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Nucleoside Syntheses, XXII[1]

Nucleoside Synthesis with Trimethylsilyl Triflate and Perchlorate as Catalysts[2]

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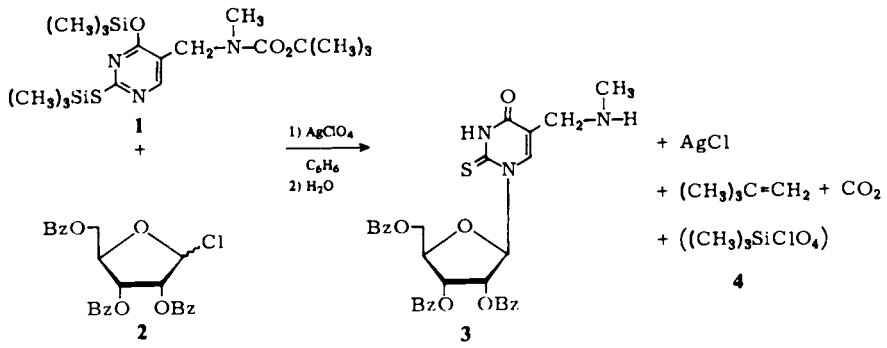
The novel Lewis acids $(CH_3)_3SiOSO_2CF_3$ (**5**), $(CH_3)_3SiOSO_2C_4F_9$ (**6**), and $(CH_3)_3SiClO_4$ (**4**) are highly selective and efficient Friedel-Crafts catalysts for nucleoside formation from silylated heterocycles and peracylated sugars as well as for rearrangements of persilylated protected nucleosides. With basic silylated heterocycles these new catalysts give much higher yields of the natural *N*-1-nucleosides than with $SnCl_4$.

Nucleosid-Synthesen, XXII[1]

Nucleosid-Synthese mit Trimethylsilyltriflat und Perchlorat als Katalysatoren

Die neuen Lewis-Säuren $(CH_3)_3SiOSO_2CF_3$ (**5**), $(CH_3)_3SiOSO_2C_4F_9$ (**6**) und $(CH_3)_3SiClO_4$ (**4**) sind sehr spezifische und effektive Friedel-Crafts-Katalysatoren für die Nucleosid-Synthese mit silylierten Heterocyclen und peracyclierten Zuckern sowie für die Umlagerung von persilylierten geschützten Nucleosiden. Insbesondere bei basischen silylierten Heterocyclen ergeben diese neuen Katalysatoren viel höhere Ausbeuten an natürlichen *N*-1-Nucleosiden als $SnCl_4$.

In the total synthesis[1] of the "rare" nucleoside 5-(methylaminomethyl)-2-thiouridine, the silylated 2-thiouracil **1** and 2,3,5-tri-*O*-benzoyl-D-ribofuranosylchloride (**2**) were reacted with $AgClO_4$[3,4,5] in absolute benzene to give unexpectedly the *O*-benzoylated nucleoside **3** in which the protecting *tert*-butoxycarbonyl (BOC) group had been lost during nucleoside formation and workup.



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Investigating this reaction, the only strong Lewis acid which could have been formed as an intermediate and could have cleaved the BOC group was $(CH_3)_3SiClO_4$ (**4**). **4** had already previously been postulated as an intermediate during nucleoside synthesis by *Birkofer* et al.[4] and *Wittenburg*[5].

We could subsequently show that $(CH_3)_3SiClO_4$ (**4**) as well as $(CH_3)_3SiOSO_2CF_3$ (**5**) are very interesting new Lewis acids or Friedel-Crafts catalysts and do indeed cleave BOC groups rather selectively in protected amino acids and peptides[6]. Further interesting applications of reagents like **4** and **5** e. g. for the preparation of trimethylsilyl enol ethers and silyl ethers of *tert.* alcohols, cleavage of epoxides and cycloadditions were subsequently described[7].

A. The New Catalysts

Recently, *Marsmann* and *Horn*[8] had measured the ^{29}Si-NMR shifts of a whole series of trimethylsilyl esters of strong acids $(CH_3)_3SiX$ with X ranging from CN, Br, F, Cl to SO_4, ClO_4 and OSO_2CF_3. They estimated the pK values of these new Lewis acids and demonstrated that $(CH_3)_3SiClO_4$ (**4**)[9] and even more so $(CH_3)_3SiOSO_2CF_3$ (**5**)[8,10] were far stronger acids than others in these series. *Marsmann* and *Horn* however did not include higher homologues of $(CH_3)_3SiOSO_2CF_3$ (**5**) like $(CH_3)_3SiOSO_2C_4F_9$ (**6**) as well as $(CH_3)_3SiOSO_2F$[11] which probably possess about the same acidic strength than $(CH_3)_3SiClO_4$ (**4**) and $(CH_3)_3SiOSO_2CF_3$ (**5**)[12].

Encouraged by these acidity data we initially tested $(CH_3)_3SiClO_4$ (**4**) and $(CH_3)_3SiOSO_2CF_3$ (**5**) as well as other acidic silyl compounds like $(CH_3)_3SiCl$ and $[(CH_3)_3Si]_2SO_4$[8] as potential new catalysts for the synthesis of nucleosides.

$(CH_3)_3SiClO_4$ (**4**)[9], $(CH_3)_3SiOSO_2CF_3$ (**5**)[8,10], and $(CH_3)_3SiOSO_2C_4F_9$ (**6**) are readily prepared by the following reactions:

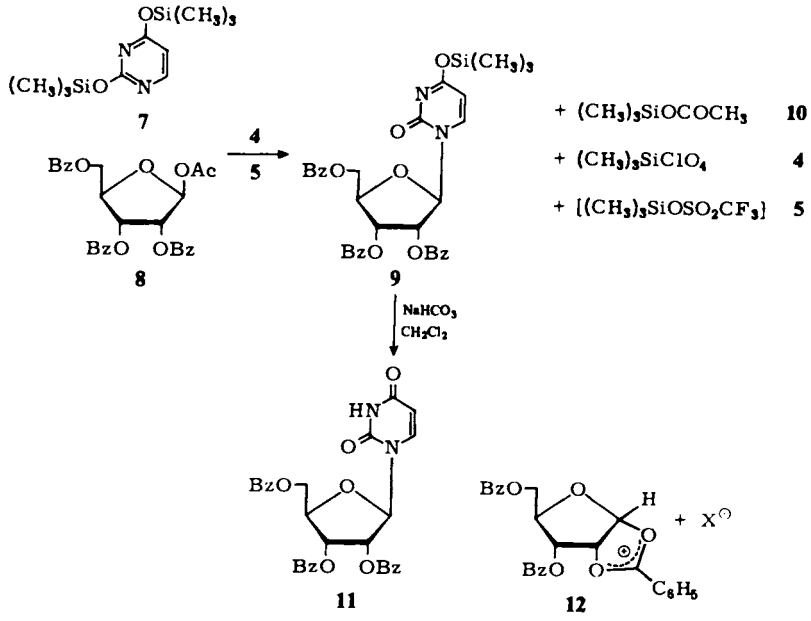
$$(CH_3)_3SiCl + AgClO_4 \xrightarrow[\text{or toluene}]{\text{benzene}} \underset{\mathbf{4}}{(CH_3)_3SiClO_4} + AgCl\downarrow$$

$$(CH_3)_3SiCl + CF_3SO_3H \xrightarrow[\Delta]{\text{neat}} \underset{\mathbf{5}}{(CH_3)_3SiOSO_2CF_3} + HCl\uparrow$$

$$(CH_3)_3SiCl + C_4F_9SO_3H \xrightarrow[\Delta]{\text{neat}} \underset{\mathbf{6}}{(CH_3)_3SiOSO_2C_4F_9} + HCl\uparrow$$

We first reacted silylated uracil **7** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**8**) in the presence of **4** and **5** in 1,2-dichloroethane or acetonitrile and obtained the silylated intermediate **9**[13] as well as the silyl ester of acetic acid **10** and regenerated **4** or **5**. The workup with aqueous $NaHCO_3/CH_2Cl_2$ did not give rise to any emulsions (as were often obtained with $SnCl_4$) to afford pure crystalline uridine tri-*O*-benzoate (**11**) in more than 80% yield.

Due to σ-complex formation between **4** or **5** and the silylated base[14], one equivalent of **4** or **5** is inactivated during nucleoside formation. Thus application of 1.1 – 1.3 equivalents of the catalysts **4** and **5** dramatically shortens the reaction time. Such a slight excess of catalyst is therefore *preferable* to working with catalytic (0.1 equ.) amounts of **4** and **5**, because much more stringent reaction conditions must then be used (compare chapter B. 1.).



In contrast to **4** and **5**, trimethylsilyl chloride $(CH_3)_3SiCl$ as well as bis(trimethylsilyl) sulfate $[(CH_3)_3Si]_2SO_4$[8] as catalysts for the reaction of **7** with **8** *did not afford any nucleoside.* Apparently neither catalyst is a strong enough Lewis acid to convert 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**8**) into the reactive electrophilic sugar cation **12**[15].

A slight excess of trimethylsilyl fluorosulfonate[11], which we also consider to be a very strong Lewis acid[12], did not give any uridine tri-*O*-benzoate (**11**). Apparently $(CH_3)_3SiOSO_2F$ causes side reactions which prevent nucleoside formation.

