4 mL of MeOH and 4 mL of 3 N aqueous HCl was heated at reflux for 3 days. The solvent was removed in vacuo to give 80.6 mg of a green solid. The ^{1}H NMR spectrum (CD_3OD) indicated the presence of three compounds: the δ- and γ-lactones and the uncyclized methyl ester. Selective recrystallization from CH_3CN gave the pure γ-lactone: ^{1}H NMR (CD_3OD) δ 4.57 (d, J = 6, 7 Hz, 1 H, H_4), 4.27 (m, 1 H, H_3), 4.12 (q, J = 6.2 Hz, H_5), 3.06 (dd, J = 18, 8.9 Hz, 1 H, H_{2a}), 2.72 (dd, J = 18, 5.4 Hz, 1 H, H_{2b}), 1.37 (d, J = 6.4, 3 H, H_6); IR (crude mixture; CH_3CN) 3420–3200, 2900, 1790, 1720 cm^{-1}.

The mixture of hydrolysis products prepared as described above (50 mg) was benzoylated with benzoyl chloride (60 μL, 0.51 mmol) by using the procedure described for preparation of **25** to give, after preparative TLC (silica gel, ether), 26 mg (48%) of **36** and 8 mg (13%) of methyl *xylo*-3-(benzoylamino)-2,3,6-trideoxyhexonate (**36b**).

Data for **36a**: mp 161–164 °C; R_f 0.42 (ether); ^{1}H NMR ($CDCl_3$) δ 7.78 (m, 3 H), 7.48 (m, 3 H), 5.19 (m, 1 H, H_3), 4.57 (dd, J = 7.7, 1.3 Hz, 1 H, H_4), 4.12 (q, J = 7.1 Hz, H_5), 2.96 (dd, J = 9, 17.9, 1 H, H_{2a}), 2.71 (dd, J = 6.4, 18 Hz, 1 H, H_{2b}), 1.39 (d, J = 6.6 Hz, 3 H, H_6); IR ($CHCl_3$) 3600, 3500–3200, 2975, 1780, 1655, 1520, 1480, 1265, 910 cm^{-1}; mass spectrum, m/e 249 (parent ion); high resolution mass spectrum for $C_{13}H_{15}NO_4$, calcd 249.1001, found 249.0095.

Data for **36b**: R_f 0.24 (ether); ^{1}H NMR ($CDCl_3$) δ 7.78 (m, 2 H), 7.46 (m, 3 H), 7.04 (br d, J = 10 Hz, NH), 4.52 (m, 1 H, H_3), 4.05 (dd, J = 3, 5.6 Hz, 1 H, H_4), 3.71 (q, J = 6 Hz, H_5), 3.69 (s, 3 H, OCH_3), 2.80 (dd, J = 2, 7 Hz, 1 H, H_{2a}), 2.63 (d, J = 7 Hz, 1 H, H_{2b}), 1.74 (br s, 1 H, OH), 1.27 (d, J = 6 Hz, 3 H, H_6); IR ($CHCl_3$) 3600, 3450, 2980, 1760, 1730, 1650, 1585, 1565, 1500, 1475, 1260 cm^{-1}; mass spectrum, m/e 282 (M^+ + H); high resolution mass spectrum for $C_{14}H_{20}NO_5$, calcd 282.1341, found 282.1341.

Epoxidation of Azetidinone 29. The standard MCPBA epoxidation procedure was used with a change in the purification procedure. The *m*-chlorobenzoic acid was removed by filtration, and the crude product was then directly chromatographed (silica gel, 1:1 ether–hexane to ether) to give an inseparable 82:18 mixture of **41** and **42** (95% yield; ratio determined by ^{13}C NMR spectroscopy). When the $Mo(CO)_6$/TBHP procedure was employed, a 79:21 mixture of **41** and **42** was obtained in 89% yield. Data for **41** (obtained on mixture): ^{1}H NMR ($CDCl_3$) δ 6.12 (br s, 1 H, NH), 3.49 (m, 1 H, H_3), 3.15 (m, 2 H), 2.97 (dd, J = 4.4, 8.0 Hz, 1 H), 2.82 (ddd, J = 15.3, 2, 3 Hz, 1 H), 1.32 (d, J = 6 Hz, 3 H, H_6); ^{13}C NMR ($CDCl_3$) δ 167.08, 58.57, 52.46, 46.38, 40.79, 13.29. Data for **42**: ^{13}C NMR ($CDCl_3$) δ 167.85, 57.54, 52.75, 45.07, 42.74, 12.88. Data for mixture: IR ($CHCl_3$) 3425, 3005, 1770, 1340, 1200, 870 cm^{-1}. Anal. Calcd for $C_6H_9O_2N$: C, 56.69; H, 7.14; N, 11.02. Found: C, 56.40; H, 7.17; N, 10.81.

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Registry No. **1a**, 110079-69-1; **1b**, 110079-70-4; **1c**, 110079-71-5; **1d**, 110079-72-6; **2a**, 110096-40-7; **2b**, 110079-73-7; **2c**, 110079-74-8; **3a**, 110079-75-9; **3b**, 110079-77-1; **3c**, 110079-78-2; **3d**, 110079-79-3; **4a**, 110169-88-5; **4c**, 110169-89-6; **5a**, 110169-90-9; **5b**, 110169-91-0; **5c**, 110169-93-2; **6a**, 110169-94-3; **6b**, 110169-92-1; **6c**, 110170-06-4; **7**, 110079-66-8; **8**, 110079-68-0; **10**, 110079-63-5; **11**, 110079-65-7; **12**, 110079-67-9; **13b**, 110079-76-0; **14a** (acetate), 110079-80-6; **14b**, 110169-95-4; **15**, 110169-96-5; **16f** (α-anomer), 110079-88-4; **16f** (β-anomer), 110079-89-5; **16p** (α-anomer), 110170-02-0; **16p** (β-anomer), 110170-03-1; **19**, 89179-22-6; **20**, 110079-83-9; **21**, 110079-84-0; **22**, 110079-85-1; **23**, 110169-97-6; **24**, 110079-86-2; **24** (acetate), 110079-87-3; **25**, 110170-00-8; **26**, 110169-98-7; **26** (acetate), 110169-99-8; **29**, 110079-90-8; **30**, 110079-91-9; **31**, 110079-92-0; **32**, 110079-93-1; **33**, 110079-94-2; **34**, 75812-87-2; **35**, 110079-96-4; **36a**, 75812-90-7; **36b**, 110170-04-2; **41**, 110079-97-5; **42**, 110170-05-3; i, 110170-01-9; propyne, 74-99-7; phenylacetaldehyde, 122-78-1; 1-phenyl-2-phthalimidopent-3-yne, 110079-64-6; 1-(triphenylphosphoranylidene)-2-propanone, 1439-36-7; (*E*)-1-phenylpent-2-en-4-one, 42762-51-6; trichloroacetonitrile, 545-06-2; [4(*R**,*S**),5(*R**,*S**),6(*S**,*R**)]-2-phenyl-4-benzyl-5-hydroxy-6-methyl-5,6-dihydro-1,3-4*H*-oxazine, 110079-82-8; *lyxo*-3-amino-2,3,6-trideoxyhexano-γ-lactone hydrochloride, 110079-95-3.

5-Aza-7-deaza-2′-deoxyguanosine: Studies on the Glycosylation of Weakly Nucleophilic Imidazo[1,2-*a*]-*s*-triazinyl Anions

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5-Aza-7-deaza-2′-deoxyguanosine (**1**) has been synthesized by glycosylation of the anions of the imidazo[1,2-*a*]-*s*-triazines **3** or **4b** with 2-deoxydi-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**7a**). Glycosylation was carried out under liquid–liquid or solid–liquid phase-transfer conditions with Bu_4NHSO_4 or the cryptand TDA-1 as catalyst as well as in the presence of NaH. In contrast to the stereospecific glycosylation occurring at hard nucleophiles, glycosylation was not stereospecific in the case of weakly nucleophilic imidazo[1,2-*a*]-*s*-triazines; α- and β-anomers were formed by applying the three different glycosylation methods. Configurational as well as conformational parameters of the deoxynucleosides **1** and **2** were determined by one- and two-dimensional FT-NMR spectroscopy. Both anomeric 2′-deoxyguanosine isosteres exhibit the anti conformation at the N-glycosylic bond, a predominant C-2′-endo sugar puckering, and a (−sc) conformation around the C-4′–C-5′ bond.

