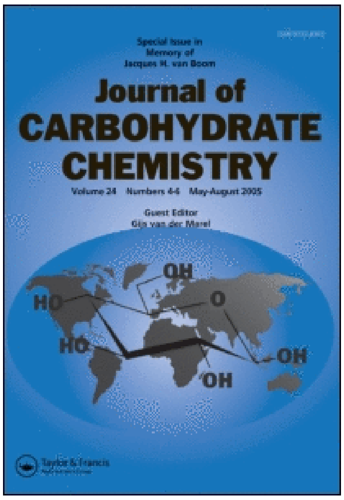

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Chiroptical Assignment of the Anomeric Configuration of 4-(α,β-D-lyxopyranosyl)- and 4-(α,β-D-lyxofuranosyl)-2-phenyl-2*H*-1,2,3-Triazole C-Nucleoside Anomeric Pairs: Extension of the CD Triazole Rule[1]

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The circular dichroism of the anomeric 4-(α,β-D-lyxopyranosyl)- and 4-(α,β-D-lyxofuranosyl)-2-phenyl-2*H*-1,2,3-triazole *C*-nucleoside analogs obtained by acid-catalyzed dehydrative cyclization of 4-(D-*galacto*-pentitol-1-yl)-2-phenyl-2*H*-1,2,3-triazole analog was studied. A correlation between the sign of the Cotton effect at the maximal UV absorption and the absolute configuration of the anomeric carbon atom was obtained and used for their anomeric configuration assignment. This correlation supports the CD triazole rule for anomeric assignment and is in accord with the assignment obtained by NMR spectral studies.

Keywords CD; *C*-Nucleosides; 1,2,3-Triazoles; D-Lyxopyranosyl; D-Lyxofuronosyl; Anomeric configuration

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[1] Part II. For part I, see reference 1.

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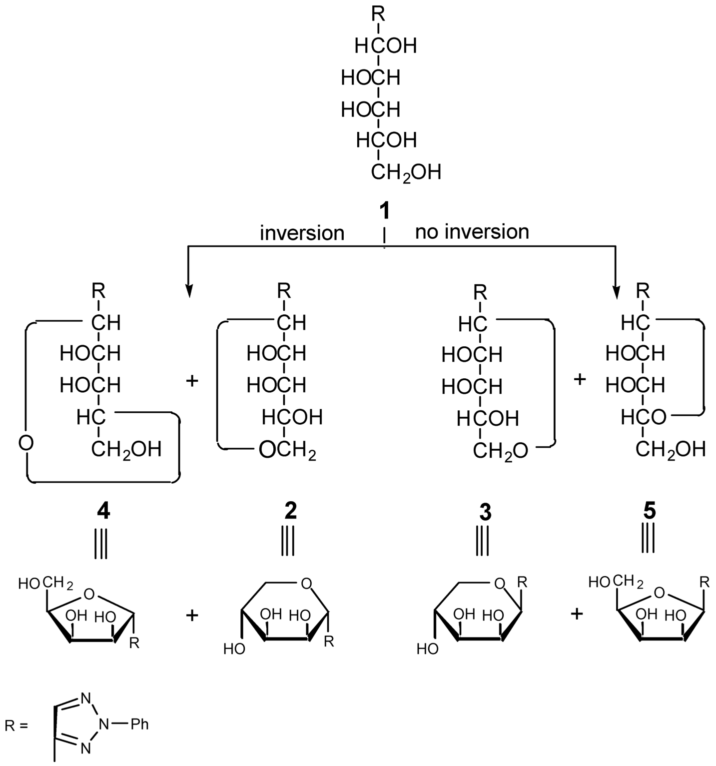
INTRODUCTION

Circular dichroism is a reliable tool for determining the stereochemistry of the asymmetric carbon atoms of saccharides.[2,3] The chromophoric base moiety of *C*-nucleosides makes them target compounds for CD measurements and anomeric assignment. We have been interested lately in the synthesis of *C*-nucleoside analogs by acid-catalyzed dehydrative cyclization of polyhydroxyalkyl heterocyclic analogs.[4–9] This reaction gives an anomeric mixture of *C*-nucleosides, whose anomeric configuration is of importance. The anomeric configuration of the products may be assigned by NMR spectroscopy that requires the presence of the two anomers on hand and applying different NMR criteria such as comparing the chemical shift values of the anomeric proton for the anomeric pair or the coupling constant values ($J_{1',2'}$) of their anomeric protons. These techniques are sometimes not reliable and cannot give unequivocal proof for the anomeric configuration. The NOE measurements are a more reliable tool for assigning the anomeric configuration by NMR spectroscopy.