Thus, we concentrated initially on $(CH_3)_3SiClO_4$ (**4**) and $(CH_3)_3SiOSO_2CF_3$ (**5**). Due to the explosive nature of pure $(CH_3)_3SiClO_4$ (**4**)[4] and the relative high cost of trifluoromethane sulfonic acid (triflic acid), we used later increasingly $(CH_3)_3SiOSO_2C_4F_9$ (**6**) which is readily prepared from the commercially available $C_4F_9SO_3K$ (potassium nonaflate)[16] either *via* the free nonaflic acid $C_4F_9SO_3H$ by heating with $(CH_3)_3SiCl$ as described above or by reaction of the stable potassium nonaflate ($KOSO_2C_4F_9$)[16] with $(CH_3)_3SiCl$ *in situ* in acetonitrile[17].

$$C_4F_9SO_3K + (CH_3)_3SiCl \xrightarrow[CH_3CN]{} \underset{\mathbf{6}}{(CH_3)_3SiOSO_2C_4F_9} + KCl\downarrow$$

$$\underset{\mathbf{13}}{HCF_2[CF_2]_3SO_3K} + (CH_3)_3SiCl \longrightarrow \underset{\mathbf{14}}{(CH_3)_3SiOSO_2C_4F_8H} + KCl$$

A further equally efficient catalyst is trimethylsilyl octaflate (**14**) which is prepared analogously from the readily available potassium octaflate **13**[16].

Persilylated polymeric perfluorinated sulfonic acids like Nafion® were not as yet tried as a catalyst. Such a catalyst would be easily recovered by filtration and reformed by heating with excess TCS.

It should be pointed out here that during workup with $NaHCO_3$, the collected mother liquors of experiments with trimethylsilyl triflate (**5**) can be evaporated and the triflate salts recrystallized from acetone[18]. In the case of trimethylsilyl nonaflate (**6**), on workup with $KHCO_3$, the slightly soluble salt $C_4F_9SO_3K$ can be easily recovered in up to 80% yield from the collected aqueous and organic phases by concentration and filtration (compare preparation of **18a**).

B. The Scope of Nucleoside Synthesis with the New Catalysts

1. Introduction

After the use of simple Friedel-Crafts catalysts like $SnCl_4$ in nucleoside synthesis had become widely accepted[19], the introduction of any new and more expensive catalysts like $(CH_3)_3SiOSO_2CF_3$ (**5**), $(CH_3)_3SiOSO_2C_4F_9$ (**6**) or $(CH_3)_3SiOSO_2C_4HF_8$ (**14**), although they can be recovered to a large extent, can only be justified if they have definite advantages over $SnCl_4$ or any of the other catalysts.

As already mentioned, in contrast to $SnCl_4$ no emulsions are formed on workup of the reaction mixture using **4**, **5** or **6** with $NaHCO_3/CH_2Cl_2$.

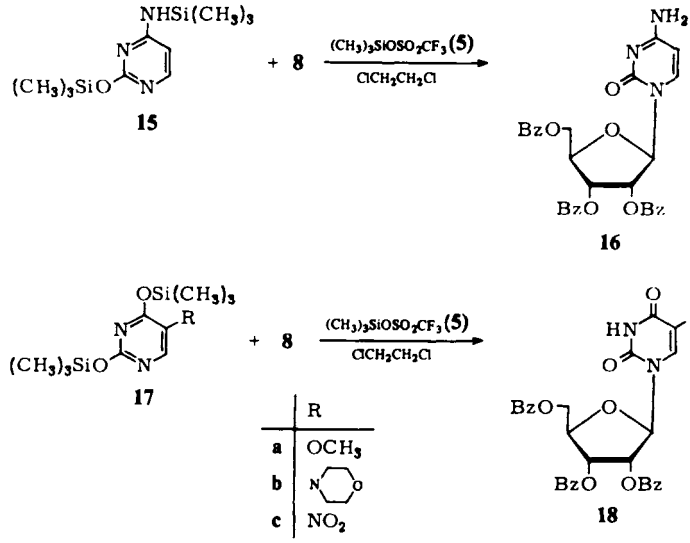
However, the major advantage which makes these new catalysts (**4**, **5**, **6**, **14**) in many cases vastly superior to $SnCl_4$ or other Friedel-Crafts catalysts[19a] is their lowered acidity as Lewis acids compared to $SnCl_4$. These new catalysts are just sufficiently acidic to form reactive sugar cations like **12** (compare also Chapter B. 6.), however they cause dramatically decreased σ-complex formation with silylated bases compared to $SnCl_4$ as discussed in the accompanying publication[14]. Consequently, much higher yields are obtained of the desired natural *N*-1-nucleosides in the case of more basic silylated heterocycles.

2. Synthesis of Pyrimidine and Pyridine Nucleosides

As we had observed and described before[19f], more basic silylated heterocycles like silylated cytosine or silylated uracils having electron donating methoxy or morpholino substituents in the 5-position lead to increasingly stable σ-complexes between the silylated bases and $SnCl_4$ and thus to longer reaction times and, most importantly, to increasing amounts of the undesired unnatural *N*-3-nucleosides.

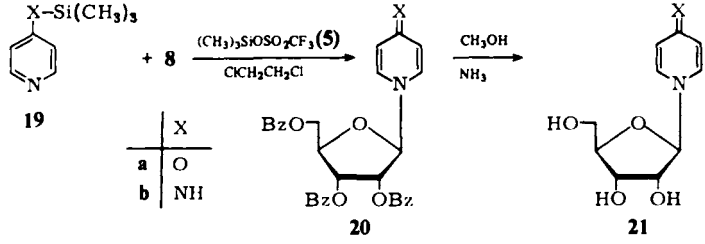
With catalytic amounts (0.1 equ.) of **5**, the basic silylated cytosine **15** reacted very slowly with **8** in boiling 1,2-dichloroethane. However, after adding a further amount of 1.1 equ. of **5** the reaction was complete after 1 h refluxing to afford a practically quantitative yield of amorphous cytidine 2′,3′,5′-tri-*O*-benzoate (**16**).

In the case of the rather basic silylated 5-methoxyuracil (**17a**) and 5-morpholinouracil (**17b**), using **5** instead of $SnCl_4$ dramatically improved the yield of the desired *N*-1-nucleosides **18a** and **18b** compared to $SnCl_4$. Thus, in 1,2-dichloroethane 89% **18a** were obtained compared to 53% using $SnCl_4$ and 95% **18b** compared to 39% with $SnCl_4$[19f].



As was expected, the reaction of the rather *weakly basic* silylated 5-nitrouracil (**17c**) with **8** using **5** as catalyst affords the 2',3',5'-tri-*O*-benzoyl-5-nitrouridine (**18c**) in 93% yield, thus showing no advantage over the corresponding reaction with $SnCl_4$ which gives also a nearly quantitative yield of **18c**[19a].

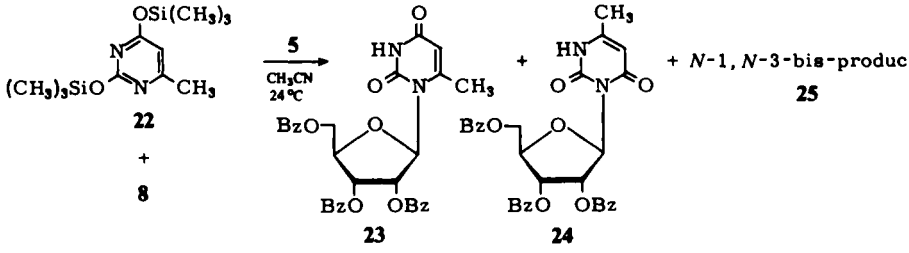
Reaction of the basic silylated 4-pyridone (**19a**) and silylated 4-aminopyridine (**19b**) with **8** and 1.2 equ. $(CH_3)_3SiOSO_2CF_3$ (**5**) afforded the nucleosides **20a** and **20b** in 83% and 80% yield. Saponification with methanolic ammonia gave the new nucleoside **21b**. The toxic 3-carboxy derivative of **21b** clitidine was recently isolated from the toadstool *Clitocybe acromelalga*[20].



It should be noted that **20a** is only formed in 63% yield under forcing conditions in the presence of $SnCl_4$[19d]. The analogous reaction of the even more basic silylated 3,4-diaminopyridine with **8** in the presence of **5** gave complicated mixtures which were not further investigated.

The less basic silylated 2-pyridone and **8** afforded with trimethylsilyl triflate (**5**) as with $SnCl_4$[19d] 85% of the desired 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone.

A further reaction which did not proceed satisfactorily with $SnCl_4$[19b] was the synthesis of benzoylated 6-methyluridine (**23**) starting from silylated 6-methyluracil (**22**).

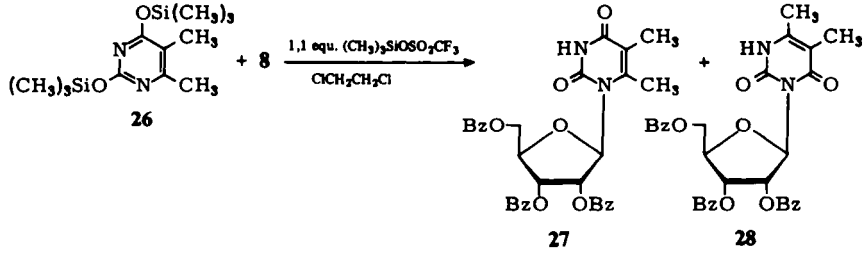


Using $(CH_3)_3SiOSO_2CF_3$ (**5**) instead of $SnCl_4$ in acetonitrile afforded 71% of **23** compared to 41% of **23** with $SnCl_4$[19b] besides varying amounts of the *N*-3 **24** as well as the *N*-1,*N*-3-bis-riboside **25**.

As described in chapter C the yield of the desired **23** can be further increased by rearrangement of silylated **24** and **25** to **23**.

In all these preparations of benzoylated 6-methyluridine (**23**)[19b], it is of paramount importance that the sugar moiety **8** is pure and absolutely free of solvent traces and the acetonitrile carefully dried by subsequent treatment with P_2O_5 and CaH_2.

The analogous reaction of silylated 5,6-dimethyluracil (**26**) with **8** and 1.1 equ. of **5** afforded in 1,2-dichloroethane 82% of the *N*-1-nucleoside **27** and only 9% of the *N*-3-nucleoside **28**.



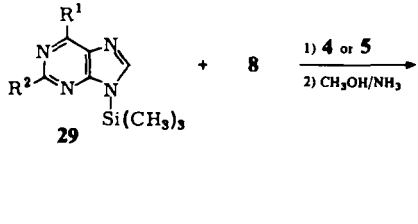
With $SnCl_4$ as catalyst[19b] in 1,2-dichloroethane *only* 10% of **27** and 60% of **28** and in acetonitrile 66% of **27** and 17% of **28** were obtained.

