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Synthesis of 5-Amino-4-sulfonamidoimidazole Nucleosides as Potential Inhibitors of Purine Nucleotide Biosynthesis, and of an Imidazothiadiazine Dioxide Analogue of Adenosine

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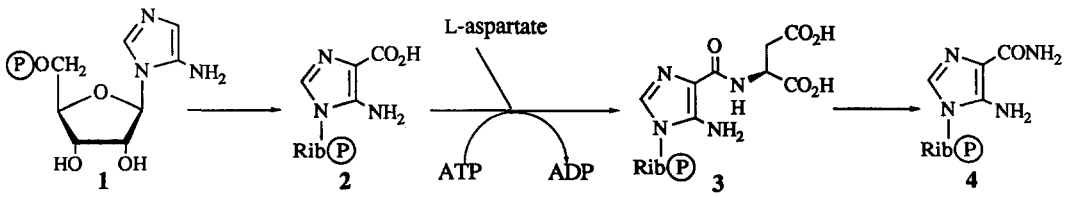
Abstract: 5-Amino-4-sulfonamido-1-(β-D-ribofuranosyl)imidazole **6** and two more complex sulfonamides, one of which (**8**) incorporates an L-aspartyl unit, have been prepared as potential inhibitors of the intermediate stages in the pathway for *de novo* biosynthesis of purine nucleotides. An intermediate in the preparation of **6** could be cyclized to give 5-(β-D-ribofuranosyl)imidazo[4,5-*e*]-1,2,4-thiadiazine-1,1-dioxide **9**, a novel analogue of adenosine and inosine, and a potential inhibitor of enzymes which effect reactions at C-6 of purine nucleosides or nucleotides. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The activity of enzymes involved in the *de novo* biosynthesis of purines has been found to be very low in a number of normal tissues,[1] where the energetically more economical salvage pathway is preferred, and indeed the rate-limiting enzyme of the pathway, phosphoribosyl pyrophosphate amidotransferase, could not be detected in rat skeletal muscle.[2] However, in rapidly proliferating cells, *de novo* purine biosynthesis has an important role,[3] and it has been shown that in Erlich ascites cells several enzymes of the pathway have elevated activity relative to appropriate control tissues.[4] Thus the inhibition of *de novo* nucleotide biosynthesis has attracted attention as a means to the development of new antitumour agents.[5]

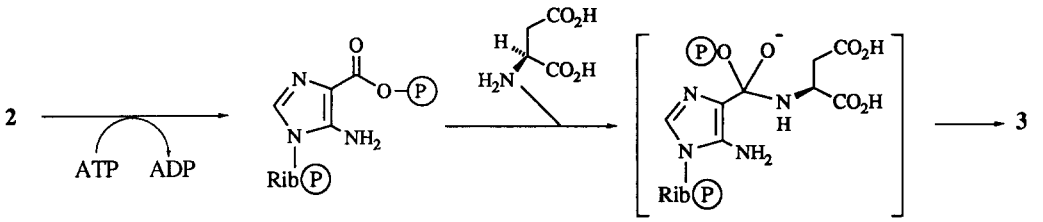


Scheme 1

In the intermediate stages of *de novo* purine nucleotide biosynthesis (Scheme 1), 5-amino-1-β-D-ribofuranosylimidazole- 5'-phosphate (AIR, **1**) undergoes carboxylation catalysed by AIR carboxylase to give the 5-amino-4-carboxyimidazole CAIR (**2**). Recent interesting studies have shown that, in *E. coli*, this enzyme consists of two subunits, one of which catalyses the ATP-dependent conversion of bicarbonate to

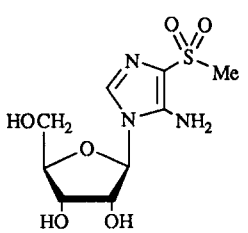
carbonyl phosphate and the subsequent carboxylation of AIR (**1**) on the aminogroup, whilst the second subunit catalyses the interconversion of this *N*-carboxy intermediate and CAIR (**2**).[6] However, it would appear that the carboxylation process is very significantly different in eukaryotes, where no cofactor requirement has been demonstrated. Indeed, in both mammalian[7] and avian[8] tissues, AIR carboxylase activity is closely linked with that of SAICAR synthetase, which catalyses the ATP-dependent conversion of CAIR (**2**) and aspartate into the *N*-succinylamide SAICAR (**3**). SAICAR is the substrate for a β-elimination catalysed by adenylosuccinase leading to 5-amino-4-carboxamido-1-(β-D-ribofuranosyl)imidazole-5'-phosphate (AICAR, **4**).

The conversion of **2** to **3**, catalysed by SAICAR synthetase [5'-phosphoribosyl-4-carboxy-5-aminoimidazole: L-aspartate ligase (ADP-forming), E.C. 6.3.2.6][9] can be assumed to involve formation of an acyl phosphate from CAIR **2** and ATP, and subsequent reaction of this acyl phosphate with aspartate via a tetrahedral intermediate (Scheme 2). Thus the enzyme may be susceptible to inhibition by transition-state analogues[10] designed to mimic either the acyl phosphate or, perhaps preferably, the tetrahedral intermediate.



Scheme 2

In a previous report from one of our laboratories, we described the synthesis of the simple sulfone **5**, together with some more complex sulfones.[11] In this paper we report the synthesis of the sulfonamide **6**, which can be regarded either as a substrate analogue of **2** or **4**,[12] or as a simple analogue of the tetrahedral intermediate in Scheme 2, and also the more complex structures **7** and **8**, which incorporate all or part of the L-aspartyl unit. We also describe the use of an intermediate in the route to **6** to give access to the imidazothiadiazine dioxide **9**, a novel analogue of adenosine and inosine.[13]



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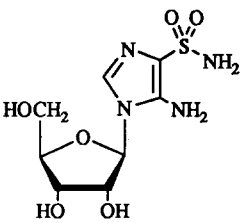

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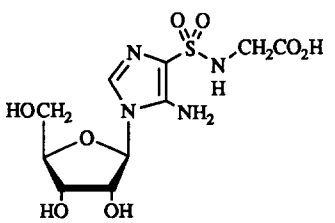

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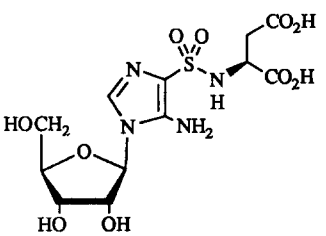

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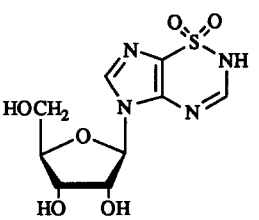

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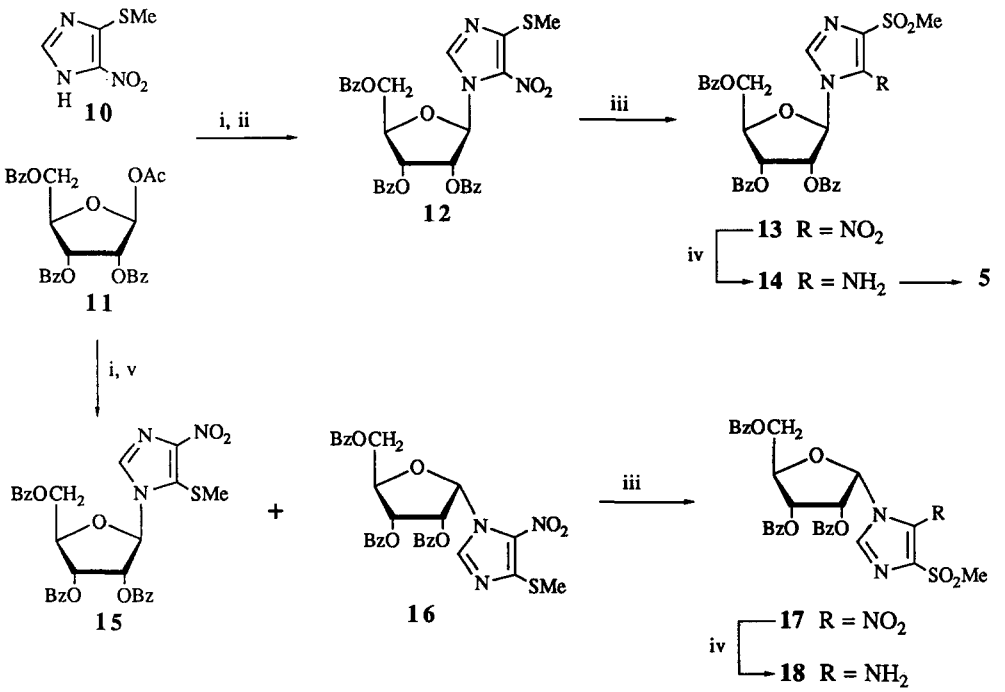
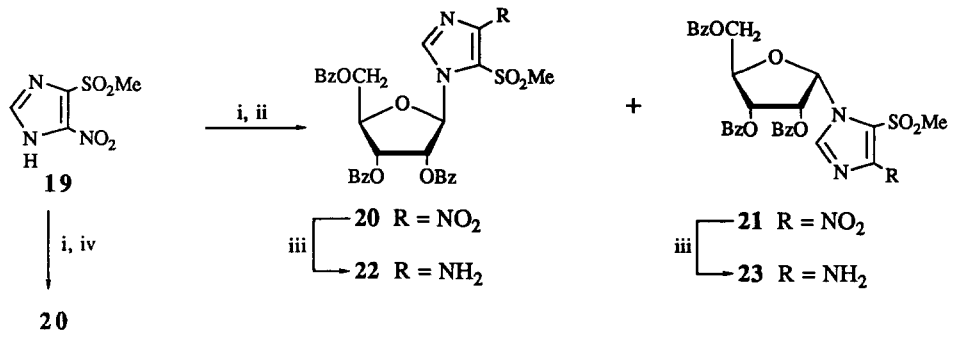
RESULTS AND DISCUSSION

We felt that **6**, **7** and **8** might well be accessible by base-sugar condensation between an appropriate 4(5)-nitro-5(4)-sulfonamidoimidazole and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11**, using the conditions developed by Vorbrüggen and coworkers.[14] However, such an approach requires that methods are available to determine unambiguously the regiochemistry of such a process (i.e. N^1- versus N^3-ribosylation), and to ensure that a β-nucleoside has been formed. To this end, we reinvestigated and extended some of our earlier work on the sulfone **5**.[11] We had prepared the protected nucleoside **12** (Scheme 3) by silylation of 4-methylthio-5-nitroimidazole **10** and condensation with **11** under conditions of kinetic control (3 min reaction time). The regiochemistry of this glycosylation was established by UV spectroscopy and ultimately rests on crystallographic evidence.[11] The nitro-sulfide **12** was converted to the aminosulfone **5** as indicated in Scheme 3. We had also shown[11] that condensation of **10** with **11** under conditions of thermodynamic control (16 h reaction time) gave as major product the 4-nitro-β-isomer **15** (Scheme 3). On reinvestigation, we have now found that another minor nucleoside product was also formed in this reaction. The UV spectrum of this product (λ_{max} 380 nm) clearly indicated the regiochemistry of ribosylation as being the opposite to that in **15**, and, since it was different from **12**, this new material must be the 5-nitro-α-isomer **16**. Oxidation of **16** gave the nitrosulfone **17**, which on catalytic hydrogenation gave the aminosulfone **18** anomeric with **14**. Interestingly, attempted oxidation of the 4-nitro-β-isomer **15** using a variety of reagents was unsuccessful, presumably due to steric factors.



