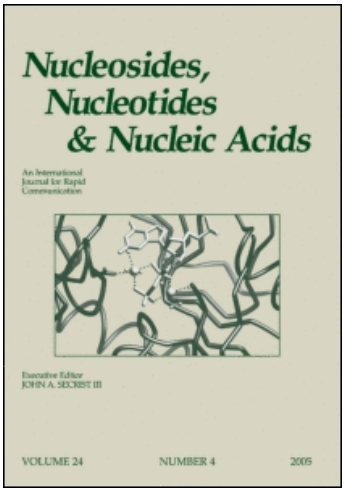

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COUPLING OF 2,6-DISUBSTITUTED PURINES TO RIBOSE-MODIFIED SUGARS

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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. ^{1}H 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

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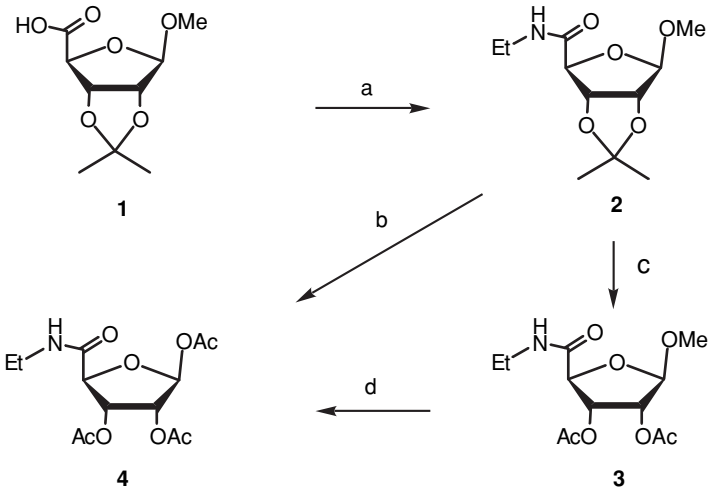
deoxyribose derivatives gave much higher yield in nucleosides than the corresponding 1-O-methyl sugars (7,8). On these bases we decided to prepare 1,2,3-tri-O-acetyl-N-ethyl-D-ribofuranuronamide, to be coupled with 2,6-dichloropurine to obtain the useful intermediate 2,3-di-O-acetyl-1-deoxy-1-(2,6-dichloro-9H-purin-9-yl) 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-isopropyliden)-β-D-ribofuranuronic acid (**1**) (9) was reacted first with tionyl chloride in dry DMF, followed by treatement 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; treatement 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 ^{1}H 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.

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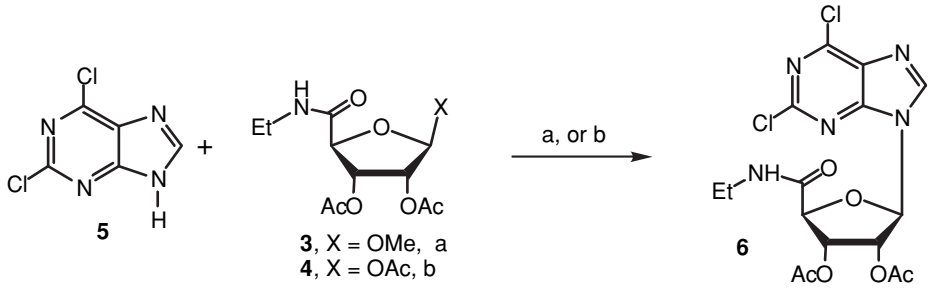

Scheme 2. a) 1. Hexamethyldisilazane, ammonium sulfate, heating; 2. Dry CH_2Cl_2, **3**, TMS triflate; b) HMDS, ammonium sulfate, heating; 2. Dry CH_2Cl_2, **4**, TMS triflate.

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 ^{1}H 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.

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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.

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