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SYNTHESES OF ALL FOUR POSSIBLE DIASTEREOMERS OF THE ACYCLONUCLEOSIDE 9-(1,3,4-TRIHYDROXY-2-BUTOXYMETHYL)GUANINE FROM CARBOHYDRATE PRECURSORS

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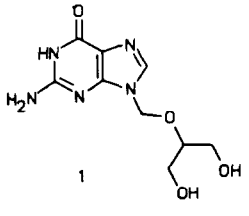
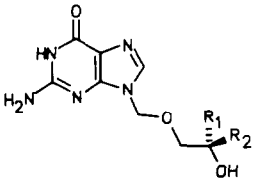
Abstract: The syntheses of all four possible diastereomers of 9-(1,3,4-trihydroxy-2-butoxymethyl)guanine, starting from D- and L-xylose and from D- and L-arabinose derivatives are described.

Recent work from this laboratory and others has described the potent antiherpetic activity of 9-(1,3-dihydroxy-2-propoxymethyl)guanine (1)[1-4] and of its linear isomer (S)-9-(2,3-dihydroxy-1-propoxymethyl)guanine (**2a**)[5]. In contrast, (R)-9-(2,3-dihydroxy-1-propoxymethyl)guanine (**2b**) was shown to have relatively poor antiviral activity[5a]. It was therefore of interest to prepare **3-6**, which possess the acyclo side-chains of both **1** and **2**, to investigate the precise stereochemical requirements for enzyme specificity and antiviral activity. The structure of 9-(1,3,4-trihydroxy-2-butoxymethyl)guanine has previously been described[4], but no stereochemistry or experimental details were given[6]. It should also be noted that **3-6** can also be regarded as guanine nucleoside analogs lacking the C1'-C2' bond.

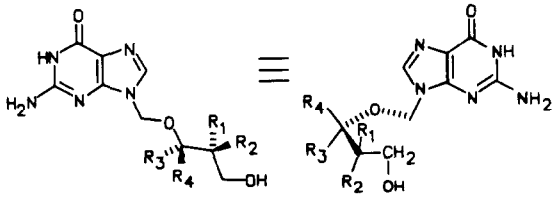


1



2a R_1 = H, R_2 = OH

2b R_1 = OH, R_2 = H



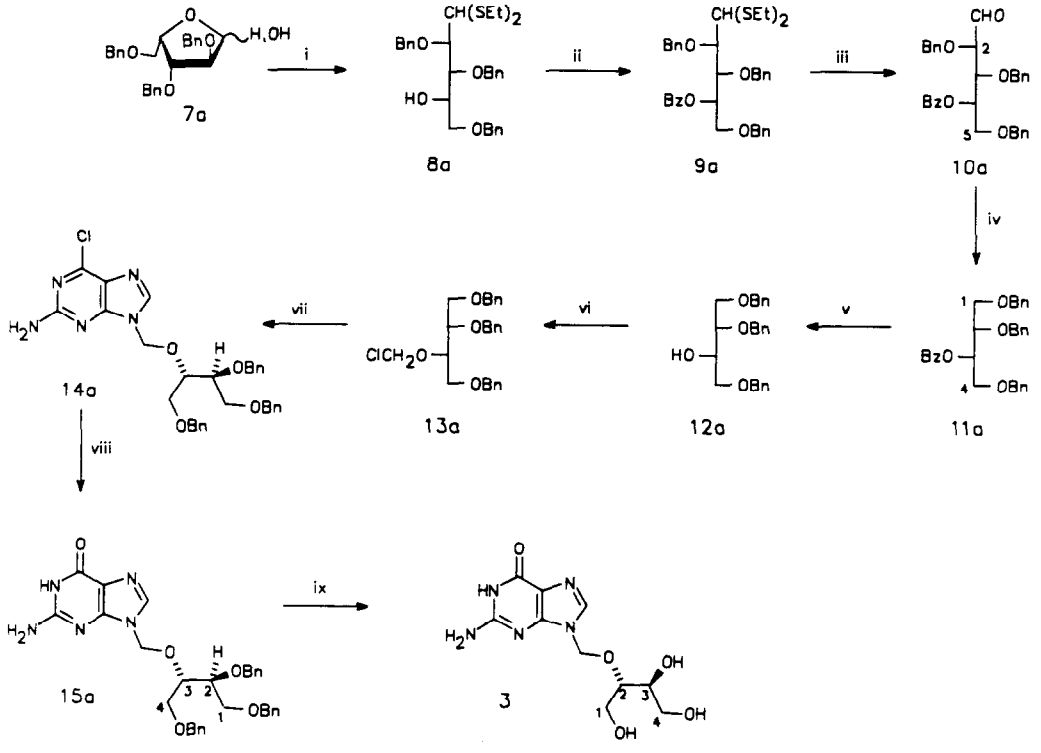
3 R_1 = H, R_2 = OH, R_3 = CH_2OH, R_4 = H

