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Levoglucosenone-derived precursors for the stereoselective synthesis of methylene-expanded analogues of C-nucleosides

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Simple chiral precursors for the preparation of methylene-expanded C-nucleosides were developed, using as key steps pyrolysis of cellulose to levoglucosenone followed by hydrogenation and introduction of vinyl and ethynyl fragments to the 2-position.

Regioselective synthesis of sugar-connected heterocycles, such as N- and C-nucleosides (**A**, Figure 1), is an important approach to biomolecules.[1] Nucleosides with heterocyclic base linked to sugar through C–C bond attract much attention because of their chemical and enzymatic stability.[2]

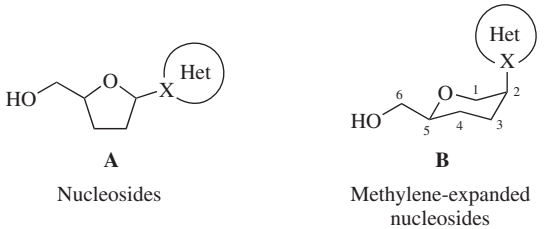


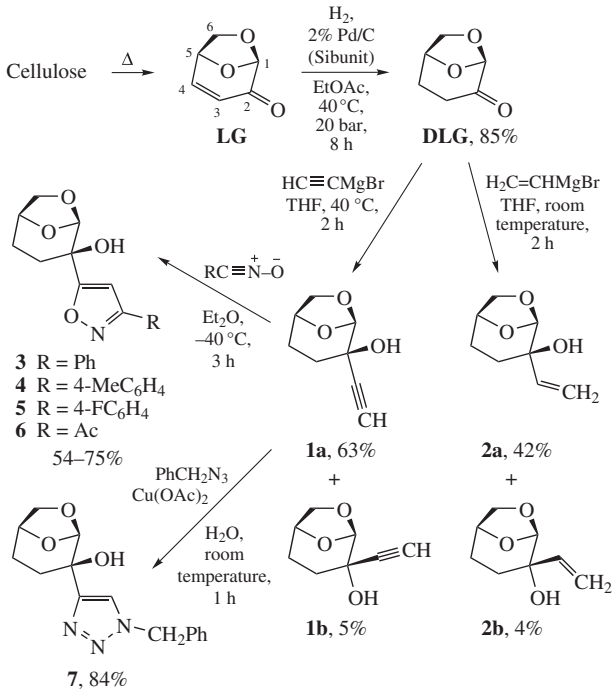
Figure 1 Structure of nucleosides.

Among the synthetic C-nucleosides, tiazofurin (2-β-D-ribofuranosylthiazole-4-carboxamide NSC-286193),[3(a)] selenazofurin (2-β-D-ribofuranosylselenazole-4-carboxamide NSC-340847),[3(b)] have gained significant recognition as potent antitumor agents.

When a methylene group is inserted between the ring oxygen and the carbon atom linked to the base moiety, such compounds are considered as ring-expanded (six-membered ring) analogues of nucleosides (**B**, Figure 1). A number of six-membered ring N-nucleoside derivatives (with pyranose,[4(a)] cyclohexane,[4(b)] cyclohexene[4(c)] rings) as well as dideoxynucleosides containing two heteroatoms within the carbohydrate moiety[4(d)] have been prepared. Several of these compounds showed potent antiviral[2,5] and antitumor[2] activity.

An efficient synthesis of 1,6-anhydrohexitol N-nucleosides (type **B**) allowing for introduction of alternative substituents at the 2′-position of the sugar has been developed from levoglucosenone (**LG**).[6] **LG**, a highly functionalized chiral synthon with proper stereochemistry at the 5-position, is susceptible to selective addition at the C=C bond on the side opposite to the anhydro bridge,[7] which opens an access to new enantiopure compounds.[8]

We consider **LG** as an excellent starting material for the synthesis of methylene-expanded C-nulceosides **B** (Scheme 1).



Scheme 1

It is obtained by acid-catalyzed pyrolysis of cellulose[9] and available from Chemical Block Ltd.

