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Nucleoside Syntheses, XXV [1]

A New Simplified Nucleoside Synthesis [2]

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The several steps of the Friedel-Crafts catalyzed silyl-Hilbert-Johnson nucleoside synthesis – silylation of the heterocyclic base, silylation of the perfluorosulfonic acids or its salts (if $SnCl_4$ is not used as catalyst) and finally the nucleoside synthesis itself – can be combined to a simple one-step/one-pot reaction which generally affords nucleosides in high yields.

Nucleosid-Synthesen, XXV [1]

Eine neue einfache Nucleosid-Synthese

Die verschiedenen Schritte der Friedel-Crafts-katalysierten Silyl-Hilbert-Johnson-Nucleosid-Synthese – Silylierung der heterocyclischen Base, Silylierung der Perfluorsulfonsäuren oder ihrer Salze (falls nicht $SnCl_4$ als Katalysator benutzt wird) und schließlich die Nucleosid-Synthese selbst – können zu einer einfachen Einstufen-Eintopf-Reaktion vereinigt werden, die allgemein Nucleoside in hohen Ausbeuten ergibt.

1) Introduction

The reaction of persilylated heterocyclic bases with peracylated sugars in the presence of Friedel-Crafts catalysts like $SnCl_4$ [3,4] or $(CH_3)_3SiSO_3CF_3$, $(CH_3)_3SiSO_3C_4F_9$ or $(CH_3)_3SiClO_4$ [5] has become a standard synthetic method for the preparation of pyrimidine, purine as well as other nucleosides.

Prior to nucleoside synthesis however, the heterocyclic bases have to be silylated by heating with excess hexamethyldisilazane (HMDS) to the highly moisture sensitive persilyl derivatives which either have to be distilled or repeatedly evaporated with absol. xylene to remove the excess of HMDS.

For the synthesis of nucleosides of more basic heterocyclic systems like persilylated 5-methoxyuracil, 4-pyridone etc., the new Lewis acids or Friedel-Crafts catalysts $(CH_3)_3SiSO_3CF_3$, $(CH_3)_3SiSO_3C_4F_9$ or $(CH_3)_3SiClO_4$ [5,6] must be employed as catalysts instead of $SnCl_4$ in order to obtain the natural *N*-1-nucleosides in high yields [5]. And these catalysts have also to be prepared *prior* to nucleoside synthesis by heating the free triflate or nonaflate acids with trimethylchlorosilane [7] or by treating a toluene solution of silver perchlorate with trimethylchlorosilane [8].

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2) The One-Step/One-Pot Reaction

Since silylations are accelerated by Lewis acids[9] and the silylation of the heterocyclic bases would consequently be quite rapid in the presence of Friedel-Crafts catalysts, we have combined the different steps of nucleoside synthesis: a) the silylation of the heterocyclic bases, b) the silylation of the triflate or nonaflate acids or salts including the perchlorates (if $SnCl_4$ is not used as a catalyst), c) the nucleoside synthesis with acylated 1-*O*-acyl or 1-*O*-alkyl sugars in the presence of Friedel-Crafts catalysts, in a one-step/one-pot procedure employing a polar solvent like acetonitrile.

Under these conditions the amounts of trimethylchlorosilane (TCS) and hexamethyldisilazane (HMDS) have to be chosen in such a way that all reactive heterocyclic hydroxy, mercapto or amino groups as well as the free triflate or nonaflate acids $C_nF_{2n+1}SO_3H$[10], their corresponding salts[10] and perchlorate salts are silylated with formation of NH_4Cl and the corresponding alkali chlorides, NaCl or KCl. Since we are dealing with Friedel-Crafts catalyzed reactions it is crucial that only NH_4Cl is obtained, NH_3 would neutralize the Friedel-Crafts catalyst!

