SYNTHESIS OF BIOLOGICALLY ACTIVE ACYCLOAZT DERIVATIVES AND RELATED COMPOUNDS

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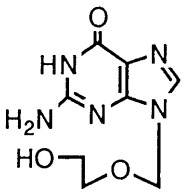
The synthesis of optically active acyclic analogues of 3'-azido-3'-deoxythymidine, which lack only the 2'-CH_2 of the sugar, is described. The synthesis of some nucleoside analogues that contain the N-acetyl-D-neuraminic acid moiety is also described.

KEYWORDS antiviral agent; acycloAZT; N-acetyl-D-neuraminic acid; sialosyl-acycloAZT

The discovery of acyclonucleosides with potent antiviral activities such as 9-(2-hydroxyethoxymethyl)guanine (1, acyclovir), 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (2, DHPG), etc[1] has recently made significant progress in the development of antiviral chemotherapy. Biological selectivity of these acyclonucleosides was found to result from monophosphorylation catalyzed selectively by virus enzymes.[2] Based on these findings, the modification of the sugar moiety of 3'-azido-3'-deoxythymidine (3, AZT) with an acyclic substituent was expected to develop compounds with high antiviral activity and low host cytotoxicity. Since the 4'-position of AZT belongs to the S configuration, we have designed to synthesize (S)-1-[[2-azido-1-(hydroxymethyl)ethoxy]methyl]thymine (4, acycloAZT).[3] Now we describe the synthesis of optically active acycloAZT derivatives from chiral starting materials. Furthermore, N-acetyl-D-neuraminic acid is widely distributed in membrane glycoproteins and glycolipids and plays an important role in animal cells. Therefore, we also prepared some nucleoside analogues that contain the N-acetyl-D-neuraminic acid (Neu5Ac) moiety for antiviral activities.



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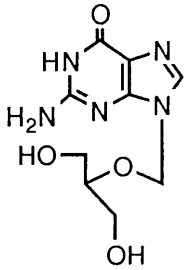

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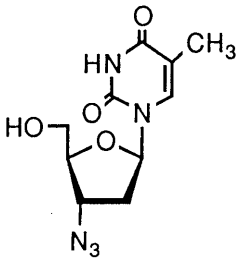

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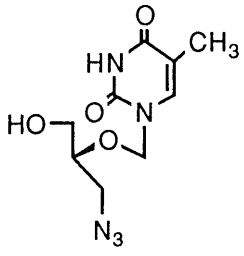

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The chiral glycerol derivative 5 was prepared by lipase-catalyzed asymmetric transesterification.[4] Treatment of 5 with p-toluenesulfonyl chloride in pyridine followed by hydrolysis with sodium hydroxide in ethanol gave 6 quantitatively (Chart 1). Hydrogenolysis of 6 over 5% Pd-C in ethanol gave 3-tosyloxy-1,2-propanediol (7) (mp 55℃, $[\alpha]^{21}_{D}$-8.4° (MeOH)) in 98% yield. After formylation of 7 with trioxane, the resulting 8 was acetylated with acetic anhydride and $ZnCl_2$ to give a mixture of the acetoxymethyl ethers 9a and 9b in 95% yield. The 9a was separated from 9b by silica gel column chromatography [benzene-EtOH(20:1)] and treated with bis(timethylsilyl)thymine (10) in the