Dihydrolevoglucosenone (**DLG**) was synthesized by hydrogenation of **LG** using 2% Pd catalyst on granulated graphite Sibunit[10] in a specially designed stainless reactor ensuring contact between a solution to be hydrogenated and a fixed layer of the catalyst.[†] In the next step vinyl and ethynyl fragments were introduced to

[†] *Dihydrolevoglucosenone* **DLG** *(1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hexopyranos-2-ulose)*. Pd/Sibunit catalyst was prepared and regenerated as described earlier.[10] A stainless steel autoclave (650 ml)[10] was charged with **LG** (35 g, 0.273 mol) in EtOAc (400 ml). A gauze container with a 2% Pd/C catalyst (8 ml) was placed in the autoclave in such a way that the catalyst was immersed in solution. **LG** was hydrogenated at 40 °C and a hydrogen pressure 20 atm for 48 h with stirring with a magnetic bar. The autoclave was discharged, washed with EtOAc (2×20 ml), combined

the 2-position of **DLG** *via* addition of the corresponding Gringard reagents.‡ The presence of the 1,6-anhydro bridge provides high stereoselectivity.[6,8(*b*)] Noteworthy, addition of MeMgI to **DLG** is less stereoselective.[11] The major isomers of target alcohols **1a** (92.9% in mixture) and **2a** (91.7%) were easily separated by column chromatography. The ethenyl and ethynyl substitutents in such molecules can be transformed to various heterocyclic rings *via* 3+2 dipolar cycloaddition reactions.[12,§] We demonstrated such transformation yielding isoxazoles **3–6** and 1,2,3-triazoles **7** with 1,5-anhydrohexitol moieties. 3-Acetylisoxazole **6** was synthesized from alkyne **1a** and acetone using ammonium cerium(IV) nitrate in one-pot procedure[13] (see Scheme 1).

Interesting biological properties have been reported for 1,2,3-triazole–carbohydrate conjugates.[14] Isoxazoles and 4,5-dihydroisoxazoles are considered as useful intermediates in organic synthesis.[15] Furanose- and pyranose-containing C-nucleosides with isoxazole group were reported previously.[16] The opening of 1,6-anhydrohexitol acetal ring, described earlier,[6] can be used for transformation of derivatives **3–7** into type **B** C-nucleosides.

The molecular structures of **1a** and **3** and stereoselectivity were unambiguously determined by X-ray crystal diffraction study (Figures 2 and 3).¶

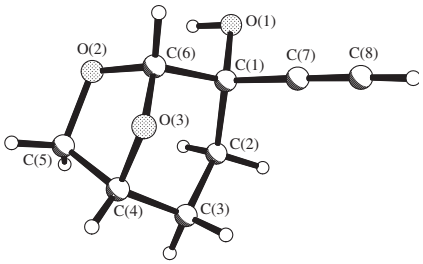


Figure 2 Molecular structure of 1,6-anhydro-3,4-dideoxy-2-*C*-ethynyl-β-D-*threo*-hexopyranose **1a**.

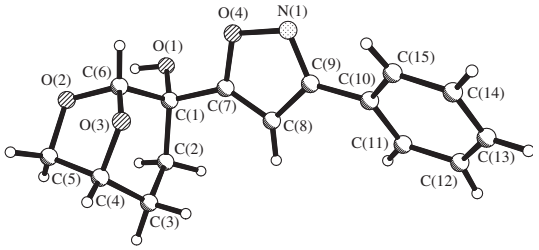


Figure 3 Molecular structure of 1,6-anhydro-3,4-dideoxy-2-*C*-(3-phenylisoxazol-5-yl)-β-D-*threo*-hexopyranose **3**.

In conclusion, we have developed the simple synthesis of C2 chiral derivatives of dihydrolevoglucosenone **1a**, **2a** and **3–7** as precursors for preparation of methylene-expanded C-nucleosides (**B**).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.01.016.

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EtOAc solution was evaporated. Residue was distilled to afford **DLG**, 30.2 g (85%), bp 52 °C/2 Torr (lit.,[17] 104 °C/16 Torr), $[\alpha]_D^{20}$ –261.8 (*c* 1.0, $CHCl_3$) {lit.,[17] $[\alpha]_D^{25}$ –246 ($CHCl_3$)}.

‡ *1,6-Anhydro-3,4-dideoxy-2*-C-*ethynyl-β-D-hexopyranose* **1a**. Purified anhydrous THF (100 ml) was placed in a 50 ml flask, acetylene was introduced through a gas-inlet tube at the rate of 0.5–1.0 dm^3 h^{-1}, and the stirrer was started. After 15 min, ethylmagnesium bromide (prepared from 0.48 g, 0.02 g-atom of magnesium turnings, and 2.4 g, 0.022 mol of bromoethane in the 25 ml of THF) was added over 2 h. The temperature was raised to 5–10 °C. The mixture was stirred at 30–35 °C for 1 h, then cooled in an ice bath and **DLG** (3.1 g, 0.024 mol) in tetrahydrofuran (15 ml) was added over 15 min. The mixture was then stirred and heated to 40–45 °C for a further 2 h, cooled and saturated aqueous NH_4Cl was added carefully to dissolve the solid components. The two layers were separated and the aqueous phase was extracted with Et_2O (3×15 ml). The combined organic fractions were dried (K_2CO_3) and solvent was evaporated *in vacuo*. The crude product (2.3 g) was purified by chromatography on silica gel to afford **1a** (1.95 g, 63%) and **1b** (0.15 g, 5%) as white crystals.