Scheme 3. i, **10**, TMSCl, HMDS, xylene, reflux; ii, **11**, TMSOTf, MeCN, 0 °C to r.t., 3 min; iii, MCPBA, CH_2Cl_2; iv, H_2, Pd/C, EtOAc; v, as ii, but 16 h.

When sulfide **10** was oxidized to the sulfone **19**[15] prior to nucleoside formation, we found that in a condensation carried out under conditions of thermodynamic control two nucleosides were obtained in similar yields, both of which were different from **13** and **17**. Therefore, both these new products must be 4-nitro-



Scheme 4. i, TMSCl, HMDS, xylene, reflux, 2 h; ii, **11**, TMSOTf, MeCN, 0 °C to r.t., 16 h; iii, H_2, Pd/C, EtOAc; iv, as ii, but 3 min.

Table. Selected NMR data for methylsulfonyl/sulfonamido-aminoimidazole nucleosides

Entry	Compound	1'-H(δ)	C-1'	Shift on reduction (ppm)[a]	C-4(δ)	C-5(δ)	$\Delta\delta_c$[b]
1	**14** (5-amino-β-)	5.98	87.1	0.80	117.4	141.2	23.8
2	**18** (5-amino-α-)	6.31	83.8	0.74	116.7	141.4	24.7
3	**22** (4-amino-β-)	6.36	87.5	0.59	153.9	104.1	49.8
4	**23** (4-amino-α)	6.78	84.7	0.41	153.3	104.2	49.1
5	**27** (4-amino-β-)	6.27	86.5	0.57	150.7	106.1	44.6
6	**28** (4-amino-α-)	6.77	85.2	0.34	151.9	106.3	45.6
7	**30** (5-amino-β-)	5.96	87.2	0.73	119.5	139.3	19.8
8	**35** (4-amino-β-)	6.27	88.4	0.55	154.2	102.4	51.8
9	**36** (4-amino-α-)	6.75	85.0	0.31	153.3	101.8	51.5
10	**37** (5-amino-α-)	6.32	83.9	0.63	115.3	141.3	26.0
11	**39** (5-amino-β-)	5.95	87.4	0.84	116.6	141.1	24.5
12	**43** (4-amino-β-)	6.36	87.3	0.46	154.0	103.0	51.0
13	**44** (4-amino-α-)	6.68	85.3	0.35	143.8	108.7	35.1
14	**46** (5-amino-β-)	5.95	87.3	0.84	117.7	140.7	23.0

[a] Upfield shift of 1'-H on reduction of the nitrocompound to the aminocompound
[b] Chemical shift difference between C-4 and C-5

isomers. The chromatographically more mobile isomer, obtained in 36% yield, was assigned as the β-anomer **20**, and the less mobile isomer (24%) as the α-anomer **21** (Scheme 4) on the basis of NMR evidence. In particular, the signal for 1'-H in the α-anomer **21** was at lower field (δ 7.19) than the equivalent signal in β-anomer **20** (δ 6.95), and for **21** the coupling constant $J_{1',2'}$ was larger (4.9 Hz) than in **20** (3.6 Hz), as would be expected.[16,17] Additionally, C-1' appeared at higher field in the α-anomer **21** than in the β-anomer **20**, as would be expected on the basis of steric effects.[18] The same correlations were observed for the 5-nitro-isomers **13** and **17**. The β-stereochemistry of **20** was also supported by the observation that it was the only isolable nucleoside product in a reaction between **19** and **11** under conditions of kinetic control (3 min reaction time), since one would expect β-products to dominate under these conditions when the sugar component **11** has a participating group at *O*-2'.

Reduction of **20** and **21** gave the aminosulfones **22** and **23** respectively. The reactions of Schemes 3 and 4 had therefore made available the four isomeric nitrosulfones **13, 17, 20** and **21**, and the aminosulfones prepared by reduction of these, namely **14, 18, 22** and **23** respectively. Comparison of NMR data for the four combinations of regiochemistry and α/β-stereochemistry enabled a number of correlations to become apparent:

(a) As noted above, for an α/β pair, 1'-H resonates at a lower field in the case of the α-anomer, and, for the nitro-compounds, the α-anomer displays a larger value for $J_{1',2'}$:

(b) For an α/β pair, C-1' appears at higher field (lower chemical shift) in the case of the α-anomer:

(c) For a regiosomeric pair, reduction of the nitrogroup to an amino-function induces a greater upfield shift for 1'-H in the case of a 5-nitro-isomer, as would be expected on the basis of the greater proximity of the nitro/amino group to 1'-H in this regioisomer;

(d) For a regioisomeric pair of aminosulfones, 1'-H appears at lower field in the 4-amino-isomer, as would be expected from the deshielding effect of the sulfonyl group at C-5 in this isomer;

(e) For a regioisomeric pair of aminosulfones, the signals for C-4 and C-5 are more widely separated in the case of the 4-amino-isomer (Δδ ~50 ppm) then is found for the corresponding 5-amino-compound(Δδ ~25 ppm). This final very useful correlation is similar to findings observed previously in one of our laboratories for nucleosides of 4/5-aminoimidazole-5/4-carboxamides and -carboxylates.[19]

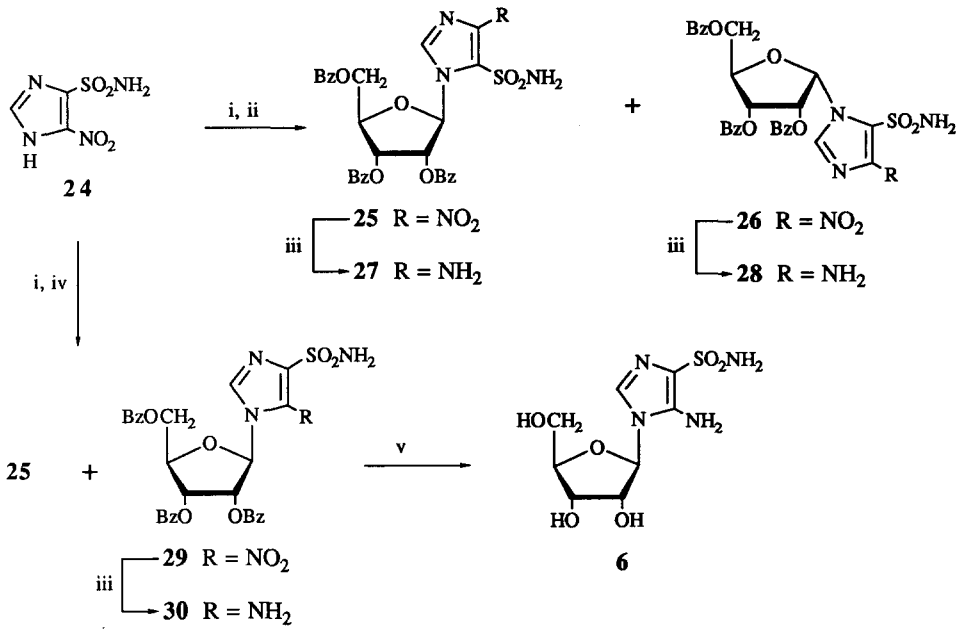
Key features of these correlations as applied to the aminosulfones **14, 18, 22** and **23** are indicated in the Table, entries 1-4, and the trends observed were maintained throughout the subsequent work described below.

We thus went on to investigate the reaction of the nitrosulfonamide **24**[20] with the ribose donor **11**, confident that the structures of nucleoside products could be determined unambiguously, but apprehensive in that the reactions of the closely related sulfone **19** (Scheme 4) had not given any of the desired 5-nitro-β-isomer.

Silylation of **24** and reaction with **11** catalysed by trimethylsilyl triflate under conditions of thermodynamic control mirrored the case of the sulfone, giving the two products **25** and **26** with the undesired regiochemistry (Scheme 5). The structures of the nitrosulfonamides **25** and **26** became apparent when they were reduced catalytically to the aminosulfonamides **27** and **28** respectively, key data for which appears in the Table, entries 5 and 6. In particular, the large difference in chemical shift between C-4 and C-5, and the relatively small shift in the position of 1'-H on reduction indicated that both compounds **27** and **28** were 4-amino-5-sulfonamides. The α/β assignment was also supported by data for the nitrocompounds (**25**, 1'-H δ 6.84, $J_{1',2}$ 2.0 Hz, C-1' δ 90.2; **26**, 1'-H δ 7.11, $J_{1',2'}$, 4.05 Hz, C-1' δ 88.2).

We were pleased to find, however, that when the condensation of silylated **24** with **11** was allowed to proceed for only 3 minutes (Scheme 5), two products were obtained, one of which (41%) was the 4-nitro-β-isomer **25**, whilst the other (44%) was a new nucleoside assigned structure **29**. The 5-nitro-4-sulfonamido-regiochemistry was apparent on reduction to the aminosulfonamide **30** which showed a difference of only 19.8 ppm between the signals for C-4 and C-5, whilst the signal from 1'-H moved upfield by 0.73 ppm on reduction (Table, Entry 7). The β-stereochemistry is supported by the observation of 1'-H in **29** at δ 6.69, $J_{1',2'}$ 2.1 Hz,

