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Carbohydrate Research 343 (2008) 855–864
Carbohydrate RESEARCH

Synthesis of new mannosyl, galactosyl and glucosyl theophylline nucleosides with potential activity as antagonists of adenosine receptors. DEMA-induced cyclization of glycosylideneiminouracils

Rodrigo Rico-Gómez,[a,*] J. Manuel López-Romero,[a] Jesús Hierrezuelo,[a] José Brea,[b] M. Isabel Loza[b] and Maykel Pérez-González[c]

[a]*Dept. de Química Orgánica, Facultad de Ciencias, Universidad de Málaga, 29071 Málaga, Spain*
[b]*Dept. de Farmacología, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain*
[c]*Centro de Química Bioactiva, Universidad Central de Las Villas, Santa Clara, 54830 Villa Clara, Cuba*

Received 29 October 2007; received in revised form 17 December 2007; accepted 10 January 2008
Available online 18 January 2008

Abstract—The synthesis of D-mannosyl, D-galactosyl and D-glucosyl theophylline nucleosides by diethoxymethyl acetate (DEMA)-induced cyclization of 4-amino-5-glycosylideneimino-1,3-dimethyluracil is reported. 8-Methyltheophylline derivatives of the same sugars were also prepared by Ac_2O/H^+-induced cyclization of their imine precursors. This approach has allowed β-D-mannopyranosyl-, α-D-galactofuranosyl- and β-D-glucofuranosyltheophylline nucleosides to be synthesized for the first time. The inhibition of specific binding at A_1, A_{2A}, A_{2B} and A_3 adenosine receptors in the mannose derivatives is also reported.

Keywords: Iminouracil; Mannosyl, galactosyl and glucosyl nucleosides; Theophylline

1. Introduction

Nucleoside analogues are amongst the most complex and promising anticancer drugs on account of the growing number of anticancer nucleoside analogues available, the abundance of molecular targets for them and the wide variety of effective drug resistance mechanisms.[1] Nucleosides additionally exhibit antiviral activity (e.g., against the human immunodeficiency virus or hepatitis B virus);[2] also, they act as antagonists of various adenosine receptors (particularly those substituted at position 8 in the purine ring).[3] New efforts should therefore be made with a view to fully exploit their synthetic potential.

7-Glycopyranosyl theophylline nucleosides have been prepared in three different ways involving direct coupling of the base and sugar moiety, namely: (i) from theophylline and glycopyranose pentaacetate (fusion method);[4] (ii) from theophylline silver[5] and mercury salts[6] and tetra-*O*-acetyl glycopyranosyl bromide (heavy-metal method); and (iii) from a silylated theophylline and glycopyranose pentaacetate (Vorbrüggen method).[7] Only the β-anomer has thus been obtained for gluco- and galactopyranosyl nucleosides, and the α-anomer for mannopyranosyl nucleosides using these condensation procedures. These results can be explained in the light of the generally accepted reaction mechanism, where glycosidation is produced by an attack of the base to an acetoxonium ion intermediate at the site opposite the 2-acetoxy group to give 1′,2′-*trans*-nucleosides alone (Scheme 1).[8]

The stereochemistry of the process is governed by the axial arrangement of the 2-acetoxy group in mannopyranose pentaacetate, which leads to the α-nucleoside (Scheme 1). To the best of our knowledge, the synthesis of a β-anomer of mannosyl theophylline nucleosides by sugar–nucleobase condensation methods

* Corresponding author. E-mail: rrico@uma.es

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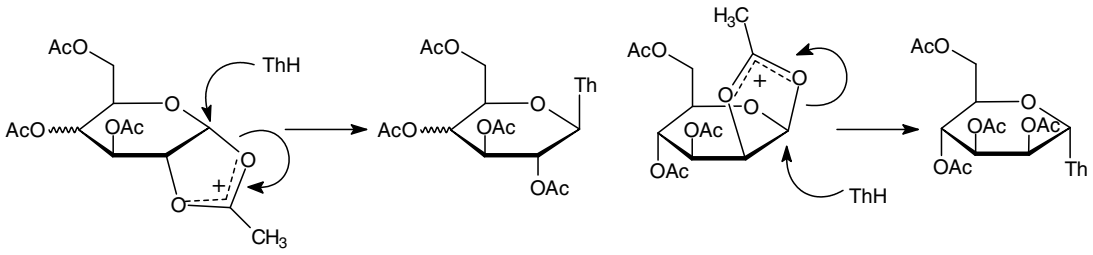
doi:10.1016/j.carres.2008.01.011