Introduction

Modified 2′-deoxyribonucleosides—in particular those with an altered nitrogen pattern compared to the parent purines—are of wide biological interest.[1] They can be used for site-directed modification of DNA fragments with respect to the study of DNA structure and DNA-protein recognition.

Recently, we have synthesized 7-deaza-2′-deoxyguanosine, which was incorporated into the recognition sequence of the endodeoxyribonuclease Eco R 1, and have studied the interaction of the resulting oligomer with this enzyme.[2] We now report on the synthesis of the 2′-

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Table I. ^{13}C NMR Chemical Shifts of Imidazo[1,2-*a*]-*s*-triazines and Their 2′-Deoxyribofuranosides[a]

compd	C-4	C-8a	C-2	C-7	C-6	C-1′	C-4′	C-3′	C-5′	C-2′	C=O	CH	CH_3	CH
3[b]	162.4	151.3	149.8	118.9	107.4									
6a[c]	163.4	154.6	154.0	127.6	106.6									
5[b]	157.0	149.9	146.4	130.4	108.5								41.0/35.0	158.8
8a/9a[d]	166.0	150.6	150.1	113.4	109.0	85.4	84.3	74.8	63.9	37.9				
	165.4	150.5	149.7	113.0	108.0	84.6	82.8	74.7	63.8	37.3				
8b[d]	160.8	150.2	149.3	114.9	109.5	85.1	83.4	74.7	63.9	38.1	176.8	35.9	19.4/19.1	
9b[d]	160.6	150.3	148.8	115.4	108.9	86.7	85.3	74.8	63.9	38.2	176.5	36.0	19.1/19.0	
1[b]	165.4	150.2	150.1	114.2	108.4	87.7	82.8	70.6	61.6	38.8				
1[e]	165.1	150.1	153.0	115.4	108.9	87.0	82.2	71.0	61.6	38.6				
2[b]	165.4	150.3	150.1	115.4	108.0	89.0	83.6	70.7	61.8	39.6				
2[e]	165.0	149.7	153.1	116.3	108.4	89.0	83.4	71.0	61.6	39.2				

[a] δ values are relative to tetramethylsilane. [b] $(CD_3)_2SO$. [c] D_2O/NaOD. [d] $CDCl_3$. [e] D_2O.

deoxyribofuranoside of 2-aminoimidazo[1,2-*a*]-*s*-triazin-4-one (1), which can be looked upon as 5-aza-7-deaza-2′-deoxyguanosine—a 2′-deoxyguanosine isostere in which N-7 and C-5 are exchanged. This exchange may cause (i) a lack of a proton donator site at N-1 as well as an acceptor site at N-7 (purine numbering) and (ii) an alteration of the dipole moment of the heterocyclic moiety. Incorporation of 5-aza-7-deaza-2′-deoxyguanosine into DNA duplexes should therefore affect stacking interactions as well as Watson–Crick base pairing.

In the proceed of the synthesis of pyrrolo[2,3-*d*]pyrimidine as well as pyrrolo[3,2-*c*]pyridine 2′-deoxyribofuranosides, it became apparent that the glycosylation reaction was regio- and diastereospecific if a nucleobase anion was reacted with the halogenose **7a**.[3,4] In particular, liquid–liquid and solid–liquid phase-transfer glycosylation of nucleobase anions which has been developed in our laboratory has been found to be advantageous with respect to both, the stereochemical as well as the regiochemical course of the glycosylation reaction.[5] In this paper we report on the glycosylation of 5-aza-7-deazaguanine by applying three different methods (i) liquid–liquid and (ii) solid–liquid phase-transfer glycosylation and (iii) NaH-mediated condensation. Furthermore, we focus on the problem of stereoselectivity during glycosylation of nucleobase anions and on the sugar conformation of the novel anomeric 2′-deoxyribonucleosides **1** and **2**.

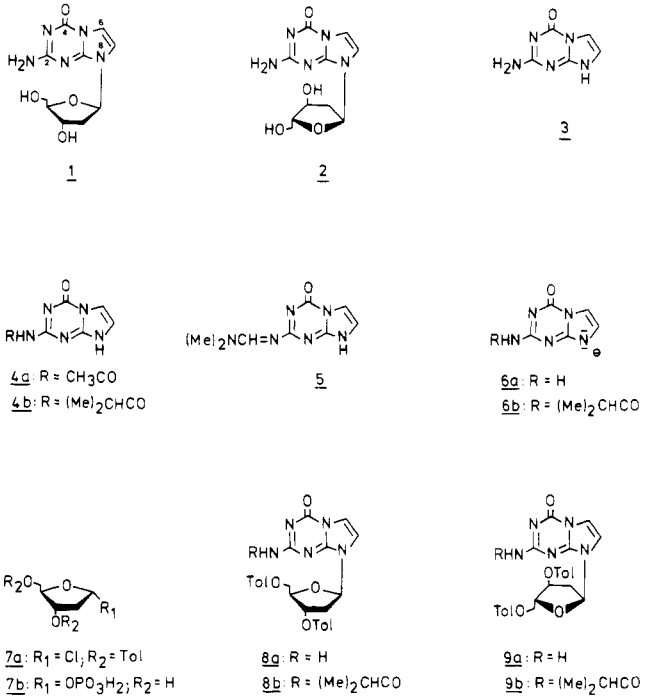
Results and Discussion

Glycosylation of 5-Aza-7-deazaguanine with the Halogenose 7a. The synthesis of 5-aza-7-deazaguanine (**3**) as well as of its β-D-ribofuranoside has been described by Kim et al.[6] Glycosylation was carried out by conventional techniques; the structure of the nucleoside was confirmed by X-ray analysis.[7] Both compounds exhibit interesting biological activities: while the nucleobase acts as a strong competitive inhibitor toward xanthine oxidase (K_i, 0.55 mM), the β-D-ribonucleoside shows antiviral activity against rhino viruses comparable with that of ribavirine.[6]

As it has been shown that nucleobase anions can be glycosylated stereospecifically with the halogenose **7a**, we considered employing this technique for the synthesis of **1**. First, we have determined the pK_a values of 5-aza-7-deazaguanine UV spectrophotometrically in Teorell–Stenhagen buffer at 260 nm.[8] Compound **3** exhibits a pK_a value of 3.7 for protonation and of 7.7 for deprotonation. In order to show from what position the proton of **3** is abstracted during anion formation, ^{13}C NMR spectra of the neutral nucleobase **3** as well as of its anion **6a** were recorded. As can be seen from Table I the signal of carbon-7 is strongly downfield shifted (8.7 ppm) during deprotonation, which designates nitrogen-8 as the deprotonation site. This makes the anion applicable for regioselective glycosylation at this position. However, the ease of deprotonation may cause stereochemical problems due to the low nucleophilicity of this anion.

