Pergamon

Tetrahedron Vol. 50, No. 23, pp. 6825-6838, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)E0316-L

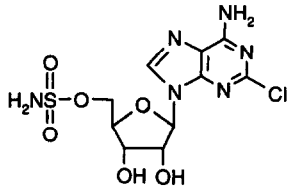
A Novel Synthesis of Sulfamoyl Nucleosides

Haukur Kristinsson, Kurt Nebel, Anthony C. O'Sullivan*, Fritz Struber, Tammo Winkler, and Yasuchika Yamaguchi

Plant Protection Division, Ciba-Geigy AG, 4002 Basel, Switzerland.

Abstract. The sulfamoylated ribose derivative **8** was prepared on a kilogram scale, and used in conjunction with various heterocycles to prepare a series of natural and unnatural 5-O-sulfamoyl nucleosides (**10** - **32**). A modification of the Vorbrüggen-Hilbert-Johnson reaction conditions for nucleoside formation was used.

Introduction. Recently in these laboratories 5'-O-sulfamoyl-2-chloroadenosine (**1**) was isolated as the agent responsible for the herbicidal activity of Streptomyces albus R 2374 (Tü-3389).[1] This compound had previously been isolated because of its antibacterial activity,[2] and even earlier had been prepared by synthesis.[3] We repeated the synthesis of this compound to prepare enough material for biological testing and found the compound to possess potent herbicidal activity especially on broad leaf weeds in post-emergant application. The discovery of the herbicidal activity of **1** was foreshadowed by the isolation of the herbicidally active 5'-O-sulfamoyl-tubercidin[4] **2** and 5'-O-sulfamoyl-2-bromoadenosine[5] **3**. The 5-O-sulfamoyl nucleosides themselves are a class of natural product which, since the isolation of nucleosidin **4** by Lederle chemists in 1957,[6] has been shown to exhibit a wide variety of biological activities,[7] accompanied unfortunately by a level of mammal toxicity, which prevented the commercialisation of any of the compounds. It has been suggested that the sulfamoyl group mimics a phosphate moiety,[8] making these molecules antimetabolites of adenosine monophosphate (ATP). These compounds have been shown to inhibit protein synthesis, more specifically aminoacyl tRNA synthase.[9] Despite the toxicity of **1**, which was found to be between 1 and 25 mg/kg oral LD_{50} in rat,[10] and the known toxicity of this class of compounds,[11] the herbicidal activity of **1** was so encouraging, that a synthesis program was started.



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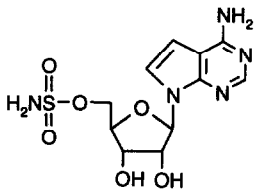
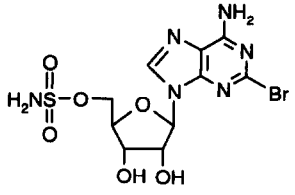


2 5'-O-sulfamoyl-tubercidin



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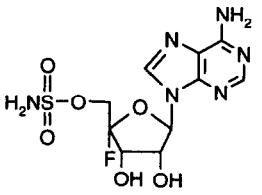
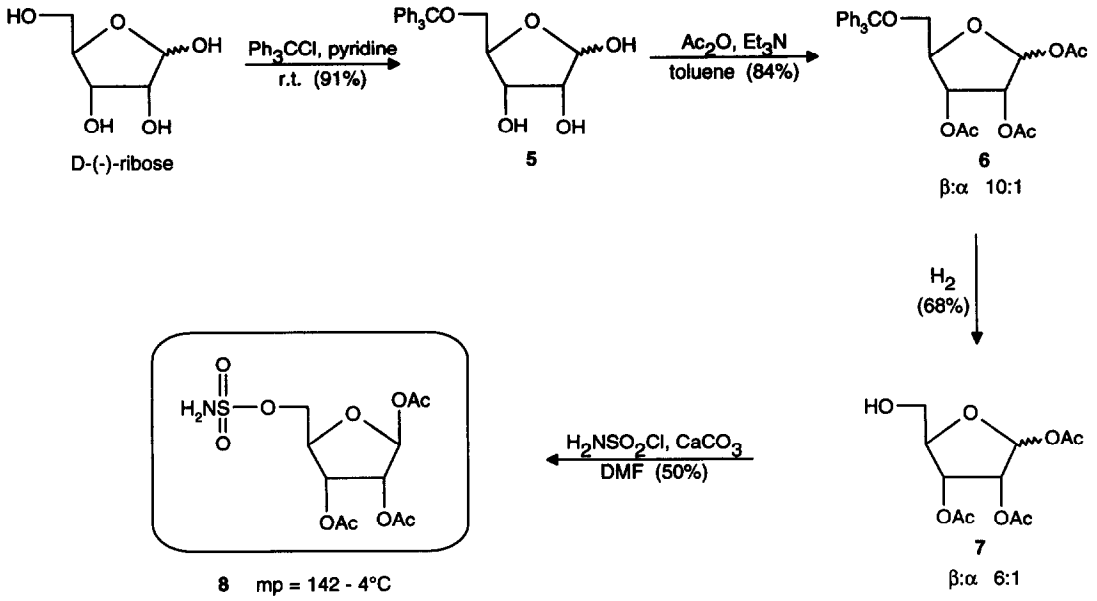


4 nucleosidin

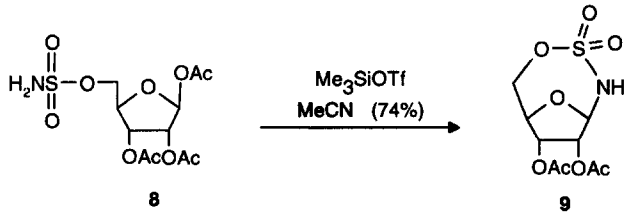
Traditionally the synthesis of 5'-O-sulfamoyl-nucleosides has always started from nucleosides, which were protected, sulfamoylated, and deprotected.[12] We have optimised this process, in particular the critical sulfamoylation step, to the point where the protecting groups could be dispensed with. This resulted in a one step synthesis of 5'-O-sulfamoyl nucleosides, albeit with a loss in yield.[13] As an alternative route it was considered that coupling of the heterocyclic base with a sulfamoylated ribose derivative would open up a new convergent synthesis of 5'-O-sulfamoyl nucleosides and also allow the synthesis of nucleosides with unnatural heterocyclic bases. This type of Hilbert-Johnson coupling of bases with ribose derivatives most commonly uses ribose derivatives with a simple acyl group protecting the 5-OH. However reactions with substrates bearing other substituents at the 5 position have been described several times,[14] providing a reasonable expectation of success in our case.

Results and Discussion. The requisite 5-O-sulfamoyl-1,2,3-triacetyl-D-ribose **8**, was prepared by sulfamoylation of 1,2,3-triacetyl-D-ribose **7** with sulfamoyl chloride in DMF using $CaCO_3$ as a base (Figure 1). Use of more conventional sulfamoylation methodology[12] resulted in long reaction times and low yields. As the ribose derivative **7** prepared by Maryanoff et al.[15] was a mixture of anomers, both α- and β-anomers of **8** were obtained by this procedure. Although theoretically both isomers of **8** could be used for the coupling reaction, only the β-anomer was crystalline. As large amounts of this crucial intermediate were needed, the synthesis of **6** was optimized with a view to increasing the β:α ratio of **8**, thus allowing its preparation on a large scale without chromatography. Using Et_3N as catalyst, the acetylation of **5** led to **6** with a 10:1 β:α ratio instead of ca 1:1 when pyridine[15] was used. Removal of the trityl group from **6** with mild acid led to **7** in only 30%-50% yield, as the anomeric acetate was also cleaved to some extent. Although hydrogenolysis was successful (68%) on a small to moderate scale (<500 g), large scale hydrogenolysis resulted in incomplete conversion despite long reaction times and repeated addition of catalyst. Of course a more readily cleavable substituted trityl group may well bring an improvement in yield of this step, but this advantage would be more than offset by the higher cost of the starting materials. Overall with this method **8** can be thus prepared from D-ribose on a kilogram scale in 26% yield.