Because practically all of these salts are rather insoluble in acetonitrile, they precipitate when formed and therefore might shift the reactions towards the desired electrophilic trimethylsilyl esters as depicted in the following equations:

$$3\ CF_3SO_3H + HMDS + TCS \longrightarrow 3\ (CH_3)_3SiSO_3CF_3 + NH_4Cl \quad (1)$$

$$C_4H_9SO_3K^{10)} + TCS \longrightarrow (CH_3)_3SiSO_3C_4F_9 + KCl \quad (2)$$

$$NH_4ClO_4 + TCS \longrightarrow (CH_3)_3SiClO_4 + NH_4Cl \quad (3)$$

$$NaBF_4 + TCS \longrightarrow (CH_3)_3SiBF_4 + NaCl \quad (4)$$

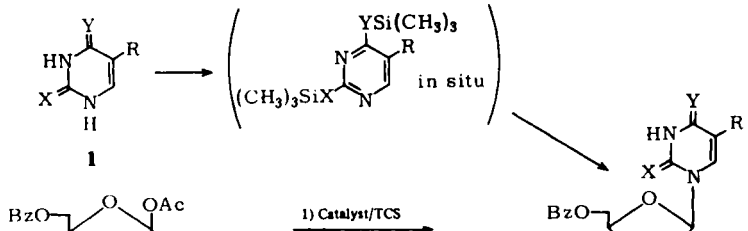
Although trimethylsilyltetrafluoroborate (equation (4)) has been described to decompose at ambient temperature to trimethylfluorosilane and BF_3[11], it might still act as a catalyst during its transient existence. It is more probable however that the BF_3 formed by decomposition of $(CH_3)_3SiBF_4$ will act as catalyst, since BF_3 has already been shown to be an effective catalyst for nucleoside formation in form of its etherate[3a].

Since potassium nonaflate ($C_4F_9SO_3K$)[10] is only partially soluble in boiling acetonitrile and potassium or ammonium perchlorate are nearly insoluble in acetonitrile, NaCl, KCl or NH_4Cl which are formed on reaction with TCS could thus occlude unreacted reagent. Therefore an excess of finely powdered $C_4F_9SO_3K$ or perchlorates was usually employed. In the case of the better soluble $NaClO_4 \cdot H_2O$ additional amounts of TCS and HMDS had to be used to eliminate the water.

As described in equation (1) for free triflic acid (CF_3SO_3H), a mixture of ca. 0.33 – 0.40 equivalents of TCS and HMDS was used whereas for potassium nonaflate ($C_4F_9SO_3K$) (equation (2)) equivalent amounts of TCS had to be employed.

For silylating uracil (**1a**), cytosine (**1d**) or a purine like N^2-acetylguanine (**14b**) containing two reactive oxygen, or oxygen and nitrogen functions, a mixture of a least 0.7 – 0.8 equ. each of TCS and HMDS are necessary to afford the persilylated uracil, cytosine or purine with concomitant formation of ca. 0.7 – 0.8 equ. of NH_4Cl. For a heterocyclic base like 4-pyridone (**7**) with only one reactive oxygen group, only half of that amount e. g. ca. 0.4 equ. each of TCS and HMDS is needed.

We studied first the formation of uridine 2',3',5'-tri-*O*-benzoate (**3a**) starting from uracil (**1a**) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) in acetonitrile trying several combinations of catalysts, TCS and HMDS. In practice, this one-pot reaction is conducted by weighing the crystalline free bases, the acylated sugars and salts into a dried reaction flask connected to a reflux condenser and a drying tube, then adding the absolute solvent and HMDS and finally the liquid Lewis acids TCS, $SnCl_4$ or CF_3SO_3H with magnetic stirring.



1 **2** **3**

	X	Y	R
a	O	O	H
b	S	O	H
c	O	O	OCH_3
d	O	NH	H
e	O	NAc	H

As is readily seen from Table 1, the synthesis of uridine 2',3',5'-tri-*O*-benzoate (**3a**), proceeded optimally in ca. 81 – 84% yield either with free triflic acid, potassium nonaflate or with $SnCl_4$ as catalysts. The stronger Friedel-Crafts catalyst $SnCl_4$[5] was effective at room temperature.