The glycosylation of the anion **6a** was first carried out under liquid–liquid phase-transfer conditions.[9] As the standard system, a biphasic mixture of either 50% aqueous NaOH or 30% aqueous KOH with dichloromethane as counterphase was employed.[4] Unfortunately **3** proved almost insoluble in both inorganic phases. However, 10% aqueous potassium carbonate was found to be sufficient for anion formation, dissolves **3** readily, and was therefore chosen as inorganic phase. As organic phase dichloromethane was employed and Bu_4NHSO_4 was selected as phase-transfer catalyst. In order to show the distribution

Chart I



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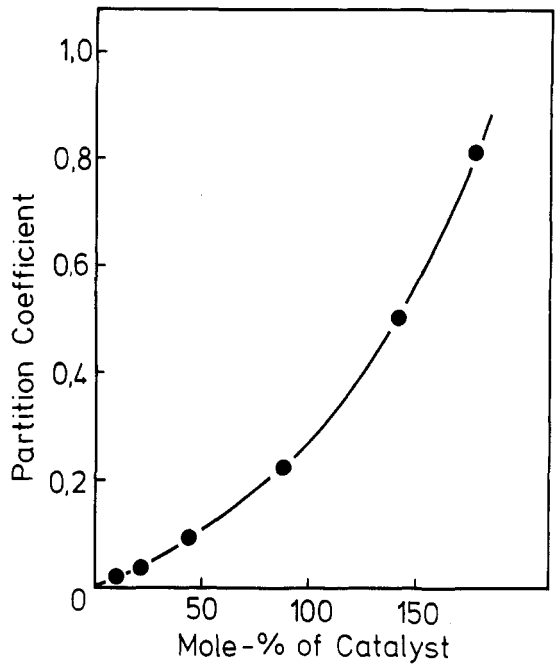

Figure 1. Partition coefficient of 5-aza-7-deazaguanine (151 mg, 1 mmol) between 10% aqueous potassium carbonate (10 mL) and dichloromethane (10 mL) as a function of tetrabutylammonium hydrogen sulfate concentration (mol % of catalyst related to chromophore). The concentration of **6a** in each phase was determined spectrophotometrically at 257 nm after 15 min of mixing of the biphasic mixture.

of **6a**, we determined its partition coefficient between 10% aqueous K_2CO_3 and CH_2Cl_2 as a function of catalyst concentration. As can be seen from Figure 1, only very small amounts of the nucleobase are extracted into the organic phase even at very high concentrations of Bu_4NHSO_4.

The fact that the mass balance (sum of nucleobase concentration in both phases) is constant over the whole range measured implies that the ion pairs of the tetrabutylammonium cation and the nucleobase anion **6a** are transferred into the organic phase and do not enrich at the phase boundary with increasing amounts of catalyst.

In a liquid–liquid phase-transfer glycosylation of **3** with the halogenose **7a**[10] employing CH_2Cl_2 as organic phase and 7 mol % of Bu_4NHSO_4, an anomeric mixture of the toluoyl-protected nucleosides **8a**/**9a** was obtained in 63% yield (10 min of vibromixing). This was in contrast to earlier glycosylation experiments with pyrrolo[2,3-*d*]pyrimidines where in most cases only the β-nucleoside was formed.[5] The anomers could not be separated chromatographically so that the estimation of the α:β ratio was difficult at this stage. Nevertheless our findings imply that the formation of the α-anomer is related (i) to the low concentration of reactive nucleobase ion pairs in the organic phase and/or (ii) to their weak nucleophilicity.

Deprotection of the anomeric mixture **8a**/**9a** with methanolic ammonia at room temperature gave the crystalline nucleosides **1**/**2** in 94% yield. The ratio of anomers was now estimated from the integrals of the H_a-2′ signals in the ^1H NMR spectrum and was found to be 1:2 (α:β). As also at this stage separation of the anomers was found to be extremely difficult and could only be performed with small amounts of material (100 mg), we tried to employ solid–liquid phase-transfer glycosylation techniques on compound **3**. First attempts, however, using acetonitrile or dichlormethane as aprotic solvents, solid K_2CO_3 or KOH as base, and either the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1)[11] or Bu_4NHSO_4 as catalyst failed due to the low solubility of the nucleobase. Therefore, we decided to enhance the solubility of **3** by introducing hydrophobic groups into the molecule.

At first, we synthesized a 2-(dimethylamino)methylene derivative (**5**) by reaction of **3** with *N*,*N*-dimethylformamide diethyl acetal in DMF.[12] Its structure was confirmed by ^1H and proton-coupled as well as decoupled ^{13}C NMR spectroscopy (Table I and Experimental Section). The protecting group causes indeed a sufficient increase of the solubility in acetonitrile. Subsequent solid–liquid phase-transfer glycosylation, however, gave side reactions at the nucleobase moiety.

As a consequence, compound **3** was next converted into **4a** according to the method of Kim et al.;[6] however, the resulting acetamido derivative **4a** did not prove soluble enough in acetonitrile or dichloromethane. In order to enhance the lipophilicity further, compound **3** was isobutyrylated, following the procedure of the acetylation. The resulting isobutyryl compound **4b** was then subjected to solid–liquid phase-transfer glycosylation with **7a** using acetonitrile as solvent, TDA-1 as catalyst, and potassium carbonate as base. From this reaction mixture, two compounds with similar R_f values and identical UV spectra were isolated. Separation by flash chromatography led to a 1:2 ratio (β:α) of anomeric nucleosides in 88% yield. ^1H and ^{13}C NMR spectra (Table I and Experimental Section) pointed to the anomers **8b** and **9b**. N-8 as glycosylation site was deduced from almost identical chemical shifts of the C-7 signals in the ^{13}C NMR spectra of **8b** and **9b** compared to that of the nucleobase **3**.

The anomeric configuration of **8b** and **9b** was first tentatively assigned from the ^1H NMR spectra. According to the large differences of the chemical shifts of the H-4′ and H-5′ signals, the fast migrating zone was assigned to the α-anomer **9b**. The slower migrating compound was therefore the β-anomer **8b**.[13,14]

Deprotection of **8b** and **9b** respectively was accomplished by using methanolic ammonia and gave the 2′-deoxyribofuranosides **1** and **2**. Their ^1H and ^{13}C NMR data (Table I and Experimental Section) confirmed the proposed structures. Nitrogen-8 was the glycosylation site which was confirmed by (i) the identical chemical shifts of the C-7 signals of both anomers compared with that of the nucleobase **3** and (ii) the ddd multiplicity of the C-7 signals in gated-decoupled ^{13}C NMR spectra (β-anomer, J(C-7/H-7) = 200.7 Hz; J(C-7/H-6) = 11.7 Hz; J(C-7/H-1′) = 4.5 Hz; α-anomer, J(C-7/H-7) = 202.5 Hz; J(C-7/H-6) = 11.9 Hz; J(C-7/H-1′) = 4.5 Hz).

Since the order of sugar signals in a ^{13}C NMR spectrum may differ from one 2′-deoxyribonucleoside to another,[15] we applied two-dimensional ^1H–^{13}C correlation spectroscopy (XHCORR)[16] on an anomeric mixture of **1** and **2** (Figure 2). From this experiment an unequivocal assignment of the order of sugar signals in the ^{13}C NMR spectra (C-4′–C-1′–C-3′–C-5′–C-2′) can be confirmed since the cross peaks of C-4′(α) and C-4′(β) with the H-4′ signals are far away from those of the C-1′ signals with the corresponding H-1′ signals. Furthermore, the XHCORR spectrum of **1** and **2** allows the assignment of H-6 and H-7

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Table II. Ratio of Anomers and Total Yield of 1 and 2 by Various Glycosylation Methods on Compound 3 or 4b[a]

method	ratio of anomers (β:α)	yield (%)
solid–liquid PTG of **4b** (TDA-1, K_2CO_3, CH_3CN)	1:2	88
NaH-mediated condensation of **4b** with **7a**, CH_3CN	1:2	74
liquid–liquid PTG of **3** (Bu_4NHSO_4, 10% aqueous K_2CO_3)	2:1	63

[a] PTG: phase-transfer glycosylation; for details see Experimental section.

