

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

COUPLING OF 2,6-DISUBSTITUTED PURINES TO RIBOSE-MODIFIED SUGARS

S. Vittori^a; S. Costanzi^a; C. Lambertucci^a; R. Volpini^a; G. Cristalli^a

^a Dipartimento di Scienze Chimiche, via s. Agostino, 1, University of Camerino, Camerino, Italy

Online publication date: 31 March 2001

To cite this Article Vittori, S. , Costanzi, S. , Lambertucci, C. , Volpini, R. and Cristalli, G.(2001) 'COUPLING OF 2,6-DISUBSTITUTED PURINES TO RIBOSE-MODIFIED SUGARS', *Nucleosides, Nucleotides and Nucleic Acids*, 20: 4, 771 – 774

To link to this Article: DOI: 10.1081/NCN-100002427

URL: <http://dx.doi.org/10.1081/NCN-100002427>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

COUPLING OF 2,6-DISUBSTITUTED PURINES TO RIBOSE-MODIFIED SUGARS

S. Vittori, S. Costanzi, C. Lambertucci, R. Volpini, and G. Cristalli*

Dipartimento di Scienze Chimiche, via s. Agostino, 1,
University of Camerino, I-62032 Camerino, Italy

ABSTRACT

1,2,3-Tri-O-acetyl-N-ethyl- β -D-ribofuranuronamide was synthesized in three steps starting from 1-O-methyl-(2,3-O-isopropylidene)- β -D-ribofuranuronic acid. Both the triacetyl and the 1-O-methyl-2,3-di-O-acetyl derivatives were coupled to the 2,6-dichloropurine to obtain the acetylated 1-(2,6-dichloro-9H-purin-9-yl)-1-deoxy-N-ethyl- β -D-*erythro*-pentofuranuronamide. ^1H NMR and n.O.e. data accounted for both anomeric and N-7/N-9 isomeric configuration.

INTRODUCTION

In the last years growing efforts have been dedicated to the discovery of adenosine receptor (AdoR) ligands as therapeutic drugs, especially in the cardiovascular system and in the CNS (1). Furthermore, purine nucleoside and deoxynucleoside analogues substituted in 2 and 6 position have been shown to possess to various extent affinity and selectivity for AdoR subtypes and to potently interact with different biological systems (2,3). In recent papers we demonstrated that 2-alkynyl-5'-N-ethylcarboxamidoadenosines (2-alkynylNECAs) possess high affinity for AdoRs combined, in some cases, with good selectivity (4-6). Taking into account these data, we set up a program to prepare 2,6-disubstituted purines coupled to N-alkylribofuranuronamide, 2'-deoxy-N-alkylribofuranuronamide and 3'-deoxy-N-alkylribofuranuronamide. Recently we reported that, in the coupling of 2,6-dichloropurine to 2'- and 3'-deoxy-N-alkylribofuranuronamides, 1-O-acetyl

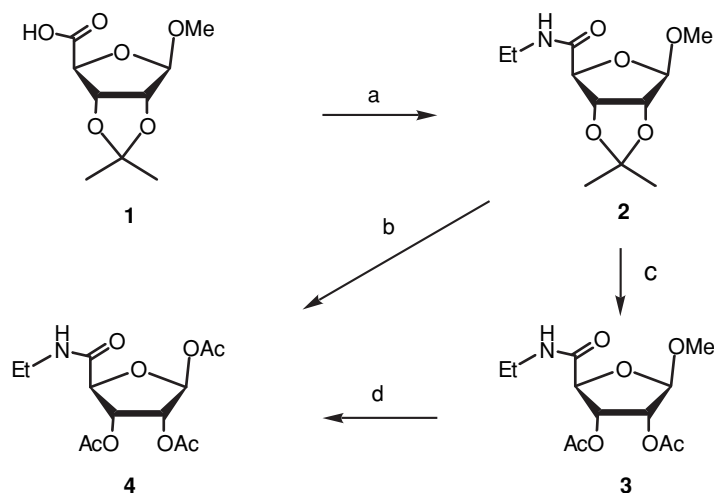
*Corresponding author.

deoxyribose derivatives gave much higher yield in nucleosides than the corresponding 1-O-methyl sugars (7,8). On these bases we decided to prepare 1,2,3-tri-O-acetyl-N-ethyl- β -D-ribofuranuronamide, to be coupled with 2,6-dichloropurine to obtain the useful intermediate 2,3-di-O-acetyl-1-deoxy-1-(2,6-dichloro-9H-purin-9-yl) N-ethyl- β -D-ribofuranuronamide.

RESULTS AND DISCUSSION

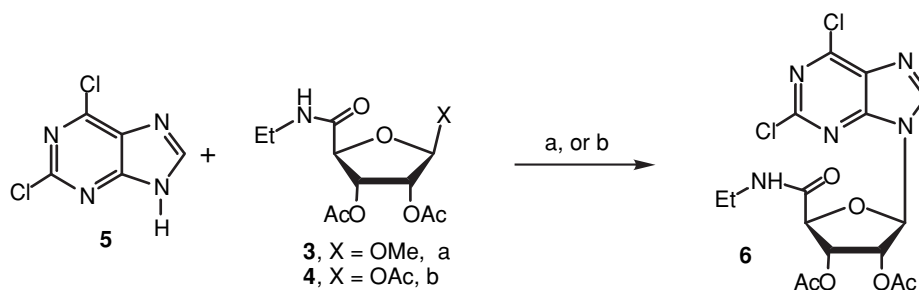
The synthesis of 1,2,3-tri-O-acetyl-N-ethyl- β -D-ribofuranuronamide was performed as reported in Scheme 1. Methyl-(2,3-O-isopropylidene)- β -D-ribofuranuronic acid (**1**) (**9**) was reacted first with thionyl chloride in dry DMF, followed by treatment with ethylamine in dry dichloromethane, to give the ethylamide derivative **2** in 90% yield. Stirring of **2** in a mixture of acetic acid, acetic anhydride, and catalytic sulfuric acid yielded 24% of the triacetyl ribofuranuronamide **4**. The same final product has been obtained from **2** also in two steps, in an attempt to improve the final yield. The isopropylidene derivative **2** was first deprotected by heating it in methanol in the presence of resin Dowex 50 (H^+), and then the two free hydroxyl groups were acetylated with acetic anhydride and dry pyridine to obtain the diacetyl sugar **3** in 43% yield; treatment of **3** with acetic anhydride and catalytic sulfuric acid gave **4** in moderate yield. All analytical data were consistent with the structure of compounds reported in Scheme 1; in particular, the β -anomeric configuration was supported by 1H NMR data and n.O.e. experiments.