An additional methyl, isopropyl or nitro group[19f] in 5-position pushes the 4-*O*-trimethylsilyl group in 4-position towards the *N*-3-nitrogen which becomes therefore hindered. Thus substitution at *N*-1 is favored over substitution at *N*-3 and smaller amounts of the *N*-3-nucleoside are obtained. However, as discussed before[19f], the decreased basicity of silylated 6-methyl-5-nitrouracil favors also the formation of benzoylated 6-methyl-5-nitrouridine in the presence of **5**.

3. Synthesis of Purine and Pteridine Nucleosides

The following examples demonstrate that purine nucleosides are also readily accessable using **5** as catalyst[21]. The crude reaction mixtures obtained were saponified

directly with methanolic ammonia to the nicely crystalline free nucleosides. Adenosine (**30a**) was thus obtained in 81%, guanosine (**30b**) in 66% and xanthosine (**30c**) in 49% yield.

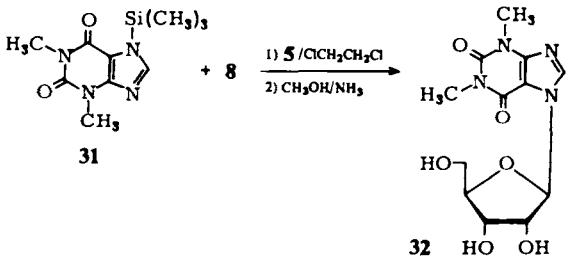


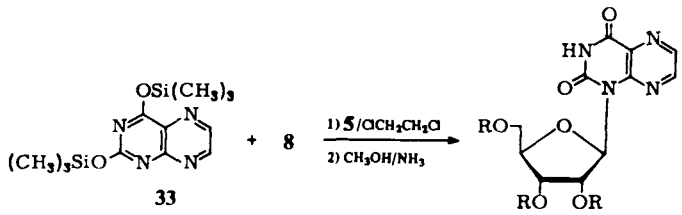
	R^1	R^2
29a	C_6H_5–CO–N–Si$(CH_3)_3$	H
b	$(CH_3)_3SiO$	$(CH_3)_3Si$–N–$COCH_3$
c	$(CH_3)_3SiO$	$(CH_3)_3SiO$

	R^1	R^2
30a	NH_2	H
b	OH	NH_2
c	OH	OH

During the synthesis of benzoylated adenosine[14], a number of intermediates are formed which are apparently gradually rearranged by **5** during the reaction to the acylated adenosine as studied in the case of the benzoylated adenine *N*-3-riboside (compare chapter C.).

Silylated theophylline (**31**) reacted analogously with **8** in the presence of **5** to give after saponification the known crystalline theophylline *N*-7-β-D-ribofuranoside[22] (**32**) in 82% yield.



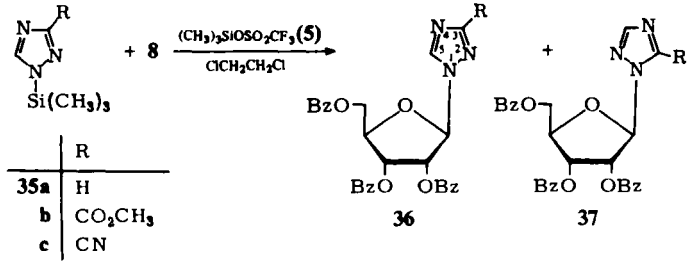


	R
34a	Bz
b	H

Silylated lumazine **33** gave after chromatography 93% of the amorphous 2',3',5'-tri-*O*-benzoylated nucleoside **34a** which had been obtained previously in 50% yield by the Wittenburg method[23]. Saponification of the tri-*O*-benzoate afforded 91% of the crystalline free nucleoside **34b**[23].

4. Synthesis of Triazole Nucleosides

Silylated 1,2,4-triazole **35a** gave on reaction with **8** in the presence of 1.2 equ. of $(CH_3)_3SiOSO_2CF_3$ (**5**) in 1,2-dichloroethane a 61% yield of the crystalline triazole riboside **36a**[24].



	R
35a	H
b	CO_2CH_3
c	CN

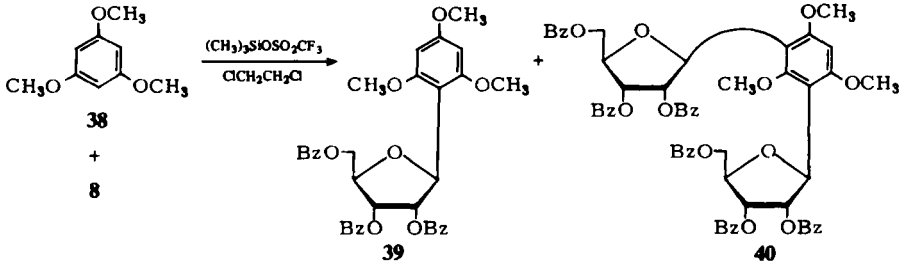
Reaction of silylated methyl 1,2,4-triazole-3-carboxylate **35b** with **8** and **5** in acetonitrile afforded 47% of the desired crystalline **36b**[25] as well as 19.6% of crystalline **37b**, 15.5% of **37c** and 2.3% of the decarboxylated product **36a**. The analogous reaction in 1,2-dichloroethane gave only 31.2% of the desired **36b** as well as 36.2% of **37b** and small amounts of **37c** and **36a**.

The mode of formation of **37c** is still unclear. It is possible that the ester moiety in methyl 1,2,4-triazolecarboxylate **35b** is partly converted during silylation, into the amide, which is subsequently dehydrated to the nitrile **37c** by HMDS or by **5** during nucleoside synthesis.

36b is readily converted by methanolic ammonia into the biologically interesting antiviral drug 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (ribavirin)[25].

5. Synthesis of *C*-Nucleosides

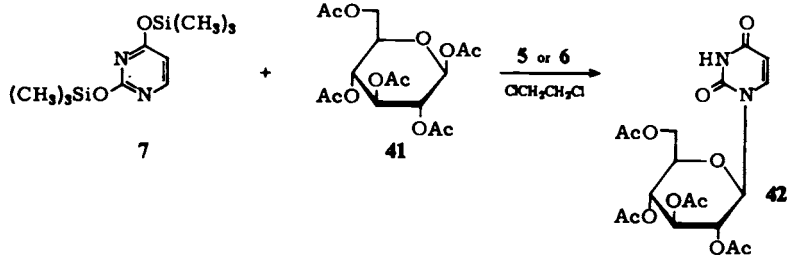
As discussed in the adjacent paper[14], the silyl-Hilbert-Johnson reaction in the presence of Friedel-Crafts catalysts is only a special version of the Friedel-Crafts reaction. Since rather stable sugar cations like **12**, which are formed during nucleoside synthesis, are only weak electrophiles, they can only react with electron-rich nucleophilic aromatic compounds. Thus while anisole did *not* react with **8**, 1,3,5-trimethoxybenzene (**38**) afforded 60% of the known crystalline β-nucleoside **39**[26] and 4.9% of the crystalline bis-product **40**. *N,N*-Dimethylaniline did not give any *C*-nucleoside. In the case of different di- or trimethoxybenzenes, other authors used stronger Lewis acids like $AlCl_3$ for the synthesis of such *C*-nucleosides and obtained α,β-mixtures[27].

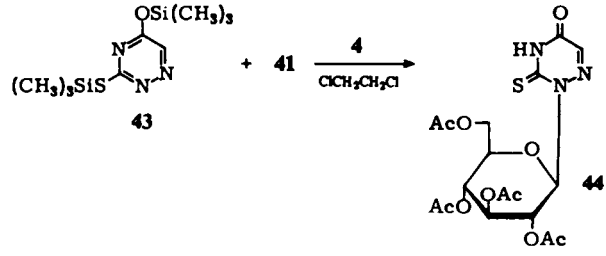


6. Variation of the Sugar Moiety

As we stated in chapter A, the new catalysts are just strong enough Friedel-Crafts catalysts to convert 1-*O*-acyl or 1-*O*-alkyl sugars into their corresponding cations e. g. 1-*O*-acetyl-2,3,5-tri-*O*-benzoylribofuranose (**8**) into the reactive intermediate **12**. Since the formation of furanosyl cations is kinetically favored over the corresponding pyranosyl cations[28], it was of interest to determine whether this difference in reactivity could be put to use.

We first reacted silylated uracil **7** with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**41**) and **5** and **6** as catalysts in boiling 1,2-dichloroethane and obtained the crystalline glucopyranoside **42**[29] in 89% and 92% yield respectively. This means that **5** and **6** give very similar results.





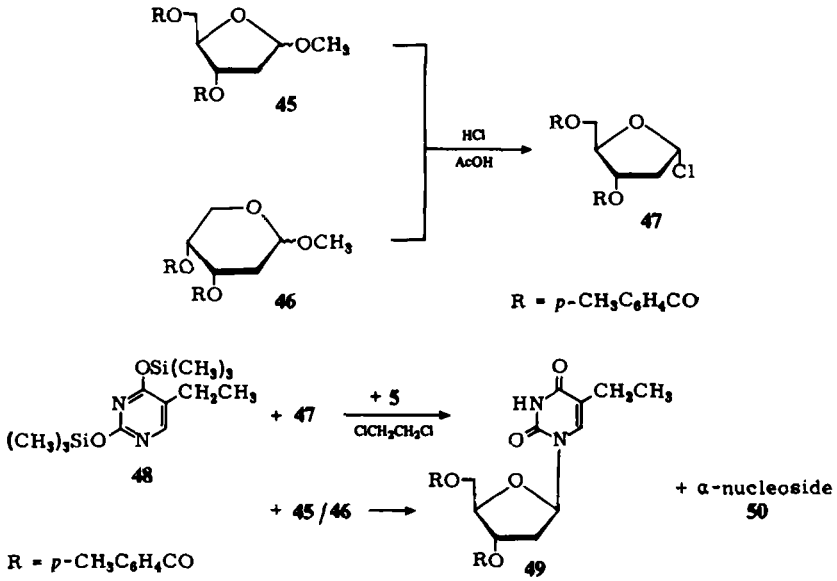
The corresponding silylated "2-thio-6-azauracil" **43** reacted analogously with $(CH_3)_3SiClO_4$ (**4**) in boiling 1,2-dichloroethane to afford a 56% yield of the nucleoside **44**[19a].