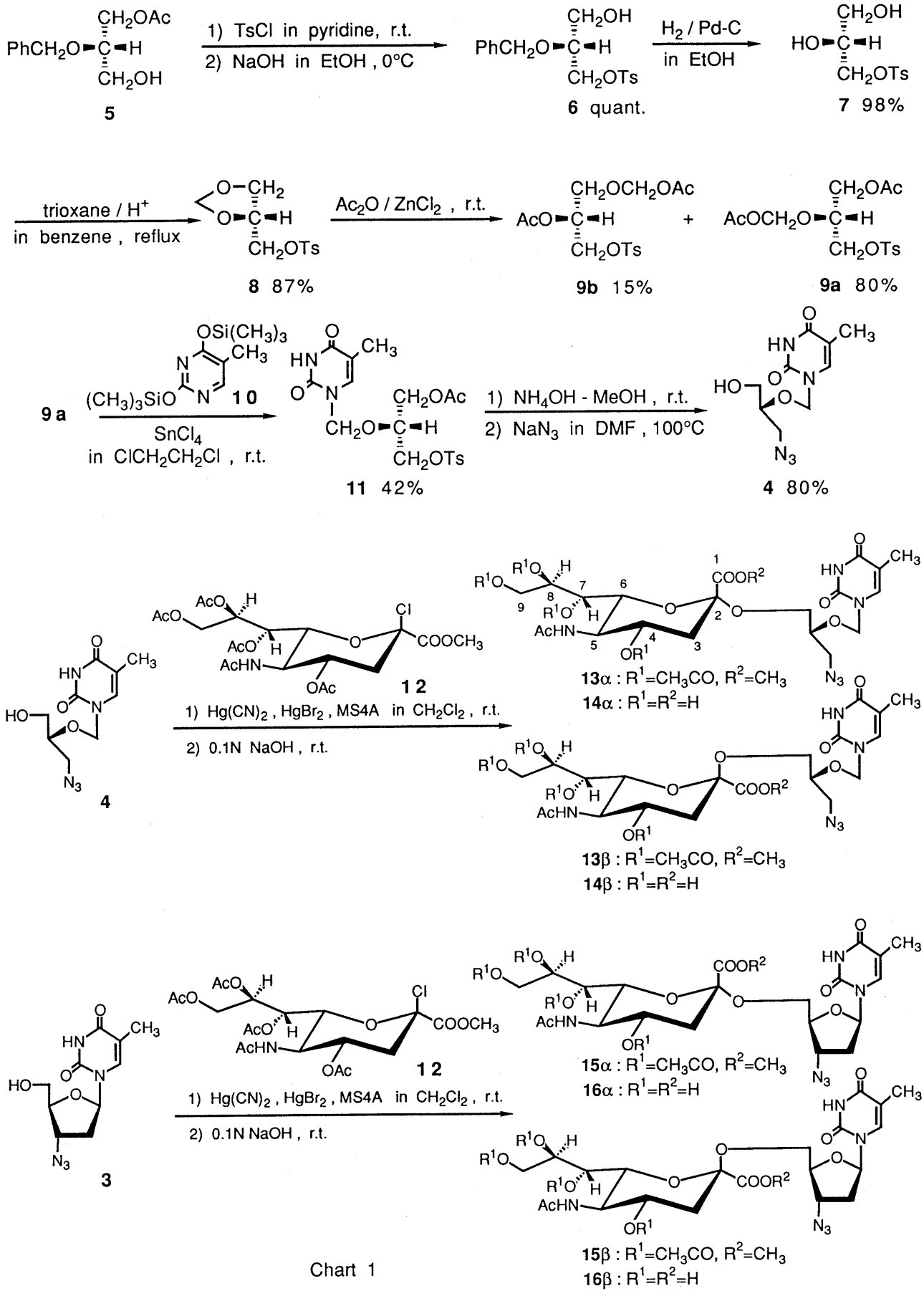

Chart 1

presence of Lewis acid in 1,2-dichloroethane to give the acyclic nucleoside 11 in 42% yield.[5] (S)-acycloAZT (4) was synthesized from 11 in 80% yield by deacetylating 11 with NH_4OH-MeOH then treating it with sodium azide in DMF.[6] Nucleoside analogues which contain Neu5Ac were prepared by Koenigs-Knorr coupling[7]: Treatment of acycloAZT with the chloride 12[7] in the presence of mercuric cyanide and mercuric bromide gave O-[methyl (5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-nonulopyranosyl)onate]-(2→2)-(S)-1-[[2-azido-1-(hydroxymethyl)ethoxy]methyl]thymine (13α) in 55% yield and its β-anomer 13β in 41% yield.[8] Deacetylation of the α-glycoside 13α and β-glycoside 13β with sodium hydroxide afforded the α- and β-anomers of N-acetyl-D-nueraminyl-(2→2)-(S)-1-[[2-azido-1-(hydroxymethyl)ethoxy]methyl]thymine (Neu5Ac-acycloAZT), 14α: mp 208℃, $[\alpha]^{21}_D$-19.4° (MeOH), 14β: mp 193℃, $[\alpha]^{21}_D$-22.2° (MeOH). We also synthesized N-acetyl-D-nueraminyl-AZT. Treatment of AZT with the chloride 12 gave O-[methyl (5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-nonulopyranosyl)onate]-(2→5')-3'-azido-3'-deoxythymidine (15α) in 60% yield and its β anomer 15β in 30% yield.[8] Deacetylation of α-glycoside 15α and β-glycoside 15β with sodium hydroxide afforded the α- and β-anomers of N-acetyl-D-nueraminyl-(2→5')-3'-azido-3'-deoxythymidine (Neu5Ac-AZT), 16α: mp 173℃, $[\alpha]^{21}_D$+24.5° (MeOH), 16β: mp 178℃, $[\alpha]^{21}_D$-7.8° (MeOH). Preliminary examination of the biological activities of 14α,β and 16α,β indicates that 14α has potent inhibitory activity against the influenza virus neuramidase.

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6) 4: ^{1}H-NMR ($CDCl_3$) δ: 1.92 (3H,s), 3.37 (2H,d,J = 5.4 Hz), 3.10-4.11 (4H,m), 5.56 (2H,s), 7.16 (1H,s), 8.02 (1H,s). IR (neat): 3300, 2100, 1720, 1660 cm^{-1}. $[\alpha]^{21}_D$+1.3° (EtOH).

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8) The stereochemistry of the products was confirmed by ^{1}H-NMR spectral comparison of the chemical shifts of the H-3e doublet of doublets [lower-field shift (δ 2.5-2.7) for the α-glycoside, higher-field shift (δ 2.3-2.5) for the β-glycoside] of various neuraminic acid derivatives.[7] 13α: 2.58 (1H,dd,J = 4.8 and 12.8 Hz), 13β: 2.46 (1H,dd,J = 4.8 and 13.9 Hz). 15α: 2.63 (1H,dd,J = 4.8 and 12.8 Hz), 15β: 2.49 (1H,dd,J = 4.8 and 13.2 Hz).

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