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Stereospecific Synthesis of Chiral Acyclic Analogues of Guanosine

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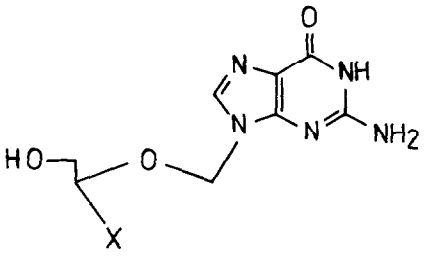
Abstract: The 3',4'-seco nucleoside **5** as well as its derivatives lacking C(3') **7** or 2'-deoxygenated **13**, all of them retaining the carbon framework and chirality of guanosine, have been synthesized by ring opening of suitably protected 9-α-L-arabinopyranosylguanines.

Acyclic nucleoside analogues have been extensively investigated in the search for therapeutically useful agents,[1,2] and among them 9-[2-(hydroxyethoxy)methyl]guanine (Acyclovir)[3] and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG)[4] (Figure 1) have been marketed for use against herpes simplex virus type 1 and human cytomegalovirus infections, respectively.

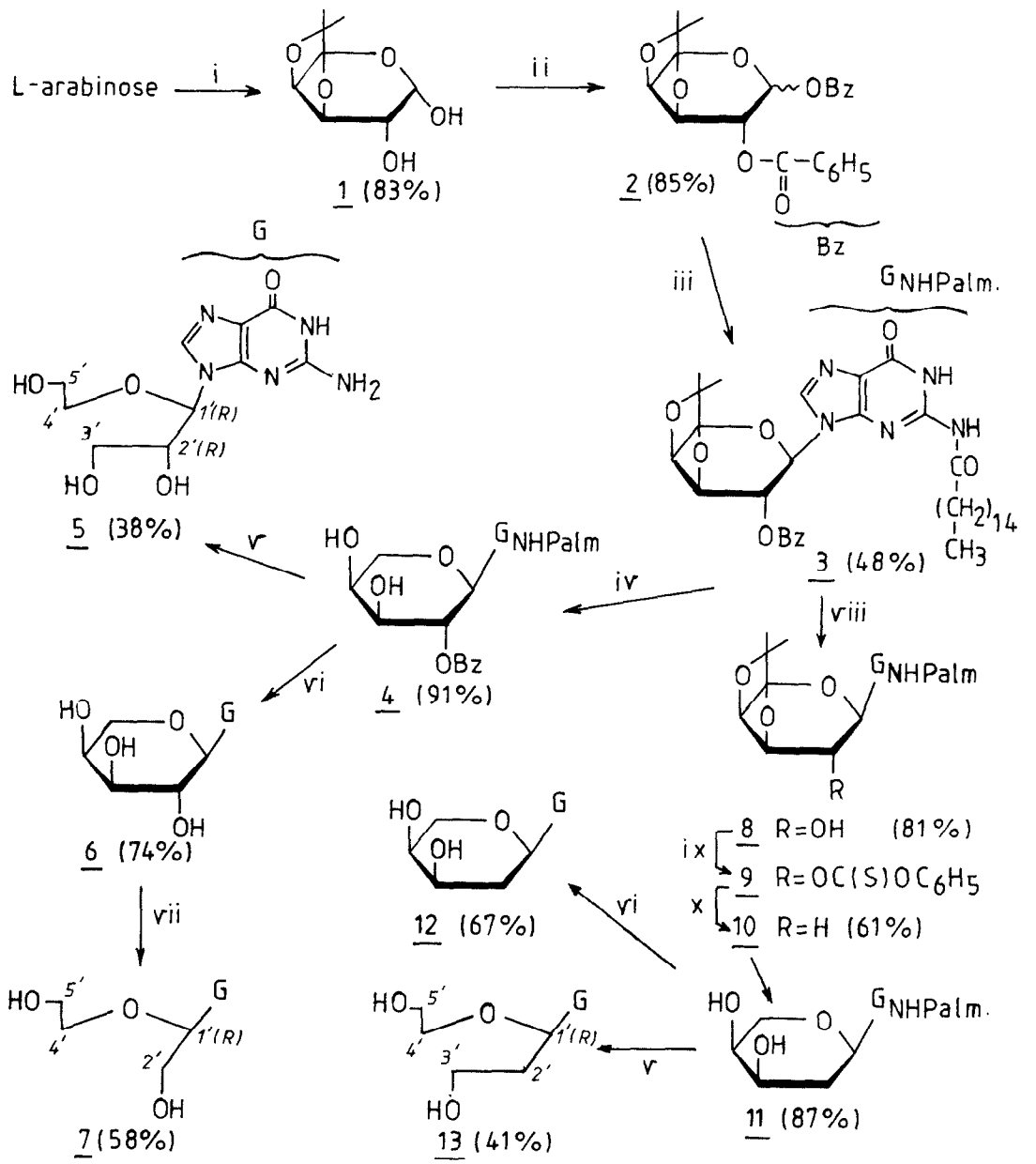
Despite the potential for chemotherapeutic activity by the acyclic nucleosides in the guanine series, to date little attention has been given to 3',4'-seco derivatives retaining the carbon framework and chirality at their asymmetrical carbon atoms of the natural β-D-ribofuranosyl moiety. Thus, prior to starting this work, only diastereoisomeric or racemic mixtures of 9-[1-(2-hydroxyethoxy)-(2,3-dihydroxy)propyl]guanine,[5] 9-[1-(2-hydroxyethoxy)-2-hydroxyethyl]guanine[6] and 9-[1-(2-hydroxyethoxy)-(3-hydroxy)propyl]guanine[7,8] had been described. The recently mentioned synthesis of the 1'(R)[9] enantiomer of the last compound[10] prompted us to report our results on the stereospecific synthesis and antiviral evaluation of open-ring guanosine derivatives lacking the C(3')-C(4') bond or the C(3') atom.