After having established that pyranosides do react with the new catalysts although under more stringent conditions than the furanosides, we turned to the synthesis of the important 2'-deoxyribosides.

The starting material for the 2'-deoxynucleosides is crude 2-deoxy-1-*O*-methyl-3,5-di-*O*-*p*-toluoylribofuranose which is actually a mixture of two furanose (**45**) and pyranose (**46**) 1-epimers. This mixture can be readily separated by chromatography and the fractions identified by NMR[30].

The mixture at hand afforded with HCl in anhydrous acetic acid 35% of the crystalline labile 1-α-chloro-2-deoxy-3,5-di-*O*-*p*-toluoylribofuranose (**47**)[31]. Silylated 5-ethyluracil (**48**) reacted readily with **47** in the presence of $(CH_3)_3SiOSO_2CF_3$ (**5**) in 1,2-dichloroethane/acetonitrile at 24°C to give a high yield of the mixture of the

desired β-nucleoside **49** and the α-nucleoside **50**. Crystallization from ethyl acetate and ethyl acetate/ether afforded 58% **49** and 31% **50**.



Since the crude mixture of the furanoside **45** and pyranoside **46** 1-epimers at hand had only furnished 35% of the crystalline 1-α-chloro sugar **47** and, as already discussed, the pyranoside 1-epimers **46** are only very slowly converted at 24°C into the corresponding pyranose cation[28], we reacted silylated 5-ethyluracil **48** directly with this mixture of **45** and **46** in the presence of **5** and obtained after simple chromatography and crystallization 27% of **49** and 15% of **50** – that means higher overall yields based on the crude 2-deoxyribose derivatives **45/46** than proceeding via the crystalline 1-α-chlor sugar **47**!

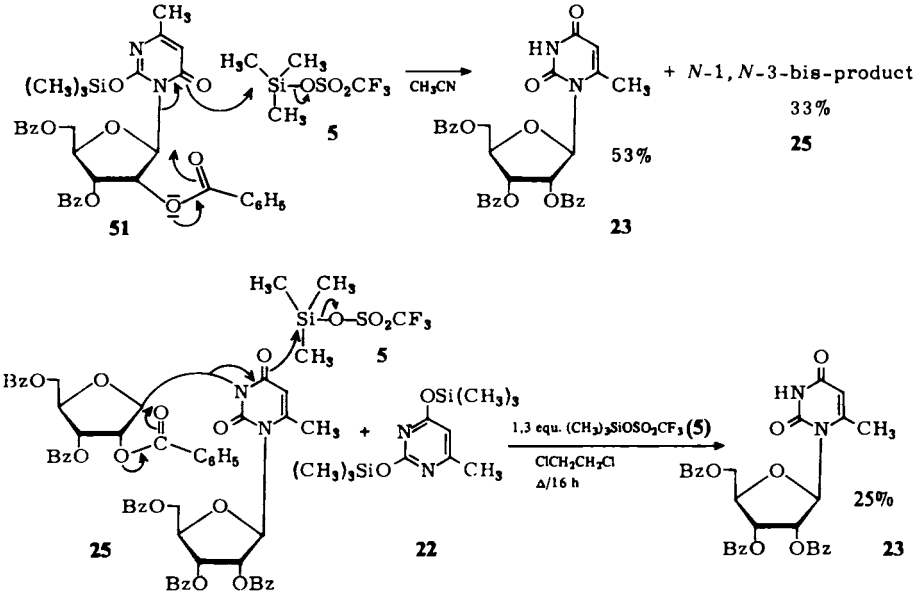
Therefore, on using the new selective catalysts like **5**, it is no longer necessary to prepare the sensitive crystalline halo sugar **47** to separate the furanose **45** from the pyranose **46** forms. $SnCl_4$[19a] as a stronger Lewis acid converts at 24°C either sugar into their corresponding cations and thus into a complex mixture of α/β-anomers of both furanosides and pyranosides[19a].

As described in the following chapter C., the yield of the desired β-anomers can be further increased by partial rearrangement of the unwanted α-anomers to the β-anomers.

C. Rearrangements of Nucleosides

During nucleoside synthesis often undesired products like the unnatural *N*-3-nucleosides are formed and isolated. If the nucleoside synthesis (cf. the accompanying paper)[14] is a reversible reaction one should be able to rearrange these undesired nucleosides in their silylated form using our new catalysts.

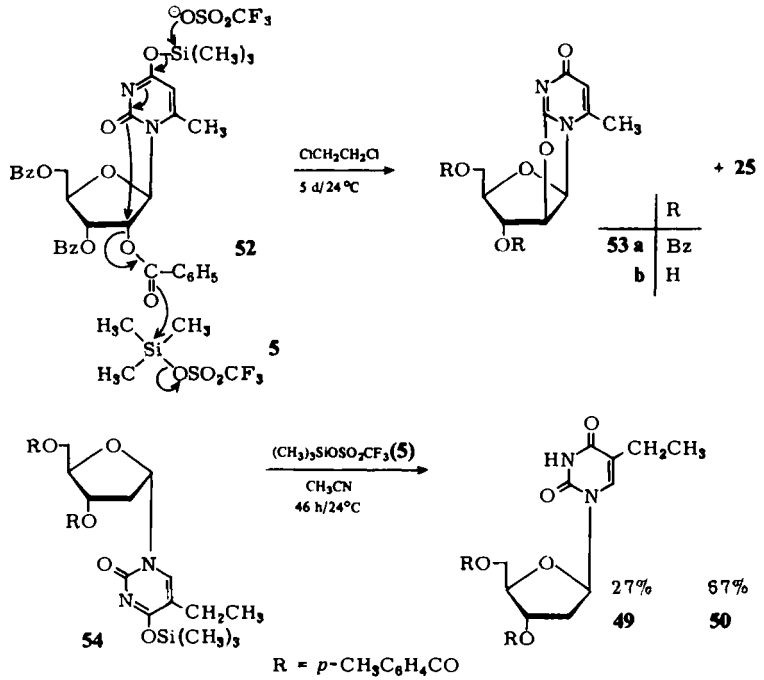
Heating the benzoylated 6-methyl-*N*-3-uridine (**24**) with hexamethyldisilazane (HMDS) followed by evaporative distillation with absol. xylene afforded the silylated product **51** which was treated for 2.5 h at 24 °C with 1.2 equ. of **5** to give, via *dissociation* to the silylated base **22** and reactive sugar cation **12** (as depicted by the arrows in **51**) and *resynthesis*, 53% of the desired *N*-1-product **23** as well as 33% *N*-1,*N*-3-product **25**.



However, in the case of the undesired *N*-1,*N*-3-bis-product **25** in which the heterocyclic carbonyl groups are sterically hindered, **25** had to be heated for 16 h with silylated 6-methyluracil (**22**) and **5** in 1,2-dichloroethane to transfer a benzoylated ribose moiety from *N*-3 to **22** and thus afford 25% of the desired **23**.

To check the chemical stability of the thermodynamically most stable silylated *N*-1-nucleoside **52**, we kept **52** with 1.2 equ. **5** for 5 days in 1,2-dichloroethane at 24 °C and obtained after chromatography ca. 24% of the 3',5'-di-*O*-benzoyl-2,2'-anhydronucleoside **53a** as well as 23.5% of the *N*-1,*N*-3-bis-riboside **25**. **53a** was identified by its NMR and MS data and saponification with methanolic ammonia to the known[32] crystalline **53b**. **53a** is probably formed via electrophilic attack of **5** on the 2'-benzoate as depicted in **52**; a process probably favored by the *syn*-configuration of **52**[33].

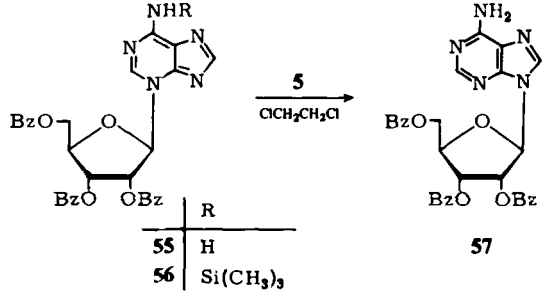
As generally observed and described in chapter B. 6., considerable amounts of the undesired α-nucleosides are always formed during the synthesis of 2'-deoxyribosides. We therefore silylated the α-nucleoside **50** by heating with HMDS and subsequent evaporative distillation with absol. xylene to **54** which was treated for 46 h at 24 °C with **5** in acetonitrile. Workup and preparative t.l.c. gave 27% of the desired β-nucleoside **49** as well as 67% recovered α-anomer **50**. In this way, the overall yield of the desired β-anomer **49** can be further increased.



Although longer reaction times might increase the yield of the β-anomer **49**, they also lead to gradual decomposition of the nucleosides e. g. with formation of furans. Thus, it is not possible to measure the equilibrium between **49** and **50** (chapter B. 6.) to determine whether the synthesis of **49** is kinetically or thermodynamically controlled.

It is interesting in this context to note that *Bardos* et al.[34] have observed that the presence of $(CH_3)_3SiCl$ during the silyl-Hilbert-Johnson reaction with 1-halo-2-deoxy sugars leads preferably to the formation of α-nucleosides.