The perchlorate and tetrafluoroborate catalysts however afforded **3a** only in 40 – 60% yield. But this is not of importance as the use of perchlorates should be avoided due to their explosion hazard.

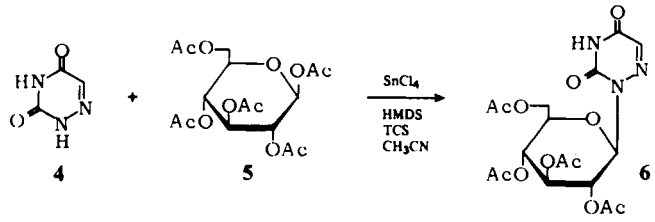
Table 1. One-step/one-pot reactions

Base/Sugar (1 equ.)	Acid or Salt	TCS/HMDS (equ.)	Reaction Time/ Temperature	Acylated Nucleoside (Yield)
1a/2	CF_3SO_3H[a]	1.2/1.1	1 h/83 °C	**3a** (81%)
1a/2	$C_4F_9SO_3K$[b]	3.1/0.7	14 h/83 °C	**3a** (84%)
1a/2	$SnCl_4$[a]	0.8/0.8	2 h/24 °C	**3a** (83%)
1a/2	NH_4ClO_4[b]	3.1/0.7	19 h/83 °C	**3a** (40%)
1a/2	$NaClO_4 \cdot H_2O$[b]	4.7/2.3	19 h/83 °C	**3a** (58%)
1a/2	$NaBF_4$[b]	3.1/0.7	2 h/83 °C	**3a** (43%)
1b/2	$SnCl_4$[a]	0.8/0.8	7 h/24 °C	**3b** (59%)
1c/2	$C_4F_9SO_3K$[b]	3.1/0.7	20 h/83 °C	**3c** (71%)
1d/2	$C_4F_9SO_3K$[b]	3.1/0.7	27 h/83 °C	**3d** (56%)

[a] 1.2 equivalents. – [b] 2.4 equivalents.

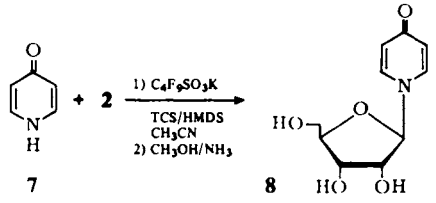
2-Thiouracil (**1b**) with $SnCl_4$ as catalyst gave 2-thiouridine 2',3',5'-tri-*O*-benzoate (**3b**) in ca. 60% yield. The more basic 5-methoxyuracil (**1c**)[3f,5] as well as cytosine (**1d**) reacted with **2** in the presence of potassium nonaflate/TCS/HMDS to afford crystalline 2',3',5'-tri-*O*-benzoyl-5-methoxyuridine (**3c**) in 71% as well amorphous cytidine 2',3',5'-tri-*O*-benzoate (**3d**) in 56% yield. The analogous reaction of N^4-acetylcytosine (**1e**) followed by saponification with methanolic ammonia gave 59% of pure crystalline cytidine.

6-Azauracil (**4**) reacted with pentaacetyl-β-D-glucopyranose (**5**) in the presence of $SnCl_4$/TCS/HMDS to furnish the known[3a] crystalline nucleoside **6** in 42% yield.



4 **5** **6**

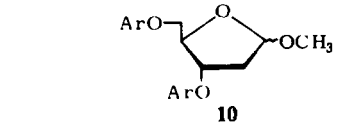
The rather basic 4-pyridone **7**[5] and **2** were converted by potassium nonaflate/TCS/HMDS and saponification in 50% yield into the known[3e] **8**.



