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Tetrahedron Letters 45 (2004) 2965–2966
Tetrahedron Letters

Simple entry into isonucleosides: synthesis of 6-amino-9-[(3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl]purine

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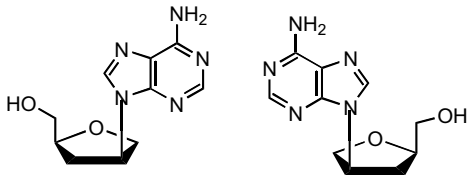
Received 16 November 2003; revised 30 January 2004; accepted 5 February 2004

Abstract—A simple and efficient method for the preparation of isonucleoside **7** is described. The preparation of 1,4-anhydroxylitol **4**, a key intermediate, is described by intramolecular cyclization of (2*S*,3*R*,4*R*)-3,5-dibenzyloxypentan-1,2,4-triol **3** using diethyl carbonate and NaH.

A number of nucleoside analogues have been found to possess antiviral and anticancer activities.[1] Modification of the sugar part of nucleosides has led to the development of several nucleoside analogues including dideoxynucleosides[2] [AZT (3-azidothymidine), ddC (dideoxycytidine), ddI (dideoxyinosine), carbocyclic nucleosides[3] (Carbovir), acyclic nucleosides[4] (Acyclovir and Ganciclovir). The natural nucleosides and nucleotides as well as many synthetic nucleosides, which are of therapeutic use are quite susceptible to both hydrolytic and enzymatic cleavage where nucleobases are attached to C-1 of the sugar moiety. In the search for modified nucleosides, which can resist hydrolysis and enzymatic degradation, there is considerable interest in the investigation of isonucleosides in which the nucleobase is linked to a position on the sugar moiety other than C-1.[5] Isonucleosides, which have proved to have therapeutic value against a broad spectrum of viruses and some tumor cell lines include both stereomers of, for example, (*S*,*S*)-iso-ddA[6] and its enantiomer (*R*,*R*)-iso-ddA[7] (Fig. 1).



(*S*,*S*)-iso-ddA (*R*,*R*)-iso-ddA

Figure 1.

The 1,4-anhydroalditol moieties in isonucleosides are usually prepared from carbohydrates through multi-step reactions. The most common strategy has been reduction of methyl glycofuranosides or 1,2-*O*-isopropylidene glycofuranoses by reaction with triethylsilane/Lewis acid[8] to obtain the anhydro derivatives.[9] The tetrahydrofurans have also been synthesized through protocols involving ring opening–ring closing of sugar precursors or through asymmetric synthesis from prochiral starting materials.[10] Bis-epoxides[11] and glycidol,[12] obtained by asymmetric synthesis, have been used for the synthesis of isonucleosides using iodo etherification as a key step. Butane-1,2,4-triol was used to synthesize 1,4-anhydroalditol stereoselectively using desilylation with NH_4F and concomitant cyclization.[13] The nucleobase can also be directly introduced by nucleophilic substitution of a sulfonate with nucleobase salts.[14] 1,4-Anhydro-3,5-di-*O*-benzyl-D-ribitol was prepared by cyclization of (2*S*,3*S*,4*R*)-3,5-dibenzyloxypentan-1,2,4-triol by a Mitsunobu reaction (DEAD/TPP) in THF.[9]

In continuation of our investigations toward the synthesis of modified nucleosides,[15] we report here a simple and efficient method for the synthesis of 6-amino-9-[(3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl]purine **7** (Scheme 1). The key intermediate,

