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SYNTHESIS OF THE CHIRAL ACYCLONUCLEOSIDE ANTIHERPETIC AGENT (S)-9-(2,3-DIHYDROXY-1-PROPOXYMETHYL)GUANINE

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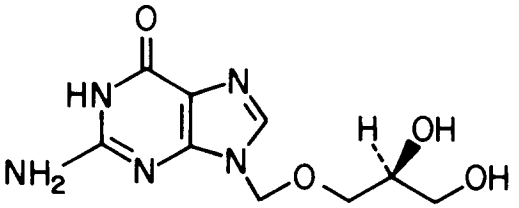
Abstract. A new synthesis of the potential antiviral agent, (S)-9-(2,3-dihydroxy-1-propoxymethyl)guanine is described, starting from the readily available methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside. The sequence utilizes the absolute configuration defined by carbons 4, 5 and 6 of the D-glucose ring and provides a ready synthesis of the single enantiomer without recourse to many chromatographic separations.

The antiherpetic activity of selected guanine acyclonucleosides has recently received much attention. In particular, 9-(2-hydroxyethoxymethyl)guanine, 9-(1,3-dihydroxy-2-propoxymethyl)guanine and R-9-(3,4-dihydroxybutyl)guanine have been shown to be promising candidates.[1] Recent work from this laboratory[2,3] has described the potent antiherpetic activity of another derivative, (S)-9-(2,3-dihydroxy-1-propoxymethyl)guanine (**1**). The initial preparations of **1** and its R enantiomer (**2**) utilized syntheses of 1,2-di-O-benzyl-L- and D-glycerol as chiral synthons which were prepared from D-mannitol in a multi-step reaction sequence.[2,3] The R enantiomer (**2**) was shown to possess relatively poor antiherpetic activity. Such a preference for a single enantiomer is usual in biological systems and of particular note for acyclonucleosides is the marked preference for a single isomer of the 9-(2-hydroxy-3-nonyl)adenines in the inhibition of adenosine deaminase[4] and the broad-spectrum antiviral activity of (S)-9-(2,3-dihydroxypropyl)adenine compared to the total lack of activity of the R enantiomer.[5]



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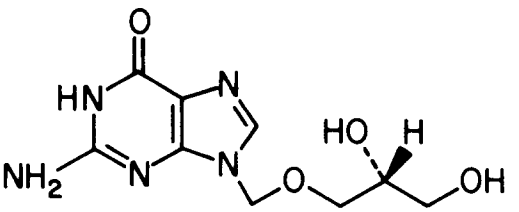

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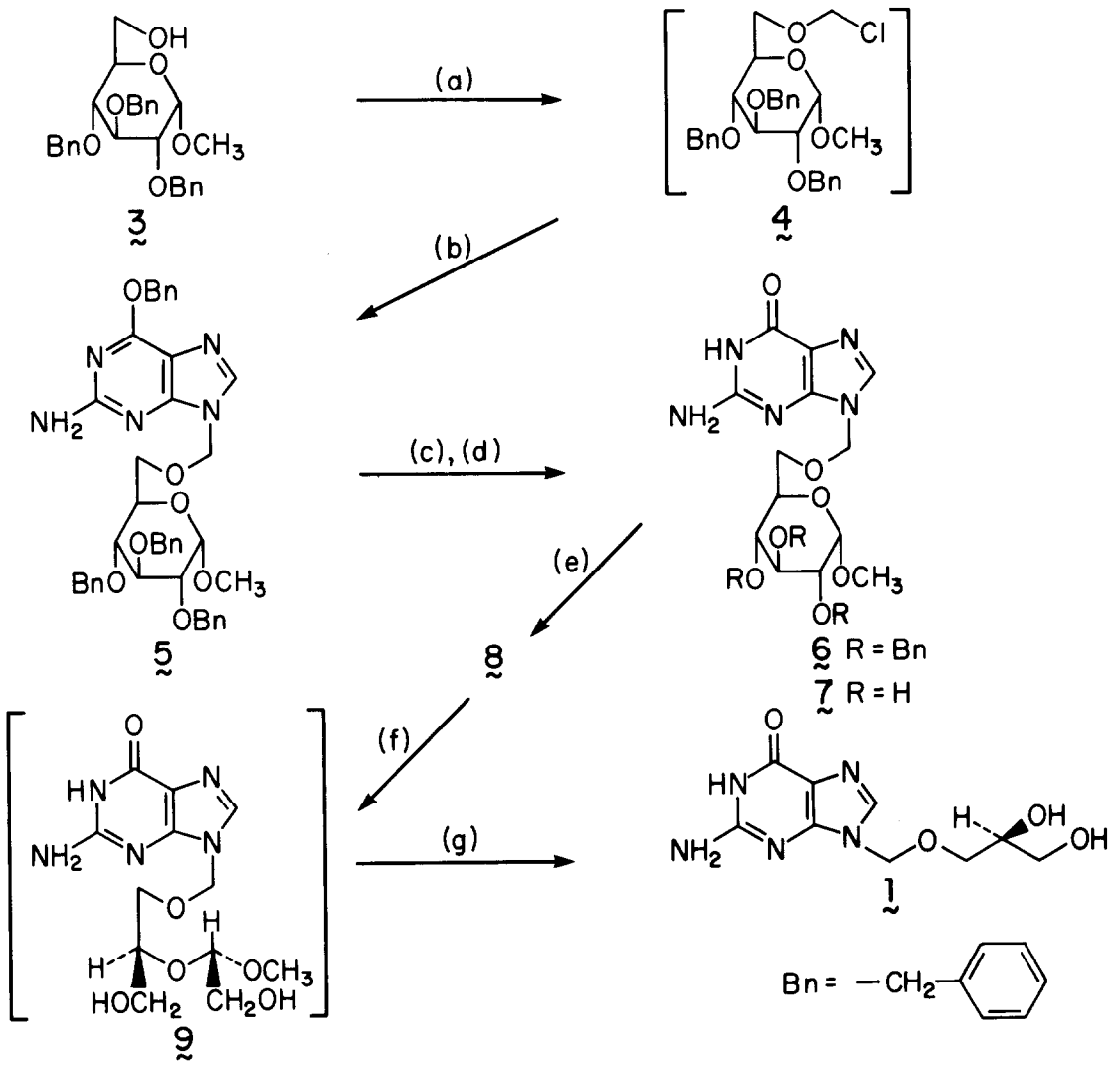
Because we anticipated a need for larger amounts of **1**, we set out to devise an alternative synthetic route which did not require several chromatographic purification steps.[6,7]