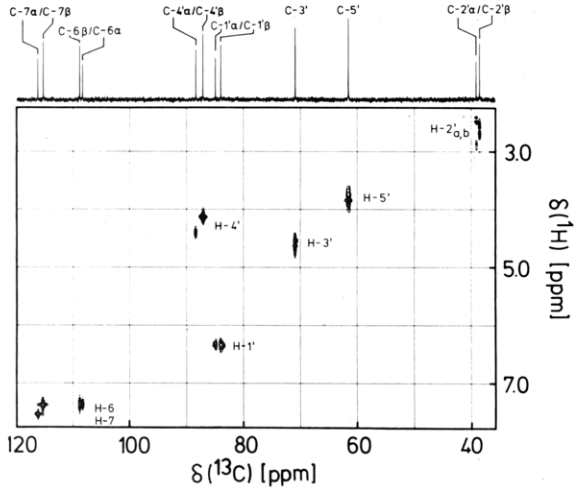


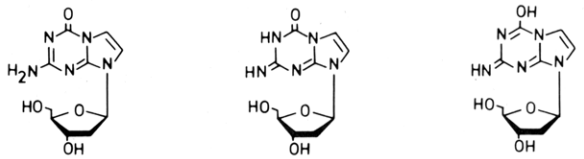
Figure 2. Two-dimensional [^{1}H,^{13}C] correlation spectrum (XHCORR) of an anomeric mixture of **1** and **2** in D_2O. For details, see Experimental Section.

of the α-anomer **2**. As the C-6 and C-7 signals of **2** appear separated and can unrequivocally be identified by their different multiplicities in the gated-decoupled ^{13}C NMR spectrum (C-6, dd; C-7, ddd), the ^{1}H NMR signal of H-7 appears at low field. The tentative assignment of the anomers on the stage of the protected nucleosides **8b** and **9b** was confirmed on the deprotected nucleosides **1** and **2**. Compound **2** exhibited a dd for H-1′, whereas the β-anomer **1** showed a pseudo-t.[17]

This empirical assignment was also proven unequivocally. For this purpose 5-aza-7-deazaguanine was incubated with 2-deoxy-α-D-ribofuranose 1-phosphate (**7b**) and purine nucleoside phosphorylase[18,19] at pH 7.5 for 2 h at room temperature. This enzyme glycosylates various purine isosteres in a stereospecific S_N2 reaction by exclusive formation of β-nucleosides. TLC analysis of the supernatant of the incubation mixture indicated that 5-aza-7-deazaguanine is accepted as substrate by the enzyme and that the β-nucleoside **1** was formed. The comparison of the chromatographic mobilities of the enzymatically synthesized nucleoside **1** with those of the nonenzymatically synthesized nucleosides **1** and **2** confirmed the NMR assignment.

Table II shows that solid–liquid as well as liquid–liquid phase-transfer glycosylation resulted in the formation of mixtures of anomeric 5-aza-7-deaza-2′-deoxyguanosine (**1**, **2**). While the liquid–liquid phase-transfer glycosylation of **6a** gave an α:β mixture of 1:2, solid–liquid phase-transfer glycosylation[20] of the isobutyrylated derivative **6b** gave the α-anomer in preponderance. Nevertheless, the latter method is preferred due to higher yields and the ease of the separation of anomers.

Chart II



I II III

As the formation of an anomeric mixture of **1** and **2** was unexpected, we focused our interest on the glycosylation of **4b** in the absence of phase-transfer catalyst. When compound **4b** was subjected to glycosylation with the halogenose **7a** using acetonitrile as solvent and sodium hydride as base,[21] again both anomers were formed in the same ratio as described before (Table II). This demonstrates clearly that the cryptand TDA-1 was not responsible for the nonstereospecific glycosylation. The finding was verified by a qualitative glycosylation experiment in the presence of K_2CO_3 but without TDA-1. TLC analysis of the reaction mixture indicated again the formation of both anomers with the α-anomer in preponderance. The formation of α-nucleosides during a glycosylation reaction may therefore be due to the following reasons: (i) a change from a S_N2 to an S_N1 reaction, (ii) intermolecular transglycosylation reactions,[22] and (iii) equilibration of the halogenose **7a** before glycosylation.

It has been shown by Kotick et al.[23] and confirmed by Hubbard et al.[24] that glycosylation of a nucleobase with an anomeric mixture of 2-deoxy-di-*O*-(*p*-toluoyl)-D-*erythro*-pentofuranosyl chloride may result in the formation of the corresponding α-nucleoside in preponderance. This is caused by the fact that the β-halogenose reacts to produce the α-nucleoside at a faster rate compared with the reaction of the α-halogenose **7a** with the nucleobase. Thus, unless the rate of sugar equilibration is probably still slower compared with the glycosylation rate, α-nucleosides may predominate no matter where the equilibrium position between the two sugar anomers lies.

The conclusions drawn from the glycosylation of imidazo[1,2-*a*]-*s*-triazinyl anions are the following: (i) weak nucleophiles such as the anions **6a** and **6b** give rise to nonstereospecific glycosylation reactions; (ii) on the other hand, hard nucleophiles such as pyrrolo[2,3-*d*]pyrimidines or pyrrolo[3,2-*c*]pyridines lead to stereospecific glycosylation reactions with exclusive β-nucleoside formation.[5] As a result, glycosylation of nucleobase anions with the halogenose **7a** does not give β-nucleosides per se; for weakly acidic nucleobases it might be advantageous to introduce electron-withdrawing substituents at the heterocyclic moiety in order to ensure the formation of a nucleobase anion. However, this strategy counteracts with the stereospecificity of the glycosylation reaction. On the other

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Table III. NOESY Connectivities between Protons of the Anomers 1 and 2[a]

	β-anomer (1)	α-anomer (2)		β-anomer (1)	α-anomer (2)
H-7,H-1′[b]	+	+	H-7,H_b-2′[b]	+	+
H-7,H-3′[b]	+	–	H-1′,H-3′[b]	–	+
H-7,H-4′[b]	–	+	H-1′,H-4′[b]	+	–
H-7,H-5′[b]	+	–	3′-OH,5′-OH[c]	+	+
H-7,H_a-2′[b]	+	–			

[a] For details, see Experimental Section. [b] D_2O. [c] $(CD_3)_2SO$.

hand, electron-donating substituents may increase the stereospecificity of the glycosylation of weakly nucleophilic nucleobases. This will be the subject of further studies.

Tautomerism and Stability of the N-Glycosylic Bond of 5-Aza-7-deaza-2′-deoxyguanosine. 5-Aza-7-deaza-2′-deoxyguanosine (1) is capable of existing in three tautomeric forms (Chart II). In order to assign the most probable structure of 1, we measured its ^1H and ^{13}C NMR spectra in $(CD_3)_2SO$. The ^1H NMR spectrum, measured in $(CD_3)_2SO$, exhibits a singlet with an integral of two protons for the primary amino group, indicating that in this solvent structure I is the most preferred tautomer. Due to the exchange of protons in D_2O, the most probable tautomeric form of 1 cannot be determined by ^1H NMR spectroscopy in D_2O. Therefore, the ^{13}C NMR spectra of compound 1, taken from D_2O and $(CD_3)_2SO$ solution, were compared. A significant downfield shift (3 ppm) of the C-2 signals was observed when changing from $(CD_3)_2SO$ to D_2O while all other chemical shifts are constant (Table I). This points to structure II as the preferred tautomer of 1 in D_2O. Structure III was excluded as its existence would cause a shift of the C-4 signal when changing the solvents.

The finding that 5-aza-7-deaza-2′-deoxyguanosine exists obviously in two different tautomeric forms depending on the solvent becomes understandable when the pK values of the nucleoside were determined. Interestingly, compound 1 exhibits a pK value of protonation of 3.7 and a pK value of deprotonation of 7.5—values which are almost identical with those of the nucleobase 3. The pK value of deprotonation near the neutral point indicates lability of the tautomeric forms I and II.