During our studies on the synthesis of purine nucleosides we had followed the formation of N^6-benzoyladenosine 2',3',5'-tri-*O*-benzoate and isolated among other products the benzoylated *N*-3-nucleoside **55**. Consequently we silylated **55**, which is readily available by the "classical" Hilbert-Johnson reaction[35], to **56**, and rearranged **56** with **5** in boiling acetonitrile in 76% yield to the amorphous adenosine 2',3',5'-tri-*O*-benzoate (**57**)[36].



For the discussion of **56** as a potential intermediate during the synthesis of adenosine compare ref.[14,21c].

Recently, Japanese and German authors have successfully used $(CH_3)_3SiClO_4$ (**4**) and $(CH_3)_3SiOSO_2CF_3$ (**5**) for replacing the pyrimidine moiety in a nucleoside antibiotic by a purine moiety[37,38].

The authors thank Prof. Dr. *H. Schmidbaur* for a sample of $(CH_3)_3SiOSO_2F$ and Dr. *J. Farkas* for an authentic sample of **39**. We are furthermore indebted to Drs. *D. Rosenberg* and *A. Seeger* for physical measurements and Dr. *K. Merz* for microanalyses.

Experimental Part

The melting points were taken on a Kofler melting point microscope and are uncorrected. The UV spectra were recorded on a Cary Model 14 spectrometer, the NMR spectra were determined on Varian A-60 and HR-100 instruments.

The thin layer chromatography (t.l.c.) was performed on E. Merck silica plates F_{254} using systems: A toluene/acetic acid/H_2O (5:5:1)[39], B ethyl acetate/methanol (5:1), C n-BuOH/acetic acid/H_2O (5:1:4)[39].

Materials: Silicagel 60 (E. Merck) 0.063 – 02. mm (70 – 230 mesh, ASTM), as well as cellulose powder (Acivel, Merck) were used for column chromatography. 1,2-Dichloroethane as well as 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (ABR) (**8**) and 3,5-bis(*p*-toluoyl)-2-deoxyribofuranosylchloride (**47**) were purified as previously described[19a]. Acetonitrile was first refluxed several hours over P_2O_5 and destilled from P_2O_5 and finally refluxed over and distilled from CaH_2. The additional CaH_2-treatment of acetonitrile is crucial for a high yield preparation of *O*-benzoylated 6-methyluridine (**23**). Trimethylsilyl perchlorate (**4**) was prepared from silver perchlorate and trimethylchlorosilane in benzene or toluene solution[9]. Trimethylsilyl triflate (**5**), bp. 133 – 134°C, and nonaflate (**6**), bp. 68 – 69°C/11 torr, were obtained in 85 – 90% yield by heating of the free triflic and nonaflic acid[18a] with a slight excess of trimethylchlorosilane for ca. 7 h until the evolution of HCl ceased and subsequent distillation with careful exclusion of humidity. For the *in situ* preparation of trimethylsilyl nonaflate from potassium nonaflate ($KOSO_2C_4F_9$) and $(CH_3)_3SiCl$ in acetonitrile compare ref.[17].

Silylations: The bases were routinely silylated by heating with excess of hexamethyldisilazane (HMDS) (for 10 mmol heterocyclic base, 20 – 30 ml HMDS). In cases, where the base did not dissolve promptly after 0.5 – 2 h either 0.1 ml trimethylchlorosilane (TCS) was added (e. g. with 5-nitrouracil, lumazine) or pyridine (ca. 10 ml) (e. g. with 4-aminopyridine, N^6-benzoyladenine, N^2-acetylguanine, xanthine) to accelerate the silylation.

Although the subsequent distillation of the silylated base is crucial as in the case of the preparation of *O*-benzoylated 6-methyluridine (**23**), in most other instances the distillation step can be omitted if the excess HMDS and pyridine is removed by codistillation with 2 × 25 – 50 ml portions of absol. xylene.

The structure of the silyl compounds was only determined and confirmed in some cases and assumed to be as indicated in the formulas (compare the NMR studies in the accompanying paper on the mechanism of nucleoside synthesis[14]).

Workup

A) *After nucleoside formation:* The workup consists routinely of diluting the reaction mixture with CH_2Cl_2 and extracting the organic phase with ice-cold sat. $NaHCO_3$ or $KHCO_3$-solution. The organic phase is then dried (Na_2SO_4) and evaporated to give the crude acylated nucleoside (compare preparation of **11**).

B. *After saponification with methanolic ammonia:* The methanolic ammonia is evaporated *in vacuo*, the residue taken up in water (for 10 mmol nucleoside 25 – 100 ml) and extracted several times with ether and $CHCl_3$ to remove benzamide and methyl benzoate as well as other material. The aqueous phase is then either concentrated for crystallization from water or evaporated for crystallization from other solvents.

Recovery of $C_4F_9SO_3K$: If only a slight excess of $KHCO_3$ is used during workup, a considerable amount of $C_4F_9SO_3K$ crystallizes out (compare preparation of **18a**) which can be reused for the preparation of nonaflic acid or for the *in situ* preparation of $(CH_3)_3SiOSO_2C_4F_9$ in acetonitrile[17] (compare preparation of **18a**).

Uridine 2',3',5'-tri-O-benzoate (**11**): To a mixture of 5.15 mmol 2,4-bis(trimethylsilyloxy)-pyrimidine (**7**) (3 ml of a 1.75 N standard solution in 1,2-dichloroethane) and 2.57 g (5 mmol) ABR (**8**) in 15 ml absol. 1,2-dichloroethane, 2.5 mmol $(CH_3)_3SiClO_4$ (**4**), (16.67 ml of a 0.15 N standard solution in benzene) were added and the mixture kept for 1 week at 24°C. The clear yellow solution was diluted with 50 ml CH_2Cl_2 and extracted with 50 ml ice-cold $NaHCO_3$-solution. After washing with 3 × 20 ml H_2O, the organic phase was dried (Na_2SO_4) and evaporated to yield 2.8 g colorless foam which crystallized from 40 ml benzene to give after 2 h at 24°C 2.25 g (81%) crystalline **11**, mp. 138 – 140°C. The mother liquors contained further amounts of **11** acc. to t.l.c. (system A) (**11**, R_F = 0.5).

When the reaction mixture was refluxed for 4 h instead of keeping it 1 week at 24°C, an analogous yield of **11** was obtained.

Cytidine 2',3',5'-tri-O-benzoate (**16**): 2.56 g (10 mmol) colorless crystalline 4-(trimethylsilyl-amino)-2-(trimethylsilyloxy)pyrimidine (**15**) and 5.04 g (10 mmol) ABR (**8**) were dissolved in 35 ml absol. 1,2-dichloroethane and 12 mmol trimethylsilyl triflate (**5**) (24 ml of 0.5 N standard solution in benzene) added and the mixture refluxed for 1 h, cooled and diluted with 100 ml $CHCl_3$. After standard workup the brownish foam was dissolved in 150 ml hot ethanol, treated with charcoal and evaporated to give 4.5 g (98%) of colorless amorphous **16** which was homogenous on t.l.c. (system A, R_F = 0.3) and exhibited the expected NMR and UV data.

5-Methoxyuridine 2',3',5'-tri-O-benzoate (**18a**)

a) *Using triflate* **5**: To 11 mmol silylated 5-methoxyuracil (**17a**)[40] (34 ml of a 0.356 N standard solution in 1,2-dichloroethane), 5.04 g (10 mmol) ABR (**8**) in 75 ml absol. 1,2-dichloroethane, 12 mmol trimethylsilyl triflate (**5**) (22.8 ml of a 0.522 N standard solution in 1,2-dichloroethane) were added and stirred for 4 h at 24°C. After dilution with $CHCl_3$ and standard workup the crude nucleoside afforded on recrystallization from ethyl acetate/hexane 5.24 g (89%) of pure crystalline **18a**, mp. 205 – 207°C (lit.[41] 210 – 212°C) which was homogenous on t.l.c. (system B).

b) *Using nonaflate* **6** (recovery of $C_4F_9SO_3K$): 33 mmol **17a**, 15.12 g (30 mmol) ABR (**8**) and 34 mmol **6** in 200 ml 1,2-dichloroethane were kept for 7 h at 24°C, diluted with CH_2Cl_2 and worked up with an ice-cold solution of 4.95 g (49.5 mmol) $KHCO_3$ in 80 ml H_2O. On repeated extraction with CH_2Cl_2, the collected CH_2Cl_2-solution was filtered to afford a first crop of $C_4F_9SO_3K$. However the major part of $C_4F_9SO_3K$ was obtained on filtration of the aqueous phase to give a combined yield of 9 g (81%) of recovered $C_4F_9SO_3K$.

The CH_2Cl_2-phase was dried (Na_2SO_4) to give after evaporation and recrystallization of the crude product (17.1 g) from ethyl acetate-hexane in several crops 15.2 g (86%) of crystalline **18a**.

5-Morpholinouridine 2',3',5'-tri-O-benzoate (**18b**) *and 5-morpholinouridine:* To a solution of 10 mmol silylated 5-morpholinouracil[42] (**17b**) 5.04 g (10 mmol) ABR (**8**) in 70 ml absol. 1,2-dichloroethane and 11 mmol trimethylsilyl triflate (**5**) (20.9 ml of a 0.522 N standard solution in 1,2-dichloroethane) were added under argon. After 24 h stirring at 24°C, dilution with $CHCl_3$ and standard workup the slightly impure **18b** was dissolved in 5 ml ethyl acetate and crude **18b** preci-

pitated with 500 ml hexane. The sticky amorphous **18b** was filtered to give after dissolving in ethyl acetate and evaporation 6.36 g (99%) of nearly pure amorphous **18b** which was practically homogenous on t.l.c. (system A, R_F = 0.5) and identical with an authentic sample[19f].

Saponification of 4 g crude **18b** with 125 ml methanolic ammonia for 1 week at 24°C, and workup gave practically pure nucleoside which crystallized on concentration of the aqueous phase in three crops to afford 1.69 g (82%) of 5-morpholinouridine, mp. 230–234°C (lit.[43] 229–231°C).