The CD chiroptical studies[10–12] are more simple and can be used for anomeric assignment from the sign of the Cotton effect at the maximal UV absorption. In this work the anomeric configuration of the *C*-nucleoside anomeric pairs 4-(α,β-D-lyxopyranosyl)-2-phenyl-2*H*-1,2,3-triazole **2,3** and 4-(α,β-D-lyxofuranosyl)-2-phenyl-2*H*-1,2,3-triazole **4,5**, obtained from acid-catalyzed dehydrative cyclization of 4-(D-*galacto*-pentitol-1-yl)-2-phenyl-2*H*-1,2,3-triazole **1**, was investigated by CD chiroptical measurements.

RESULTS AND DISCUSSION

The anomeric mixture 4-(α,β-D-lyxopyranosyl)-2-phenyl-2*H*-1,2,3-triazole analogs **2** and **3**, and 4-(α,β-D-lyxofuranosyl)-2-phenyl-*2H*-1,2,3-triazole **4** and **5** were obtained by acid-catalyzed dehydrative cyclization of 4-(D-*galacto*-pentitol-1-yl)-2-phenyl-2*H*-1,2,3-triazole **1** (Scheme 1). The four isomeric *C*-nucleosides were separated by chromatography. The anomeric configuration of compounds **2–5** was assigned by NMR spectroscopy. In a recent publication,[1] the anomeric configuration was subjected to CD measurements, which reversed the anomeric assignment obtained by NMR measurements. In order to confirm the anomeric configuration of compounds **2–5**, chiroptical methods were applied. As expected, the sign of rotation of the cyclic nucleosides **2–5** did not follow the sign of the specific rotation at the D-line, as it does in the El-Khadem triazole rule.[13,14] The latter deals specifically with the rotation of the chiral centers in acyclic polyhydroxyalkyl chains attached to aromatic or heterocyclicrings. In addition, these compounds did not obey Hudson isorotation rules[15,16] for glycosides. The α anomers **2** and **4** were not more dextrorotatory than the corresponding β anomers **3** and **5** (Table 1). Other examples in the literature[17] showed opposition to Hudson isorotation rules.



Scheme 1: Acid catalyzed dehydrative cyclyzation of 4-(D-*galacto*-pentitol-1-yl)-2-phenyl-2*H*-*1,2,3-triazol* ***1***

The β anomer was more dextrorotatory than the corresponding α anomer. These results did not allow anomeric assignment for compounds **2–5** from their specific rotation at the D-line. The CD chiroptical properties of these compounds showed a correlation similar to that obtained for the D-arabinoglycosyl

Table 1: Specific rotation, observed CD, and UV spectra of compounds **1–5**

Compound	$(\alpha)_D$	Obs CD $\lambda(\Delta\varepsilon)$	λ_{max}	Log ε
1	+80.3° (c 0.84, pyridine)(20)	266.4 (+2.7)	266.6	4.31
2	+4.3° (c 2.4, methanol)(8)	258.6 (–0.4)	266.4	4.28
3	+52.3° (c 0.52, methanol)(8)	256.4 (+2.0)	256.2	4.32
4	+39.3° (c 1.08, methanol)(8)	253–225 (–0.1)	266.4	4.41
5	+72.7° (c 1.08, methanol)(8)	266.4 (+3.3)	256.8	4.31