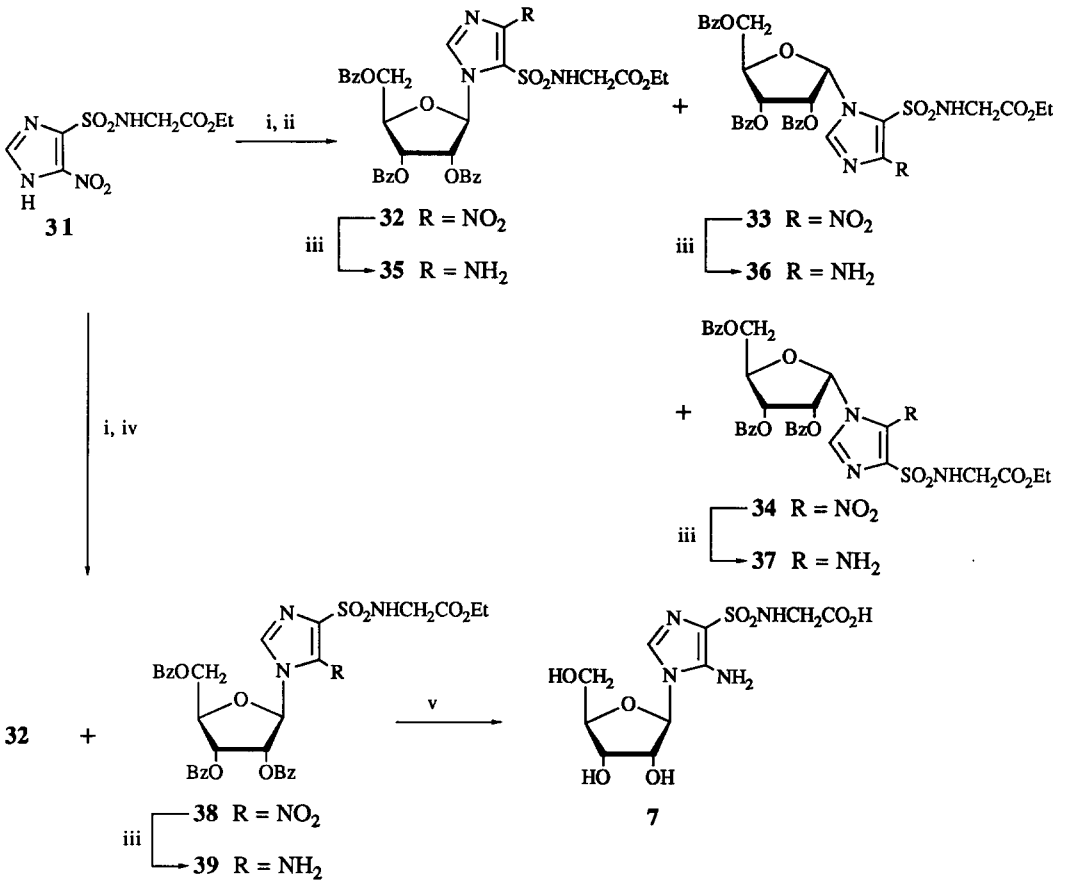
by the very close similarity of the position of 1'-H in **30** with the equivalent signal in **14**, and by the fact that **29** is the product of a reaction under kinetically-controlled conditions. Routine debenzoylation of **29** then gave **6**, the first and simplest of our targets.



Scheme 5. i, TMSCl, HMDS, xylene, reflux, 2 h; ii, **11**, TMSOTf, MeCN, 0 °C to r.t., 16 h; iii, H_2, Pd/C, EtOAc; iv, as ii, but 3 min; v, NH_3, MeOH.

For the synthesis of the more complex analogue **7** (Scheme 6), the nitrosulfonamide **31** was firstly prepared by the reaction of 4(5)-chlorosulfonyl-5(4)-nitrimidazole[20] with ethyl glycinate. Reaction of silylated **31** with the ribose unit **11** under conditions of thermodynamic control gave, in order of elution from a silica column, the 4-nitro-β-isomer **32** (32%), the 4-nitro-α-isomer **33** (27%), and a lesser amount (14%) of the 5-nitro-α-isomer 34 . The structures of **32** and **33** were readily apparent from data obtained for their reduction products **35** and **36** respectively (Table, entries 8 and 9). Reduction of **34** gave the 5-amino-compound **37**. The close similarity of NMR data for **37** with data for **18** (Table, entries 10 and 2) strongly suggested that **37** was an α-anomer. This was confirmed when a reaction of silylated **31** and **11** under conditions of thermodynamic control (3 minutes reaction time) gave a mixture of **32** (38%) and a new nucleoside (34%), which was identified as the required 5-nitro-β-isomer **38** after reduction to the aminosulfonamide **39**. Data for **39** and its anomer **37** (Table, entries 11 and 10 respectively) clearly establish their structures. The anomeric stereochemistries (α /β) of **32** and **33** and of **34** and **38**, were also indicated by both of the NMR criteria (a) and (b) above. A chromatographic correlation also became apparent at this point; for any series of isomeric nitrosulfonamido or nitrosulfonyl nucleosides, the order of mobility of the *O*-benzoylated compounds on silica was in the order 4-nitro-β- > 4-nitro-α- > 5-nitro-β- > 5-nitro-α-, and the same order of mobility applied after reduction to the *O*-protected aminosulfonamides or aminosulfones. A similar observation has been made previously in one of our laboratories for 4/5-amino-5/4-carboxyimidazole nucleosides,where the inverse order of mobility was found when using a reverse-phase column.[19] Deprotection of the 5-nitro-β -isomer **39** gave the target nucleoside **7.**

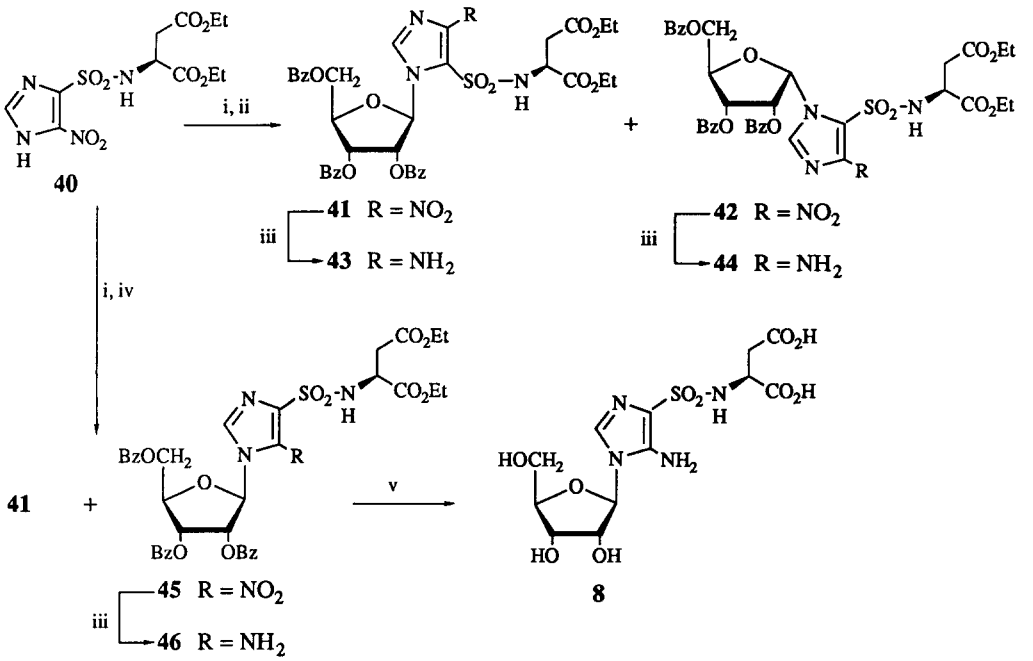
To prepare analogue **8**, incorporating the aspartate unit, the nitrosulfonamide **40** (Scheme 7) was prepared by treatment of the sulfonyl chloride[20] with diethyl-L-aspartate. The reactions of **40** with the ribosyl acetate **11** parallelled those found with the simpler sulfonamides. Thus, under thermodynamically-controlled



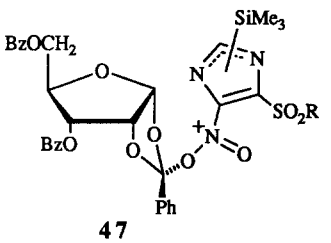
Scheme 6. i, TMSCl, HMDS, xylene, reflux, 2 h; ii, **11**, TMSOTf, MeCN, 0 °C to r.t., 16 h; iii, H_2, Pd/C, EtOAc; iv, as ii, but 3 min; v, NaOMe (cat.), MeOH, then NaOH aq.

conditions, the 4-nitro-β-isomer **41** (40%) and 4-nitro-α-isomer **42** (31%) were obtained, their structures being confirmed by data on their reduction products **43** and **44** respectively (Table, entries 12 and 13) as well as by data on the nitrosulfonamides themselves (**41**, 1'-H δ 6.82, $J_{1',2'}$ 2.6 Hz, C-1' δ 89.9; **42**, 1'-H δ 7.03, $J_{1',2'}$, 5.3 Hz, C-1' δ 87.3). Under conditions of kinetic control, the 4-nitro-β–isomer 41 (38%) and the 5-nitro-β-isomer **45** (29%) were the products obtained. Catalytic hydrogenation of **45** gave the amine **46**, the NMR spectra of which (Table, entry 14) confirmed the β-stereochemistry as well as the regiochemistry of glycosylation. Deprotection of **46** gave the target nucleoside **8**.

The fact that the reactions of Schemes 4-7 gave significant quantities of α-nucleosides under conditions of thermodynamic control is somewhat surprising. However, Verheyden and coworkers have observed that reaction of silylated 2-nitroimidazole with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11** in the presence of tin (IV) chloride gave the α-nucleoside as the major product.[17] They tentatively ascribed their observation to the intermediacy of a nitronate formed by interaction of the nitrogroup with the 1,2-benzoxonium ion, derived from **11**, and application of this idea to our cases would involve intermediates of type **47**. On the other hand, Srivastava and coworkers have shown that interaction of silylated 4-bromo-5-nitroimidazole with **11**, again in the presence of $SnCl_4$, gave a mixture of two regioisomers, both of β-configuration.[21] The situation is thus somewhat unclear, but it seems probable that the conditions we have employed, with trimethylsilyl triflate present, are ones which are, over a prolonged time scale, likely to lead to true products of thermodynamic control.



Scheme 7. i, TMSCl, HMDS, xylene, reflux, 2 h; ii, **11**, TMSOTf, MeCN, 0 °C to r.t., 16 h; iii, H_2, Pd/C, EtOAc; iv, as ii, but 3 min; v, NaOMe (cat.), MeOH, then NaOH aq.



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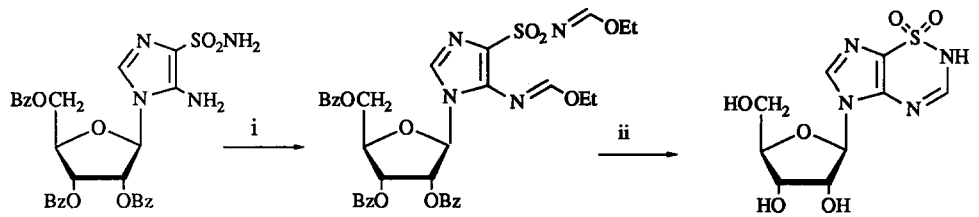
The availability of the aminosulfonamide **30** prompted us to investigate its cyclization to form the imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide **9**. Huang and Parham have studied cyclizations of this type, and they found that the ring closure required more stringent conditions in the case of a 1-alkylated-5-aminoimidazole-4-sulfonamide (analogous to **30**) than were necessary to cyclise the isomeric 1-alkyl-4-aminoimidazole-5-sulfonamide. They also found that reactions of the preformed bicyclic imidazothiadiazine dioxide with **11** led to ribosylation on the imidazole ring, but with the undesired regiochemistry.[22] The conditions we used for the cyclisation were based on the observations of Huang and Parham. Thus, heating the aminosulfonamide **30** with triethylorthoformate at 120 °C for 4 hours led to the formation of the bis-(ethoxymethylene) compound **48** (Scheme 8). Selective hydrolysis of the substituent on the sulfonamide gave an intermediate which cyclized at pH 10 with concomitant debenzoylation to give the imidazothiadiazine dioxide **9** in 71% yield. This compound is an analogue of adenosine or inosine with tetrahedral geometry at C-6 (purine numbering); it can therefore be envisaged as a potential inhibitor of enzymes which effect reactions at this position, such as adenosine deaminase, or, after phosphorylation at *O*-5', of adenylosuccinate synthetase.