(a) CH_2O, HCl (g), CH_2Cl_2, 0°
(b) 2-amino-6-benzyloxypurine, NaH, DMF, r.t.
(c) 20% $Pd(OH)_2$ on carbon, H_2 (50 psi), EtOH
(d) 20% $Pd(OH)_2$ on carbon, H_2 (50 psi), TsOH, EtOH / H_2O
(e) $NaIO_4$ in H_2O
(f) $NaBH_4$
(g) HAc-HCl (20 : 3 v/v), 55-60°, 1 $\frac{1}{2}$ hr. or CF_3CO_2H—H_2O (1:9 v/v), r.t., overnight

The readily available methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside[8] (**3**) was chloromethylated at the 6-position using paraformaldehyde and HCl gas in CH_2Cl_2 as solvent under conditions similar to those described earlier for related compounds.[2,3,9-11] (**Caution**: Bis-chloromethyl ether, a potent carcinogen, is presumably formed as a by-product in this reaction and the procedure should be carried out in a well ventilated hood.) The product, methyl 2,3,4-tri-O-benzyl-6-O-chloromethyl-α-D-glucopyranoside,[12] **4**, was obtained in high yield. Purity was checked by NMR and the material was used without purification to alkylate 2-amino-6-benzyloxypurine.[13,15,16] The product, methyl 2,3,4-tri-O-benzyl-6-O-(2-amino-6-benzyloxypurin-9-ylmethyl)-α-D-glucopyranoside, **5**[17] was obtained in 43% yield after a straightforward silica gel column separation. Debenzylation was carried out by hydrogenation over 20% $Pd(OH)_2$ on carbon. In this deblocking step, the presence or absence of p-toluenesulfonic acid determined the nature of the product formed. Thus, when the acid was omitted, debenzylation of the heterocycle occurred leaving the blocking groups on the sugar moiety intact. In this way, the intermediate **6** could be readily isolated.[18] If 3 molar equivalents of p-toluenesulfonic acid were added to the hydrogenation, complete deblocking occurred to give methyl 6-O-(guanin-9-ylmethyl)-α-D-glucopyranoside[19] **7**, in an overall yield of 67% from **5**.

The methyl 6-O-(guanin-9-ylmethyl)-α-D-glycopyranoside, **7**, was dissolved in water and treated with sodium periodate (3 molar equivalents). After removal of excess periodate by precipitation with strontium chloride, the intermediate dialdehyde **8** was not isolated but was reduced immediately with sodium borohydride to give the presumed (2S,1'S)-2-O-(2'-hydroxy-1'-methoxyethyl)-1-O-(guanin-9-ylmethyl)glycerol **9**.[20,21] Acidic hydrolysis of **9** with HAc-HCl (20:3 v/v) at 55-60° for 1-1/2 hr or with CF_3CO_2H-H_2O (1:9 v/v) at room temperature overnight[22] gave the required **1** in 60% overall yield from **7**. The final product **1** was identical to authentic material[2,3] by TLC, HPLC, MP, NMR and UV, and the enantiomeric integrity of the synthesis was verified by the behavior of **1** in the staggered enzyme assay[23] which unequivocally differentiates **1** and **2**.[3]

Acknowledgment. We thank J. D. Karkas, J. Germershausen and R. Liou for enzymatic evaluations.