Scheme 1. The Synthesis of the Sulfamoyltriacetate **8.**

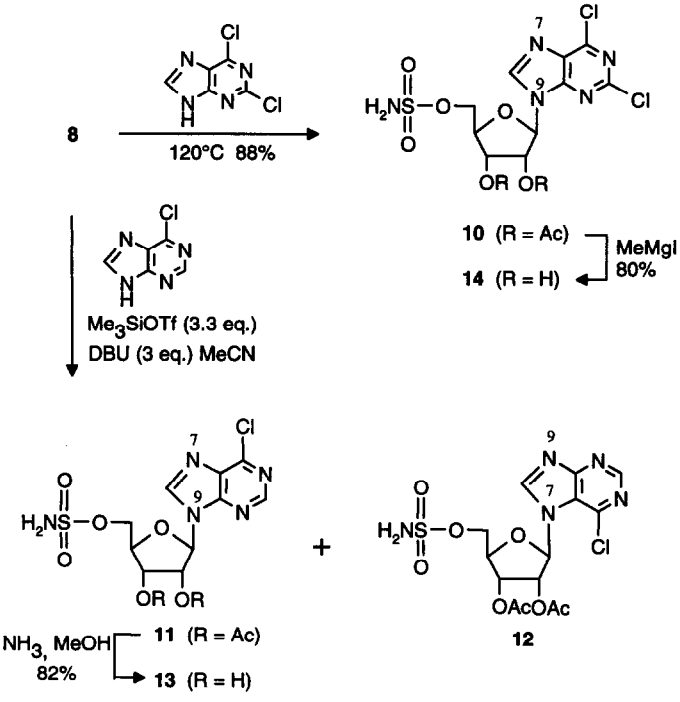
The Hilbert-Johnson[16] coupling of **8** with heterocyclic bases required special reaction conditions. Use of Vorbrüggen's conditions[17] for this reaction resulted only in the formation of the bicyclo-compound **9** (Scheme 2). One possible cause for the formation of this compound could be adventitious protic acid arising from traces of water in the reaction mixture. Indeed the problem was solved by performing the reaction in the presence of base. It was thought at first that a nucleophilic base would react with the intermediate glycosyl cation, therefore 2,6-ditert-butyl-pyridine was used, and indeed successfully. However it transpired that even DBU or 2,6-lutidine were suitable, offering a considerable cost improvement. In practice DBU had the advantage of increasing the solubility of the heterocyclic bases and thus the volume yield. It was necessary to use an excess of Me_3SiOTf over the base or no reaction took place, and for most of the reactions described here 3 eq. base and 3.5 eq. Me_3SiOTf were used. Me_3SiOTf reacts first with water in the medium and presumably silylates the purine base. Thus in addition to the use of the reagent combination to destroy protic acids, its drying ability proved advantageous. The meticulous drying of reagents and solvents necessary for the success of the Vorbrüggen coupling could be dispensed with, and in all the reactions described here acetonitrile was used without prior drying.



Scheme 2. Attempted Nucleoside Formation with **8** under Vorbrüggen's conditions.

With 2,6-dichloropurine and in particular 6-chloropurine, mixtures of 7-ribosides and 9-ribosides were obtained (Scheme 3). With DBU as a base at low temperature almost sole formation of the 7-riboside **12** was observed. Warming the reaction mixture to 60°C before quenching mobilised an equilibrium in favour of the 9-riboside as described by Höfle and Vorbrüggen,[18] and the pure 9-riboside **11** was isolated in good yield. 2,6-Dichloropurine was also coupled with **8** in high yield by simply stirring the two components together under vacuum at 120°C,[19] but on a large scale (ca 30mmol) the yield was much lower. It appeared that decomposition had set in before both reaction partners had completely melted and mixed. Similarly the high melting 6-chloropurine afforded only a low yield of **11** with this procedure.

The 2' and 3' acetate groups of **10** and **11** were easily cleaved. Mild treatment of **11** with NH_3 in MeOH led to the free nucleoside **13** in 82% yield. Prolonged reaction under these conditions led to 5-O-sulfamoyl adenosine resulting from replacement of the 6-chloro substituent with NH_3. An analogous substitution reaction with **10** was so facile that NH_3 in MeOH only gave low yields of the free nucleoside **14**. However treatment with MeMgI in Et_2O resulted in selective acetate cleavage and **14** was isolated in 80% yield.



Temp. (°C)	Ratio **11**:**12**	Yield (%)
0	5:95	53
0→60	100:0	84

Scheme 3. Nucleoside Formation from **8** using modified conditions.

In addition to the synthesis of purine nucleosides similar to the natural product **1**, it was considered interesting to find out if replacement of the purine nucleus by other heterocycles was compatible with herbicidal activity. A number of different heterocycles were coupled with **8** using the conditions optimised for the synthesis of **11** (Table 1). Although the two purine derivatives were used without prior silylation, the same was not possible for the synthesis of some of the unnatural heterocycles. For example formation of the imidazolidinone **19** was achieved in 45% yield from the silylated base, but no trace of **19** was formed from the NH compound itself. Several triazole derivatives were used without prior silylation yielding a mixture of regioisomeric ribosides. Interestingly only 1H- and 3H- isomers were isolated, and no 2H- isomers were found.[20] The structures of the regioisomers **16** were determined by spectroscopic methods. The regiochemistry at the benztriazole ring was established by means of a complete assignment of the proton coupled ^{13}C-NMR spectrum of the two compounds, the chemical shifts of which are incompatible with 2H- substitution.[21] No attempt was made to couple pyrimidines to the sulfamoyl ribosylating agent **8**, as these compounds, which were prepared by another method, showed no herbicidal activity in our tests.

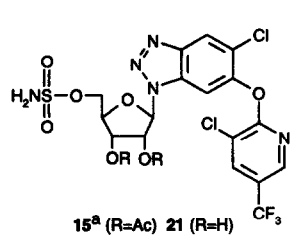
Table 1. Formation of Various Natural and Unnatural Nucleosides.

8 **10 - 20**

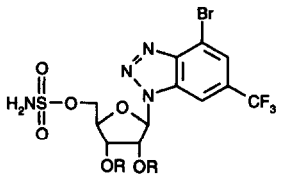
TMSOTf (equivs)	Base	Conditions (°C)	Conditions (time)	Prior Silylation	Product	Yield (%)
5	DBU (3 eq.)	r.t.	1 h	no	**10**	84[a]
4	DBU (3 eq.)	60	4 h	no	**11**	88
4	DBU (3 eq.)	0	5 min	no	**12**	50
3.2	lutidine (3 eq.)	r.t.	1 h	no	**15**[b]	54
3.2	dit.bupyridine (3 eq.)	r.t.	1 h	no	**16**[b]	85
3.2	dit.bupyridine (3 eq.)	r.t.	1.5 h	no	**17**	51
3.2	lutidine (3 eq.)	r.t.	1 h	no	**18**[b]	95
1.2	DBU (1 eq.)	50	2 h	yes	**19**	45
1.2	DBU (1 eq.)	reflux	6 h	yes	**20**[b]	48

a) Also prepared in 80% yield by a thermal reaction on an 11 mmol scale.

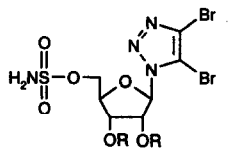
b) Mixture of 1H- and 3H- substituted regioisomers.