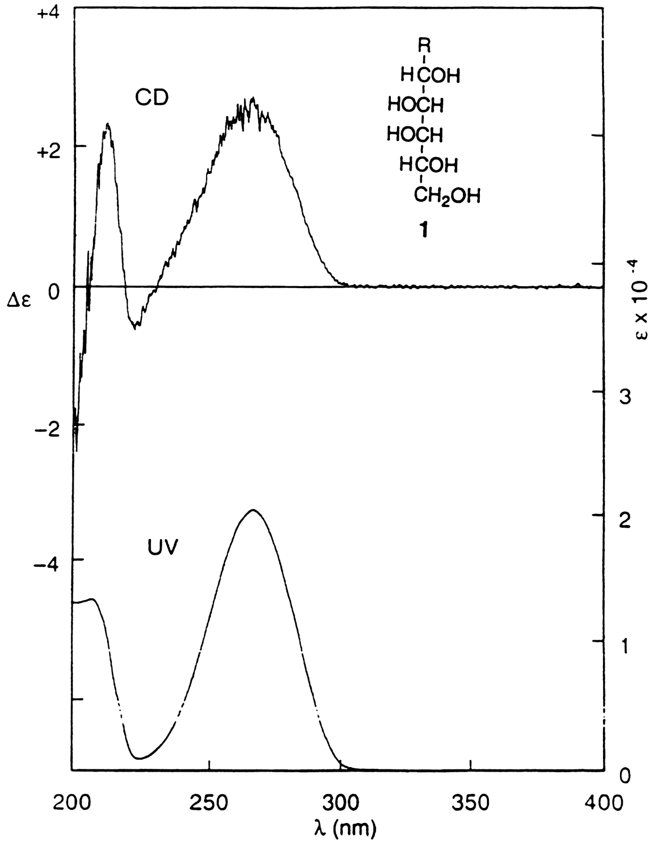


Figure 1: CD Spectrum of 4-(D-*galacto*-pentitol-l-yl)-2-phenyl-2*H*-1,2,3-triazole 1, in methanol.

stereoisomeric *C*-nucleoside analogs.[1] The CD spectrum of the acyclic analog **1**, having the hydroxyl group α- to the triazole base moiety to the right D-glycero-(*S*) configuration, showed a positive Cotton effect at the maximal UV absorption (Fig. 1). The CD spectra of the D-lyxorpyranosyl anomeric pair **2** and **3** showed a single Cotton effect of the opposite sign at the maximal UV absorption (Fig. 2). Compound **3** showed a positive Cotton effect of the same sign of the acyclic analog **1**, in accord with the right configuration of the ring oxygen of the Fischer projection formula (i.e., the β-D-lyxopyranosyl configuration of the glycosyl group formed). Compound **2** showed a negative Cotton effect at the same region, manifested by the left configuration of the ring oxygen at the Fischer projection formula (i.e., the α-D-lyopyranosyl configuration of the glycosyl group formed). The CD spectra of the D-lyxofuranosyl anomeric pair **4** and **5** showed a single Cotton effect at the maximal UV absorption (Fig. 3). Compound **5** showed a positive Cotton effect, manifested by the right configuration of the ring oxygen of the Fischer projection formula (i.e., the β-D-lyxofuranosyl

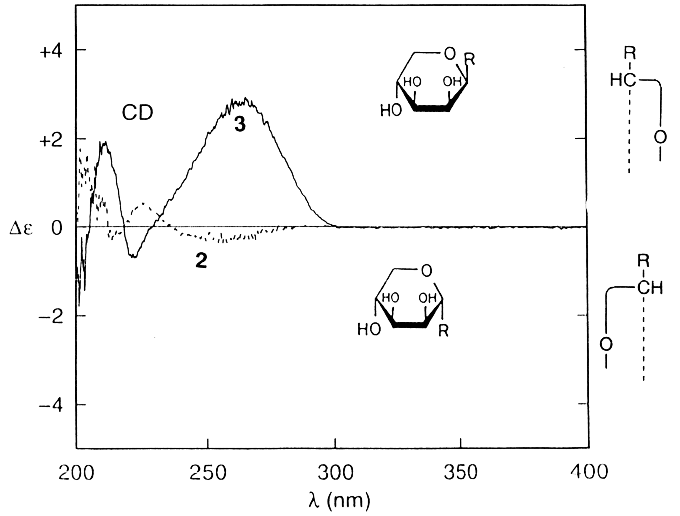


Figure 2: CD Spectra of 4-(α-D-lyxopyranosyl)-2-phenyl-2*H*-1,2,3-triazole **2**(– – – – –), and 4-(β-D-lyxopyranosyl)-2-phenyl-2*H*-1,2,3-triazole **3** (————), in methanol.