Scheme 1. Mechanism for glucosyl and galactosyl (left) and mannosyl (right) nucleosides.

has previously never been reported. Lichtenthaler and Nakagawa, however, have reported a theophylline β-nucleoside of 3-amino-3-deoxy-β-D-mannopyranose (and derivatives) formed by periodate oxidation and ring expansion via nitromethane reaction with 7-(β-D-ribofuranosyl)theophylline.[9]

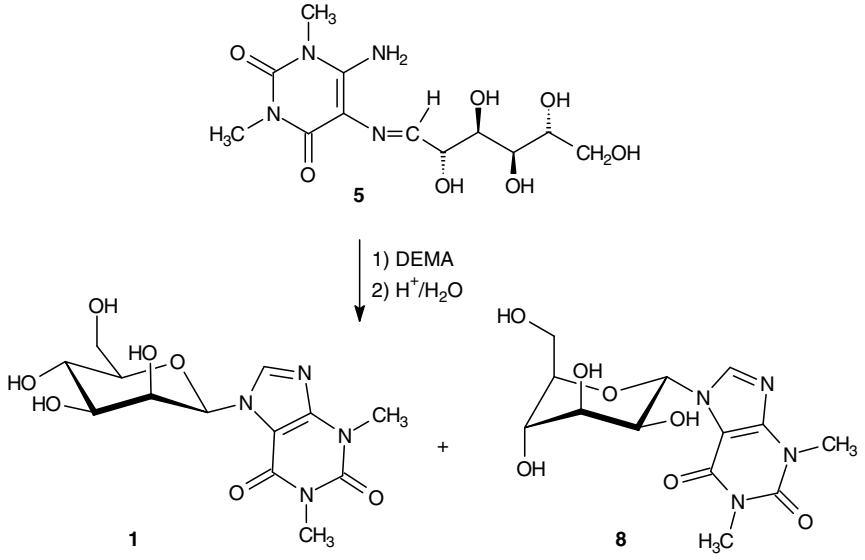
In previous work, we accomplished the synthesis of theophylline nucleosides with D-ribose, D-glucose and L-arabinose by building the imidazole and sugar rings from acyclic imine precursors such as 4-amino-1,3-dimethyl-5-*N*-glycosylideniminouracil as an alternative to direct glycosidation.[10,11] In this work, we developed the first synthesis for β-mannosides 7-(β-D-mannopyranosyl)theophylline (**1**) and 7-(β-D-mannopyranosyl)-8-methyltheophylline (**2**). Also, we further explored this synthetic approach and extended it to mannosyl, glucosyl and galactosyl nucleosides by preparing new nucleoside derivatives for α-D-galactofuranose (**3**) and β-D-glucofuranose (**4**). The starting imines (**5**–**7**) were obtained by the condensation of 4,5-diamino-1,3-dimethyluracil with D-mannose, D-galactose and D-glucose, respectively, in methanol, following the previously reported procedures.[12]

2. Results and discussion

2.1. DEMA-induced cyclization

2.1.1. Mannose derivatives. Treating the imine of mannose **5** with diethoxymethyl acetate (DEMA)[11] at 120 °C for 1 h and workup, provided a crude product whose ^{1}H NMR spectrum in D_2O showed the presence of a mixture containing two main products. After separation by column chromatography and purification by crystallization from ethanol, the major compound was identified as 7-(β-D-mannopyranosyl)theophylline (**1**) (yield 62%) and the minor one 7-(α-D-mannopyranosyl)theophylline (**8**) (yield 20%) (see Scheme 2).

The ^{1}H NMR spectrum for **1** in D_2O exhibits a singlet at 8.05 ppm corresponding to H-8 in theophylline. The anomeric proton gives a broad doublet at 5.92 ppm, whose coupling constant (J <1 Hz) is consistent with an axial–equatorial arrangement with H-2′. This, together with the triplet at 3.53 ppm for H-4′ (J 9.7 Hz), which reflects a *trans*-diaxial arrangement with H-3′ and H-5′, is consistent with the presence of the β-anomer in a $^4C_1$ conformation.



Scheme 2.