Scheme 8. i, $HC(OEt)_3$, 120 °C, 4 h; ii, MeOH, NaOH aq, pH 8, 2 h, then adjust to pH 10, 2 h.

Compounds **6** - **9** were tested for cytotoxicity against the MAC I5A cell line, but none of them displayed significant cytotoxicity at concentrations below 10 μg. cm^{-3}. Phosphorylation of **6** - **9**, and the evaluation of the 5'-phosphates as enzyme inhibitors, will be described elsewhere.

EXPERIMENTAL

NMR spectra were recorded on Bruker WP 200 SY and WH 400 spectrometers. Unless otherwise stated, ^1H-spectra were obtained at 200 MHz, and ^{13}C-spectra at 50 MHz, in $CDCl_3$ as solvent. Coupling constants are measured in Hz. Mass spectrometry was performed using V.G. updated MS9 and V.G. ZABE high resolution EI/FAB instruments. Specific rotations were measured at room temperature using a Bendix-NPL 143D automatic polarimeter (path length 1 cm); units for $[\alpha]_D$ values are 10^{-1} deg cm^2 g^{-1}. Melting points were determined using an Electrothermal MK II melting point apparatus and are uncorrected. UV spectra were obtained on a Shimadzu 160 spectrophotometer.

Reactions were monitored by TLC on precoated aluminium-backed plates, Kieselgel HF_{254} type 60 (Merck). Detection was effected using u.v. light or 5% aqueous ammonium molybdate solution to which concentrated sulphuric acid had been added. Column chromatography was carried out using Kieselgel H type 60 (Merck), an external pressure being applied to the top of columns. Organic extracts were dried over anhydrous sodium sulfate.

4-Methylsulfonyl-5-nitro-1-(2,3,5-tri-O-*benzoyl*-β-D-*ribofuranosyl)imidazole* **(13)** -This compound was prepared in 84% yield as previously described,[11] m.p. 147-148 °C (lit.[11] 147-148 °C), R_F 0.2 (toluene-ethyl acetate, 4:1); additional data, δ_C 42.1 (Me), 62.7 (C-5'), 69.8, 75.7 (C-2', C-3'), 81.0 (C-4'), 90.1 (C-1'), 128.0 (C-4), 128.2-129.6 (Ph), 133.0-134.8 (Ph), 135.2 (C-2), 141.7 (C-5), 164.7, 165.0 and 166.0 (COPh).

5-Amino-4-methylsulfonyl-1-(2,3,5-tri-O-*benzoyl*-β-D-*ribofuranosyl)imidazole* **(14)** - This was prepared (95%) as previously reported,[11] R_F 0.28 (ethyl acetate); additional data, δ_C 43.3 (Me), 62.9 (C-5'), 70.1, 73.2 (C-2', C-3'), 80.4 (C-4'), 87.1 (C-1'), 117.4 (C-4), 127.9-129.7 (C of Ph, C-2), 133.6-134.0 (Ph), 141.2 (C-5), 165.1, 165.5 and 166.0 (COPh).

5-Methylthio-4-nitro-1-(2,3,5-tri-O-*benzoyl*-β-D-*ribofuranosyl)imidazole* **(15)** *and 4-methylthio-5-nitro-1-(2,3,5-tri*-O-*benzoyl*-α-D-*ribofuranosyl)imidazole* **(16)** - A mixture of sulfide **10** (0.40 g, 2.5 mmol), chlorotrimethylsilane (0.32 cm^3, 2.5 mmol), hexamethyldisilazane (3.5 cm^3) and xylene (5 cm^3) were stirred and heated at 130° C. After *ca* 1h all the solid had dissolved to give a clear brown solution. Ammonium chloride sublimed into the condenser during the course of the reaction. The solution was evaporated to dryness under reduced pressure to give a brown residue. This was dissolved in acetonitrile (5 cm^3) and a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11**[23] (1.29 g, 2.5 mmol) in acetonitrile (15 cm^3)was added with stirring. The mixture was cooled to 0°C, trimethylsilyl trifluoromethanesulfonate (0.85 cm^3, 3.77 mmol) was added, and after warming to room temperature the solution was stirred for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (30 cm^3) and diluted with dichloromethane (30 cm^3). The layers were separated and the aqueous layer extracted with further

dichloromethane (2 x 30 cm^3). The combined organic extracts were dried and evaporated to give a yellow foam which was chromatographed on silica, with toluene-ethyl acetate (20:1) as eluent , to give firstly the *5-nitro-α- isomer* **16** (0.25 g, 16%) as a yellow amorphous solid, R_F 0.55 (toluene-ethyl acetate, 4:1), $[\alpha]_D$ -36.0 (*c* 0.50, CH_2Cl_2); λ_{max} ($CHCl_3$) 240, 278 and 380 nm; δ_H 2.61(3 H, s, Me), 4.62 (1H, dd, $J_{4',5'a}$ 3.8, J_{gem} 12.35, 5'-H_a), 4.79 (1H, dd, $J_{4,5'b}$ 3.4, J_{gem} 12.35, 5'-H_b), 5.05 (1H, app. q, *J* 3.5, 4'-H), 5.97 (1H, dd, *J* 3.4 and 5.4, 3'-H), 6.27 (1H, t, *J* 5.4, 2'-H), 7.08 (1H, d, *J* 5.35, 1'-H), 7.32-7.70 (9H, m, *m*- and *p*- H of Ph), 7.86-8.18 (7H, m, *o*-H of Ph, 2-H); δ_C 13.6 (Me), 63.7 (C-5'), 71.7, 71.9 (C-2', C-3'), 82.3 (C-4'), 87.5 (C-1'), 127.8 (C-4), 128.2-129.8 (Ph), 133.5-133.7 (Ph), 138.5 (C-2), 149.9 (C-5), 163.9, 164.9, 165.9 (COPh) (Found: C, 59.4; H, 3.9; N, 7.2; S, 5.7. $C_{30}H_{25}N_3O_9S$ requires C, 59.69; H, 4.18; N, 6.97; S, 5.30%).

Further elution of the column afforded **15**[11] (1.10 g, 70%) as an amorphous solid with data as previously reported; additional data, δ_C 19.0 (Me), 63.3 (C-5'), 71.1, 74.6 (C-2', C-3'), 81.0 (C-4'), 87.2 (C-1'), 126.1 (C-4), 127.9-129.7 (C of Ph), 133.6-134.0 (Ph and C-2), 149.8 (C-5), 164.7, 165.1 and 165.9 (COPh).

*4-Methylsulfonyl-5-nitro-1-(2,3,5-tri-*O*-benzoyl-α-*D*-ribofuranosyl)imidazole* **(17)** - A solution of the sulfide **16** (0.15 g, 0.25 mmol) and *m*-chloroperbenzoic acid (0.135 g, 0.78 mmol) in dichloromethane (10 cm^3) was stirred at 20°C for 1.5h. The solution was filtered and washed with saturated sodium bicarbonate solution (10 cm^3) followed by water (10 cm^3). The organic layer was dried filtered and evaporated. Chromatography on silica, with toluene-ethyl acetate (5:1) as eluent, yielded the *sulfone* **17** (0.14 g, 89%), as an amorphous white solid, R_F 0.15 (toluene - ethyl acetate 4:1); $[\alpha]_D$ -80.7 (*c* 1.165, CH_2Cl_2); δ_H 3.34 (3H, s, Me), 4.62 (1H, dd, $J_{4',5'a}$ 3.7, J_{gem} 12.45, 5'-H_a), 4.79 (1H, dd, $J_{4',5'b}$ 3.4, J_{gem} 12.3, 5'-H_b), 5.16 (1H, app. q, *J* 3.1, 4'-H), 5.97 (1H, dd, *J* 2.6 and 5.5, 3'-H), 6.32 (1H, t, J 5.5, 2'-H), 7.05 (1H, d, *J* 5.51, 1'-H), 7.18-7.40 (9H, m, *m*- and *p*- H of Ph), 7.90-8.14 (7H, m, *o*-H of Ph and 2-H); δ_C 42.0 (Me), 63.7 (C-5'), 71.5, 71.7 (C-2', C-3'), 83.2 (C-4'), 88.1 (C-1'), 127.1 (C-4), 127.9-129.6 (Ph), 133.6-135.0 (Ph), 135.6 (C-2), 141.6 (C-5), 163.7, 164.8, 165.8 (COPh); (Found: C, 56.4; H, 4.1; N, 6.7, S, 5.4. $C_{30}H_{25}N_3O_{11}S$ requires C, 56.68; H, 3.97; N, 6.61; S 5.03%).

*5-Amino-4-methylsulfonyl-1-(2,3,5-tri-*O*-benzoyl-α-*D*-ribofuranosyl)imidazole* **(18)** - The nitrosulfone **17** (0.10 g, 0.16 mmol) in ethyl acetate (15 cm^3) was hydrogenated at 1 atm. over palladium-on-charcoal (5%, 50mg). The reaction was monitored by TLC and when reaction was complete the mixture was filtered and evaporated. Chromatography of the residue on silica, with toluene-ethyl acetate (1:1) as eluent, gave the *amine* **18** (0.09 g, 95%) as a white amorphous solid, R_F 0.25 (toluene-ethyl acetate), $[\alpha]_D$ +16.4 (*c* 0.915, CH_2Cl_2); δ_H 2.91 (3H, s, Me), 4.65 (4H, m, collapses to 2H, m, on D_2O shake, 5'-H_2, NH_2), 4.92 (1H, app. q, *J* 3.7 , 4'-H), 5.97 (1H, dd, *J* 3.7 and 6.0, 3'-H), 6.05 (1H, t, *J* 5.8, 2'-H), 6.31 (1H, d, *J* 5.7, 1'-H), 7.18-7.57 (9H, m, *m*- and *p*- H of Ph), 7.62-8.14 (7H, m, *o*-H of Ph and 2-H); δ_C 43.3 (Me), 63.7 (C-5'), 71.4, 71.6 (C-2', C-3'), 81.2 (C-4'), 83.8 (C-1'), 116.7 (C-4), 127.6-129.6 (Ph), 131.0 (C-2), 133.5-134.1 (Ph), 141.4 (C-5), 164.9, 165.4, 166.0 (COPh) (Found: C, 59.2; H, 4.7; N, 6.9; S, 5.7. $C_{30}H_{27}N_3O_9S$ requires C, 59.49; H, 4.50, N, 6.94; S, 5.28%).