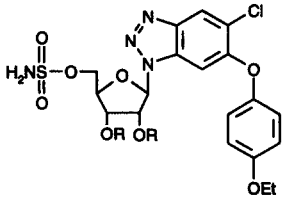
15[a] (R=Ac) **21** (R=H)



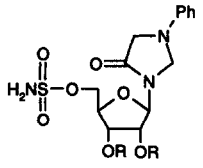
16[a] (R=Ac) **22** (R=H)



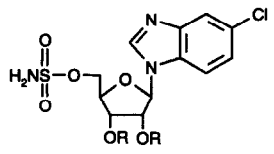
17 (R=Ac) **23** (R=H)



18[a] (R=Ac) **24** (R=H)



19 (R=Ac) **25** (R=H)



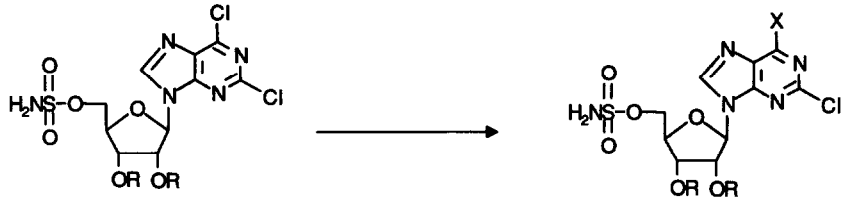
20[a] (R=Ac) **26** (R=H)

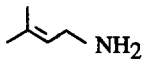
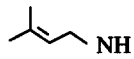
a) These compounds were isolated as a mixture of 1H- and 3H- substituted isomers

The chloro derivatives **10** and **11** proved to be useful intermediates for the synthesis of a variety of derivatives. Happily the sulfamoyl group proved stable to the appropriate reaction conditions. Treatment of **10** or its free nucleoside analog **14** with nucleophiles led to the 6-substituted 2-chloro-adenosine derivatives shown in Table 2, with concomitant deprotection of the acetate groups. One of the compounds thus prepared was the natural compound 5'-O-sulfamoyl-2-chloro-adenosine **1**. Apart from replacement with nucleophiles, **10** was also labile to hydrogenation producing **31** (Table 2), which was deprotected with NH_3 in MeOH as usual, yielding **32** in 76% yield.

Biological Activity. All of the compounds prepared were tested against a number of monocot and dicot plants in greenhouse trials. Although most of the compounds were inactive in these tests, many were interesting herbicides and **32** showed a particularly high activity approximately equipotent to **1**. Because these compounds are known to inhibit protein synthesis,[9] which is an intracellular process, the toxicity of the compounds observed in rodents can be assumed to be mirrored by a cytotoxicity found in cell cultures. Therefore cytotoxicity was used as an *in vitro* screening tool in the hope that potent herbicidal activity could be found in compounds that were not toxic. The cytotoxicity of several compounds was examined in a mammalian cell line,[22] but unfortunately the herbicidally active compounds tested were all cytotoxic. In fact many of the weakly active or inactive herbicides were also cytotoxic, giving the impression that toxicity was in fact more common than herbicidal activity in this series.

Table 2. Derivatisation of the Sulfamoyl-Nucleosides **10** and **14**.



Starting Material	R	Conditions	Product	X	R	Yield
10	Ac	NH_3, MeOH	**1**	H_2N	H	63%
10	Ac	"	**27**	MeO	H	22%
10	Ac	$MeNH_2$	**28**	MeNH	H	43%
10	Ac		**29**		H	78%
14	H	MeSNa	**30**	MeS	H	75%
10	Ac	H_2, Pd/C	**31**	H	Ac	52%
31	Ac	NH_3, MeOH	**32**	H	H	76%

Conclusion. The sulfamoylated ribose derivative **8** was prepared on a kilogram scale, and used in conjunction with various heterocycles to prepare a series of natural and unnatural nucleosides. A modification of the Vorbrüggen-Hilbert-Johnson reaction conditions for nucleoside formation was necessary for the success of the reaction. With a base buffering the reaction solution, high yields of the desired nucleosides were obtained. As a further bonus prior drying of the solvent was unnecessary, and silylation of the heterocyclic base could be dispensed with. Many of the new sulfamoyl nucleosides were herbicidally as potent as the naturally occurring lead compound **1.** Using an in vitro method, the toxicity of the compounds was examined.

EXPERIMENTAL

The multiplicities of the signals in the ^{13}C NMR were assigned on the basis of DEPT experiments. Assignments marked with + refer to multiplicity in the fully proton coupled spectrum.

A: Preparation of 8

5-O-Triphenylmethyl-D-ribose (**5**)

Triphenylchloromethane (2.79 kg, 10 mol) was added with stirring to a mixture of D-ribose (1.55 kg, 10.5 mol) and pyridine (5 L)(no exotherm). The mixture was heated at 45°C with stirring for ca. 60 min, whereupon the solution became homogenous. The solvent was removed under vacuum, and the residue taken up in CH_2Cl_2 (10 L), washed twice with water (5 L), dried, and the solvent evaporated. The residue was again

taken up in CH_2Cl_2 (3 L) and added dropwise with stirring to a mixture of hexane (10 L) and CH_2Cl_2 (1 L), whereby the product crystallised out of solution. After stirring at room temperature for 60 minutes the product was filtered off, washed with hexane and water, and dried under vacuum at 50°C to yield 1.85 kg (47%) of **5** mp 123-127°C (Lit[23] 125°C). This reaction was repeated on approximately this scale six times. The yields were 47%, 52%, 45%, 51%, 60%, and 62%; in total (54mol) 51%. From the combined mother liquors a further small amount of product was isolated.

5-O-Triphenylmethyl-D-ribofuranose-1,2,3-triacetate (**6**)

Acetic anhydride (8.56 kg, 83.8 mol) was added dropwise over 4 h to a solution of **5** (9.4 kg, 23.9 mol) and triethylamine (14 L, 94.4 mol) in toluene (25 L) under stirring (slight exotherm) and the mixture was stirred overnight at room temperature. Ice (10 kg) and water (15 L) were added, the mixture was stirred thoroughly for 10 min, and the phases separated. The aqueous phase was extracted with toluene (5 L) and the combined toluene phase was washed with water (twice with 5 L) and the solvent evaporated to yield 12.9 kg (>100%) of crude **6** as a 9:1 mixture of 1β-acetoxy:1α-acetoxy anomers, as determined by integration of the signals in the NMR ($CDCl_3$) at δ= 6.22 (1β-acetoxy) and 6.58 (1α-acetoxy).

1,2,3-Tri-O-acetyl-D-ribofuranose (**7**)

a) A solution of **6** (309 g, 90%pure +10% toluene, 536 mmol) in acetic acid (2 L) was treated with 5% Pd/C (30 g) and hydrogenated under normal pressure at room temperature for 40 h when the hydrogen uptake stopped (an additional 30 g catalyst was added during this time). 13.5 L (111%) of hydrogen was taken up. The catalyst was filtered off with Celite, which was washed with acetic acid (thrice 100 mL). The solvent was evaporated and the residue (280 g) stirred with water (1 L) overnight. The triphenylmethane (137 g) was filtered off, and washed with water. The aqueous phase (1.7 L) was saturated with NaCl (500 g) and extracted with CH_2Cl_2 (once 500 ml + thrice 300 ml). The combined organic phase was dried with Na_2SO_4 and evaporated to yield 101 g (69%) of **7** as a 6:1 mixture of 1β-acetoxy:1α-acetoxy anomers.

b) Water (1.2 L) was added over 30 min with stirring to a solution of **6** (2.875 kg, 5.55 mol) in acetic acid (6 L) at 70°C. After stirring at 70°C for 2.5 h, the reaction mixture was poured into ice/water (5 L), and after stirring for 30 min, the precipitated triphenylcarbinol (1.75 kg) was filtered off. The aqueous phase was saturated with NaCl (3 Kg) and extracted with CH_2Cl_2 (thrice 2 L), and the organic phase dried and evaporated to yield crude 515 g (34%) **7** as a 6:1 mixture of β:α anomers. The yields obtained by this method on various batches were 34%, 42%, 45%, 56%, 52%.