The pK value of protonation of 3 is similar to that of its parent nucleoside 2′-deoxyguanosine (pK = 3.5).[25] While the latter is protonated in the five-membered ring, which is a prerequisite for N-glycosyl hydrolysis,[26] compound 1 can only be protonated in the triazine ring. This should cause a higher stability of 1 toward acidic hydrolysis compared to 2′-deoxyguanosine, which is found to be hydrolyzed in 0.5 N HCl at 25 °C with a half-life value of 10.6 min.[27] Under these conditions compound 1 is stable. In order to test the stability of 5-aza-7-deaza-2′-deoxyguanosine, it was treated with 3 N hydrochloric acid at 70 °C (($\pm$)1°). Under these conditions the intact nucleobase was released from the nucleoside as shown by comparison of the pH-dependent UV spectra of the hydrolysis product with that of the authentic nucleobase. Data were obtained from the decrease of the UV absorbance differences between the nucleoside and the corresponding aglycon at 260 nm, the wavelength where the UV differences are most pronounced. From an A_{260}–time scan the half-life value of 1 was calculated to be 33 min ($k = 2.1 \times 10^{-2}$ min^{-1}).

Conformational Studies on 5-Aza-7-deaza-2′-deoxyguanosine. From the ^1H NMR spectra of 1 and 2 conformational data of the sugar moieties can be derived. On the basis of a method of Cadet et al.,[28] sugar puckering can be estimated from J(3′,4′) coupling constants. This coupling constant is about 1 Hz in the C-2′-endo conformer (S-type) and about 10 Hz in the C-3′-endo conformer (N-type). The population can be derived by interpolation and are found to be as follows: 68% S for compound 1 and 78% S for compound 2. This preponderance of the C-2′-endo conformation for both anomers is in line with findings on other anomeric nucleosides.[29]

The coupling constants of C-7 with the anomeric proton (4.5 Hz) of both anomers, taken from the gated-decoupled ^{13}C NMR spectra, gives a torsion angle Φ = 145° which corresponds to a glycosylic torsion angle of χ = 25° and −95°, both in the anti region.[30,31] The conformation of the exocyclic C-4′–C-5′ bond can be estimated from the ^1H NMR spectra by applying the following equation: %gg = 10[13 − (J(4′,5′) + J(4′,5″))].[32] For both anomers a gg population of about 10% can be deduced. The conformation around the C-4′–C-5′ bond (tg or gt) can be derived from two-dimensional nuclear Overhauser enhancement spectroscopy (NOESY).[33] When the NOESY spectra of the anomers 1 and 2 were run in $(CD_3)_2SO$, significant cross peaks between 5′-OH and 3′-OH can be observed for both anomers. CPK model building shows a close proximity of the sugar hydroxyls. As a consequence tg (= −sc) conformation around the C-4′–C-5′ bond occurs.

When run in D_2O, the NOESY spectra of 1 and 2 exhibit several connectivities which confirm the conformation of both anomers. As Table III shows, the β-anomer 1 shows cross peaks between H-7 and H-3′/H-5′ as well as between H-1′ and H-4′ while connectivities between H-7 and H-4′ and H-1′ and H-3′ are missing. In contrast to this, the α-anomer exhibits cross peaks between H-7 and H-4′ as well as between H-1′ and H-3′. These findings underline the anti conformation as well as the anomeric assignment of the nucleosides 1 and 2. Furthermore, the NOESY spectrum of the β-anomer 1 exhibits connectivities between H-7 and both H-2′ protons of similar intensity. This points to a C-2′-endo conformation of the sugar moiety for χ values of around 150°.[34]

Additionally, information about sugar geometry can be obtained from homonuclear correlation spectroscopy (COSY)[35] by looking at the relative intensities of H-1′–H_a-2′ and H-1′–H_b-2′ cross peaks. For C-2′-endo geometry, both coupling constants are large (6–7 Hz) and would produce strong cross peaks in the COSY spectrum. On the other hand, for C-3′-endo geometry the two cross peaks of H-1′–H_a-2′ and H-1′–H_b-2′ would have very different intensities.[34] As Figures 3 and 4 indicate, both anomers exhibit a C-2′-endo sugar puckering.

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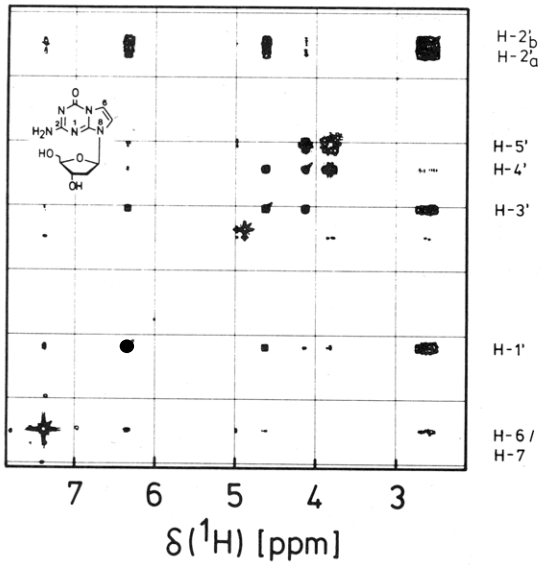

Figure 3. Symmetrized two-dimensional [^{1}H,^{1}H] correlation spectrum (COSY-long range) of **1** in D_2O. For details, see Experimental Section.

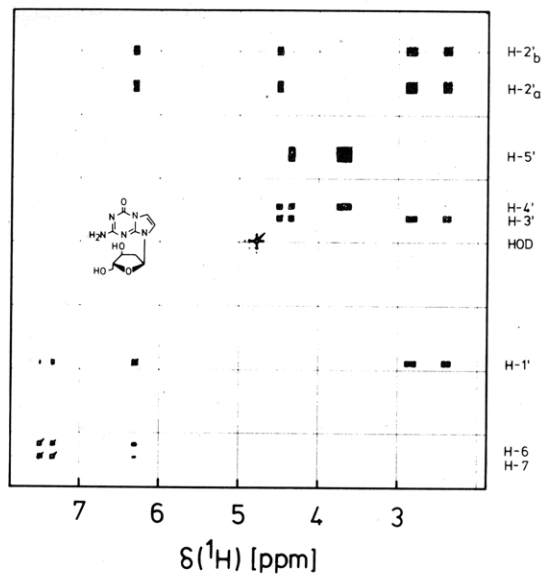

Figure 4. Symmetrized two-dimensional [^{1}H,^{1}H] correlation spectrum (COSY) of **2** in D_2O. For details, see Experimental Section.

Table IV. Spin–Lattice Relaxation Times of Protons of 1 and 2 in D_2O[a]

	T_1 (s) ± 0.1 s			T_1 (s) ± 0.1 s	
	β-anomer (1)	α-anomer (2)		β-anomer (1)	α-anomer (2)
H-7	1.7	2.5	H-3′	1.1	1.1
H-6	1.7	1.3	H-4′	1.4	1.3
H-1′	1.5	1.1	H-5′	0.4	0.4
H-2′	0.4	0.4			

[a] For details see Experimental Section.

CPK models of the anomers **1** and **2**—constructed by using the conformational parameters derived from 1D and 2D FT-NMR spectra—indicate that only the α-anomer exhibits a close spatial proximity between the O-3′ and the H-7 atom. This should cause a weakening of the C-7/H-7 bond which would induce an enhanced mobility of H-7 compared with H-6. In order to verify this assumption, we measured the spin–lattice relaxation times (T_1) of all protons of both anomers by applying inversion–recovery techniques (Table IV). As Table IV shows there is indeed a difference by a factor of 2 in the T_1 values of H-6/H-7 of the α-anomer whereas in the β-anomer H-6 and H-7 exhibit identical T_1 values. Moreover, the T_1 value of H-7 of the α-anomer is 0.4 s longer than that of the β-anomer.