1,6-Anhydro-3,4-dideoxy-2-C-*ethenyl-β-D-hexopyranose* **1b**. A solution of ethenylmagnesium bromide (prepared from 0.48 g, 0.02 g-atom of magnesium turnings, and 2.4 g, 0.022 mol of bromoethene) in dry THF (100 ml) was cooled to 5 °C. Solution of **DLG** (3.12 g, 0.02 mol) in THF (15 ml) was added. After stirring for 2 h at room temperature, the reaction was cooled to 0 °C and quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×20 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a mixture of **2a** and **2b**. The crude product was purified by flash chromatography to yield **2a** (1.3 g, 42%) and **2b** (0.12 g, 4%) as white solid products.

§ *1,6-Anhydro-3,4-dideoxy-2*-C-*(3-phenylisoxazol-5-yl)-β-D*-threo-*hexopyranose* **3** *(typical procedure)*. Compound **1a** (0.31 g, 0.002 mol) was dissolved in Et_2O (10 ml). PhCCl=NOH (0.47 g, 0.003 mol) in Et_2O (10 ml) was added at –40 °C. Et_3N (0.6 g, 0.006 mol) was added dropwise over 2 h. Stirring was continued at –40 °C until the reaction was complete according to TLC (2–3 h) and 2 h at room temperature. The mixture was quenched with saturated aqueous NH_4Cl (10 ml), extracted with diethyl ether and dried with Na_2SO_4. After evaporation of the solvent resulting oil was purified by flash chromatography to give **3** as a white solid, yield 0.37 g (67%).

1,6-Anhydro-3,4-dideoxy-2-C-*(1-benzyl-1,2,3-triazol-4-yl)-β-D*-threo-*hexopyranose* **7**. A mixture of **1a** (0.162 g, 0.00105 mol), benzyl azide (0.133 g, 0.001 mol), and $Cu(OAc)_2 \cdot H_2O$ (36 mg, 0.2 mmol) in water (5 ml) was vigorously stirred for 1 h and extracted with EtOAc (2×5 ml). The solvent was removed *in vacuo* and the residue was crysrallized from benzene to yield **7** (241 mg, 84%) as a white solid.

For more synthetic details and characteristics of compounds **1–7**, see Online Supplementary Materials.

¶ *Crystallographic data* were collected on an Enraf-Nonius CAD-4 diffractometer using MoKα radiation, *ω*/2*θ* scan mode. Structures were solved by full-matrix least-squares method.

For **1a**: crystals of $C_8H_{10}O_3$ (*M* = 154.16) are orthorombic, space group $P2_12_12_1$, at 293 K: *a* = 6.623(1), *b* = 9.427(2) and *c* = 12.076(2) Å, *V* = = 754.0(3) $Å^3$, *Z* = 4, d_{calc} = 1.358 g cm^{-3}. 1061 reflections were collected, from which 1395 unique (R_{int} = 0.0209), *F*(000) = 328. Refinement converged to R_1 = 0.0386, wR_2 = 0.0848 (all data) and R_1 = 0.0308, wR_2 = 0.0827 [$I > 2\sigma(I)$], GOF = 1.103.

For **3**: crystals of $C_{15}H_{15}NO_4$ (*M* = 273.28) are hexagonal, space group $P3_1$, at 293 K: *a* = 9.809(1), *b* = 9.809(1) and *c* = 11.856(2) Å, *γ* = 120°, *V* = 987.9(3) $Å^3$, *Z* = 3, d_{calc} = 1.378 g cm^{-3}. 2045 reflections were collected, from which 1288 unique (R_{int} = 0.0197), *F*(000) = 432. Refinement converged to R_1 = 0.0331, wR_2 = 0.0612 (all data) and R_1 = 0.0224, wR_2 = 0.0594 [$I > 2\sigma(I)$], GOF = 1.033.

CCDC 961718 and 961719 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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