Sulfamoyl Chloride[24]

Formic acid (711 g, 15.5 mol) was added dropwise with stirring over a period of 3 h to a solution of chlorosulfonyl isocyanate (2.122 kg, 15 mol) in CH_2Cl_2 (6 L) under argon. There was a slight exotherm and vigourous gas evolution. After stirring overnight, the mixture was heated to reflux for 60 min (vigourous gas evolution), and then stirred overnight. This 3M solution of sulfamoyl chloride was either used as such, or the solution was cooled to -30°C, and after 60 min at this temperature the crystalline sulfamoyl chloride was filtered off, washed with CH_2Cl_2 (-30°C) and dried under vacuum. Yield = 92%. m.p. = 40°C. (Lit[24] = 40°C).

5-O-Sulfamoyl-1,2,3-tri-O-acetyl-β-D-ribofuranose (**8**)

A 3M solution of sulfamoyl chloride in CH_2Cl_2 (3.3 L, 10 mol) was added dropwise with stirring to a suspension of $CaCO_3$ (1.9 kg, 19 mol) in a solution of **7** (2.109 kg, 7.63 mol, β:α = 6:1) in DMF (4 L) at 5-10 °C. There was evolution of gas during this process. After stirring for 1 h at 20-25 °C, the mixture was poured onto ice/water (100 L). After stirring for 30 min, the product was filtered off. It was dissolved in acetone (15 L) and filtered through Celite, washing with warm acetone (5 L), to remove inorganic material. After removing the solvent the residue was recrystallised from ethanol (5 L) to yield 1.259 kg (50%, two crops) **8**. Samples of this material stored at 5 °C have been stable for more than 3 years, and those stored at room temperature (20-35 °C) have proven stable for several months, before decomposition set in. mp 142-4°C. ^{1}H-NMR (300MHz; $CDCl_3$): 2.12, 2.15, 2.16 (3s, 3OAc); 4.32 - 4.46 (m, H-C(4), 2H-C(5)); 4.95 (br s, NH_2); 5.38 (m, H-C(2), H-C(3)); 6.12 (s, H-C(1)).

Chromatography of the mother liquors (50% EtOAc/hexane) yielded 5-O-sulfamoylribose-1α,2,3-triacetate. ^{1}H-NMR (300MHz; $CDCl_3$): 2.12, 2.14, 2.15 (3s, 3OAc); 4.41 (m, 2H-C(5)); 4.45 (m, H-C(4)); 5.12 (br s, NH_2); 5.20 (dd, J= 5 and 8Hz, H-C(3)); 5.30 (dd, J=4 und 8Hz, H-C(2)); 6.43 (d, J= 4Hz, H-C(1)).

B: Coupling Reactions

Acetic Acid 7-Acetoxy-3,3-dioxo-4,9-dioxa-3-thia-2-aza-bicyclo[4.2.1]non-8-yl Ester (**9**)

Trifluoromethane sulfonic acid trimethylsilyl ester (Me_3SiOTf, 90 µL, 500 µmol) was added to a suspension of **8** (3.55 g, 10 mmol) in acetonitrile (20 ml). The material went into solution over ca 2-3 min. After 30 min the solvent was evaporated, the mixture shaken between water and CH_2Cl_2 (2x), the solvent evaporated and the residue (2.9 g) chromatographed (EtOAc/hexane 7:3) to yield 1.8 g (61%) **9** and 0.4 g (13%) material that was slightly impure. ^{1}H-NMR (300MHz; $CDCl_3$): 2.12, 2.14 (2s, 2OAc); 4.38 (dd, J=13 and 1 Hz, H-C(5)); 4.58 (dd, J=13 and 2 Hz, H-C(5)); 4.63 (m, H-C(6)); 5.18 (s, H-C(1)); 5.43 (d, J=7 Hz, H-C(8)); 5.59 (dd, J=7 and 2 Hz, H-C(7)); 5.71 (s, NH). Analysis: Calculated C 36.61 H 4.44 N 4.74 S 10.86 O 43.35 Found C 36.80 H 4.51 N 4.74 S 10.71 O 43.31

9-(2',3'-Di-O-acetyl-5'-O-sulfamoyl-β-D-ribofuranosyl)-2,6-dichloropurine (**10**)

a) A mixture of **8** (4.07 g; 11.46 mmol) and 2,6-dichloropurine (2.16 g; 11.46 mmol) was stirred under vacuum at 130°C until the mixture had completely melted. The temperature was reduced to 120°C and the mixture sturred for 60 min, cooled and chromatographed (EtOAc/ hexane 7:3) yielding 4.86 g (88%) **10**. ^{1}H-NMR (300MHz; $CDCl_3$): 2.06, 2.16 (2s, 2OAc); 4.52 (m, H-C(4'), 2H-C(5')); 5.54 (br s, NH_2); 5.63 (br d,J=5Hz, H-C(3')); 5.74 (dd, J=5 and 5Hz, H-C(2')); 6.30 (d, J=5Hz, H-C(1')); 8.45 (s, H-C(8)).

b) Me_3SiOTf (110 mL, 600 mmol) was added slowly with ice cooling to a solution of **8** (42.6 g, 120 mmol), 2,6-dichloropurine (22.6 g, 120 mmol), and DBU (72 mL, 480 mmol) in MeCN (800 mL). After 60 min at room temperature the reaction mixture was shaken between $NaHCO_3$ (1M) and CH_2Cl_2, the organic phase was dried with Na_2SO_4, the solvent evaporated and the crude product chromatographed (70% EtOAc/hexane) to yield 48.5 g (84%) of **10**.

6-Chloro-9-(2,3-di-O-acetyl-5-O-sulfamoyl-β-D--ribofuranosyl)-purine (**11**)

Me_3SiOTf (88.9 g, 400 mmol) was added slowly with ice cooling to a solution of **8** (35.5 g, 100 mol), 6-chloropurine (17.0 g, 110 mmol), and DBU (45.7 g, 300 mmol) in MeCN (200 mL). After stirring at 60°C for 4 h the reaction mixture was shaken between $NaHCO_3$ (1M) and CH_2Cl_2, the organic phase was dried with Na_2SO_4, the solvent evaporated and the crude product (134.7 g) chromatographed (EtOAc) to yield 39.6 g (88%) of **11**. ^{1}H-NMR (300MHz; $CDCl_3$): 2.03, 2.14 (2s,2OAc); 4.47-4.58 (m,H-C(4'),2H-C(5')); 5.63 (m, H-C(3')); 5.83 (m,H-C(2'), NH_2); 6.32 (d, J=7Hz, H-C(1')); 8.47, 8.77 (H-C(2),H-C(8)). MS(CI): 449[M]$^-$, 484[M+Cl]$^-$.