Studies on other pairs of anomeric nucleosides will show if spin–lattice relaxation measurements can be used to identify the configuration at the anomeric center.

Experimental Section

General. Melting points were determined on a Linström apparatus (Wagner-Munz, West Germany) and are not corrected. UV spectra and kinetics were assayed on a UV-3200 spectrophotometer (Hitachi, Japan) equipped with a RCS-6 thermostat (Lauda, West Germany). TLC was performed on silica gel SIL G-25 UV_{254} plates (Macherey-Nagel, West Germany) with solvent systems (A) $CHCl_3$–MeOH (99:1); (B) $CHCl_3$–MeOH (95:5); (C) $CHCl_3$–MeOH (7:3); (D) $CHCl_3$–MeOH (9:1). Silica gel 60, 230–400 mesh ASTM (Merck, West Germany), was used for column chromatography and silica gel 60 H (Merck) for flash chromatography with eluants indicated for TLC. The columns were connected to a Uvicord S UV detector and a MultiRac fractions collector (LKB Instruments, Sweden). TLC scanning was performed with a thin-layer Chromatoscanner CS 950 (Shimadzu, Japan). p*K* values were determined spectrophotometrically in Teorell–Stenhagen buffer.[8] Purine nucleoside orthophosphate ribosyltransferase (nucleoside phosphorylase, from bovine spleen, EC 2.4.2.1) and xanthine oxidase from cow's milk (EC 1.2.3.2) were purchased from Sigma Chemicals Co. (St. Louis, MO).

NMR Measurements. 1D and 2D FT NMR spectra were measured at 25 °C on an AC 250 spectrometer equipped with an Aspect 3000 data system and an array processor (Bruker, West Germany). Operational frequencies: ^{1}H, 250.133 MHz; ^{13}C, 62.898 MHz. δ values are relative to Me_4Si as internal standard for ^{1}H and ^{13}C nuclei. The solvents were as indicated in Table I. Digital resolutions: ^{1}H, 0.275 Hz/pt; ^{13}C, 0.526 Hz/pt. Homonuclear correlation spectroscopy ([^{1}H,^{1}H]-COSY)[35] was performed by using the pulse sequence D_1–90°–D_0–90°–FID with a relaxation period D_1 of 1 s and an initial delay D_0 of 3 μs. The experiments were carried out with 2048 data points and 512 data points in the t_2 and t_1 directions. In order to emphasize long-range couplings with small coupling constants, a modified COSY spectrum (COSYLR)[36] with an additional delay D_2 of 80 ms was run using the pulse sequence D_1–90°–D_0–D_2–90°–D_2–FID. The experiments were carried out with the same parameters as described for the COSY spectra. 2D nuclear Overhauser enhancement spectra (NOESY, magnitude mode)[33] were carried out with 2048 data points and 1024 data points in the t_2 and t_1 dimensions. The pulse sequence was as follows: D_1–90°–D_0–90°–D_9–90°–FID. The initial delay was set to 3 μs, the relaxation delay D_1 to 5 s, and the mixing time D_9 to 500 ms. The latter was calculated from a mean value of the spin–lattice relaxation times (T_1) shown in Table IV.

For all 2D NMR experiments a typical 90° pulse width of 10.8 μs was used. After zero-filling, sine-bell multiplication of the time domain data, and fourier transformation, the contour plots with a digital resolution of 2.9 Hz/pt were obtained.

Spin–lattice relaxation time (T_1) measurements were performed by using the pulse sequence D_1–180°–VD–90°–FID (inversion–recovery technique). After a relaxation delay D_1 of 10 s and the 180° pulse, 16 variable delays of 0.1–1.5 and 2.0 s were incorporated. In cases of nonsufficiently resolved 1D ^{1}H NMR spectra, coupling constants were taken from two-dimensional homonuclear *J*-resolved spectra; pulse sequence D_1–90°–D_0–180°–D_0–FID with D_1 = 1 s and D_0 = 3 μs. The number of data points in the t_2 dimension was 2048 and the sweep width in the t_1 dimension was half the width of the largest multiplet.

2-[[(Dimethylamino)methylene]amino]-8*H*-imidazo[1,2-*a*]-*s*-triazin-4-one (5). Compound **3** (100 mg, 0.66 mmol) was dissolved in dry dimethylformamide (3 mL). After addition of *N*,*N*-dimethylformamide diethyl acetal (3 mL, 2.6 g, 17.7 mmol) the reaction mixture was stirred for 14 h under nitrogen at room temperature. After evaporation to dryness in high vacuo the

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residue was chromatographed on silica gel 60 (15 × 6 cm). Solvent D eluted one main peak which was pooled and evaporated to dryness. Crystallization from MeOH afforded 88 mg (70%) of colorless needles: mp 198–205 °C dec; TLC (D) R_f 0.5; UV (MeOH) λ_{max} 304 nm (ϵ 17100), 241 (11500); ^{1}H NMR ($(CD_3)_2SO$) δ 8.71 (s, CH), 7.41 (d, J = 1.8 Hz, H-7), 7.10 (d, J = 1.8 Hz, H-6), 3.20, 3.10 (s, 2 CH_3). Anal. Calcd for $C_8H_{10}N_6O$: C, 46.60; H, 4.89; N, 40.76. Found: C, 46.81; H, 4.91; N, 40.53.

2-[(2-Methylpropionyl)amino]-8*H*-imidazo[1,2-*a*]-*s*-triazin-4-one (4b). Compound **3** (1 g, 6.62 mmol) was dissolved in isobutyric anhydride (25 mL). After addition of one drop of 85% phosphoric acid the reaction mixture was refluxed for 1 h. After filtration, the excess of anhydride was evaporated under high vacuo and the residue was treated with ice water (20 mL). After storage at 4–8 °C overnight, the precipitate was filtered off and crystallized from aqueous MeOH: 950 mg (65%) of colorless needles, mp 228–231 °C; TLC (D) R_f 0.68; UV (MeOH) λ_{max} 280 nm (ϵ 7800), 222 (16900); ^{1}H NMR ($(CD_3)_2SO$) δ 10.7 (s, br, NH), 7.55 (d, J = 2.3 Hz, H-7), 7.39 (d, J = 2.3 Hz, H-6), 2.84 (pseudo-sept., J = 6.8 Hz, CH), 1.08, 1.05 (s, 2 CH_3). Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.68; H, 5.02; N, 31.48.

Liquid–Liquid Phase-Transfer Glycosylation of 3 with 7a. Anomeric 2-Amino-8-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-D-*erythro*-pentofuranosyl]-8*H*-imidazo[1,2-*a*]-*s*-triazin-4-ones (8a/9a). Compound **3** (500 mg, 3.31 mmol) in 10% aqueous potassium carbonate (25 mL) was dissolved by gentle warming. The solution was cooled to room temperature and covered with a solution of Bu_4NHSO_4 (80 mg, 0.24 mmol) in dichloromethane (20 mL). The layers were thoroughly mixed with a vibromixer (1 min) and a solution of 2-deoxydi-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**7a**) (1.4 g, 3.57 mmol) in dichloromethane (5 mL) was added in one portion. Mixing was continued for another 10 min. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2 and acidified (pH 4–5) by addition of 6 N hydrochloric acid. After 24 h, unreacted chromophore could be recovered as crystals from the aqueous phase (120 mg, 24%).

The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was dissolved in solvent B and chromatographed on a silica gel column (45 × 6 cm). Solvent B eluted one main zone from which colorless crystals of **8a/9a** could be obtained upon evaporation and trituration with ether (1.05 g, 63%): TLC (B) R_f 0.75; UV ($CHCl_3$) λ_{max} 246 nm (ϵ 36100); ^{1}H NMR ($CDCl_3$) δ 7.8, 7.7, and 7.25 (m, CH, toluoyl), 7.01 (d, J = 2.6 Hz, H-7(α)), 6.85 (m, H-6/H-7(α/β)), 6.35 (m, H-1'), 5.6 (m, H-3'), 4.74 (m, H-4'(α)), 4.65 (m, H-4'(β) and H-5'(α/β)), 2.95 (m, H_a-2'), 2.75 (m, H_b-2'), 2.37, 2.35 (s, 2 CH_3, toluoyl). Anal. Calcd for $C_{26}H_{25}N_5O_6$: C, 62.02; H, 5.00; N, 13.91. Found: C, 61.81; H, 5.17; N, 13.69.