configuration of the glycosyl group formed). Compound **4** showed a weak negative Cotton effect at the same region, in accord with the left configuration of the ring oxygen of the Fischer projection formula (i.e., the α-D-lyxofuranosyl configuration of the glycosyl group formed). The anomeric configuration of compound **4** was supported by X-ray crystallography measurements.[8] The β-D-lyxopyxopyranosyl and β-D-lyxofuranosyl anomers **3** and **5**, respectively, showed higher spectrum amplitude than the corresponding α-D-lyxopyranosyl and α-D-lyxofuranosyl anomers **2** and **4**, respectively. The difference in the CD spectrum amplitude is attributed to the different conformational population of the glycosyl part. The chiroptical assignment of compounds **2–5** is in accord with the anomeric assignment obtained from NMR spectroscopy. Compounds **2** and **4** are obtained from **1** with inversion at the configuration of the carbon atom α- to the triazole base moiety (C-1′). Compounds **3** and **5** are obtained from **1**, without inversion at C-1′, during the dehydrative cyclization process.

These CD results are an additional example supporting the CD triazole rule for anomeric configuration assignment of 4-glycosyl-2-phenyl-2*H*-1,2,3-triazole *C*-nucleoside analogs. *C*-Nucleosides having the β-D-configuration show a positive Cotton effect at the maximal UV absorption, and the corresponding α-D-anomers show a negative Cotton effect at the same region. In addition, the CD triazole rule is applicable for acyclic polyhydroxyalkyl-2-phenyl-2*H*-1,2,3-triazole analogs, supporting the El-Khadem triazole rule for specific rotation at the D-line. It is also applicable for *C*-nucleosides having different cyclic glycosyl parts: D-glycopyranosyl,[1] D-glycofuranosyl,[18] 5′-hydroxymethyl-D-glycofuranosyl,[1] and L-glycofuranosyl[19] analogs.

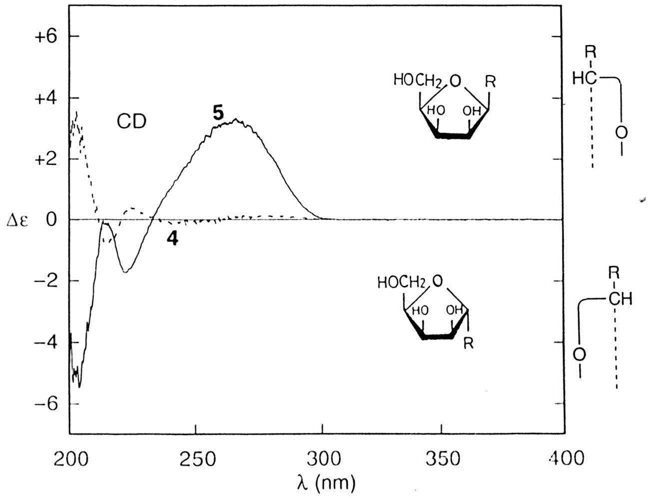


Figure 3: CD Spectra of 4-(α-D-lyxofuranosyl)-2-phenyl-2*H*-1,2,3-triazole **4**(– – – – –), and 4-(β-D-lyxofuranosyl)-2-phenyl-2*H*-1,2,3-triazole **5** (————), in methanol.

MATERIALS AND METHODS

Compounds **2–5** have been prepared by standard methods and separated by column chromatography.[8] Their structure and anomeric configuration were assigned using NMR spectroscopy. The CD measurements were recorded for solutions in methanol on Jasco 500 H and Jasco 720 WI spectrometers at concentrations 0.25 to 0.30 mg/mL methanol using 0.2-mL micro-cell.

CONCLUSION

The chiroptical properties of the anomeric 4-(α,β-D-lyxopyranosyl) and 4-(α,β-D-lyxofuranosyl)-2-phenyl-2*H*-1,2,3-triazole analogs were studied. These compounds are obtained by the dehydrative cyclization of 4-(D-*galacto*-pentitol-1-yl)-2-phenyl-2*H*-1,2,3-triazole with inversion or retention of the configuration at C-1′. The anomeric configuration of these compounds obtained by CD studies is in accord with NMR spectral assignment. The chiroptical anomeric assignment of these compounds reports an additional example supporting the CD triazole rule for anomeric assignment of glycosyl-2-phenyl-2*H*-1,2,3-triazole analogs.

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