References and Notes

1) See J. L. Kelley and L. Beauchamp, Ann. Rep. Med. Chem. **18**, 139 (1983) for a recent review.

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6) While this manuscript was in preparation, a synthesis of the racemic 9-(2,3-dihydroxy-1-propoxymethyl)guanine was described[7] which utilized 1,2-di-O-acetyl-glycerol as the side-chain precursor. In our hands, acyl migration occurs under the acidic chloromethylation conditions and leads to a mixture of products.

7) T.-S. Lin and M.-C. Liu, Tetrahedron Lett. **25**, 905 (1984).

8) Readily prepared in two steps from the commercially available methyl α-D-glucopyranoside; see R. Eby and C. Schuerch, Carbohydrate Res. **34**, 79 (1974).

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10) J. C. Martin, C. A. Dvorak, D. F. Smee, T. R. Matthews and J. P. H. Verheyden, J. Med. Chem. **26**, 759 (1983).

11) European Patent Appl. No. 072,027, assigned to the Wellcome Foundation Ltd., February, 1983.

12) Characterized by 60 MHz NMR in $CDCl_3$: δ (from TMS) 7.28 (s, aromatics), 5.42 (s, OCH_2Cl), 5.02-4.42 (m's, $-CH_2\phi$'s and H1), 4.18-3.38 (m's, sugar protons), 3.35 (s, OCH_3).

13) Prepared by addition of 2-aminopurin-6-yltrimethylammonium chloride[14] in dry DMSO to sodium benzyl oxide (2 equiv.) and benzyl alcohol (3.6 equiv.) in DMSO. The reaction was carried out at room temperature, and after a single work-up, the final product was obtained in 92% yield. An analytical sample could be obtained by crystallization from EtOH-H_2O which had an mp and UV spectrum identical to that quoted for material prepared by a different route.[15,16] Calc. for $C_{12}H_{11}N_5O_1 \cdot 0.25\ H_2O$: C 58.65; H 4.72; N 28.50. Found: C 59.02; H 4.58; N 28.47. 200 MHz NMR (d_6-DMSO): δ (from TMS) 7.87 (s, H8); 7.62-7.36 (m's, aromatics), 6.32 (s, NH_2), 5.52 (s, $O-CH_2-O$).

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17) Calc. for $C_{41}H_{43}N_5O_7$: C 68.60, H 6.04, N 9.76. Found: C 68.65, H 5.98, N 9.76. 200 MHz NMR ($CDCl_3$): δ (from TMS) 7.90 (s, H8), 7.56-7.04 (m's, aromatics), 5.52 (s) and 5.45 (ABq) ($N-CH_2O$ and $O^6-CH_2-\phi$), 5.00-4.28 (m's, sugar $O-CH_2\phi$'s, H1', NH_2), 4.04-3.44 (m's, H2', H3', H4', H5', H6', H6", 3.34 (s, OCH_3); mp 107-110° (dec.).

18) 200 MHz NMR (d_6-DMSO): δ (from TMS) 7.85 (s, H8), 7.40-7.03 (m's, aromatics), 6.52 (s, NH_2), 5.40 (s, $N-CH_2-O$), 4.88-4.28 (m's, $O-CH_2-O$'s and H1'), 3.80-3.15 (m's, H2', H3', H4', H5', H6', H6", and HDO), 3.29 (s, OCH_3).

19) Calc. for $C_{13}H_{19}N_5O_7 \cdot 1.7\ H_2O$: C 40.24, H 5.81, N 18.05. Found: C 39.87, H 5.39, N 17.82. 200 MHz NMR (d_6-DMSO): δ (from TMS) 7.80 (s, H8), 6.66 (s, NH_2), 5.35 (ABq, $N-CH_2-O$), 5.13-4.62 (bm's, OH's), 4.49 (d, J = 3.4 Hz, H 1'), 3.74-2.92 (m's, H 2', H 3', H 4', H 5', H 6', H 6", and HDO), 3.24 (s, OCH_3); mp 210° (dec. softens at 169°).

20) See K. W. Buck, F. A. Fahim, A. B. Foster, A. R. Perry, M. H. Qadir and J. M. Webber, Carbohydrate Res. **2**, 14 (1966) for a related oxidation-reduction sequence.

21) It should be noted that this reaction sequence can be utilized to give ready access to radiolabeled material by the use of NaB^3H_4 in place of $NaBH_4$ in the preparation of **9**.

22) We thank Dr. A. Rosegay for this modification.

23) A. K. Field, M. E. Davies, C. DeWitt, H. C. Perry, R. Liou, J. Germershausen, J. D. Karkas, W. T. Ashton, D. B. R. Johnston and R. L. Tolman, Proc. Natl. Acad. Sci. USA **80**, 4139 (1983).

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