Anomeric 2-Amino-8-(2-deoxy-D-*erythro*-pentofuranosyl)-8*H*-imidazo[1,2-*a*]-*s*-triazin-4-ones (1/2). The anomeric mixture (**8a/9a**) of the protected nucleosides (3.97 mmol) was dissolved in 4% methanolic ammonia (40 mL) and stirred at room temperature for 48 h. During this period 752 mg (72%) of **1/2** precipitated as colorless needles. The filtrate was evaporated to dryness and the residue distributed between water and CH_2Cl_2 (25 mL, each). Evaporation of the aqueous phase and recrystallization of the residue from MeOH afforded another 227 mg of crystalline **1/2**: total yield 979 mg (94%): TLC (C) R_f 0.55; UV (H_2O) λ_{max} 256 nm (ϵ 13500); ^{1}H NMR (D_2O) δ 7.54 (d, J = 2.9 Hz, H-7(α)), 7.38 (m, H-6/H-7(α/β)), 6.35 (m, H-1'(α/β)), 4.59 (pseudo-q, H-3'(β)), 4.54 (pseudo-q, H-3'(α)), 4.38 (pseudo-q, H-4'(α)), 4.12 (pseudo-q, H-4'(β)), 3.76 (m, H-5'(α/β)), 2.88 (pseudo-q, J = 7 Hz, H_a-2'(α)), 2.68 (pseudo-q, J = 7 Hz, H_a-2'(β)), 2.51 (m, H_b-2'(α/β)).

2-Amino-8-(2-deoxy-β-D-*erythro*-pentofuranosyl)-8*H*-imidazo[1,2-*a*]-*s*-triazin-4-one (1). The anomeric mixture of **1/2** (100 mg, 0.37 mmol) was dissolved in MeOH, adsorbed on silica gel 60 H (10 g), and applied on the top of a column with silica gel 60 H (30 × 6 cm). Flash chromatography (0.5 bar) with solvent C eluted two zones. From the faster migrating zone 60 mg (60%) of the β-anomer **1** was obtained as colorless needles (MeOH): mp 195–198 °C; TLC (C) R_f 0.55; UV (pH 1) λ_{max} 265 nm (ϵ 14200); UV (pH 7) λ_{max} 257 (13300); UV (pH 13) λ_{max} 256 nm (ϵ 14800); ^{1}H NMR (D_2O) δ 7.41, 7.39 (2 d, J = 2.8 Hz, H-7/H-6), 6.37 (pseudo-t, $J(1',2'_{a,b})$ = 6.7 Hz, H-1'), 4.62 (dt, $J(3',4')$ = 3.8 Hz, $J(3',2'_a)$ = 6.2 Hz, H-3'), 4.13 (pseudo-q, $J(4',3')$ = 4 Hz, $J(4',5')$ = 8.2 Hz, H-4'), 3.83 (m, $J(5',4')$ = 8.2 Hz, H-5'), 2.69 (pseudo-q, $J(2',1')$ = 6.4 Hz, H-2'$_a$), 2.54 (dq. $J(2',1')$ = 6.6 Hz, J = 2.5 Hz, H-2'$_b$); ^{1}H NMR ($(CD_3)_2SO$) δ 7.44 (d, J = 2.7 Hz, H-7), 7.36 (d, J = 2.7 Hz, H-6), 6.91 (s, br, 2 H, NH_2), 6.18 (pseudo-t, $J(1',2')$ = 6.7 Hz, H-1'), 5.27 (d, J = 4 Hz, 3'-OH), 4.95 (t, J = 5.3 Hz, 5'-OH), 4.33 (m, H-3'), 3.82 (m, H-4'), 3.53 (m, H-5'), 2.39 (pseudo-q, J = 6 Hz, H_a-2'), 2.20 (dq, J = 2.8 Hz, H_b-2'). Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 45.29; H, 4.95; H, 26.26.

2-Amino-8-(2-deoxy-α-D-*erythro*-pentofuranosyl)-8*H*-imidazo[1,2-*a*]-*s*-triazin-4-one (2). From the slower migrating zone 32 mg (32%) of the α-anomer **2** was obtained as colorless needles (MeOH): mp 136–138 °C; TLC (C) R_f 0.55; UV (pH 1) λ_{max} 265 nm (ϵ 14000); UV (pH 7) λ_{max} 257 nm (ϵ 13300); UV (pH 13) λ_{max} 257 nm (ϵ 14700); ^{1}H NMR (D_2O) δ 7.50 (d, J = 2.8 Hz, H-7), 7.33 (d, J = 2.8 Hz, H-6), 6.30 (dd, $J(1',2'_b)$ = 2.9 Hz, $J(1',2'_a)$ = 8.9 Hz, H-1'), 4.52 (dt, $J(3',4')$ = 3.0 Hz, $J(3',2'_a)$ = 6.6 Hz, H-3'), 4.63 (pseudo-q, $J(4',3')$ = 3.2 Hz, $J(4',5')$ = 8.3 Hz, H-4'), 3.71 (m, $J(5',4')$ = 8.3 Hz, H-5'), 2.87 (pseudo-q, J = 7 Hz, H-2'$_a$), 2.40 (dt, $J(2'_b,1')$ = 2.9 Hz, H-2'$_b$); ^{1}H NMR ($(CD_3)_2SO$) δ 7.53 (d, J = 2.7 Hz, H-7), 7.34 (d, J = 2.7 Hz, H-6), 6.94 (s, br, 2 H, NH_2), 6.18 (dd, $J(1',2'_b)$ = 2.8 Hz, $J(1',2'_a)$ = 8.8 Hz, H-1'), 5.53 (d, J = 3.4 Hz, 3'-OH), 4.87 (t, J = 5 Hz, 5'-OH), 4.30 (m, H-3'), 4.10 (m, H-4'), 3.41 (m, H-5'), 2.68 (pseudo-q, J = 6.8 Hz, H_a-2'), 2.50 (m, H_b-2'). Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.81; H, 5.06; N, 26.14.

Solid–Liquid Phase-Transfer Glycosylation of 3. The chromophore **4b** (500 mg, 2.26 mmol) was dissolved in dry acetonitrile (60 mL) under gentle warming. After addition of K_2CO_3 (1 g, 7.2 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (100 μL, 0.31 mmol) the solution was stirred for 10 min at room temperature. After addition of the halogenose **7a** (1.4 g, 3.57 mmol), stirring was continued for another 60 min. After filtration the reaction mixture was evaporated to dryness. The residue was dissolved in $CHCl_3$ and chromatographed on silica gel (10 × 6 cm). Solvent A separated the anomeric mixture from byproducts. Subsequently, the anomers were separated by flash chromatography on silica gel 60 H (20 × 6 cm, 0.5 bar, A).