Acyclovir (X = H)
DHPG (X = CH_2OH)

- Figure 1 -

The most appropriate synthetic plan to reach the chiral acyclic analogues **5**, **7**, **13** (Scheme 1) appeared to first prepare suitable pyranonucleosides and to open them by periodate oxidation followed by reduction of the resulting dialdehydes with sodium borohydride.[11] As intermediary nucleosides, we chose α-L-arabinopyranosylguanines as these compounds: i) possess the requisite R configuration at their 1' (and 2') carbon; ii) are not well-documented, and the biological evaluation of the hitherto unknown **6** and **12** seemed us also of interest.



- Scheme 1 - *Reaction conditions* : i) $(CH_3O)_2C(CH_3)_2$, $CH_3C_6H_4SO_3H$/DMF; ii) C_6H_5COCl/C_5H_5N; iii) 2-N-palmitoylguanine, BSA, TMSF/CH_3CN; iv) CH_3COOH-H_2O; v) $NaIO_4$, then $NaBH_4$/dioxane-H_2O, then NH_3/CH_3OH; vi) NH_3/CH_3OH; vii) $NaIO_4$, then $NaBH_4$/dioxane-H_2O; viii) $NaOH/C_5H_5N$-C_2H_5OH; ix) DMAP, C_6H_5OCSCl/CH_3CN; x) Bu_3SnH, AIBN/toluene.

Thus, inexpensive commercial L-arabinose was first conveniently converted on a large scale into its 3,4-O-isopropylidene derivative **1**[12] according to an effective procedure published for the D-enantiomer.[13] Benzoylation of **1** gave the hitherto unknown starting sugar **2**[14] which on reaction with 2-N-palmitoylguanine[15] following the procedure of Wright and Dudycz[16] afforded a separable mixture of the expected α-L-9-N **3**[14] and undesirable α-L-7-N isomers. Removal of the O-isopropylidene protecting group from **3** with aqueous acetic acid afforded the key intermediate **4**.[14] On the one hand scission of the 3',4'-bond of **4** by periodate oxidation,[17] followed first by sodium borohydride reduction of the formed dialdehyde and then by deacylation with ammonia in methanol, resulted in the formation of the desired 9-[1(R)-(2-hydroxyethoxy)-(2(R), 3-dihydroxy)propyl]guanine **5**.[14,18] On the other hand, deacylation of **4** in methanol ammonia yielded 9-α-L-arabinopyranosylguanine **6**.[14,18] When **6** was treated with two equivalents of sodium metaperiodate and then with sodium borohydride, successive scissions of the 3',4' and 2',3' bonds resulted in the formation of the expected 9-[1(R)-(2-hydroxyethoxy)-2-hydroxyethyl]guanine **7**.[14,18]

Finally, selective 2'-O-debenzoylation of the protected nucleoside **3** by aqueous sodium hydroxide in a pyridine-ethanol mixture gave the 3',4'-O-isopropylidene derivative **8**[14] which on reaction with phenyl chlorothionocarbonate and 4-(dimethylamino)pyridine in acetonitrile afforded the corresponding 2'-O-(phenoxythiocarbonyl) derivative **9**.[19] This latter was directly treated with tributyltin hydride and the free-radical initiator α,α'-azobisisobutyronitrile in toluene to give the protected 2'-deoxygenated product **10**.[14] 9-(2-Deoxy-α-L-*erythro*-pentopyranosyl)guanine **12**[14,18] was obtained by deisopropylidenation in acidic condition of **10**, followed by N-deacylation with methanolic ammonia of the intermediate **11**. Scission of the 3',4' bond by periodate oxidation followed by sodium borohydride reduction and methanolic ammonia deacylation resulted in the formation of the desired 9-[1(R)-(2-hydroxyethoxy)-(3-hydroxy)propyl]guanine **13**.[10,14,18]

Compounds **5-7**, **12**, **13** were tested for their *in vitro* inhibitory effects on the replication of a number of DNA and RNA viruses in several cell systems and in two anti-HIV assays. None of them showed a marked antiviral effect at the highest concentration tested (1mM). Furthermore, except for compounds **12** and **13** which were significantly cytotoxic against MT-4 cells ($10^2 > CD_{50} > 10$ and $10 > CD_{50} > 1$ μM, respectively), none of them showed a detectable alteration of host cell morphology at 1 mM.

Further data and studies on the use of sugar **2** in the synthesis of other α-L-arabinopyranosyl and subsequently acyclic nucleosides will be reported in a full paper.

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