6-Chloro-7-(2,3-di-O-acetyl-5-O-sulfamoyl-β-D-ribofuranosyl)-purine (**12**)

Me_3SiOTf (70 mL, 87.8 g, 386 mmol) was added slowly with ice cooling to a solution of **8** (34.2 g, 96.4 mmol), 6-chloropurine (16.33 g, 106 mmol), and DBU (43.1 mL, 44.1 g, 289 mmol) in MeCN (200 mL). After 5 min at 0°C, the reaction mixture was shaken between $NaHCO_3$ (1M) and CH_2Cl_2, the organic phase was washed with HCl (2M, 300 mL), again with $NaHCO_3$, dried with $MgSO_4$, the solvent evaporated and the crude product chromatographed (70% EtOAc/hexane) to yield 23 g (53%) of **12** which was contaminated with ca 5% **11**. A pure sample of **12** was obtained by chromatography (EtOAc/hexane 7:3). ^{1}H-NMR (300MHz, $CDCl_3$): 2.02 (s, 2Me); 4.52 (m,H-C(4'), 2H-C(5')); 5.44 (dd, J=6 and 6 Hz, H-C(3')); 5.58 (dd, J=6 and 6 Hz, H-C(2')); 6.37 (br s, NH_2); 6.77 (d, J=6, H-C(1')); 8.85 (s, H-C(2), H-C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$) 20.3 and 20.4 (2Me); 67.8 (C(5')); 69.8 (C(3')); 74.6 (C(2')); 80.6 (C(4')); 87.8 (C(1')); 122.2 (C(5)); 142.9 (C(6)); 147.1 (C(8)); 152.5 (C(2)); 161.6 (C(4)); 169.5 and 169.9 (2C=O). MS (DCI, NH_3): pos. 450 $[M+H]^+$ neg. 449 $[M]^-$

5-Chloro-6-(3-chloro-5-trifluoromethyl-2-pyridoxy)-1(and3)-(2,3-di-O-acetyl-5-O-sulfamoyl-β-D-ribofuranosyl)-1H (and 3H)-benztriazole (**15**)

To a solution of the 3-chloro-5-trifluoromethyl-2-pyridoxybenztriazole[25] (3.7 g, 10.6 mmol) and **8** (3.77 g, 10.6 mmol) in acetonitrile (150 mL) was added 2,6-lutidine (3.4 g, 31.8 mmol) at room temperature. To the mixture was added Me_3SiOTf (6.20 mL, 33.93 mmol) at the same temperature over 15 min. After stirring at room temperature for 1 h, the reaction mixture was poured into aq sat $NaHCO_3$ (150 mL) and the mixture extracted with dichloromethane (4 x 50 mL). The combined extracts were washed with brine (50 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel 100 g, hexane / ethyl acetate 1:1) to give 3.7 g (54%) of a 1:1 mixture of the title compounds **15** as a colorless amorph. ^{1}H-NMR (D_6-DMSO, 300 MHz) 2.08, 2.11, 2.12, 2.13 (s, 2Ac),

4.12-4.33 (m, 2H-C(5'')), 4.58 (m, H-C(4'')), 5.68 (m, H-C(3'')), 6.00 (m, H-C(2'')), 6.81 (d, J=3.0, 0.5H-C(1'')), 6.90 (d, J=3.0, 0.5H-C(1'')), 7.57 (bs, 0.5NH_2), 7.60 (bs, 0.5NH_2), 8.28 (s, 0.5H, Ar), 8.39 (s, 0.5H, Ar), 8.50-8.60 (m, 2H, Ar), 8.67 - 8.72 (m, 1H, Ar).

4-Bromo-1 (and 3)-(2,3-di-O-acetyl-5-O-sulfamoyl-β-D-ribofuranosyl)-6-trifluoromethyl-1H (and 3H)-benztriazole (**16**)

To a solution of 4-bromo-6-trifluoromethylbenztriazole[25] (4.8 g, 18.04 mmol) and **8** (6.41 g, 18.04 mmol) in acetonitrile (140 mL) was added 2,6-di-tert-butylpyridine (12.2 mL, 54.13 mmol) at room temperature. To the mixture was added Me_3SiOTf (10.48 mL, 57.77 mmol) at the same temperature over 10 min. After stirring at room temperature for 1 h, the reaction mixture was poured into aq sat $NaHCO_3$ (300 mL). The mixture was extracted with dichloromethane (4 x 200 mL). The combined extracts were washed with brine (200 mL) and dried over $MgSO_4$. After evaporation under reduced pressure, the residue was purified by flash column chromatography (silica gel 400 g, hexane / ethyl acetate 1:1) to give 8.58 g (85%) of a 1:1 mixture of the title compounds **16** as a colorless amorph. ^{1}H-NMR (D_6-DMSO,300 MHz) 2.12, 2.13, 2.14, 2.17 (s, 2Ac), 4.00-4.33 (m, 2H-C(5')), 4.59 (m, H-C(4')), 5,71 (dd, J=6.0 and 6.0, 0.5H-C(3')), 5.79 (dd, J=5.5 and 7.0, 0.5H-C(3')), 6.05 (dd, J=3.0 and 5.5, 0.5H-C(2'), 6.27 (dd, J=2.0 and 5.0, 0.5H-C(2')), 7.04 (d, J=3.0, 0.5H-C(1')), 7.14 (d, J=2.0, 0.5H-C(1')), 7.51 (bs, 0.5NH2), 7.57 (bs, 0.5NH2), 8.12 (bs, 0.5H, Ar), 8.29 (bs, 0.5H, Ar), 8.68 (bs, 0.5H, Ar), 8.77 (bs, 0.5H, Ar). ^{13}C-NMR (D_6-DMSO, 75 MHz) 20.3 (q, 2Me), 67.3 (t, 0.5C(5')), 67.7 (t, 0.5C(5')), 70.0 (d, C(3')), 73.2 (d, 0.5C(2')), 73.4 (d, 0.5C(2')), 79.7 (d, 0.5C(4')), 79.8 (d, 0.5C(4')), 88.2 (d, 0.5C(1')), 88.3 (d, 0.5C(1')), 104.1 (s, C(4), 3H-isomer), 109.5 (d, C(7), 1H-isomer), 113.7 (s, C(4), 1H-isomer), 118.1 (d, C(7), 3H-isomer), 123.2 (q, J_{CF}=275, CF3), 124.0 (d, C(5), 1H-isomer), 126.9 (q, J_{CF}=33Hz, C(6), 3H-isomer), 129.0 (d, C(5), 3H-isomer), 129.7 (q, J_{CF}=33, C(6), 1H-isomer), 132.8 (dd$^+$, C(3a), 3H-isomer), 133.1 (s$^+$, C(7a), 1H-isomer), 145.5 (dd$^+$, C(3a), 1H-isomer), 145.7 (s$^+$, C(7a), 3H-isomer).

1-(2,3-Di-O-acetyl-5-O-sulfamoyl-β-D-ribofuranosyl]-4,5-dibromo-1H-triazole (**17**)

To a solution of 4,5-dibromo-1,2,3-triazole[26] (2.55 g, 11.26 mmol) and **8** (4.00 g, 11.26 mmol) in acetonitrile (80 mL) was added 2,6-di-tert-butylpyridine (7.58 mL, 33.77 mmol) at room temperature. To the solution was added Me_3SiOTf (6.54 mL, 36.02 mmol) at room temperature over 5 min. After stirring at room temperature for 1.5 h, the mixture was poured into 100 mL of aq sat $NaHCO_3$. The mixture was extracted with dichloromethane (2 x 200 mL) and the combined extracts were dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel 400 g, hexane / ethyl acetate 1:1) to give 3.0 g (51%) of the title compound **17** as a colorless amorph. ^{1}H-NMR (D_6-DMSO, 300 MHz): 2.10, 2.12 (s, 2Ac), 4.05 (dd, J=6.0 and 11.5, H-C(5')), 4.23 (dd, J=3.0 and 11.5, H-C(5')), 4.56 (m, H-C(4')), 5.56 (dd, J=5.5 and 7.0, H-C(3')), 5.96 (dd, J=2.5 and 5.5, H-C(2')), 6.26 (d, J=2.5, H-C(1')), 7.58 (s, NH_2). ^{13}C-NMR (D_6-DMSO, 75 MHz): 20.1 (q, Me), 20.2 (q, Me), 67.4(t, C(5')), 69.7 (d, C(3')), 72.6 (d, C(2')), 79.9 (d, C(4')), 89.1 (d, C(1')), 114.8 (s, C(5)), 123.4 (s, C(4)), 169.1 (s, CO), 169.3 (s, CO).