Both sugars **3** and **4** were coupled to commercially available 2,6-dichloropurine (Scheme 2), to compare reactivity between 1-O-methyl- and 1-O-acetyl-ribofuranuronamide derivatives. 2,6-Dichloropurine was refluxed with hexamethyldisilazane



Scheme 1. a) 1. Dry DMF, $SOCl_2$; 2. Dry CH_2Cl_2 , $EtNH_2$; b) $AcOH$, Ac_2O , cat. H_2SO_4 ; c) 1. $MeOH$, Dowex 50 (H^+); 2. Dry CH_2Cl_2 , dry Pyr., Ac_2O ; d) Ac_2O , cat. H_2SO_4 .





Scheme 2. a) 1. Hexamethyldisilazane, ammonium sulfate, heating; 2. Dry CH_2Cl_2 , **3**, TMS triflate; b) HMDS, ammonium sulfate, heating; 2. Dry CH_2Cl_2 , **4**, TMS triflate.

in the presence of a catalytic amount of ammonium sulphate; the silylated base was reacted with the sugar **3** in dry dichloromethane in the presence of HMDS. After usual work-up the desired nucleoside **6** was obtained in 23% yield.

The reaction of the 1-O-acetyl sugar **4** with 2,6-dichloropurine was performed in a very similar manner, giving 78% of the β -nucleoside **6** after chromatographic purification.

Analytical data were consistent with the structure of compound **6** proposed in Scheme 2; in particular, the β -anomeric configuration was supported by ^1H NMR data and n.O.e. experiments. In fact, the H-1' proton signal appears as a doublet ($J = 5.9$ Hz) at 6.43 ppm, doublet typical of β configuration; furthermore, saturation of H-1' signal gave an n.O.e. effect of 4% on H-4', clearly establishing the β configuration. In the same n.O.e. experiment the enhancement of the H-8 signal upon saturation of the H-1' one resulted to be 14.4%; this very high value is possible only when the two protons are very close, i.e. when the sugar and the heterocyclic moiety are in the *endo* configuration; this configuration would not be possible in the case of the N-7 isomer, since the 6-chloro substituent would push the nucleoside toward the *exo* configuration. Thus, these n.O.e. data also account for N-9 substitution.

ACKNOWLEDGMENTS

Financial support by the Italian Ministry of Research (Grant n° 9905155535, 1999) and by the University of Camerino (Fondo di Ricerca d'Ateneo 1999) is gratefully acknowledged.

REFERENCES

1. Poulsen, S.A.; Quinn, R.J. *Bioorg. Med. Chem.*, **1998**, *48*, 619–641.
2. Cristalli, G.; Camaioni, E.; Costanzi, S.; Vittori, S.; Volpini, R.; Klotz, K.-N. *Drug Dev. Res.*, **1998**, *45*, 176–181.
3. Vittori, S.; Lorenzen, A.; Stannek, C.; Costanzi, S.; Volpini, R.; IJzermann, A.P.; von Frijtag Drabbe Kunzel, J.K.; Cristalli, G. *J. Med. Chem.*, **2000**, *43*, 250–260.



4. Cristalli, G.; Volpini, R.; Vittori, S.; Camaioni, E.; Monopoli, A.; Dionisotti, S.; Conti, A.; Zocchi, C.; Ongini, E.; *J. Med. Chem.*, **1994**, *37*, 1720–1726.
5. Cristalli, G.; Camaioni, E.; Vittori, S.; Volpini, R.; Conti, A.; Dionisotti, S.; Ongini, E.; Monopoli, A. *J. Med. Chem.*, **1995**, *38*, 1462–1472.
6. Camaioni, E.; Di Francesco, E.; Vittori, S.; Volpini, R.; Cristalli, G. *Bioorg. Med. Chem.*, **1997**, *5*, 2267–2275.
7. Volpini, R.; Camaioni, E.; Di Francesco, E.; Vittori, S.; Fein, T.; Schwabe, U.; Cristalli, G. *Collect. Czech. Chem. Commun.*, **1996**, *61*, 33–36.
8. Volpini, R.; Camaioni, E.; Vittori, S.; Barboni, L.; Lambertucci, C.; Cristalli, G. *Helv. Chim. Acta*, **1998**, *81*, 145–152.
9. De Voss, J.J.; Hangeland, J.J.; Townsend, C.A. *J. Org. Chem.*, **1994**, *59*, 2715–2723.



Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the [U.S. Copyright Office](#) for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on [Fair Use in the Classroom](#).

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our [Website User Agreement](#) for more details.

[Order now!](#)

Reprints of this article can also be ordered at

<http://www.dekker.com/servlet/product/DOI/101081NCN100002427>