8-[2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl]-2-[(2-methylpropionyl)amino]-8*H*-imidazo[1,2-*a*]-*s*-triazin-4-one (9b). From the faster migrating zone 760 mg (59%) of the α-anomer was obtained as colorless needles (MeOH), mp 130–132 °C: TLC (B) R_f 0.65; UV (MeOH) λ_{max} 278 nm (ϵ 14000), 242 (38100); ^{1}H NMR ($CDCl_3$) δ 8.14 (s, NH), 7.93 (d, J = 8.2 Hz, toluoyl), 7.64 (d, J = 8.2 Hz, toluoyl), 7.46 (d, J = 2.8 Hz, H-6), 7.28 (d, J = 2.8 Hz, H-7), 7.27 (d, J = 8.2 Hz, toluoyl), 7.20 (d, J = 8.2 Hz, toluoyl), 6.51 (dd, J = 2.4 Hz, 5.8 Hz, H-1'), 5.64 (m, H-3'), 4.86 (m, H-4'), 4.58 (d, J = 4.0 Hz, H-5'), 3.03 (m, H-2' and CH), 2.42 and 2.39 (s, 2 CH_3, toluoyl), 1.22 and 1.20 (s, 2 CH_3, isobutyryl). Anal. Calcd for $C_{30}H_{31}N_5O_7$: C, 62.82; H, 5.45; N, 12.21. Found: C, 62.79; H, 5.41; N, 12.17.

8-[2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-2-[(2-methylpropionyl)amino]-8*H*-imidazo[1,2-*a*]-*s*-triazin-4-one (8b). From the slower migrating zone 380 mg (29%) of the β-anomer was obtained as colorless needles (MeOH), mp 195–197 °C: TLC (B) R_f 0.60; UV (MeOH) λ_{max} 250 nm (ϵ 13700), 242 (38100); ^{1}H NMR ($CDCl_3$) δ 8.22 (s, NH), 7.94 (d, J = 8.2 Hz, toluoyl), 7.85 (d, J = 8.2 Hz, toluoyl), 7.36 (d, J = 2.7 Hz, H-6), 7.26 (d, J = 8.2 Hz, toluoyl), 7.21 (d, J = 8.2 Hz, toluoyl), 7.11 (d, J = 2.7 Hz, H-7), 6.47 (pseudo-t, $J(1',2'_b)$ = 7.0 Hz, H-1'), 5.73 (m, H-3'), 4.75 (m, H-4'), 4.63 (m, H-5'), 3.14 (pseudo-q, $J(2'_b,1')$ = 6.8 Hz, H_b-2'), 2.85 (m, H_a-2' and CH), 2.42 and 2.39 (s, 2 CH_3, toluoyl), 1.23 and 1.21 (s, 2 CH_3, isobutyryl). Anal. Calcd for $C_{30}H_{31}N_5O_7$: C, 62.82; H, 5.45; N, 12.21. Found: C, 62.85; H, 5.47; N, 12.25.

Glycosylation of 4b in the Presence of Sodium Hydride. Compound **4b** (100 mg, 0.45 mmol) was dissolved in dry acetonitrile (20 mL) and NaH (20 mg, 0.83 mmol) was added. After stirring for 10 min at room temperature under nitrogen, the halogenose **7a** (250 mg, 0.64 mmol) was added and stirring was continued for 60 min at ambient temperature and then for another 15 min at 50 °C. The reaction mixture was filtered and evaporated to dryness, and the residue was chromatographed on silica gel 60H (20 × 6 cm, 0.5 bar) with solvent A. From the faster migrating

zone 125 mg (49%) of the α-anomer was obtained as colorless needles upon crystallization from MeOH. From the slower migrating zone 65 mg (25%) of the β-anomer was crystallized (MeOH). Both compounds were identical with those obtained by solid–liquid phase-transfer glycosylation in all respects.

Glycosylation of 3 with 7b Employing Purine Nucleoside Phosphorylase. Compound **3** (5 mg, 0.033 mmol) was suspended in Sörensen phosphate buffer (0.07 M, pH 7.5), and 2-deoxy-α-D-ribofuranose 1-phosphate (**7b**) (10 mg, 0.049 mmol) was added after addition of purine nucleoside phosphorylase from bovine spleen (3.25 units); the reaction mixture was stirred at 25 °C for 2 h. From the supernatant solution a sample of 10 μL was taken and applied on a TLC plate. As reference compounds authentic samples of the β-nucleoside **1** and the α-nucleoside **2** were used. Tenfold development of the plate in solvent D identified the enzymatically prepared nucleoside as the faster migrating β-anomer.

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Registry No. 1, 110457-87-9; 2, 110457-88-0; 3, 67410-64-4; 4b, 110472-07-6; 5, 110457-84-6; 7a, 4330-21-6; 7b, 17039-17-7; 8a, 110457-85-7; 8b, 110457-90-4; 9a, 110457-86-8; 9b, 110457-89-1; *N,N*-dimethylformamide diethyl acetal, 1188-33-6.

Practical Enantioselective Synthesis of a Homotyrosine Derivative and (*R,R*)-4-Propyl-9-hydroxynaphthoxazine, a Potent Dopamine Agonist

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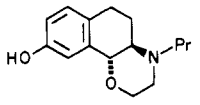
Two enantioselective routes were developed to prepare chiral amino acid derivative **4**. The key step in the first route was catalytic hydrogenation of acrylate derivative **3** using chiral rhodium catalysts. In the second route the key step was acylation of 2-chloroanisole with (*R*)-aspartic anhydride (**8**), wherein chlorine acts as a removable directing group. Cyclization of (*R*)-homotyrosine **4b** to tetralone **13** and reduction to tetralol **14** occurred with preservation of enantiomeric purity. The process for converting amide **19** to (*R,R*)-4-propyl-9-hydroxynaphthoxazine [(+)-PHNO, **1**] has been simplified and optimized.

Introduction

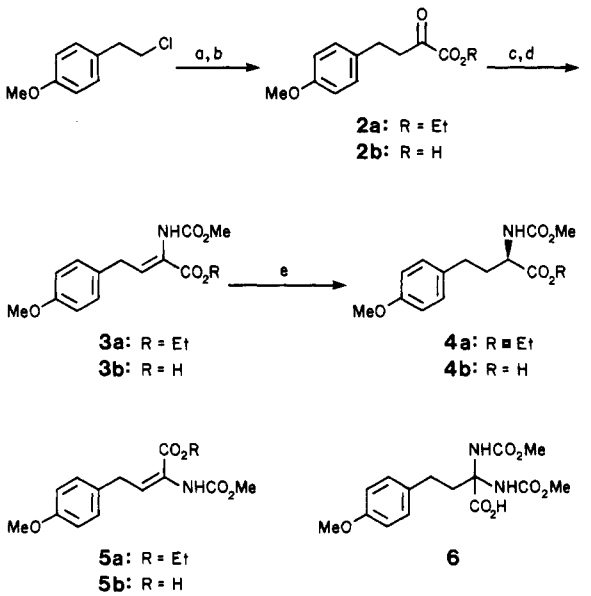
A new class of dopamine agonists recently has attracted attention[1] due to tremendous potency and a selective mode of action at the D_2 receptors. In particular, (*R,R*)-4-propyl-9-hydroxynaphthoxazine [(+)-PHNO, **1**] has therapeutic potential for treatment of Parkinson's disease.[2] The previously reported[1] syntheses of **1** began with 7-methoxy-1-tetralone and required a resolution to obtain the pharmacologically active *R,R* enantiomer. Herein we describe the first enantioselective synthesis of **1**.



1

In designing a practical, asymmetric synthesis we chose (*R*)-homotyrosine **4** as our intermediate target.[3] Incentive for this approach was provided by the intramolecular Friedel–Crafts cyclization of aryl amino acids developed by McClure and co-workers[4] and more recently by Nordlander[5] and Rapoport.[6] Based on these reports, we believed that enantiomeric purity could be preserved in going from (*R*)-homotyrosine **4b** to the enantiomerically secure bicyclic intermediate **14**. Furthermore, we concluded that a practical, enantioselective synthesis of the requisite am-

Scheme I[a]



[a] (a) Mg/THF; (b) $(EtO_2C)_2$; H_3O^+; (c) H_2NCO_2Me/*p*-TSA/tol/reflux/$-H_2O$; (d) HCl/tol/80 °C; (e) H_2 (3 atm)/[Rh(NBD)-((*S,S*)-chiraphos)]ClO_4/MeOH.

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