4 R_1 = OH, R_2 = H, R_3 = H, R_4 = CH_2OH

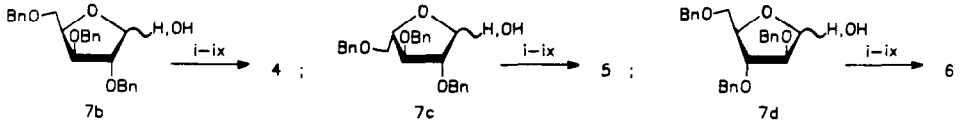
5 R_1 = OH, R_2 = H, R_3 = CH_2OH, R_4 = H

6 R_1 = H, R_2 = OH, R_3 = H, R_4 = CH_2OH

SCHEME 1



[Note the numbering system used in the side-chain]



Bn = benzyl ; Bz = benzoyl

(i) EtSH, HCl, $MgSO_4$, 0° for 1 hr.
(ii) BzCl, pyridine, r.t. overnight
(iii) $HgCl_2$, $CdCO_3$, acetone–H_2O, r.t. overnight
(iv) $(Ph_3P)_3RhCl$, CH_3CN, reflux 2 hr.
(v) NaOMe, MeOH, reflux 20 min.
(vi) CH_2O, HCl(g), CH_2Cl_2, 0°
(vii) per-Me_3Si-2-amino-6-chloropurine, $Hg(CN)_2$, PhH reflux
(viii) 20% aq. Et_4NOH, glyme, 25% aq. Me_3N, r.t. 3 hr.
(ix) cyclohexene, EtOH, 20% $Pd(OH)_2/C$, reflux overnight

The synthetic sequence to prepare **3** is shown in Scheme 1 starting from the readily available 2,3,5-tri-*O*-benzyl-L-xylose (**7a**). Isomers **4**, **5** and **6** were prepared in an identical fashion starting from 2,3,5-tri-*O*-benzyl-D-xylose (**7b**), 2,3,5-tri-*O*-benzyl-L-arabinose (**7c**), and 2,3,5-tri-*O*-benzyl-D-arabinose (**7d**), respectively[8].

The straight-chain form of the sugar was readily obtained as the di(ethythio)acetal (**8a-d**) using standard procedures[10] and the 4-position was immediately benzoylated[10] to give **9a-d**[11] in 70-80% yield overall from **7a-d**. The free aldehydes **10a-d**[11](obtained as oils in essentially quantitative yield) were generated by treatment with $HgCl_2$ and $CdCO_3$[12] and these were immediately decarbonylated with $[(C_6H_5)_3P]_3RhCl$ (Wilkinson's catalyst) in CH_3CN solvent at reflux[13] to give the protected butane tetrols **11a-d**[11] in 40-60% yield. Removal of the benzoyl group with NaOMe gave the desired side-chain precursors **12a-d**[11] in 65%-95% yield, and chloromethylation of **12a-d** was carried out with CH_2O and HCl gas at 0^0C in CH_2Cl_2 using conditions described elsewhere for related compounds[3,5]. This gave the 1,2,4-tribenzyloxybut-3-yl chloromethyl ethers **13a-d**[11] which were used without purification to alkylate pertrimethylsilylated 2-amino-6-chloropurine using $Hg(CN)_2$ as catalyst[14]. The 9-alkylated products **14a-d**[11] were obtained in 20-46% yield after silica gel chromatography. Conversion of **14a-d** to the blocked guanine acyclonucleosides **15a-d** was accomplished in high yield (60-84%) by a facile double displacement at C-6, using a mixture of NMe_3 and $Et_4N^+OH^-$ in aqueous glyme[15]. The blocked products **15a-d** were crystallized and fully characterized[16] by elemental analysis, NMR and UV spectroscopy. Measurement of the optical rotations[16] indicated that the stereochemical integrity of the side-chain had been maintained throughout the synthetic sequence. Final deprotection was carried out by transfer hydrogenation over Pearlman's catalyst[14a] to give **3-6**[11] in 68-85% yields after final purification by crystallization from water or by HPLC (Partisil M9 10/50 ODS-3 using H_2O as eluant).