5-Chloro-1 (and 3)-(2,3-di-O-acetyl-5-O-sulfamoyl-β-D-ribofuranosyl)-6-(4-ethoxyphenoxy)-1H (and 3H)-benztriazole (**18**)

To a solution of 5-(4'-ethoxyphenoxy)-6-chlorobenztriazole[25] (1.5 g, 5.2 mmol) and **8** (1.85 g, 5.2 mmol) in 60 mL of acetonitrile was added 2,6-lutidine (1.7 g, 16.6 mmol) at room temperature. To the mixture was added Me_3SiOTf (3.7 g, 16.6 mmol) at the same temperature over 10 min. After stirring at room temperature for 1 h, the reaction mixture was poured into 100 mL of aq sat $NaHCO_3$. The mixture was extracted with dichloromethane (4 x 50 mL). The combined extracts were washed with brine (50 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel 100 g, hexane / ethyl acetate 1:1) to give 2.9 g (95%) of a 1:1 mixture of the title compounds **18** as a colorless amorph. ^{1}H-NMR (D_6-DMSO, 300 MHz) 1.31 ,1.35 (2t, J=7Hz, Me), 2.09, 2.11, 2.14, 2.16 (4s, 2Ac), 3.98-4.30 (m, 4H, -CH_2-OAr, 2H-C(5')), 4.48 (m, 0.5H-C(4')), 4.54-4.60 (m, 0.5H, H-C(4')), 5.64 (m, H-C(3')), 5.96 (m, 0.5H-C(2')), 6.02 (m, 0.5H-C(2')), 6.80 (d, J=3.0, 0.5H-C(1')), 6.85 (d, J=3.0, 0.5H-C(1')), 6.94-7.10 (m, 4H, Ar), 7.49 - 7.60 (m, 3H, NH_2, Ar), 8.42 (s, 0.5H, Ar), 8.45 (s, 0.5H, Ar).

1-Phenyl-3-trimethylsilylimidazolidin-4-one

A mixture of 1-phenyl-imidazolin-4-one (4.9 g, 30 mmol) and hexamethyldisilazane (14.5 g, 90 mmol)

in acetonitrile (30 mL) was heated at reflux for 60 min. Evaporation of the solvent afforded nearly pure 1-phenyl-3-trimethylsilyl-imidazolidin-4-one as a crystalline solid (mp 90-92°C). This compound was used without purification for the next step, but a sample was distilled with a bulb to bulb apparatus. (140°C/1mbar). ^{1}H-NMR ($CDCl_3$, 250MHz) 0.45 (s, 3Me-Si); 3.88 (s, 2H-C(5)); 4.75 (s, 2H-C(2)); 6.5-7.3 (m, Ph).

3-(2,3-Di-O-acetyl-5-O-sulfamoyl-β-D-ribofuranosyl)-4-oxo-1-phenyl-imidazolidine (**19**)

Me_3SiOTf (4.3 g, 19 mmol) was added slowly with ice cooling to a solution of **8** (5.7 g, 16 mmol), 1-phenyl-3-trimethylsilyl-imidazolidin-4-one (3.75 g, 16 mmol), and DBU (2.77 g, 16 mmol) in MeCN (50 mL). After heating at 50°C for 2 h, the solvent was evaporated and the residue chromatographed (70% EtOAc/hexane) to yield 3.3 g (45%) **19.** ^{1}H-NMR ($CDCl_3$, 300MHz) 2.09 and 2.15 (2s, 2OAc); 3.95 (s, 2H-C(5)); 4.32 (m, H-C(4')); 4.41 (dd, J=7 and 2 Hz, H-C(5')); 4.43 (dd, J=7 and 2 Hz, H-C(5')); 4.86 (m, H-C(2)); 4.98 (m, H-C(2)); 5.04 (br s, NH_2); 5.44 (m, H-C(2'), H-C(3')); 5.95 (d, J=7 Hz, H-C(1')); 6.58 (d, J=8 Hz, H-C(2"), H-C(6")); 6.85 (dd, J=8 and 8 Hz, H-C(4")); 7.32 (dd, J=8 and 8 Hz, H-C(3"), H-C(5")); .NOE between H-C(1') and H-C(4'). ^{13}C NMR (75 MHz, $CDCl_3$) 20.4 and 20.6 (2Me); 50.6 (C(5)); 61.2 (C(2)); 69.1 (C(5')); 69.9 and 71.1 (C(2'),C(3')); 79.2 (C(4')); 82.5 (C(1')); 111.7 (C(2"),C(6")); 118.4 (C(4")); 129.5 (C(3"),C(5")); 144.8 (C(1")); 170.2 and 170.3 (2MeCO); 170.9 (C(4)).

5-Chloro-1 (and 3)-(2,3-di-O-acetyl-5-O-sulfamoyl-β-D-ribofuranosyl)-1H (and 3H) benzimidazole (**20**)

Me_3SiOTf (4.3 mL, 5.27 g, 23.7 mmol) was added slowly to a solution of **8** (7.1 g, 20 mmol), 2,6-lutidine (3.5 mL, 30 mmol), and a 2:1 mixture of 1-trimethylsilyl-6-chlorobenzimidazole and 1-trimethylsilyl-5-chlorobenzimidazole[27] (4.5 g, 20 mmol) in MeCN (30 mL). After heating at reflux for 6 h, the reaction mixture was shaken between EtOAc and HCl (0.5M), the organic phase was then washed with water, $KHCO_3$ (aq.) and again with water. After evaporation of the solvent the residue was chromatographed (100% EtOAc) to yield 4.3 g (48%) of the isomeric mixture **20**. ^{1}H-NMR (250MHz, $CDCl_3$) 2.00, 2.05, 2.15, 2.15 (4s, 2OAc); 4.5 (m, H-C(4'),2H-C(5')); 5.5 (m, H-C(2'), H-C(3')); 6.05 (m, H-C(1')); 6.3 (br s, NH_2); 7.2-7.75 (m, H-C(4),H-C(6),H-C(7)); 8.28 (s, 0.5H-C(2)); 8.29 (s, 0.5H-C(2).

C. Derivatisation of 10 And 14

2-Chloro-5'-O-sulfamoyladenosine **1** and 2-Chloro-6-methoxy-9-(5-O-sulfamoyl-β-D-ribofuranosyl)purine (**27**)

10 (11.0 g; 22.7 mmol) in 20% NH_3/MeOH (100 mL) was stirred at room temperature for 3 days. Evaporation of the solvent and crystallization from MeOH/CH_2Cl_2 yielded 2.9 g **1**. Chromatography of the mother liquors (methanol/CH_2Cl_2 1:4) produced 2.0 g (22%) **27** and a mixture (4.2 g) from which a further 2.5 g **1** (total 63%) was isolated by crystallization from MeOH/Et_2O. Its NMR spectrum was identical to that of the natural product. ^{1}H-NMR (**27**) (250MHz; D_6-DMSO): 4.13 (s, MeO); 4.15-4.35 (m, H-C(2'), H-C(3'), 2H-C(5')); 4.55 (m, H-C(4')); 5.50 and 5.70 (2d, 2OH); 5.95 (d, J=6, H-C(1')); 7.6 (s, NH_2); 8.6 (s, H-C(8));