*5-Methylsulfonyl-4-nitro-1-(2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranosyl)imidazole* **(20)** - A mixture of the sulfone **19**[15] (0.15g, 0.786 mmol), chlorotrimethylsilane (0.10 cm^3, 0.786 mmol), hexamethyldisilazane (1 cm^3), and xylene (1 cm^3) were stirred and heated at 130 °C. After *ca* 2h all the solid had dissolved to give a clear brown solution. Ammonium chloride sublimed into the condenser during the course of the reaction. The solution was evaporated to give a brown residue. This was dissolved in acetonitrile (2 cm^3) and a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11** (0.39 g, 0.786 mmol) in acetonitrile (8 cm^3) was added with stirring. The mixture was cooled to 0°C and trimethylsilyl trifluoromethanesulfonate (0.218 cm^3, 1.178 mmol) was added. After 3 min, during which time the cooling bath was removed, the reaction mixture was quenched with saturated sodium bicarbonate solution (15 cm^3) and diluted with dichloromethane (15 cm^3). The layers were separated and the aqueous layer extracted with more dichloromethane (2 x 15 cm^3). The combined organic extracts were dried and evaporated to leave a brown foam which was chromatographed on silica gel, with toluene-ethyl acetate (5:1) as eluent, to give the *4-nitro-β- isomer* **20** (0.26 g, 52%) as a white amorphous solid, R_F 0.6 (toluene-ethyl acetate, 4:1), $[\alpha]_D$ +30.8 (*c* 1.17, CH_2Cl_2); δ_H 3.50 (3H, s, Me), 4.62-4.93 (3H, m, 4'-, 5'-H_2), 5.60-5.92 (1H, m, 3'-H), 5.99 (1H, dd, *J* 3.7 and 5.6, H-2'), 6.95 (1H, d, *J* 3.6, 1'-H), 7.21-7.61 (9H, m, *m*- and *p*- H of Ph), 7.82-8.15 (7H, m, *o*-H of Ph and 2-H); δ_C 45.1 (Me), 62.5 (C-5'), 71.7,

75.4 (C-2', C-3'), 80.8 (C-4'), 89.0 (C-1'), 125.4 (C-5), 128.1-129.9 (Ph), 133.1-133.9 (Ph), 134.9 (C-2), 149.5 (C-4), 164.9, 165.2 and 166.0 (COPh) (Found: C, 56.5; H, 4.1; N, 6.5; S, 5.4. $C_{30}H_{25}N_3O_{11}S$ requires C, 56.68; H, 3.97; N, 6.61; S, 5.03%).

*5-Methylsulfonyl-4-nitro-1-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazole* **(20)** *and 5-Methylsulfonyl-4-nitro-1-(2,3,5-tri-*O*-benzoyl-*α*-D-ribofuranosyl)imidazole* **(21)** - Sulfone **19**[15] (0.15g, 0.786 mmol), chlorotrimethylsilane (0.10 cm^3, 0.786 mmol), hexamethyldisilazane (1 cm^3), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11** (0.39 g, 0.786 mmol) and trimethylsilyl trifluoromethanesulfonate (0.218 cm^3, 1.178 mmol) were treated as described in the above preparation of **20**, except that a reaction time of 16 h was used for nucleoside formation. Chromatography on silica, with toluene-ethyl acetate (7:1) as eluent, yielded firstly the *nucleoside* **20** (0.18 g, 36%) as a white amorphous solid, R_F 0.6 (toluene-ethyl acetate, 4:1), with properties as given above.
Further elution of the column afforded the *4-nitro-α-isomer* **21** (0.12 g, 24%) as a white amorphous solid, R_F 0.55 (toluene-ethyl acetate, 4:1); $[\alpha]_D$ +15.4 (*c* 0.81, CH_2Cl_2); δ_H 3.48 (3H, s, Me), 4.63 (1H, dd, $J_{5'a,4'}$ 3.9, J_{gem} 12.4, 5'-H_a), 4.75 (1H, dd, $J_{4',5'b}$ 3.4, J_{gem} 12.4, 5'-H_b), 5.10 (1H, app. q, *J* 4.0, 4'-H), 5.94 (1H, t, *J* 5.0 , 3'-H), 6.30 (1H, t, *J* 5.1 , 2'-H), 7.19 (1H, d, *J* 4.9, 1'-H), 7.12-7.55 (9H, m, *m*- and *p*- H of Ph), 7.58-8.12 (7H, m, *o*-H of Ph and 2-H); δ_C 45.0 (Me), 63.8 (C-5'), 71.8, 72.0 (C-2', C-3'), 81.5 (C-4'), 87.5 (C-1'), 125.9 (C-5), 127.6-129.7 (C of Ph), 133.6-134.2 (C of Ph), 135.9 (C-2), 148.2 (C-4), 164.3, 165.0 and 165.9 (COPh) (Found: C, 56.4; H, 4.1; N, 6.4; S, 5.3. $C_{30}H_{25}N_3O_{11}S$ requires C, 56.68; H, 3.97; N, 6.61; S, 5.03%).

*4-Amino-5-methylsulfonyl-1-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazole* **(22)** - A solution of the nitrosulfone **20** (0.15 g, 0.237 mmol) in ethyl acetate (15 cm^3) was hydrogenated at 1 atm with palladium-on-charcoal (5%: 0.1g) as catalyst. The reaction was monitored by TLC and when reaction was complete the mixture was filtered and evaporated. The residue was chromatographed on silica, with toluene-ethyl acetate (1:1) as eluent, to give the *aminosulfone* **22** (0.135 g, 94%), R_F 0.48 (ethyl acetate), m.p. 144-146 °C (dec.); $[\alpha]_D$ -16.5 (*c* 0.90, CH_2Cl_2); δ_H 3.15 (3H, s, Me), 4.58-4.91 (5H, m, 4'-, 5'-H_2, NH_2), 5.88 (1H, dd, *J* 4.95 and 6.0, 3'-H), 6.11 (1H, t, *J* 5.9, 2'-H), 6.36 (1H, d, *J* 5.7, 1'-H), 7.19-7.68 (9H, m, *m*- and *p*- H of Ph), 7.83-8.15 (7H, m, *o*-H of Ph and 2-H); δ_C 44.9 (Me), 63.3 (C-5'), 70.7, 73.1 (C-2', C-3'), 80.5 (C-4'), 87.5 (C-1'), 104.1 (C-5), 128.5-129.9 (Ph), 133.5-133.8 (Ph), 136.7 (C-2), 153.9 (C-4), 164.7, 165.2 and 166.0 (COPh) (Found: C, 59.2; H, 4.7; N, 6.6; S, 5.7. $C_{30}H_{27}N_3O_9S$ requires C, 59.49; H, 4.50; N, 6.94; S, 5.28%).

4-Amino-5-methylsulfonyl-1-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)imidazole **(23)** - The nitrosulfone **21** (0.10g, 0.158 mmol) was hydrogenated and processed as described in the preparation of isomer **22** above, to give the *4-amino-α-product* **23** (0.089 g, 93%) as a white amorphous solid, R_F 0.45 (ethyl acetate), $[\alpha]_D$ -44.9 (*c* 0.51, CH_2Cl_2); δ_H 3.18 (3H, s, Me), 4.57-4.91 (5H, m, 4'-, 5'-H_2, NH_2), 5.92 (1H, dd, *J* 5.1 and 5.9 , 3'-H), 6.08 (1H, t, *J* 5.6, 2'-H), 6.78 (1H, d, *J* 5.2, 1'-H), 7.10-7.58 (9H, m, *m*- and *p*-H of Ph), 7.64-8.13 (7H, m, *o*-H of Ph and 2-H); δ_C 45.1 (Me), 63.7 (C-5'), 71.1, 71.6 (C-2', C-3'), 80.4 (C-4'), 84.7 (C-1'), 104.2(C-5), 128.1-129.7 (Ph), 133.5-133.9 (Ph), 138.6 (C-2), 153.3 (C-4), 164.4, 165.2 and 166.0 (COPh) (Found: C, 59.7; H, 4.7; N, 7.0; S, 5.7. $C_{30}H_{27}N_3O_9S$ requires C, 59.49; H, 4.50; N, 6.94; S, 5.28%).

*4-Nitro-5-sulfonamido-1-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)imidazole* **(25)** *and 4-Nitro-5-sulfonamido-1-(2,3,5-tri-*O*-benzoyl-*α*-D-ribofuranosyl)imidazole* **(26)** - Imidazole **24**[20] (1.0g, 5.21mmol), chlorotrimethylsilane (0.664 cm^3, 5.21 mmol), hexamethyldisilazane (7 cm^3) and xylene (7 cm^3) were stirred and heated at 130°C. After 2h all the solid had dissolved to give a clear brown solution. The solution was evaporated to give a brown residue. This was dissolved in acetonitrile (4 cm^3) and a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11** (2.64 g, 5.21 mmol) in acetonitrile (16 cm^3) was added. The mixture was stirred at 0°C and trimethylsilyl trifluoromethanesulfonate (1.44 cm^3, 7.81 mmol) was added. This solution was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (30 cm^3) and diluted with dichloromethane (30 cm^3). The layers were separated and the aqueous layer extracted with further dichloromethane (2 x 30 cm^3). The combined organic extracts were dried and evaporated to leave a brown foam. Chromatography on silica, with toluene-ethyl acetate (10:1) as eluent, yielded firstly the *4-nitro-β- isomer* **25** (1.6 g, 48%) as a white amorphous solid, R_F 0.65 (toluene-ethyl acetate, 3:2), $[\alpha]_D$ -7.3 (*c* 1.23, CH_2Cl_2); δ_H 4.63-4.90 (3H, m, 4'-H, 5'-H_2), 5.73 (1H, app.t, *J* 6.6, 3'-H),

5.98 (1H, dd, *J* 2.0 and 5.6, 2'-H), 6.51 (2H, broad s, exchangeable, NH_2), 6.84 (1H, d, *J* 2.0, 1'-H), 7.12-7.66 (9H, m, *m*-and *p*- H of Ph), 7.73-8.14 (7H, m, *o*- H of Ph and 2-H); δ_C 62.4 (C-5'), 69.5, 75.7 (C-2', C-3'), 80.0 (C-4'), 90.2 (C-1'), 128.1-129.8 (Ph, C-2, C-5), 113.6-133.9 (Ph), 146.5 (C-4), 165.1, 165.4, and 166.1 (COPh); (Found: C, 54.5; H, 3.8; N, 9.1; S, 5.4. $C_{29}H_{24}N_4O_{11}S$ requires C, 54.71; H, 3.80; N, 8.81; S, 5.03%).

Further elution of the column afforded the *α-anomer* **26** (1.3 g, 39%) as a white amorphous solid, R_F 0.62 (toluene: ethyl acetate 3:2); δ_H 4.63 (1H, dd, $J_{4',5'a}$ 4.0, J_{gem} 12.4, 5'-H_a), 4.80 (1H, dd, $J_{4',5'b}$ 3.4, J_{gem} 12.4, 5'-H_b), 5.12 (1H, q, *J* 3.45, 4'-H), 5.90 (1H, dd, *J* 5.0 and 6.5, 3'-H), 6.09 (2H, broad s, disappears on D_2O shake, NH_2), 6.36 (1H, t, *J* 4.5, 2'-H), 7.11 (1H, d, *J* 4.05, 1'-H), 7.26-7.53 (9H, m, *m*- and *p*-H of Ph), 7.59-8.10 (7H, m, *o*- H of Ph and 2-H); δ_C 63.6 (C-5'), 71.6, 72.2 (C-2', C-3'), 80.6 (C-4'), 88.2 (C-1'), 127.3 (C-5), 128.1-129.7 (Ph, C-2), 133.6-134.4 (Ph), 145.7 (C-4), 163.4, 165.0, 166.0 (COPh).