5-Nitrouridine 2',3',5'-tri-O-benzoate (**18c**): To a solution of 11 mmol silylated 5-nitrouracil (**17c**) (18.33 ml of a 0.6 N solution in 1,2-dichloroethane) and 5.04 g (10 mmol) ABR (**8**) in 75 ml absol. 1,2-dichloroethane, 12 mmol trimethylsilyl triflate (**5**) (23 ml of a 0.528 N standard solution in 1,2-dichloroethane) were added and the reaction mixture stirred for 2 h at 24°C. After standard workup, the crude product (6.8 g) afforded on recrystallization from ethanol in three crops 5.7 g (93%) pure crystalline **18c**, mp. 184–185°C (lit.[44] mp. 183–184°C) which was homogenous on t.l.c. (system A, R_F = 0.52).

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4(1H)-pyridinone (**20a**): To a solution of 11 mmol 4-(trimethylsilyloxy)pyridine (**19a**) (17.3 ml of a 0.637 N solution in 1,2-dichloroethane) and 5.04 g (10 mmol) ABR (**8**) in 100 ml absol. 1,2-dichloroethane, 12 mmol trimethylsilyl triflate (**5**) (16.4 ml of a 0.732 N standard solution in 1,2-dichloroethane) were added and the reaction mixture refluxed for 3.5 h, diluted with 100 ml CH_2Cl_2 and worked up as described above. The crude foam (5.75 g) was dissolved in ethyl acetate and chromatographed on 200 g silicagel. After elution with ethyl acetate (ca. 4 l) and ethyl acetate-methanol (97:3, 1l) further elution with the same mixture (1.5 l) afforded 4.72 g (87%) amorphous **20a** which gave on saponification with methanolic ammonia crystalline 1-(β-D-ribofuranosyl)-4(1*H*)-pyridinone (**21a**), mp. 128–130°C, identical with a previously obtained authentic sample[19d].

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4(1H)-pyridinimine (**20b**): 1.89 g (11.37 mmol) redistilled, crystalline 4-(trimethylsilylamino)pyridine (**19b**) and 5.04 g (10 mmol) ABR (**8**) in 70 ml absol. 1,2-dichloroethane were treated with 16.4 ml (12 mmol) of a standard solution of trimethylsilyl triflate (**5**) in 1,2-dichloroethane under argon. After 2.5 h reflux, dilution with CH_2Cl_2 and standard workup afforded 7.15 g crude **20b**. Chromatography on 350 g SiO_2 with ethyl acetate gave after a forrun of 1 l on further elution with ethyl acetate (7.5 l) 4.34 g (80%) pure homogenous (t.l.c., system A, R_F = 0.17; system B, R_F = 0.65) amorphous **20b** which had the expected UV and NMR data.

1-(β-D-Ribofuranosyl)-4(1H)-pyridinimine (**21b**): 2 g (3.7 mmol) **20b** was stirred with 150 ml methanolic ammonia for 18 h, and worked up as usual to give the free nucleoside **21b** which has as yet refused to crystallize and was homogenous on t.l.c. (system C, R_F = 0.23). – UV (CH_3OH): λ_{max} (log ε) = 205 (3.84), 275 nm (3.97). – NMR (D_2O): δ = 5.68 (d, *J* = 5 Hz, 1'-H), 6.9 (d, *J* = 8 Hz, 3-H, 5-H), 8.18 (d, *J* = 8 Hz, 2-H, 6-H).

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-2(1H)-pyridinone: 5 mmol 2-(trimethylsilyloxy)-pyridine (5 ml of a standard solution in 1,2-dichloroethane) and 2.52 g (5 mmol) ABR (**8**) in 25 ml absol. 1,2-dichloroethane were refluxed for 1.5 h with 5 mmol trimethylsilyl triflate (**5**) (10 ml of a 0.5 N solution in benzene). After dilution of the light brown reaction mixture with $CHCl_3$ and standard workup the crude light brown oil (2.8 g) gave on crystallization from 75 ml CCl_4 and concentration of the mother liquor to 25 ml in two crops 2.31 g (86%) of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyridinone, mp. 136–138°C which was identical with an authentic sample[19d].

6-Methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione (**23**) *and 6-methyl-3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione* (**24**): 11 mmol

(29.2 ml of a 0.377 N standard solution in 1,2-dichloroethane) of redistilled silylated 6-methyluracil (**22**) and 5.04 g (10 mmol) ABR (**8**) in 100 ml absol. acetonitrile (refluxed first over P_2O_5 and subsequently over CaH_2!) in a carefully dried glas apparatus were reacted at +4 °C with 12 mmol **5** (25 ml of a 0.48 N standard solution in 1,2-dichloroethane). After warming up and 2 h at 24 °C, no **8** could be any more detected on t.l.c. (system A). After dilution with 200 ml chloroform and standard workup the crude yellowish foam (6.38 g) was chromatographed on 350 g silicagel with chloroform (4 l). Further elution with chloroform (3 l) and chloroform-isopropyl alcohol 99:1 (1 l) and 98.5:1.5 (1 l) gave 1.1 g (10.8%) *N*-1,*N*-3-bis-riboside **25**. Elution with chloroform-isopropyl alcohol 98:2 (1.75 l) gave 4.29 g (75.3%) homogenous *N*-1-riboside **23**. Further elution with the 98:2 mixture (3 l) afforded 0.22 g (3.85% of the *N*-3-riboside **24**, mp. 165 – 167 °C (lit.[19b] 108 – 109 °C) from ethyl acetate-hexane which was identified with an authentic sample[45].

The *N*-1-riboside **23** was recrystallized from CH_2Cl_2-pentane to give in three crops 4.05 g (71.1%) analytically pure **23**, mp. 181 – 183 °C (lit.[19b] 126 – 129 °C) which was identical with an authentic sample, t.l.c. (system A, R_F = 0.55). When the authentic sample, mp. 126 – 129 °C was recrystallized from ethyl acetate-hexane, the same higher melting crystalls, mp. 182 – 183 °C were obtained.

5,6-Dimethyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione (**27**) *and 5,6-dimethyl-3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione* (**28**): 11 mmol silylated 5,6-dimethyluracil (**26**) and 5.04 g (10 mmol) ABR (**8**) in 50 ml absol. 1,2-dichloroethane were reacted with 12 mmol trimethylsilyl triflate (**5**) (25 ml standard solution in 1,2-dichloroethane) for 3 h at 24 °C under argon. Dilution with chloroform and standard workup gave 6.5 g crude product which was chromatographed on 350 g neutral alumina (A III) with hexane-ethyl acetate (1:1). After discarding the first 250 ml eluate, the next 300 ml eluted 0.5 g (8.6%) *N*-3-riboside **28** (mp. 200 – 201 °C) (lit.[19b] 200 – 201 °C). The subsequent fractions (2 l) eluted 4.8 g (82.2%) of **27** which crystallized from hexane-CH_2Cl_2 to give analytically pure **27**, mp. 175 – 176 °C (lit.[19b] 176 – 178 °C).

Adenosine (**30a**): 2.393 g (10 mmol) N^6-Benzoyladenine was refluxed for 7 h with 35 ml HMDS and 0.5 ml TCS (clear solution after 2 h) and the solvents were removed at 50 °C/0.1 torr. The solid yellowish silyl compound **29a** and 5.04 g (10 mmol) ABR (**8**) were dissolved in 25 ml absol. 1,2-dichloroethane and refluxed for 12 h with 1 mmol (6.7 ml standard solution in benzene) trimethylsilyl perchlorate (**4**). After dilution with CH_2Cl_2 and standard workup the crude protected adenosine (7.1 g) was dissolved in 250 ml methanolic ammonia and kept for 16 h at 24 °C. After workup the residue was evaporated in vacuum to give 4.1 g crude product. Recrystallization from methanol-H_2O (2:1; 200 ml) afforded in several crops 2.16 g (80.9%) of pure crystalline adenosine (**30a**) which was homogenous on t.l.c. (system C, R_F = 0.43).

Guanosine (**30b**): 4.09 mmol (13.5 ml of a 0.303 N standard solution in absol. 1,2-dichloroethane) silylated N^2-acetylguanine (**29b**) and 1.86 g (3.7 mmol) ABR (**8**) in 35 ml absol. 1,2-dichloroethane were refluxed with 4.46 mmol (6.32 ml of a 0.705 N standard solution in 1,2-dichloroethane) trimethylsilyl triflate (**5**) for 1.5 h. After dilution with CH_2Cl_2 and the usual workup, the crude product (2.32 g) was kept for 42 h in 125 ml methanolic ammonia at 24 °C. After standard workup, recrystallization from water gave two crops of pure guanosine (**30b**) (0.69 g = 66%) which was homogenous on t.l.c. (system C, R_F = 0.3) and identified with an authentic sample.

Xanthosine (**30c**): 11 mmol (22 ml of a 0.5 N standard solution in 1,2-dichloroethane) silylated xanthine **29c**, 5.04 g (10 mmol) ABR (**8**) in 80 ml absol. 1,2-dichloroethane were refluxed for 1 h with 12 mmol (17.5 ml standard solution) of trimethylsilyl triflate (**5**). After dilution with CH_2Cl_2 and the usual workup the crude product (6.18 g) showed on t.l.c. (system A) besides the main

product (R_F = 0.38) a number of minor faster moving spots. After saponification with 200 ml methanolic ammonia for 3 days/24 °C, and standard workup, concentration of the aqueous phase afforded in 6 crops 0.95 g pure xanthosine (**30c**). The mother liquor was evaporated with 2 g cellulose-powder which was packed on top of a column of cellulose-powder (40 g, Avicel, E. Merck) and chromatographed with methanol. After a forrun of 250 ml the next fractions (350 ml) eluted a further amount of 0.43 g xanthosine which was homogenous on t. l. c. (system C, R_F = 0.3) and identical with an authentic sample. Combined yield of **30c** 1.38 g (48.8%).