2-Chloro-6-methylamino-9-(5-O-sulfamoyl-β-D-ribofuranosyl)purine (**28**)

10 (2.02 g, 4.2 mmol) was dissolved in a solution of methylamine (4 g), water (6 mL), and methanol (20 mL). After 3 h the solvents were evaporated and the crude product crystallised from methanol to yield 702 mg (44%) of **28**. ^{1}H-NMR (300MHz, CD_3OD): 3.07 (s, MeNH) 4.28-4.45 (m, H-C(2') H-C(4'), 2H-C(5')); 4.58 (dd, J=6 und 6Hz, H-C(3')); 5.99 (d, J=6Hz, H-C(1')); 8.21 (s, H-C(8)). MS(CI): 394(M-H$^-$)

2-Chloro-6-(3-methylbut-2-en-1-ylamino)-9-(5-O-sulfamoyl-β-D-ribofuranosyl)purine (**29**)

3-Methylbut-2-en-1-ylamine[28] (3.5 g, 42 mmol) was added to a solution of **10** (2.6 g, 7.5 mmol) in MeOH (25 mL). After 3 h at room temperature the solvent was evaporated and the crude product (5.5 g) chromatographed (10% MeOH/CH_2Cl_2) to yield 2.6 g (78%) **29**. ^{1}H-NMR (250MHz, D_6-DMSO) 1.67 and 1.72 (2s, 2Me); 4.00 (m, 2H-C(1")); 4.19 (m, H-C(3'), H-C(4'), 2H-C(5')); 4.52 (m, H-C(2')); 5.25 (m, H-C(2")); 5.48 and 5.68 (2d, J=6Hz, 2OH); 5.87 (d, J=7Hz, H-C(1')); 7.62 (s, NH_2); 8.30 (s, H-C(8)); 8.48 (m, NH).

2-Chloro-6-methylthio-9-(5-O-sulfamoyl-β-D-ribofuranosyl)purine (**30**)

14 (1.6 g, 4.0 mmol) and NaSMe (400 mg, 5.5 mmol) were dissolved in THF and stirred for 24 h at room temperature. It was then shaken between NaCl (satd) and THF. The organic phase was dried Na_2SO_4 and the crude product chromatographed (20% MeOH/CH_2Cl_2). The product (1.3 g) was crystallised from EtOAc/hexane to yield 1.2 g (75%) **30**. ^{1}H-NMR (D_6DMSO + $CDCl_3$) 2.69 (s, SMe); 4.24 (m, H-C(3'), H-

C(4'), 2H-C(5'), 2OH); 4.56 (m, H-C(2')); 6.02 (d, J=6 Hz, H-C(1')); 7.58 (br s, NH_2); 8.56 (s, H-C(8)). MS (FD) 411 M^+.

2-Chloro-9-(2,3-di-O-acetyl-5-O-sulfamoyl-β-D-ribofuranosyl)purine (**31**)

A solution of **10** (9.7 g, 20 mmol) and Et_3N (2.02 g) in THF (100 mL) with 500 mg 5%Pd/C was hydrogenated at normal temperature and pressure for 7.5 h, when 442 ml (19.6 mmol) of hydrogen had been taken up. The catalyst was filtered off, the filtrate was concentrated under vacuum and the crude product (9.6 g) chromatographed (100% EtOAc) to yield 4.7 g **31** (52%) and 650 mg 9-(2',3'-di-O-acetyl-5'-O-sulfamoyl-1' β-ribofuranosyl)purine (7%). ^{1}H-NMR (250MHz, D_6-DMSO) 2.03 and 2.18 (2s, 2Me)); 4.38 (m, 2H-C(5')); 5.61 (dd, J=6 and 6 Hz, H-C(3')); 5.89 (dd, J=6 and 6 Hz, H-C(2')); 6.36 (d, J=6 Hz, H-C(1')); 7.69 (s, NH_2); 8.82 and 9.18 (2s, H-C(6), H-C(8)).

D: Deprotection of the 2',3'- Hydroxyl Groups

6-Chloro-9-(5-O-sulfamoyl-β-D-ribofuranosyl)purine (**13**)

11 (615 mg, 1.37 mmol) was dissolved in 20% NH_3/MeOH (10 mL), and the solvents evaporated after 24 h at room temperature. Chromatography (10-20% MeOH/CH_2Cl_2) yielded 411 mg (82%) of **13**. ^{1}H-NMR (300MHz, CD_3OD): 4.32-4.49 (m, H-C(4'), 2H-C(5')); 4.75 (dd, J=6 and 6, H-C(3')), 6.20 (d, J=6, H-C(1')); 8.71, 8.77 (2s,H-C(2), H-C(8)). MS(CI): 365(M^-).

2,6-Dichloro-9-(5-O-sulfamoyl-β-D-ribofuranosyl)purine (**14**)

A Solution of MeMgI (100 mmol) in Et_2O (50 mL) was added to a solution of **10** (2.42 g, 5 mmol) in THF (10 mL) at room temperature with stirring. After 3 h the reaction was quenched with NH_4Cl (40 ml satd.). The aqueous phase was extracted with 3 × 50ml THF/Et_2O 1:1, and the combined organic phase was dried with Na_2SO_4 and evaporated. The crude product (1.6 g) was recrystallized from EtOAc/hexane to yield 1.6g (80%) **14**.

^{1}H-NMR: (250MHz, D_6-DMSO) 4.26 (m, H-C(3'), H-C(4'), 2H-C(5')); 4.57 (m, H-C(2')); 5.56 and 5.78 (2d, J=7 Hz, 2 OH); 6.03 (d, J=6 Hz, H-C(1')); 7.63 (s, NH_2); 8.83 (s, H-.C(8)). MS: (DCI, NH_3) +ve 400 M^+

5-Chloro-6-(3-chloro-5-trifluoromethyl-2-pyridyloxy)-1 (and 3)-(5-O-sulfamoyl-β-D-ribofuranosyl)-1H (and 3H)-benztriazole (**21**)

To a solution of **15** (4.5 g, 7.0 mmol) in methanol (85 mL) was added triethylamine (21 mL) at room temperature. After stirring at room temperature for 5 h, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel 300 g, dichloromethane / methanol 9:1) to give 2.9 g (74%) of a 1:1 mixture of the title compounds **21** as a colorless amorph. ^{1}H-NMR (D_6-DMSO, 300 MHz), 4.07-4.31 (m, H-C(4'), 2H-C(5')), 4.38 (m, H-C(3')), 4.72 (m, H-C(2')) , 5.55 (d, J=5.0, 0.5HO-C(3')), 5.58 (d, J=5.0, 0.5HO-C(3')), 5.82 (d, J=6.0, 0.5HO-C(3')), 5.84 (d, J=6.0, 0.5HO-C(2')), 6.37 (d, J=4.0, 0.5H-C(1')), 6.45 (d, J=4, 0.5H-C(1')), 7.52 (bs, 0.5NH_2), 7.56 (bs, 0.5NH_2), 8.36 (s, 0.5H, Ar), 8.44 (s, 0.5H, Ar), 8.45-8.54 (m, 2H, Ar), 8.67-8.70 (m, 2H, Ar).

