KBr): 1744, 1571, 1369, 1232, 1034, 722 cm⁻¹; ¹H NMR (CDCl₃): δ 8.10–8.06 (m, 2H, H-17 and H-21), 7.54– 7.46 (m, 3H, H-18, H-19 and H-20), 5.90 (d, 1H, J =10.2 Hz, H-14), 5.80 (ddd, 1H, J=10.2, 2.7, 2.2 Hz, H-15), 5.30 (dd, 1H, J=9.7, 1.5 Hz, H-13) 5.18 (sl, 1H, H-10), 4.28 (dd, 1H, J = 13.1, 5.4 Hz, H-23 or H-23'), 4.20 (dd, 1H, J =13.1 Hz, $J \le 1.0$ Hz, H-23 or H-23'), 4.15 (m, 1H, H-8), 4.04 (dd, 1H, J=9.7, 5.4 Hz, H-12), 3.01–3.20 (m, 2H, H-6 and H-6'), 2.20–2.06 (m, 2H, H-7 and H-7'), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 1.26 (d, 3H, J=6.0 Hz, H-22). Anal. Calcd for (C₂₂H₂₆O₇N₂): C, 61.39 H, 6.09 N, 6.51. Found: C, 61.58 H, 6.14 N, 6.26.

5. Supplementary material

Details of the crystallographic data (CCDC) for compound **5d** has been deposited with the Cambridge Crystallographic Data Center. These data may be acquired from the Director of CCDC, 12 Union Road, Cambridge CB2 1DEZ, UK (Tel.: +44-1223-336408, fax: +44-1223-33-6033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be

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