The biochemical and biological evaluation of these derivatives will be described elsewhere.

References and Notes

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6. For use as an intermediate in the preparation of **1**, the unresolved diastereomeric mixture of 2,6-diamino-9-(1,3,4-trihydroxy-2-butoxymethyl)purines has also been previously described, but a different synthetic sequence was used[7].

7. U. K. Patent Application 2,104,070A assigned to the Wellcome Foundation (1982).

8. Each of the starting materials **7a** and **7b** was synthesized in a fashion identical to that described for **7c**[9].

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11. In all cases, the 200MHz spectra of purified **9-15** and of **3-6** were consistent with their proposed structures. It should be noted that the spectra of compounds in the **a**-series were identical to those in the b-series (enantiomers), and similarly those in the **c**-series were identical to those in the d-series.

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16. *^{1}H-NMR (200MHz, CDCl3) ppm from TMS*: **15a,b**: 7.61(s,H8), 7.41-7.14(m, aromatics), 5.87(br s, NH_2),5.61-5.46(AB_q, NCH_2O, J_{gem}=10.8Hz), 4.70-4.49(ABq, CH_2Ph, J_{gem}=12Hz), 4.49-4.37(AB_q, CH_2Ph, J_{gem}=12Hz), 4.37(s, CH_2Ph), 4.07(d of d of d, H3', $J_{3'-2'}$=4.4Hz, $J_{3'-4'}$=6.2Hz, $J_{3'4''}$=4.4Hz), 3.69(d of t, H2', $J_{2'-1'}$=$J_{2'-1''}$=5.2Hz, $J_{2'-3'}$=4.4Hz), 3.61-3.42(m's, H4',H4'', H1',H1''). **15c,d**: 7.58(s, H8), 7.38-7.20(m, aromatics), 6.00(br s, NH_2), 4.66-4.47(AB_q, CH_2Ph, J_{gem}=12Hz), 4.51-4.47(AB_q, CH_2Ph, J_{gem}=12Hz), 4.46(s, CH_2Ph), 4.06(m, H3'), 3.74-3.48(m, H2',H4',H4'',H1',H1'').

UV(MeOH): **15a**,λ_{max}255(13,980), sh 270(9,890),λ_{min}227(4,100); **15b**, λ_{max}255(14,420), sh 270(9,100), λ_{min}225(3,420); **15c**, λ_{max}255(14,520), sh 270(10,300), λ_{min}225(3,470); **15d**,λ_{max}255(14,520), sh 270(10,300),λ_{min}225(3,470).

Anal.(15a-d): Calc'd for $C_{31}H_{33}N_5O_5.0.25H_2O$: C 66,47, H 6.03, N 12.50; Found: (**15a**) C 66.16, H 5.60, N 12.38; (**15d**) C 66.60, H 6.09, N 12.39; Calc'd for $C_{31}H_{33}N_5O_5.0.5H_2O$: C 65.94, H 6.07, N 12.40; Found: (**15b**) C 66.02, H 6.03, N 12.22; (**15c**) C 66.24, H 5.93, N 12.39.

α*D's(MeOH)*: **15a**,+14.45; **15b**,-15.60; **15c**,+4.18; **15d**, -4.42.

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