7 **8**

The oily anomeric mixture of 2-deoxy-1-*O*-methyl-3,5-di-*p*-toluoyl-D-ribofuranose (**10**) and 2-deoxy-1-*O*-methyl-3,4-di-*p*-toluoylribopyranose (**11**) is commonly used as starting material for the preparation of crystalline 1α-chloro-2-deoxy-3,5-di-*p*-toluoyl-β-D-ribofuranose[12]. Since the formation of the 1-cation from the furanosides **10** is kinetically favored over the 1-cation from the pyranosides **11**[13], we reacted the mixture of **10** and **11** with 5-ethyluracil (**9**)[5] in the presence of potassium nonaflate/TCS/HMDS and obtained after chromatography and crystallization 26% of the pure crystalline β-anomer **12** as well as 21% of the corresponding α-anomer **13**. As expected[5] no pyranoside nucleosides were formed.

The purine bases N^6-benzoyladenine (**14a**) and N^2-acetylguanine (**14b**) afforded on reaction with **2** in the presence of potassium nonaflate/TCS/HMDS and subsequent saponification with methanolic ammonia, crystalline adenosine (**15a**) in 63% and cristalline guanosine (**15b**) in 44% yield.



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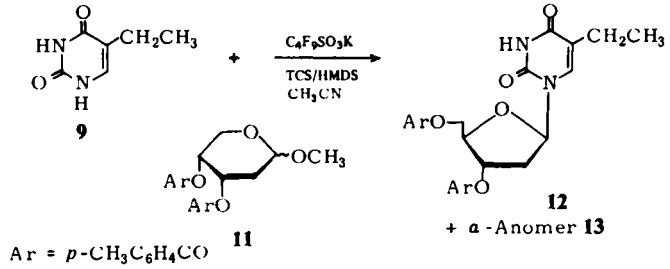
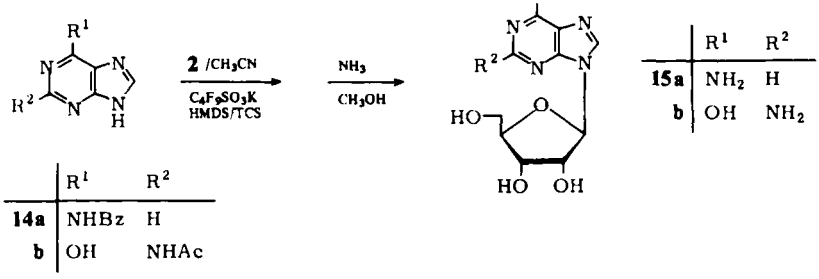


9 11 12

+ α-Anomer 13

Ar = p-$CH_3C_6H_4CO$



	R^1	R^2
14a	NHBz	H
b	OH	NHAc

	R^1	R^2
15a	NH_2	H
b	OH	NH_2

3) Solvents

Besides acetonitrile, which appears to be optimal in respect to polarity, solubility of inorganic salts and boiling point, other polar solvents like nitromethane can probably also be used.

On conducting the one-step/one-pot reaction between uracil (**1a**), **2** and $SnCl_4$ in the unpolar solvent 1,2-dichloroethane, ca. 30% of the *N*-3-nucleoside as well as ca. 5 – 10% *N*-1,*N*-3-bis-riboside were formed in addition to the desired uridine 2′,3′,5′-tri-*O*-benzoate (**3a**).

This is probably due to the increased salt concentration in the reaction mixture and enhanced σ-complex formation at N-1 of the silylated uracil[3f,6] in 1,2-dichloroethane.

Since the polar solvent acetonitrile competes with the silylated bases for the Lewis acids, these salts usually do not interfere with nucleoside formation in acetonitrile[14].

An exception is however the one-step reaction between 6-methyluracil, **2** and potassium nonaflate/TCS/HMDS in acetonitrile which afforded only ca. 20 – 25% of the desired 2′,3′,5′-tri-*O*-benzoyl-6-methyluridine besides 20 – 25% of the undesired benzoylated *N*-3-riboside and 15 – 20% of the benzoylated *N*-1,*N*-3-bis-riboside.