Theophylline 7-β-D-ribofuranoside (**32**): 2 mmol silylated theophylline **31**, 1.08 g (2 mmol) ABR (**8**) and 2.2 mmol **5** (2.2 ml of 1 M standard solution in 1,2-dichloroethane) were kept for 1 h at 24 °C. After workup, the crude product (1.35 g) was kept for 18 h at 24 °C in 50 ml methanolic ammonia to give after workup and crystallization from 5 ml H_2O 0.54 g (81.8%) pure **32**, mp. 191 – 193 °C (lit.[22] 189 °C), which had a UV spectrum quite similar to the one of coffeine. – NMR ([D_6]DMSO): δ = 3.22 (s, N – CH_3); 3.42 (s, N – CH_3); 6.05 (d, J = Hz, 1'-H); 8.4 (s, 8-H).

$C_{12}H_{16}N_4O_6 \cdot H_2O$ (333.3) Calcd. C 43.63 H 5.49 N 16.96 Found C 43.69 H 5.86 N 16.7

Lumazine riboside (**34b**): 1.64 g (10 mmol) silylated lumazine **33** and 5.04 g (10 mmol) ABR (**8**) in 30 ml absol. 1,2-dichloroethane were reacted with 12 mmol (23.7 ml of a 0.53 N standard solution in 1,2-dichloroethane) trimethylsilyl triflate (**5**) at 24 °C. After 10 min the reaction mixture turned very dark green and t. l. c. (system D) showed that only traces of starting material were left. After 1.3 h 50 ml chloroform were added and the reaction mixture worked up as usual to afford 6.34 g of foam which was practically homogenous. On chromatography on silicagel with toluene-ethyl acetate 5.68 g (93.4%) pure amorphous tribenzoate **34a** was obtained. 4.8 g (7.9 mmol) amorphous **34a** were dissolved in 350 ml methanol and sat. at + 4 °C with NH_3 and kept for 80 h at 24 °C. After standard workup and evaporation of the aqueous phase the yellowish residual foam (2.68 g) was dissolved and crystallized from ethanol-isopropyl alcohol to afford in two crops 2.13 g (91%) crystalline **34b**, mp. 152 – 155 °C. A further crystallization from ethanol-isopropyl alcohol gave the analytical sample, mp. 192 – 194 °C (lit.[23] 182 – 184 °C) which showed the same physical data (UV, NMR) as described in the literature[23].

$C_{11}H_{12}N_4O_6$ (296.4) Calcd. C 44.92 H 4.12 N 18.72 Found C 44.60 H 4.08 N 18.91

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole (**36a**): To a mixture of 11 mmol (24 ml of a 0.461 N standard solution in 1,2-dichloroethane) silylated triazole **35a** and 5.04 g (10 mmol) ABR (**8**) in 75 ml absol. acetonitrile 12 mmol **5** (23 ml of a 0.528 N standard solution in 1,2-dichloroethane) were added under argon. After 3 h at 24 °C and workup, the residue (6 g) was chromatographed on 300 g silicagel. Toluene (1.5 l) and toluene-ethyl acetate 19:1 (500 ml) and 4:1 (50 ml) eluted impurities. Further elution with the 4:1 mixture (750 ml) gave first 0.89 g of a product, which decomposed on saponification with methanolic ammonia. Further elution with the 4:1 mixture (5 l) afforded 3.12 g (61%) of **36a** which crystallized from ethanol to give 2.94 g pure **36a**, mp. 105 – 106 °C (lit.[24] 103 – 105 °C).

$C_{28}H_{23}N_3O_7$ (513.5) Calcd. C 65.49 H 4.51 N 8.18 Found C 65.40 H 4.57 N 8.00

Saponification of 2.02 crude **36a** with 125 ml methanolic ammonia for 24 h and usual workup gave from methanol in three crops 0.54 g (67.5%) free 1-(β-D-ribofuranosyl)-1,2,4-triazole, mp. 144 – 145 °C (lit.[24] 143 – 145 °C). – NMR (D_2O): δ = 6.0 (d, J = 5 Hz; 1'-H) 8.1 (s, 5-H) 8.63 (s, 3-H).

Methyl 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylate (**36b**): 11 mmol (24.55 ml of a 0.488 N standard solution in 1,2-dichloroethane) silylated methyl 1,2,4-triazole-3-carboxylate **35b** and 5.04 (10 mmol) ABR (**8**) in 100 ml absol. acetonitrile were cooled to + 4 °C and 12 mmol **5** (26.76 ml of a 0.499 N standard solution in 1,2-dichloroethane) added under argon. After 4 h at + 4 °C and workup the crude product (6.1 g) was chromatographed on 300 g

silicagel. After elution with toluene (2.5 l), toluene-ethyl acetate 9.5:0.5 (2.5 l) and 9:1 (1 l) afforded only some ribose derivatives whereas the 9:1 mixture (1.5 l) eluted 0.886 g (15.5%) of the cyano derivative **37c**, mp. 158–160°C (ethanol). – IR (KBr): 2250 cm^{-1} (weak, nitril). – ^{1}H-NMR ($CDCl_3$): δ = 6.2 (d, *J* = 1.5 Hz, 1'-H), 8.4 (s, 5-H). – MS: *m/e* = 538 (M^+), 445 (M – 3-cyano-1,2,4-triazole), 416 (M – $C_6H_5CO_2H$), 364 (M – $(CN)_2$), 322 (M – $C_6H_5CO_2H$ – 3-cyano-1,2,4-triazole).

$C_{29}H_{22}N_4O_7$ (538.5) Calcd. C 64.82 H 4.16 N 9.58 Found C 64.68 H 4.12 N 10.41

Further elution with the 9:1 solvent mixture (2.5 l) gave 1.12 g (19.6%) of the methyl ester **37b**, mp. 142–144°C (ethanol) (lit.[25] mp. 123–124°C)[45]. – NMR ($CDCl_3$): δ = 4.0 (s, CO_2CH_3).

$C_{30}H_{25}N_3O_9$ (571.5) Calcd. C 63.04 H 4.41 N 7.35 Found C 63.34 H 4.44 N 7.23

After some intermediate fractions (750 ml, 23 mg) the 9:1 mixture (1.5 l) and 4:1 mixture (1 l) gave 0.132 g (2.3%) of the benzoylated triazole riboside **36a**, mp. 144–145°C. Further elution with 3 l of a 4:1 solvent mixture afforded 2.684 g (47%) of **36b**, mp. 141–142°C (lit.[25] 137–139°C) identical with an authentic sample. – ^{1}H-NMR ($CDCl_3$): δ = 3.98 (s, OCH_3), 6.32 (d, *J* = 2 Hz, 1'-H), 8.4 (s, 5-H). – MS: *m/e* = 571 (M^+), 540 (M – CH_3OH), 449 (M – $C_6H_5CO_2H$), 445 (M – methyl triazolecarboxylate), 390 (M – $C_6H_5CO_2H$ – CO_2CH_3), 364 (M – $C_6H_5CO_2H$ – CH_3O_2C – CN), 242 (M – 2 $C_6H_5CO_2H$ – CH_3O_2C – CN).

$C_{30}H_{25}N_3O_9$ (571.5) Calcd. C 63.04 H 4.41 N 7.35 Found C 63.40 H 4.43 N 7.50

2-(β-D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide: 0.34 g (0.59 mmol) **37b** were kept in 50 ml methanolic ammonia at 24°C and worked up as usual. The residue was homogeneous on t.l.c. (system C, R_F = 0.76) and crystallized from ethyl acetate-methanol, mp. 111–113°C (lit.[25] mp. 148–150°C)[45]. The ^{1}H and especially the ^{13}C-NMR data in 10% DMSO were identical with the literature data[46].

1-(β-D-Ribofuranosyl)-1,2,4-triazole-3-carboxamide: 1.0 g (1.75 mmol) **36b** was kept in 150 ml sat. methanolic ammonia over night. After the usual workup, the product was recrystallized from ethanol to give 0.39 g (91.3%) of the free amide, mp. 176–178°C (lit.[25] 174–176°C) which was identical with an authentic sample.

$C_8H_{12}N_4O_5$ (244.2) Calcd. C 39.34 H 4.95 N 22.94 Found C 39.66 H 5.10 N 23.25

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-2,4,6-trimethoxybenzene (**39**) *and 1,3-bis(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4,6-trimethyoxybenzene* (**40**): To 0.845 g (5 mmol) 1,3,5-trimethoxybenzene (**38**) and 2.5 g (5 mmol) ABR (**8**) in 65 ml absol. 1,2-dichloroethane 6 mmol (10.66 ml of a 0.563 N solution in 1,2-dichloroethane) trimethylsilyl triflate (**5**) were added under argon, whereupon the solution turned red. After 30 min at 24°C and dilution with 50 ml CH_2Cl_2, standard workup gave the crude product (3.3 g) which was chromatographed on 150 g silicagel. Elution with toluene (3 l), toluene-ethyl acetate 99:1 (5 l) yielded only some impurities whereas the 98.5:1.5 mixture (2 l) gave 0.164 g of ribose derivatives. Further elution with the solvent mixtures 98.5:1.5 (1 l), 98:2 (3 l) and 97.5:2.5 (1 l) afforded 1.846 g (60.3%) of **39** which crystallized on seeding with an authentic sample[26], mp. and mixted mp. 102–103°C (lit.[26] mp. 102–103°C). – NMR ($CDCl_3$): δ = 3.8 (s, 4-OCH_3), 3.88 (s, 2, 6-OCH_3), 5.75 (d, *J* = 4 Hz, 1'-H), 6.1 (s, 3, 5-H). Elution with the 97.5:2.5 solvent mixture (4 l) and 90:10 (0.7 l) afforded 0.244 g of impurities and 0.108 g 2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, whereas the 80:20 solvent mixture (1 l) gave 0.517 g (4.9%) of **40**, mp. 95–97°C (isopropylalcohol). – NMR ($CDCl_3$): δ = 3.9 + 3.9 (s, OCH_3), 5.63 (d, *J* = 6 Hz, 1'-H), 6.33 (s, 3-H).