Keywords: Isonucleosides; Alditol; Nucleobase.
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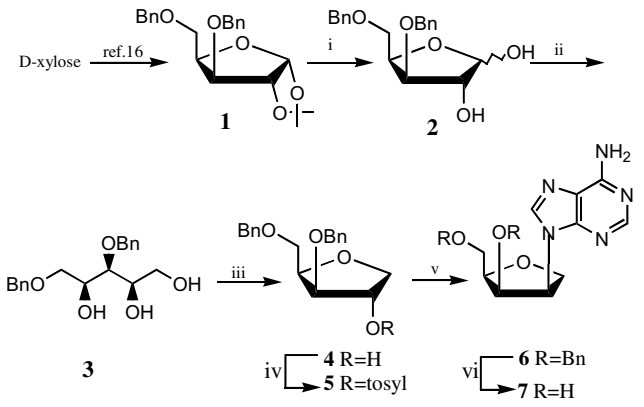
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.02.021



Scheme 1. Reagents and conditions: (i) IR-120 (H^+) resin, H_2O, 90 °C, 5 h, 95%; (ii) $NaBH_4$, MeOH, rt, 4 h, 88%; (iii) $EtOCO_2Et$ (2 mol equiv), THF, NaH, reflux, 3 h, 83%; (iv) tosyl chloride, pyridine, CH_2Cl_2, rt, 4 h, 98%; (v) adenine (2 mol equiv), 18-crown-6 (1.2 mol equiv), DMF, 100 °C, 16 h, 58%; (vi) 10% Pd/C, H_2, rt, 12 h, MeOH, 93%.

1,4-anhydro-3,5-di-*O*-benzyl-D-xylitol was elegantly prepared from 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose **1**.[16] Compound **1**, on reaction with IR-120 (H^+) resin in water at 90 °C for 5 h resulted in the formation of 3,5-di-*O*-benzyl-D-xylofuranose **2**. Reduction of **2** with $NaBH_4$/MeOH gave (2*S*,3*R*,4*R*)-3,5-di-*O*-benzyloxypentan-1,2,4,-triol **3**. Stereoselective cyclization of triol **3** using diethyl carbonate and NaH in THF at reflux for 3 h resulted in the formation of 1,4-anhydro-3,5-di-*O*-benzyl-D-xylitol **4** as a syrup in 83% yield.[17] Compound **4** was characterized by its ^1H NMR spectrum from the appearance of H-2 at δ 3.80 (dd, $J = 11.0$, 3.7 Hz), H-2′ at δ 4.08 (dd, $J = 11.0$, 3.1 Hz), and H-3 at δ 4.12 as a multiplet.

Compound **4** on tosylation gave the corresponding derivative **5** in quantitative yield, which was characterized by ^1H NMR analysis from the appearance of H-2 and H-2′ at δ 3.80 and δ 4.14, respectively, as multiplets and H-3 at δ 5.00 as a multiplet shifted downfield. Reaction of derivative **5** with adenine in the presence of K_2CO_3/18-crown-6 in DMF at 100 °C for 16 h resulted in the formation of 6-amino-9-[(3*S*,4*S*,5*R*)-4-benzyloxy-5-(benzyloxymethyl)tetrahydrofuran-3-yl]purine **6** in 58% yield as a solid, mp 162–164 °C. Compound **6** was characterized by ^1H NMR analysis from the appearance of H-2′ at δ 4.20 (dd, $J = 11.4$, 3.5 Hz), H-2″ at δ 4.45 (dd, $J = 11.4$, 3.2 Hz), and H-3′ at δ 5.25 as a multiplet and by its ^{13}C NMR spectrum from the appearance of C-2′ at δ 68.4 and C-3′ at δ 82.4. Reductive debenzylation (10% Pd/C/H_2/MeOH/rt) of **6** for 12 h resulted in the formation of 6-amino-9-[(3*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl]purine **7** as a solid, mp 260 °C (dec).

In summary, a simple method for obtaining 1,4-anhydroxylitol **4**, a key intermediate required for the synthesis of isonucleoside **7** from the corresponding triol **3** by intramolecular cyclization using diethyl carbonate/NaH/THF is described.

Acknowledgements

S.K.M. is thankful to the Council of Scientific and Industrial Research (CSIR, New Delhi) for financial support in the form of a senior research fellowship.

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