4-Bromo-1 (and 3)-(5-O-sulfamoyl-β-D-ribofuranosyl)-6-trifluoromethyl-1H-(and 3H) benztriazole (**22**)

To a solution of **16** (6.45 g, 11.49 mmol) in methanol (120 mL) was added triethylamine (30 mL) at room temperature. After stirring at room temperature for 14 h, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel 500 g, dichloromethane / methanol 20:1) to give 1.3 g (24%) of the 3H-isomer, 2.22 g (41%) of a mixture of the 3H-isomer and the 1H-isomer (1:2.3) and 1.0 g (18%) of the 1H-isomer as a colorless amorph, in order of elution. 1H-NMR (3H-isomer) (D_6-DMSO, 300MHz) 3.97 (dd, J=6.5 and11, H-C(5')), 4.21 (dd, J=3.5 and 11.0, H-C(5')), 4.28 (m, H-C(4')), 4.47 (dd, J=6.0 and 11.0, H-C(3')), 4.96 (dd, J=5.0 and 8.0, H-C(2')), 5.61 (d, J=6.0, HO-C(3')), 5.91 (d, J=5.0, HO-C(2')), 6.91 (d, J=3.0, H-C(1')), 7.49 (bs, NH_2), 8.25 (bs, 1H, Ar), 8.72 (bs, 1H, Ar). 1H-NMR (1H-isomer) (D_6-DMSO, 300MHz) 4.02-4.34 (m, H-C(4'), 2H-C(5')), 4.42 (m, H-C(3')), 4.74 (m, H-C(2')), 5.58 (d, J=6.0, OH), 5.86 (d, J=5.5, OH), 6.60 (d, J=3.5, H-C(1')), 7.51 (bs, NH_2), 8.08 (bs, 1H, Ar), 8.68 (bs, 1H, Ar). FAB-MS (mixture): 499(M+Na), 477(M+H). $C_{12}H_{12}BrF_3N_4O_6S$ Calcd. C = 30.20 %, H = 2.53 %, Br = 16.74 %, F = 11.94 %, N = 11.74 %, S = 6.72 %, Found, C = 30.55 %, H = 2.77 %, Br = 16.74 %, F= 11.98 %, N = 11.85 %, S = 6.72 %.

4,5-Dibromo-1-(5-O-sulfamoyl-β-D-ribofuranosyl)triazole (**23**)

To a solution of **17** (2.95 g, 5.65 mmol) in methanol (80 mL) was added triethylamine (20 mL) at room temperature. After stirring at room temperature for 48 h, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel 600 g, dichloromethane / methanol 9:1) to give 1.83 g (74%) of **23** as a colorless amorph. ^{1}H-NMR (D_6-DMSO, 300 MHz) 3.97-4.30 (m, H-C(3'), H-C(4'), 2H-C(5')), 4.66 (m, H-C(2')), 5.58 (d, J=6.0, H-C(1')), 5.87 (d, J=4.0Hz, 2OH), 7.55 (s,NH_2). ^{13}C-NMR (D_6-DMSO, 75 MHz) 68.7 (t, C(5')), 70.5, 73.3 (2d, C(2'), C(3')), 82.3 (d, C(4')), 91.6 (d, C(1')), 114.6 (s, C(5)), 122.9 (s, C(4)).

5-Chloro-6-(4-ethoxy-phenoxy)-1 (and 3)-(5-O-sulfamoyl-β-D-ribofuranosyl)-1H (and 3H)-benztriazole (**24**)

To a solution of **18** (4.9 g, 8.4 mmol) in methanol (50 mL) was added triethylamine (23 mL) at room temperature. After stirring at room temperature for 24 h, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel 300 g, dichloromethane / methanol 9:1) to give 3.5 g (83%) of the mixture of the title compounds **24** as a colorless amorph. ^{1}H-NMR (D_6-DMSO, 300 MHz) 1.31 (t, , J=7Hz, 0.5Me), 1.32 (t, J=7Hz, 0.5Me), 3.90-4.40 (m, 6H, -CH_2OAr, 2H-C(5'), H-C(4'), H-C(3')), 4.70 (m, H-C(2')), 5.49 (d, J=7, 0.5HO-C(3')), 5.56 (d, J=7.0, 0.5HO-C(3')), 5.72 (d, J=7.0, 0.5HO-C(2')), 5.80 (d, J=7.0, 0.5HO-C(2')), 6.30 (d, J=3.5, 0.5H-C(1')), 6.42 (d, J=4.0, 0.5H-C(1')),6.94-7.09 (m, 4H, Ar), 7.43 (s, 0.5H, Ar), 7.52 (s, 0.5NH_2), 7.55 (s, 0.5H, Ar), 7.58 (s, 0.5NH_2), 8.40 (s, 0.5H, Ar), 8.43 (s, 0.5H, Ar). $C_{19}H_{21}ClN_4O_8S$ Calcd. C = 45.56 %, H = 4.23 %, N = 11.18 %, S = 6.40 %, Cl = 7.08 %, Found, C = 46.0 %, H = 4.4 %, N = 11.2 %, S = 6.3 %, Cl = 7.0 %.

4-Oxo-1-phenyl-3-(5-O-sulfamoyl-β-D-ribofuranosyl)imidazolidine (**25**)

A solution of **19** (2.45 g, 6.6 mmol) in saturated NH_3/MeOH (50 mL) was stirred at room temperature for 45 min. After evaporation of the solvent the solid residue was recrystallised from water to yield 1.7 g (70%) **25**. ^{1}H-NMR (250MHz, $CDCl_3$ + D_6-DMSO) 3.9 (s, 2H-C(5)); 4.1-4.3 (m, H-C(2'), H-C(3'), H-C(4'), 2H-C(5')); 4.7-5.0 (m, 2H-C(2)); 5.75 (d, J=7 MHz, H-C(1')); 6.5-7.3 (m, Ph). ^{13}C-NMR (75MHz, D_6-DMSO) 50.3 (C(5)); 60.8 (C(2)); 68.8 (C(5')); 70.5 and 70.7 (C(2'),C(3')); 80.3 (C(4')); 84.3 (C(1')); 112.0 (C(2''),C(6'')); 117.7 (C(4'')); 129.1 (C(3''),C(5'')); 145.3 (C(1'')); 169.5 (C(4)).

5-Chloro-1-(5-O-sulfamoyl-β-D-ribofuranosyl)-1H (and 3H) benzimidazole (**26**)

The mixture **20** (4.2 g, 9.4 mmol) in saturated NH_3/MeOH (50 mL) was stirred at room temperature for 45 min. After evaporation of the solvent the solid residue was shaken between EtOAc and water. Drying and evaporation of the solvent left 2.5 g (74%) of **26** (ratio 1H:3H = 3:1). ^{1}H-NMR (250MHz, $CDCl_3$ + D_6-DMSO) 4.4 (m, H-C(2'), H-C(3'), H-C(4'), 2H-C(5')); 5.85 (m, H-C(1')); 7.15-7.7 (m, H-C(4),H-C(6),H-C(7)); 8.20 (s, H-C(2).

2-Chloro-9-(5-O-sulfamoyl-β-D-ribofuranosyl)-purine (**32**)

31 (485 mg, 1.08 mmol) in methanol (3 mL) was treated with saturated NH_3/MeOH (7 mL). After leaving the mixture overnight, TLC (20% EtOH/CH_2Cl_2) indicated complete reaction, so the solvent was evaporated and the residue crystallised from MeOH/Et_2O to yield 300 mg (76%) **32**. ^{1}H-NMR (250MHz, D_6-DMSO) 4.22 (m, H-C(4'), 2H-C(5')); 4.32 (m, H-C(3')); 4.61 (m, H-C(2')); 5.56 and 5.76 (2d, J=7Hz, 2 OH); 6.04 (d, J= 6Hz, H-C(1')); 7.66 (br s, NH_2); 8.82 (s, H-C(6)); 9.28 (s, H-C(8)).

Acknowledgement.

We would like to thank Thomas Fischer, Kurt Geiser, Beat Kohler, Rainer Tschan for technical assistance. We are also grateful to Peter Riebli and Charles Hary for performing the kilogram scale preparation of **8**.

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(*Received in Germany* 8 *February* 1994; *accepted* 31 *March* 1994)