$C_{61}H_{52}O_{17}$ (1057.0) Calcd. C 69.31 H 4.96 Found C 69.29 H 5.19

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)uracil (**42**): To a solution of 11 mmol silylated uracil **7** (16.41 ml of a 0.67 N standard solution in 1,2-dichloroethane) and 3.9 g (10 mmol)

1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**41**) in 100 ml absol. 1,2-dichloroethane 12 mmol (24.2 ml of a 0.496 N standard solution in 1,2-dichloroethane) of trimethylsilyl nonaflate (**6**) were added and the reaction mixture refluxed for 2.5 h. After dilution with CH_2Cl_2 and standard workup, the crude product (5 g) was recrystallized from ethanol to afford in two crops 4.07 g (92.1%) of pure **42**, mp. 149 – 150 °C (lit.[29b,29c] mp. 149 – 151 °C).

The analogous reaction with trimethylsilyl triflate (**5**) as catalyst gave 3.92 g (88.7%) of pure **42**.

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-1,2,4-triazine-5(4H)-one-3(2H)-thione (**44**): To a solution of 10 mmol silylated "2-thio-6-azauracil" (**43**) (10 ml of a N standard solution in 1,2-dichloroethane) and 3.9 g (10 mmol) 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**41**) in 25 ml absol. 1,2-dichloroethane, 1 mmol of trimethylsilyl perchlorate (**4**) (6.7 ml of a standard solution in absol. benzene) was added and the reaction mixture refluxed for 3.5 h. After dilution with $CHCl_3$ and standard workup, the crude reddish product (3.5 g) was recrystallized with charcoal from 200 ml methanol to afford in two crops 2.56 g (55.8%) of pure **44**, mp. 221 – 223 °C (lit.[19a] mp. 225 – 226 °C) which was identical with an authentic sample.

1-(2-Deoxy-3,5-di-O-p-toluoyl-β-D-ribofuranosyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione (**49**): 1) To a solution of 5.5 mmol silylated 5-ethyluracil (**48**) (8.23 ml of a 0.668 N standard solution in 1,2-dichloroethane) and 1.94 g (5 mmol) crystalline 1-α-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-D-ribofuranose (**47**) in 35 ml absol. acetonitrile and 15 ml 1,2-dichloroethane, 1 mmol trimethylsilyl triflate (**5**) (1.3 ml of a 0.773 N standard solution in 1,2-dichloroethane) was added at 0 °C and the reaction mixture stirred for 3 h at 24 °C. After dilution with CH_2Cl_2 and workup the crude product (2.5 g) afforded on recrystallization from ethyl acetate in 4 crops 1.34 g (57.8%) of the pure crystalline β-anomer **49**, mp. 199 – 201 °C (lit.[19a] mp. 197 – 198 °C) which was homogenous on t.l.c. in ether (R_F = 0.83). Crystallization of the mother liquor from ethylacetate-ether and finally acetone afforded 0.073 g (31.5%) of the crystalline α-anomer **50**, mp. 157 – 159 °C (lit.[19a] mp. 160 – 161 °C) which was homogenous on t.l.c. (ether, R_F = 0.54). The total yield of both anomers was 2.07 g (89%).

2) To a solution of 3.5 mmol **48** and 1.3 g (3.38 mmol) sugar mixture **45/46** in 20 ml absol. acetonitrile was added 4.06 mmol **5** in 1,2-dichloroethane and the mixture kept at 24 °C for 3 h. After workup the crude product (1.08 g) was chromatographed on a column of 50 g silicagel with ether-hexane (1 : 1). After discarding the first 250 ml eluate, the next 500 ml afforded on recrystallization from ethanol 0.1 g of the pure β-anomer **49**. On eluting with ether-hexane (3 : 2) the first 750 ml gave a mixture of **49** and **50** from which 0.19 g of pure **49** crystallized from ethanol. The mother liquor gave a second crop of 0.14 g of **49** and 0.12 g of the α-anomer **50**[19a]. Further elution with 1.5 l of the 3 : 2 solvent mixture gave 0.1 g of the α-anomer **50**. Total yield 0.43 g (27.4%) **49** and 0.24 g (15.3%) **50**.

Rearrangement of 6-methyl-3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione (**24**): 2.85 g (5 mmol) of **24** were heated for 18 h with 15 ml HMDS and 10 ml absol. xylene at 140 °C oil bath temperature. After evaporating the solvents first at normal pressure and finally in the vac. (60 °C/12 Torr), the residue was taken up in 50 ml absol. acetonitrile and the solution stirred for 2.5 h at 24 °C after adding 6 mmol **5** (10.27 ml of a 0.584 N standard solution in 1,2-dichloroethane). After dilution with CH_2Cl_2 and the usual workup, the crude product (2.83 g) was chromatographed on silicagel as described (compare preparation of **23**) to afford 1.575 g (53.3%) of the desired *N*-1-nucleoside **23** and 0.83 g (32.8%) of the benzoylated *N*-1,*N*-3-bis-riboside **25**, which were identified with authentic samples.

Cleavage of 6-methyl-1,3-bis(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione (**25**): 1.0 g (0.99 mmol) **25** and 0.99 mmol **22** (2.79 ml of a 0.354 N standard solution in 1,2-dichloroethane in 40 ml absol. 1,2-dichloroethane) were refluxed for 16 h with 1.26 ml **5** (2.2 ml

of a 0.85 N standard solution in 1,2-dichloroethane). After addition of CH_2Cl_2 and workup the residue (0.74 g) was chromatographed with $CHCl_3$ on 15 g silicagel and crystallized to afford 0.287 g (25.4%) of pure crystalline **23**.

Cyclization of 6-methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4(1H,3H)-pyrimidinedione (**23**) *to 2,2'-anhydro-1-(3,5-di-O-benzoyl-β-D-arabinofuranosyl)-6-methyl-2,4(1H,3H)-pyrimidinedione* (**53a**): 1.14 g (2 mmol) **23** in 10 ml HMDS and 15 ml xylene was heated until **23** had dissolved. After evaporation of the solvents *in vacuo* the silylated nucleoside was dissolved in 10 ml 1,2-dichloroethane, 2.4 mmol **5** (4.38 ml of a 0.548 N standard in 1,2-dichloroethane) added at +4°C under argon and the reaction mixture kept for 5 days at 24°C. After dilution with $CHCl_3$ and workup, the residue (1.5 g) was chromatographed on 150 g silicagel with $CHCl_3$ and $CHCl_3$-isopropyl alcohol. After obtaining the *N*-1,*N*-3-bis-riboside **25** (0.228 g = 23.5%) and the starting *N*-1-riboside **23** (0.215 g) the anhydronucleoside **53a** (0.225 g = 24.2%) was eluted with $CHCl_3$-isopropyl alcohol (99.5:0.5 → 99:1). – NMR ($CDCl_3$): δ = 4.35 (br. s, 6-CH_3); 5.65 (br. s, 5-H); 6.53 (*J* = 5 Hz, 1'-H). – MS: *m/e* = 448 (M^+), 343 (M – C_6H_5CO), 327 (M – C_6H_5COO), 229 (327 – $C_6H_5CO_2H$), 201, *126*.

$C_{24}H_{20}N_2O_7$ (448.4) Calcd. C 64.28 H 4.50 N 6.25 Found C 63.99 H 4.71 N 6.07

Saponification of 0.1 g (0.22 mmol) **53a** with 10 ml methanolic ammonia for 18 h at 25°C afforded after workup crude **53b** which was recrystallized from ethanol to give 40 mg (75.5%) of **53b**, mp. 211 – 213°C (partly 220 – 221°C) (lit.[32a] mp. 213 – 215°C).

UV (CH_3OH): λ_{max} (ε) = 225 (8050), 250 nm (8830). – NMR (D_2O): δ = 2.43 (s, 6-CH_3), 3.6 (d, 4 Hz, 5'-H_2), 4.38 (m, 4'-H), 5.45 (d, *J* = 6 Hz, 2'-H), 6.0 (s, 5-H), 6.52 (d, 6 Hz, 1'-H).

$C_{10}H_{12}N_2O_5$ (240.2) Calcd. C 50.00 H 5.04 N 11.66 Found C 50.04 H 4.96 N 11.43

Rearrangement of the silylated 1-(2-deoxy-3,5-di-O-p-toluoyl-α-D-ribofuranosyl)-5-ethyl-2,4(1H,3H)-pyrimidinedione (**54**): 2.3 g (5 mmol) **50** were heated in 25 ml HMDS and 25 ml xylene until **50** dissolved. The solvents were removed *in vacuo*, the residue taken up in 40 ml absol. acetonitrile and 6 mmol **5** (7.76 ml of a 0.773 N standard solution in 1,2-dichloroethane) added. After 46 h at 24°C the dark reaction mixture was diluted with CH_2Cl_2 and worked up. 137 mg of the residue (2.26 g) were separated on two preparative (20 × 20 cm) silicagel plates with ether to afford 94.5 mg α-anomer **50** and 37.5 mg β-anomer **49** which amounts to the formation of 27% of the desired β-anomer **49** and recovery of 67% of the α-anomer **50**.

Rearrangement of 3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)adenine (**55**) *to 2',3',5'-tri-O-benzoyladenosine* (**57**): 1.5 g (2.6 mmol) **55** was refluxed for 8 h with 75 ml HMDS and 20 ml absol. xylene. After removal of the solvents *in vacuo*, the residue was dissolved in 50 ml absol. acetonitrile and 3.12 mmol **5** (4.55 ml of a 0.685 N standard solution in 1,2-dichloroethane) added. After 15.5 h reflux with careful exclusion of humidity, the reaction mixture was diluted with CH_2Cl_2 and worked up to give 1.45 g brownish residue. Chromatography on 80 g silicagel with CH_2Cl_2-methanol 99:1 and 98:2 afforded 1.14 g (76%) of amorphous adenosine 2',3',5'-tri-*O*-benzoate (**57**), which was homogenous on t.l.c. (system A, R_F = 0.4) and gave on saponification with methanolic ammonia pure adenosine.

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