In comparison, silylated 6-methyluracil reacted with **2** and trimethylsilyl triflate [$(CH_3)_3SiSO_3CF_3$] in acetonitrile to give 2′,3′,5′-tri-*O*-benzoyl-6-methyluridine in more than 70% yield[5]. This striking difference in yield is due to the fact that this particular

reaction is especially sensitive towards humidity, alcohols, acetic acid or inorganic salts[3b,5] and therefore *not* suitable for this one-step/one-pot nucleoside synthesis. Apart from this exception however, the present procedure can be applied to practically any type of nitrogen heterocycle containing a reactive oxygen, sulfur or nitrogen function.

Although some of the yields obtained with this simple one-step/one-pot reaction are lower compared to the conventional two-step reaction[3-5], the new procedure is so simple and rapid that it can also be applied by biochemists, biologists and physicists with very limited chemical training. Since our preliminary publication[2] we have used this one-step nucleoside synthesis for the preparation of 3-amino-6-β-D-ribofuranosyl-6*H*-1,2,6-thiadiazine 1,1-dioxide[15] and have furthermore heard from quite a number of colleagues about successful applications of this simple nucleoside synthesis[16].

We thank Drs. *D. Rosenberg* and *A. Seeger* for the spectral data and Dr. *K. Merz* for the analyses.

Experimental Part

Materials: The solvents acetonitrile and 1,2-dichloroethane were purified as previously described[3,5]. Trimethylchlorosilane (TCS), hexamethyldisilazane (HMDS) and $SnCl_4$ were redistilled materials. The heterocyclic bases and standard sugars were commercial samples and purified by recrystallization as described[3,5]. The potassium nonaflate ($C_4F_9SO_3K$) was obtained from Dr. *Niederprüm*[10] (Bayer AG). All products were identified with authentic samples.

Thin layer systems[3,5]: A toluene/acetic acid/H_2O (5:5:1), B n-butanol/acetic acid/H_2O (5:1:4).

Workup after nucleoside synthesis: Employing ca. 75 ml absol. acetonitrile ca. 100 ml CH_2Cl_2 were added and the mixture extracted with sat. $NaHCO_3$-solution. After reextracting the aqueous phase with CH_2Cl_2, the combined organic phase was washed with sat. NaCl-solution, dried (Na_2SO_4) and evaporated.

Workup after saponification with methanolic ammonia[5]*:* After evaporation of the methanolic ammonia the residue was taken up in water and extracted twice with ether to remove methyl benzoate and benzamide. The aqueous phase was then evaporated and the residue recrystallized.

Uridine 2',3',5'-tri-O-benzoate (**3a**): a) *With CF_3SO_3H/HMDS/TCS as catalyst:* To 1.12 g (10 mmol) uracil (**1a**) and 5.04 g (10 mmol) 1-*O*-acetyl-2,3,5-tri-benzoyl-β-D-ribofuranose (**2**) in 100 ml absol. acetonitrile 2.3 ml (11 mmol) HMDS, 1.5 ml (12 mmol) TCS and 1.05 ml (12 mmol) trifluoromethane sulfonic acid were added consecutively whereupon the reaction temperature rose to ca. 35°C. After ca. 1 h the clear solution became turbid. Since acc. to t.l.c. (system A) the reaction had only partially proceeded after 4 h, the mixture was refluxed for $1\frac{1}{2}$ h with exclusion of humidity. After workup the crude product (5.85 g) was crystallized partially from ethanol to afford in two crops 2.05 g pure **3a**. The mother liquor was evaporated and chromatographed in toluene-ethyl acetate on a column of ca. 200 g silicagel. Elution with toluene-ethyl acetate 99:1 (1 l) and 98:2 (3 l) afforded impurities, whereas elution with 95:5 (2 l), 90:10 (2.5 l) as well as 80:20 (2 l) gave 2.55 g of crystalline **3a**. Combined yield 4.50 g (80.8%) **3a**.