*4-Amino-5-sulfonamido-1-(2,3,5-tri-*O*- benzoyl-*β*-D-ribofuranosyl)imidazole*(**27**) - The nitrosulfonamide **25** (0.5 g, 0.786 mmol) in ethyl acetate (50 cm^3) was hydrogenated and processed as in the preparation of **22** above, to give the *aminosulfonamide* **27** (0.35 g, 73%) as a white amorphous solid, R_F 0.25 (ethyl acetate); $[\alpha]_D$ -18.5 (*c* 0.92, DMSO); δ_H [$(CD_3)_2SO$] 4.69-4.93 (5H, m, collapses to 3H, m, on D_2O shake, 4'-H, 5'-H_2, NH_2), 5.38 (2H, broad, s, disappears on D_2O shake, NH_2), 5.83 (1H, app. t, *J* 6.1, 3'-H), 6.13 (1H, dd, *J* 4.8 and 6.15, 2'-H), 6.27 (1H, d, *J* 4.8, 1'-H), 7.32-7.68 (9H, m, *m*- and *p*- H of Ph), 7.87-8.11 (7H, m, *o*-H of Ph and 2-H); δ_C [$(CD_3)_2SO$] 63.5(C-5'), 70.0, 74.2 (C-2', C-3'), 78.8 (C-4'), 86.5 (C-1'), 106.1 (C-5), 128.4-129.4 (Ph), 133.5-133.8 (Ph), 136.3 (C-2), 150.7 (C-4), 164.3, 164.5, 165.4 (COPh); (Found: C, 57.2; H, 4.3; N, 9.5; S, 5.6. $C_{29}H_{26}N_4O_9S$ requires C, 57.41; H, 4.32; N, 9.24; S, 5.27%).

*4-Amino-5-sulfonamido-1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)imidazole* (**28**) - The nitrosulfonamide **26** (0.10 g, 0.157 mmol) in ethyl acetate (10 cm^3) was hydrogenated and processed as in the preparation of **22** above, to give the aminosulfonamide **28** (0.085 g, 89%) as an amorphous solid, R_F 0.23 (ethyl acetate); δ_H 4.58-4.92 (5H, m, collapses to 3H, m, on D_2O shake, 4-H', 5'-H, NH_2), 5.16 (2H, br s, exchangeable, NH_2), 5.87 (1H, dd, *J* 5.7 and 7.25, 3'-H), 6.13 (1H, app. t, *J* 4.45, 2'-H), 6.77 (1H, d, *J* 4.7, 1'-H), 7.23-7.61 (9H, m, *m*- and *p*- H of Ph), 7.71-8.16 (7H, m, *o*-H of Ph and 2-H); δ_C 63.1 (C-5'), 71.3, 71.9 (C-2', C-3'), 80.5 (C-4'), 85.2 (C-1'), 106.3 (C-5), 128.1-129.9 (Ph), 133.4-133.9 (Ph), 135.9 (C-2), 151.9 (C-4), 164.8, 165.2 and 166.1 (COPh).

*4-Nitro-5-sulfonamido-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole* (**25**) *and 5-nitro-4-sulfonamido-1-(2,3,5-tri-*O*-benzoyl- β-D-ribofuranosyl)imidazole* (**29**) - 4(5)-Nitro-5(4)-sulfonamidoimidazole **24** (2.0 g, 10.42 mmol), chlorotrimethylsilane (1.33 cm^3, 10.42 mmol), hexamethyldisilazane (14 cm^3), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11** (5.28 g, 10.42 mmol) and trimethylsilyl trifluoromethanesulfonate (2.88 cm^3, 15.62 mmol) were treated as in the preparation of **25** and **26** above but with a reaction time of 3 min. Chromatography on silica with toluene-ethyl acetate (9:1) as eluent yielded firstly the *4-nitro-β- isomer* **25** (2.7 g, 41%), with properties as described above.

Further elution of the column afforded the *5-nitro-β- isomer* **29** (2.9g, 44%) , R_F 0.35 (toluene-ethyl acetate 3:2), m.p. 168-170 °C (dec.), $[\alpha]_D$ +22.2 (*c* 1.17, CH_2Cl_2); δ_H 4.60-4.90 (3H, m, 4'-H, 5'-H_2), 5.85 (1H, app.t, *J* 6.3, 3'-H), 6.06 (1H, dd, *J* 2.25 and 5.4, 2'-H), 6.69 (1H, d, *J* 2.1, 1'-H), 7.10-7.61 (9H, m, *m*-and *p*- H of Ph), 7.69-8.30 (7H, m, *o*-H of Ph and 2-H) δ_C 64.1 (C-5'), 69.8, 75.6 (C-2', C-3'), 80.4 (C-4'), 90.9 (C-1'), 128.1-129.9 (Ph, C-4), 133.5-135.8 (Ph, C-2), 143.4 (C-5), 164.8, 165.0, 166.1 (COPh) (Found: C, 54.5; H, 4.0; N, 9.0; S, 5.3. $C_{29}H_{24}N_4O_{11}S$ requires C, 54.71; H, 3.80; N, 8.81; S. 5.03%).

*5-Amino-4-sulfonamido-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole* (**30**) - The nitro-compound **29** (2.0 g, 3.14 mmol) in ethyl acetate (200 cm^3) was hydrogenated and processed as in the preparation of **22** above to give the *5-amino-β- isomer* **30** (1.85 g, 97%) as a white amorphous solid, R_F 0.1 (ethyl acetate); $[\alpha]_D$ -25.2 (*c* 1.07, CH_2Cl_2); δ_H 4.73 (3H, m, 4-H, 5'-H), 5.08 (2H, broad s, disappears on D_2O shake, NH_2), 5.83 (4H, m, collapses to 2H, m, on D_2O shake, 2'-H, 3'-H, NH_2), 5.96 (1H, d, *J* 4.35, 1'-H), 7.23-7.59 (9H, m, *m*- and *p*- H of Ph), 7.84-8.16 (7H, m, *o*-H of Ph and 2-H); δ_C 60.3 (C-5'), 70.3, 73.3 (C-2' , C-3'), 80.3 (C-4'), 87.2 (C-1'), 119.5 (C-4), 128.1-129.9 (Ph, C-2), 133.5-133.9 (Ph), 139.3 (C-5), 165.2, 165.5 and 166.1 (COPh) (Found: C, 57.2; H, 4.5; N, 9.3; S, 5.7. $C_{29}H_{26}N_4O_9S$ requires C, 57.41; H, 4.32; N, 9.24; S, 5.27%).

5-Amino-4-sulfonamido-1-(β-D-ribofuranosyl)imidazole **(6)** - A solution of the tri-*O*-benzoyl compound **30** (0.30 g, 0.495 mmol) in methanolic ammonia (25 cm^3) was stirred overnight at room temperature. The solvent was evaporated and the residue was partitioned between water (20 cm^3) and diethyl ether (4 x 20 cm^3). The aqueous layer was evaporated and the residue was chromatographed on silica, with ethyl acetate-methanol (10:1) as eluent, to give the *triol* **6** (0.12 g, 82%) as a white amorphous solid, R_F 0.3 (ethyl acetate-methanol 4:1), $[\alpha]_D$ -42.5 (*c* 1.64, H_2O); δ_H (400 MHz, D_2O) 3.76 (1H, dd, $J_{4',5'a}$ 3.7, J_{gem} 12.6, 5'-H_a), 3.81(1H, dd $J_{4',5'b}$ 3.1, J_{gem} 12.6, 5'-H_b), 4.16 (1H, q, *J* 3.45, 4'-H), 4.29 (1H, dd, *J* 3.7 and 5.4, 3'-H), 4.56 (1H, t, *J* 5.8, 2'-H), 5.62 (1H, d, *J* 6.2, 1'-H), 7.55 (1H, s, 2-H); δ_C 61.7 (C-5'), 71.0, 73.7 (C-2', C-3'), 86.1 (C-4'), 88.8 (C-1'), 117.0 (C-4), 132.2 (C-2), 141.4 (C-5) [Found: MH^+ (FAB) 295.0695. $C_8H_{15}N_4O_6S$ requires 295.0712].

Ethyl N-*[4(5)-nitroimidazole-5(4)-sulfonyl]-glycinate* **(31)** - To a solution of 4(5)-chlorosulfonyl-5(4)-nitroimidazole[20] (1.5 g, 7.12 mmol) in dimethyl-formamide (15 cm^3) and triethylamine (2.19 cm^3, 14.22 mmol) was added dropwise with stirring a solution of ethyl glycinate hydrochloride (0.99 g, 7.12 mmol) in dimethylformamide (15 cm^3). The mixture was stirred at room temperature for 16 h and then evaporated onto silica. The resultant silica was applied to the top of a column of more silica. Elution with ethyl acetate-methanol (7:1) gave the *sulfonamide* **31** (1.1 g, 56%) as a pale yellow solid, R_F 0.85 (ethyl acetate-methanol, 2:1), m.p. 156-159 °C; δ_H [$(CD_3)_2SO$] 1.07 (3H, t, *J* 7.1, $CO_2CH_2\mathit{Me}$), 3.95 (4H, m, $CO_2\mathit{CH_2}Me$, NCH_2), 7.90 (1H, s, 2-H), 8.78 (1H, br s, exchangeable, NH); δ_C [$(CD_3)_2$ SO] 13.8 ($CO_2CH_2\underline{C}H_3$), 44.2 (NCH_2), 60.8 ($CO_2\underline{C}H_2CH_3$), 129.3 (C-4), 135.3 (C-2), 142.7 (C-5), 168.8 ($\underline{C}O_2CH_2CH_3$); *m/z* 279 (MH^+), 205 ($M-CO_2Et)^+$ (Found: C, 30.3; H, 3.6; N, 19.9; S, 11.4. $C_7H_{10}N_4O_6S$ requires C, 30.21; H, 3.62; N, 20.15; S, 11.50%).

Ethyl N-*[4-nitro-1-(2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranosyl)imidazole-5-sulfonyl]-glycinate* **(32)**, *ethyl* N-*[4-nitro-1-(2,3,5-tri*-O-*benzoyl*-α-D-*ribofuranosyl)imidazole-5-sulfonyl]-glycinate* **(33)**, *and ethyl* N-*[5-nitro-1-(2,3,5-tri*-O-*benzoyl*-α-D-*ribofuranosyl)imidazole-4-sulfonyl]-glycinate* **(34)** - A mixture of the imidazole **31** (0.5 g, 1.80 mmol), chlorotrimethylsilane (0.23 cm^3, 1.80 mmol), hexamethyldisilazane (2.5 cm^3) and xylene (2.5 cm^3) was heated with stirring at 130°C. After about 2 h all the solid had dissolved to give a clear brown solution, which was evaporated to give a brown residue. To a solution of this residue in acetonitrile (5 cm^3) was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11** (0.89g, 1.80 mmol) in acetonitrile (20 cm^3). The mixture was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (0.50 cm^3, 2.70 mmol) was added. This solution was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (30 cm^3) and diluted with dichloromethane (30 cm^3). The layers were separated and the aqueous layer extracted with more dichloromethane (2 x 30 cm^3). The combined organic extracts were dried and evaporated to leave a brown foam which was chromatographed on silica, with toluene-ethyl acetate (12:1) as eluent, to give firstly the *4-nitro-β- isomer* **32** (0.42 g, 32%) as a white amorphous solid, R_F 0.6(toluene-ethyl acetate, 4:1), $[\alpha]_D$ +13.7 (*c* 1.24 in CH_2Cl_2); δ_H 1.13 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 4.07 (4H, m, $CO_2C\underline{H}_2CH_3$, NCH_2), 4.71-4.93 (3H, m, 4'-H, 5'-H_2), 5.82 (1H, dd, *J* 5.5 and 7.1, 3'-H), 6.11 (1H, dd, *J* 2.7 and 5.4, 2'-H), 6.82 (2H, collapses to 1H, d, *J* 2.8 on D_2O shake, 1'-H, NH), 7.24-7.53 (9H, m, *m*- and *p*-H of Ph), 7.78-8.15 (7H, *o*-H of Ph and 2-H); δ_C 13.8 ($CO_2CH_2\underline{C}H_3$), 44.9 (CH_2), 62.1, 62.6 (C-5', $CO_2\underline{C}H_2CH_3$), 69.4, 75.3 (C-2', C-3'), 80.3 (C-4'), 89.7 (C-1'), 126.7 (C-5), 128.2-129.9 (Ph, C-2), 133.7-134.0 (Ph), 147.3 (C-4), 164.9, 165.1 and 166.0 ($\underline{C}OPh$), 168.8 ($\underline{C}O_2CH_2CH_3$); (Found: C, 54.8; H, 4.4; N, 7.7; S, 4.8. $C_{33}H_{30}N_4O_{13}S$ requires C, 54.84; H, 4.19; N, 7.76; S, 4.43%).

Further elution of the column yielded the *4-nitro-α- isomer* **33** (0.35 g, 27%) as a white amorphous solid, R_F 0.56 (toluene-ethyl acetate 4:1), $[\alpha]_D$ -57.02° (*c* 1.21, CH_2Cl_2); δ_H 1.06 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 3.81-4.20 (4H, m, $CO_2C\underline{H}_2CH_3$, NCH_2), 4.62 (1H, dd, $J_{4',5'a}$, 3.95, J_{gem} 12.4, 5'-H_a), 4.78 (1H, dd, $J_{4',5'a}$, 3.3, J_{gem} 12.4, 5'-H_b), 5.06 (1H, q, *J* -4, 4'-H), 5.95 (1H, t , *J* 5.2, 3'-H), 6.29 (1H, t, *J* 5.0, 2'-H), 6.60 (1H, t, *J* 5.68, exchangeable, NH), 7.06 (1H, d, *J* 4.8, 1'-H), 7.24-7.58 (9H, m, *m*- and *p*-H of Ph), 7.60-8.16 (7H, *o*-H of Ph, 2-H); δ_C 13.8 ($CO_2CH_2\underline{C}H_3$), 44.9 (CH_2), 62.0, 63.6 (C-5', $CO_2\underline{C}H_2CH_3$), 71.7, 71.9 (C-2', C-3'), 81.2 (C-4'), 87.6 (C-1'), 127.8 (C-5), 127.7-129.7 (Ph), 133.6-133.9 (Ph), 134.9 (C-2), 146.1 (C-4), 164.4, 165.1 and 166.0 ($\underline{C}OPh$), 168.2 ($\underline{C}O_2CH_2CH_3$); (Found: C, 54.6; H, 4.1; N, 7.8; S, 4.6. $C_{33}H_{30}N_4O_{13}S$ requires C, 54.84; H, 4.19; N, 7.76; S, 4.43%).

Further elution of the column yielded the *5-nitro-α- isomer* **34** (0.18 g, 14%) as a white amorphous solid, R_F 0.25 (toluene-ethyl acetate 4:1), $[\alpha]_D$ -65.6 (*c* 1.26, CH_2Cl_2); δ_H 1.13 (3H, t, *J* 7.11, $CO_2CH_2C\underline{H}_3$), 3.82-4.11 (4H, m, $CO_2C\underline{H}_2CH_3$,CH_2), 4.62 (1H, dd, $J_{4',5'a}$ 3.73, J_{gem} 12.43, 5'-H_a), 4.79 (1H, dd, $J_{4',5'b}$, 3.3, J_{gem} 12.4, 5'-H_b), 5.12 (1H, app. q, *J* 3.1, 4'-H), 5.97 (1H, dd, *J* 2.7 and 5.5, 3'-H), 6.21 (1H, t, *J* 5.74, exchangeable, NH), 6.31 (1H, t, *J* 5.5, 2'-H), 7.06 (1H, d, *J* 5.5, 1'-H), 7.22-7.55 (9H, m, *m*- and *p*-H of Ph), 7.57-8.13 (7H, m, *o*- H of Ph, H-2); δ_C 13.9 ($CO_2CH_2\underline{C}H_3$), 44.8 (CH_2), 61.7, 63.8 (C-5', $CO_2\underline{C}H_2CH_3$),71.6, 71.7 (C-2', C-3'), 83.2 (C-4'), 88.2 (C-1'), 127.3 (C-4), 127.9-129.7 (Ph), 133.6-134.5 (Ph), 135.7 (C-2), 142.0 (C-5), 163.9, 165.0 and 165.9 (<u>C</u>OPh), 168.7 (<u>C</u>$O_2CH_2CH_3$); (Found: C, 54.1; H, 4.2; N, 7.4; S, 4.8. $C_{33}H_{30}N_4O_{13}S$ requires C, 54.84; H, 4.19; N, 7.76; S, 4.43%).

Ethyl N-*[4-Amino-1-(2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranosyl)imidazole-5-sulfonyl]-glycinate* (**35**) - The nitrosulfonamide **32** (0.2 g, 0.277 mmol) in ethyl acetate (20 cm^3) was hydrogenated and processed as in the above preparation of **22** to give the *aminosulfonamide* **35** (0.17 g, 89%) as a white amorphous solid, R_F 0.3 (ethyl acetate), $[\alpha]_D$ +6.22 (*c* 1.125, CH_2Cl_2); δ_H 1.13 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 3.63 (1H, dd, *J* 4.3 and 17.8, collapses to d, *J* 17.8 on D_2O shake, NCH_a), 3.80 (1H, dd, *J* 7.2 and 17.9, collapses to d, *J* 17.9 on D_2O shake, NCH_b), 4.04 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.56-4.89 (4H, m, collapses to 3 H, m, on D_2O shake, 4'-H, 5'-H_2, NH), 5.84 (2H, s, exchangeable, NH_2), 6.11 (1H, dd, *J* 4.35 and 7.1, 3'-H), 6.27 (2H, m, 2'-H, 1'-H), 7.12-7.59 (9H, m, *m*- and *p*-H of Ph), 7.79-8.12 (7H, m, *o*-H of Ph, 2-H); δ_C 14.0 ($CO_2CH_2\underline{C}H_3$), 44.0 (CH_2), 61.8, 63.0 (C-5', $CO_2\underline{C}H_2CH_3$), 70.3, 73.5 (C-2', C-3'), 80.2 (C-4'), 88.4 (C-1'), 102.4 (C-5), 128.5-129.9 (Ph), 133.5-133.9 (Ph), 136.4 (C-2), 154.2 (C-4), 164.0, 165.1, 166.0 (<u>C</u>OPh), 169.0 (<u>C</u>$O_2CH_2CH_3$); (Found: C, 56.9; H, 4.9; N, 8.4; S, 5.0. $C_{33}H_{32}N_4O_{11}S$ requires C, 57.21; H, 4.66; N, 8.09; S 4.62%).

Ethyl N-*[4-Amino-1-(2,3,5-tri*-O-*benzoyl*-α-D-*ribofuranosyl)imidazole-5-sulfonyl]-glycinate* (**36**) - The nitrosulfonamide **33** (0.2 g, 0.277 mmol) in ethyl acetate (20 cm^3) was hydrogenated and processed as in the above preparation of **22** to give the *aminosulfonamide* **36** (0.18 g, 94%) as a white amorphous solid, R_F 0.28 (ethyl acetate); $[\alpha]_D$ +4.9 (*c* 1.835, CH_2Cl_2); δ_H 1.11 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 3.65 (2H, m, CH_2), 3.98 (2H, q, *J* 7.1, $CO_2C\underline{H}_2CH_3$), 4.54-4.75 (4H, m, collapses to 2H, 2 x dd, $J_{4',5'a}$ 4.5, $J_{4',5'b}$ 3.5, J_{gem} 12.1, on D_2O shake, 5'-H_2, NH_2), 4.86 (1H, app. q. *J* 4.5, 4'-H), 5.91 (1H, t, *J* 5.6, 3'-H), 6.14 (2H, m, 2'-H, NH), 6.75 (1H, d, *J* 4.9, 1'-H), 7.10-7.58 (9H, m, *m*- and *p*- H of Ph), 7.70-8.10 (7H, m, *o*- H of Ph, 2-H); δ_C 13.9 ($CO_2CH_2\underline{C}H_3$), 43.7 (CH_2), 61.8, 63.9 (C-5', $CO_2\underline{C}H_2CH_3$), 71.1, 71.6 (C-2', C-3'), 80.0 (C-4'), 85.0 (C-1'), 101.8(C-5), 128.4-129.6 (Ph), 133.3-133.7 (Ph), 138.3 (C-2), 153.3 (C-4), 164.5, 165.2 and 166.0 (<u>C</u>OPh), 169.0 (<u>C</u>$O_2CH_2CH_3$) (Found: C, 57.0; H, 4.8; N, 8.1; S, 4.8. $C_{33}H_{32}N_4O_{11}S$ requires C, 57.21; H, 4.66; N, 8.09; S, 4.62%).