b) *With $C_4F_9SO_3K$ as catalyst:* 0.56 g (5 mmol) uracil (**1a**), 2.52 g (5 mmol) **2** and 4.06 g (12 mmol) $C_4F_9SO_3K$ were refluxed in 70 ml acetonitrile for 14 h with 0.74 ml (3.5 mmol) HMDS and 1.89 ml (15 mmol) TCS. Workup, crystallization and chromatography of the mother liquor afforded 2.32 g (83.5%) **3a**.

c) *With $SnCl_4$ as catalyst:* To 0.56 g (5 mmol) uracil (**1a**) and 2.52 g (5 mmol) **2** in 75 ml acetonitrile were added 0.84 ml (4 mmol) HMDS, 0.51 ml (4 mmol) TCS and finally 0.71 ml (6 mmol) $SnCl_4$ in 25 ml acetonitrile. After 2 h stirring at 24 °C, workup gave 2.94 g crude **3a**, which cristallized from ethanol to furnish in 2 crops 1.72 g **3a**. Chromatography of the mother liquor as described above afforded another crop of 0.59 g **3a**. Combined yield of **3a** 2.31 g (83%).

2-Thiouridine 2',3',5'-tri-O-benzoate (**3b**): To 0.64 g (5 mmol) 2-thiouracil (**1b**) and 2.52 g (5 mmol) **2** in 50 ml absol. acetonitrile were added 0.84 ml (4 mmol) HMDS, 0.51 ml (4 mmol) TCS and finally 0.71 ml (6 mmol) $SnCl_4$ in 25 ml acetonitrile. After a short period of magnetic stirring everything had dissolved. The mixture was worked up after $6\frac{1}{2}$ h at 24 °C to give 2.75 g crude **3b** which crystallized from ethanol to afford in two crops 1.68 g (58.5%) of pure crystalline **3b**, mp. 105 – 106 °C (lit. 105 – 106 °C)[17]. Acc. to t.l.c. (system A) the mother liquor still contained some additional **3b**.

5-Methoxyuridine 2',3',5'-tri-O-benzoate (**3c**): To 0.53 g (5 mmol) 5-methoxyuracil (**1c**), 2.52 g (5 mmol) **2** and 3.84 g (12 mmol) $C_4F_9SO_3K$ in 50 ml acetonitrile were added 0.74 ml (3.5 mmol) HMDS and 1.89 ml (15 mmol) TCS and the mixture refluxed for 20 h. After workup the crude product (3.72 g) crystallized in two crops from ethyl acetate-hexane to afford 2.09 g (71.3) of pure crystalline **3c**, mp. 206 – 208 °C. Acc. to t.l.c. the mother liquor still containing some **3c**.

Cytidine 2',3',5'-tri-O-benzoate (**3d**): To 0.55 g (5 mmol) cytosine (**1d**), 2.52 g (5 mmol) **2** and 4.06 g (12 mmol) $C_4F_9SO_3K$ in 70 ml absol. acetonitrile were added 0.74 ml (3.5 mmol) HMDS and 1.96 ml (15.5 mmol) TCS and the mixture refluxed for 26 h. After workup, the crude product (3.26 g) gave on chromatography on 100 g silicagel and elution with toluene-ethyl acetate 4:1 → 3:2 /5 l) impurities. Elution with ethyl acetate (3.5 l) afforded 1.55 g (56%) of homogenous amorphous **3d** which was identical with an authentic sample.

Cytidine: 1.53 g (10 mmol) N^4-acetylcytosine (**1e**), 50.4 g (10 mmol) **2**, 8.12 g (24 mmol) $C_4F_9SO_3K$ in 140 ml absol. acetonitrile were refluxed for 21 h with 1.48 ml (7 mmol) HMDS and 3.92 ml (31 mmol) TCS. After workup, the crude **3d** was dissolved in 150 ml methanolic ammonia and kept for 3 days at 24 °C. After workup, recrystallization from ethanol-H_2O afforded in three crops 1.68 g (59%) of pure crystalline cytidine, homogeneous in system B.

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-1,2,4-triazine-3,5(2H,4H)-dione (**6**): To 1.13 g (10 mmol) 6-azauracil (**4**), 3.9 g (10 mmol) 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**5**) and 1.68 ml (8 mmol) HMDS in 100 ml absol. acetonitrile were added 1.01 ml (8 mmol) TCS and finally 1.77 ml (15 mmol) $SnCl_4$ in 50 ml absol. acetonitrile. After 7 h stirring at 24 °C and workup, the crude product (4.5 g) crystallized from ethanol to afford 0.93 g of **6**, mp. 205 – 206 °C. Chromatography of the mother liquor on 50 g silicagel gave on elution with toluene-ethyl acetate 9:1 (1.5 l) and 8:2 (1.5 l) impurities, whereas elution with 7:3 (1 l) afforded on evaporation and crystallization from ethanol in several crops 0.94 g crystalline **6**. Total yield of **6** 1.87 g (42.2%), mp. 205 – 206 °C, which was identical with an authentic sample[3a].

1-(β-D-Ribofuranosyl)-4(1H)-pyridinone (**8**): To 0.47 g (5 mmol) 4(1*H*)-pyridinone (**7**), 2.52 g (5 mmol) **2** and 3.38 g (10 mmol) $C_4F_9SO_3K$ in 70 ml absol. acetonitrile were added 0.42 ml (2 mmol) HMDS and 1.52 ml (12 mmol) TCS and the mixture refluxed for 24 h, worked up and the crude product (2.7 g) saponified with 80 ml methanolic ammonia. After 2 days at 24 °C and workup the residue (1.68 g) was chromatographed on 75 g silicagel with isopropyl alcohol. After a 300 ml forun the subsequent fractions (1 l) eluted slightly impure **8** (0.7 g). Crystallization from ethanol gave 0.56 g (49.6%) of pure **8**, mp. 128 – 130 °C, which was identical with an authentic sample[3d].

1-(2-Deoxy-3,5-di-p-toluoyl-β-D-ribofuranosyl)-5-ethyluracil (**12**): To 2.60 g (6.76 mmol) anomeric sugar mixture **10/11**, 0.95 g (6.76 mmol) 5-ethyluracil (**9**) and 5.49 g (16.22 mmol)

$C_4F_9SO_3K$ in 70 ml absol. acetonitrile were added 0.99 ml (4.73 mmol) HMDS and 2.65 ml (21 mmol) TCS and the mixture refluxed for 12 h. After workup the crude product (4.92 g) was chromatographed on 250 g silicagel. Elution with hexane-ether 8:2 (1 l), 3:2 (1 l) and 1:1 (3 l) gave only impurities, whereas elution with hexane-ether 1:1 (1 l) and 2:3 (4 l) afforded 1.48 g (47.1) of a partly crystalline mixture of **12** and the corresponding α-anomer **13** which was separated by crystallization from ethanol to give 0.81 g (25.8%) crystalline β-anomer **12**, mp. 197 – 198 °C [3a] and about 0.67 g (21%) crystalline α-anomer **13**, mp. 160 – 161 °C [3a,5].

Adenosine (**15a**): To 1.19 g (5 mmol) N^6-benzoyladenine (**14a**), 2.52 (5 mmol) **2**, 4.06 g $C_4F_9SO_3K$ and 0.74 ml (3.5 mmol) HMDS in 70 ml acetonitrile were added 1.96 ml (15.5 mmol) TCS and the mixture refluxed for 21 h. After workup the crude product (3.9 g) was stirred with 100 ml sat. methanolic ammonia for 3 days at 24 °C. Workup and crystallization from a small volume of H_2O afforded in 4 crops 0.84 g (62.7%) pure adenosine (**15a**), homogeneous in system B.

Guanosine (**15b**): Exactly as described for the preparation of adenosine, N^2-acetylguanine (**14b**) was reacted with **2** and the crude acylated nucleoside saponified with methanolic ammonia to afford on crystallization from water in two crops 43.8% of crystalline guanosine (**15b**), homogeneous in system B.

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[1] Nucleoside Syntheses, Part XXIV cf. ref.[15].

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