Ethyl N-*[5-Amino-1-(2,3,5-tri*-O-*benzoyl*-α-D-*ribofuranosyl)imidazole-4-sulfonyl]-glycinate* (**37**) - The nitrosulfonamide **34** (0.1 g, 0.139 mmol) in ethyl acetate (10 cm^3) was hydrogenated and processed as described for the preparation of **22** above to give the *5-amino-α- isomer* **37** (0.09 g, 94%) as an amorphous solid, R_F 0.1 (ethyl acetate); $[\alpha]_D$ +8.8 (*c* 0.90, CH_2Cl_2); δ_H 1.09 (3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 3.57 (2H, m, NCH_2), 3.98 (2H, q, *J* 7.0, $CO_2C\underline{H}_2CH_3$), 4.50-4.74 (2H, m, 5'-H_2), 4.80-5.07 (3H, m, collapses to 1H, m, on D_2O shake, 4'-H, NH_2), 5.90-6.13 (3H, m, collapses to 2H, m, on D_2O shake, 2'-H, 3'-H, NH), 6.32 (1H, d, *J* 5.4, 1'-H), 7.22-7.59 (9H, m, *m*- and *p*- H of Ph), 7.61-8.12 (7H, m, *o*-H of Ph, H-2); δ_C 13.9 ($CO_2CH_2\underline{C}H_3$), 44.1 (CH_2), 61.5, 63.8 (C-5', $CO_2\underline{C}H_2CH_3$), 71.5 , 71.6 (C-2', C-3'), 81.2 (C-4'), 83.9 (C-1'), 115.3 (C-4), 127.7-129.6 (Ph), 131.0 (C-2), 133.4-134.0 (Ph), 141.3 (C-5), 165.0, 165.4, 166.0 (<u>C</u>OPh), 168.8 (<u>C</u>$O_2CH_2CH_3$) (Found: C, 56.9; H, 4.5; N, 8.2; S, 5.0. $C_{33}H_{32}N_4O_{11}S$ requires C, 57.21; H, 4.66; N, 8.09; S, 4.62%).

Ethyl N-*[4-nitro-1-(2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranosyl)imidazole-5-sulfonyl]-glycinate* (**32**) *and ethyl* N-*[5- nitro-1-(2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranosyl)imidazole-4-sulfonyl]-glycinate* (**38**) - The imidazole **31** (1.0g, 3.60 mmol), chlorotrimethylsilane (0.46 cm^3, 3.60 mmol), hexamethyldisilazane (5.0 cm^3), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11** (1.78 g, 3.60 mmol) and trimethylsilyl trifluoromethanesulphonate (1.0 cm^3, 5.40 mmol) were treated as in the preparation of **32** - **34** above, but with a reaction time of 3 min for nucleoside formation. Chromatography on silica with toluene-ethyl acetate (9:1) as eluent yielded firstly the *4-nitro-β- isomer* **32** (0.87 g, 33%) with properties as described above.

Further elution of the column yielded the *5-nitro-β- isomer* **38** (0.89 g, 34%) as a colourless amorphous solid, R_F 0.3 (toluene-ethyl acetate 4:1), $[\alpha]_D$ +5.1 (*c* 0.59, CH_2Cl_2); δ_H 1.12 (3H, t, *J* 7.15, $CO_2CH_2\underline{CH_3}$), 3.99 (4H, app. q, J 7.1, $CO_2\underline{CH_2}CH_3$, CH_2), 4.69-4.92 (3H, m, 4'-H, 5'-H_2), 5.86 (1H, app. t., *J* 5.9, 3'-H), 5.95 (1H dd, *J* 3.3 and 5.5, 2'-H), 6.25 (1H, t, *J* 5.8, exchangeable, NH), 6.79(1H, d, *J* 3.2, 1'-H), 7.14-7.60 (9H, m, *m*- and *p*- H of Ph), 7.77-8.21 (7H, m, *o*-H of Ph, 2-H); δ_C 13.9 ($CO_2CH_2\underline{CH_3}$), 44.8 (CH_2), 61.8, 62.8 (C-5', $CO_2\underline{CH_2}CH_3$), 69.8, 75.8 (C-2', C-3'), 80.9 (C-4'), 90.3 (C-1'), 125.2 (C-4), 128.2-129.9 (Ph and C-2), 133.6-134.3 (Ph), 142.0 (C-5), 164.6, 165.0 and 166.0 (COPh), 168.8 ($\underline{C}O_2CH_2CH_3$) (Found: C, 54.6; H, 4.2; N, 7.5; S, 4.7. $C_{33}H_{30}N_4O_{13}S$ requires C, 54.84; H, 4.19; N, 7.76; S, 4.43%).

Ethyl N-*[5-amino-1-(2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranosyl)imidazole-4-sulfonyl]-glycinate* **(39)** - The nitrosulfonamide **38** (0.80 g, 1.112 mmol) in ethyl acetate (80 cm^3) was hydrogenated and processed as for the preparation of **22** above to give the *aminosulfonamide* **39** (0.75 g, 98%) as an amorphous solid, R_F 0.14 (ethyl acetate), $[\alpha]_D$ -24.4 (*c* 1.06, CH_2Cl_2); δ_H 1.19 (3H, t, *J* 7.6, $CO_2CH_2\underline{CH_3}$), 3.83 (2H, d, *J* 6.5, becomes s on D_2O shake, CH_2), 4.09 (2H, q, *J* 7.0, $CO_2\underline{CH_2}CH_3$), 4.79 (3H, m, 4'-H, 5'-H_2), 5.16 (2H, broad s, exchangeable, NH_2), 5.59 (1H, br t, exchangeable, NH), 5 79 (1H, m, 3'-H), 5.89 (1H, t, *J* 5.0, 2'-H), 5.95 (1H, d, *J* 4.6, 1'-H), 7.29-7.63 (9 H, m, *m*- and *p*- H of Ph), 7.84-8.12 (7H, m, *o*-H of Ph, 2-H); δ_C 14.0 ($CO_2CH_2\underline{CH_3}$), 44.4 (CH_2), 61.7, 63.0 (C-5', $CO_2\underline{CH_2}CH_3$), 70.3, 73.2 (C-2', C-3'), 80.6 (C-4'), 87.4 (C-1'), 116.6 (C-4), 128.0-129.9 (Ph and C-2), 133.7-134.2 (Ph), 141.1 (C-5), 165.2, 165.6, 166.2 (COPh), 168.9 ($\underline{C}O_2CH_2CH_3$); (Found: C, 57.3; H, 4.9; N, 8.2; S, 5.0 . $C_{33}H_{32}N_4O_{11}S$ requires C, 57.21; H, 4.66; N, 8.09; S, 4.62%).

N-[*5-Amino-1-*(β-D-*ribofuranosyl)imidazole-4-sulfonyl]glycine* **(7)** - A catalytic quantity of sodium methoxide was added to a solution of the tri-*O*-benzoyl compound **39** (0.40 g, 0.578 mmol) in methanol (40 cm^3) and the mixture was stirred for 16 h at 20 °C. The mixture was neutralized with resin (Amberlite IRC-50, H^+), filtered and evaporated to give an off-white residue which was partitioned between water (40 cm^3) and ether (4 x 40 cm^3). The aqueous layer was evaporated to dryness yielding an off white residue which was dissolved in sodium hydroxide solution (1M, 40 cm^3) and stirred for 2 h at 20 °C. The solution was acidified to pH 5.5 with resin (Amberlite IRC-50, H^+) and filtered. Evaporation yielded the *triol* **7** (0.17 g, 84%) as an off-white solid, $[\alpha]_D$ -17.0 (*c* 0.765 in H_2O); δ_H (400 MHz, D_2O) 3.52 (2H, s, CH_2), 3.75 (1H, dd, $J_{4',5'a}$ 3.6, J_{gem} 12.7, 5'-H_a), 3.81 (1H, dd, $J_{4',5'b}$ 3.0, J_{gem} 12.6, 5'-H_b), 4.15 (1H, app. q, *J* 3.4, 4'-H), 4.29 (1H, app.t, *J* 4.6, 3'-H), 4.55 (1H, t, *J* 5.7, 2'-H), 5.62 (1H, d, *J* 6.08, 1'-H), 7.54 (1H, s, 2-H); δ_C (100 MHz, D_2O). 45.9 (CH_2), 61.7 (C-5'), 70.9, 73.6 (C-2', C-3'), 86.1 (C-4'), 89.0 (C-1'), 113.7 (C-4), 132.5 (C-2), 141.6 (C-5), 176.3 (CO_2H) (Found: MH^+ 353.0755. $C_{10}H_{17}N_4O_8S$ requires 353.0767).

Diethyl N-*[4(5)-nitroimidazole-5(4)-sulfonyl]*-L-*aspartate* **(40)** - To a solution of 4(5)-chlorosulfonyl-5(4)-nitroimidazole[20] (1.5 g, 7.12 mmol) in dimethylformamide (15 cm^3) and triethylamine (2.19 cm^3, 14.22 mmol) was added dropwise with stirring a solution of diethyl L-aspartate hydrochloride (1.60 g, 7.12 mmol) in dimethylformamide (15 cm^3). After 16 h the mixture was evaporated to dryness with silica. The resultant material was applied to the top of a column of more silica and the column was eluted with ethyl acetate-methanol (6:1) to yield the *sulfonamide* **40** (1.3 g, 50%) as a pale yellow solid, m.p. 133-135 °C, R_F 0.55 (ethyl acetate-methanol, 2:1), $[\alpha]_D$ -1.6 (*c* 1.25, DMSO); $\delta_H[(CD_3)_2SO]$ 1.01 (3H, t, J 7.1, $CO_2CH_2\underline{CH_3}$), 1.13 (3H, t, *J* 7.09, $CO_2CH_2\underline{CH_3}$), 2.72 (1H, dd, *J* 16.4 and 7.3, CH_2), 2.79 (1H, dd, *J* 16.4 and 6.5, CH_2), 3.82-4.13 (4H, m, 2 x $CO_2\underline{CH_2}CH_3$), 4.35 (1H, app. t, *J* 6.8, CH), 7.86 (1H, s, 2-H); $\delta_C[(CD_3)_2SO]$ 13.5, 13.8 (2 x $CO_2CH_2\underline{CH_3}$), 36.8 ($\underline{CH_2}CO_2Et$), 51.9 (CH), 60.4 and 61.2 ($CO_2\underline{CH_2}CH_3$), 129.8 (C-4), 136.0 (C-2), 142.8 (C-5), 169.4 and 169.6 ($\underline{C}O_2CH_2CH_3$) (Found: C, 36.6; H, 4.6; N, 15.3; S, 9.2. $C_{11}H_{16}N_4O_8S$ requires C, 36.26; H, 4.43; N, 15.39; S, 8.78%).

Diethyl N-*[(4-nitro-1-(2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranosyl)imidazole-5-sulfonyl]*-L-*aspartate* **(41)** *and diethyl* N-*[(4-nitro-1-(2,3,5-tri*-O-*benzoyl*-α-D-*ribofuranosyl)imidazole-5-sulfonyl]*-L-*aspartate* **(42)** - The imidazole **40** (0.25 g, 0.687 mmol), chlorotrimethylsilane (0.088 cm^3, 0.687 mmol), hexamethyldisilazane (1 cm^3) and xylene (1 cm^3) were stirred and heated at 130° C. After about 90 min all the solid had dissolved to give a clear brown solution. Ammonium chloride sublimed into the condenser during the course of the reaction. The solution was evaporated to give a brown residue which was dissolved with stirring in

acetonitrile (5 cm^3). A solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11** (0.345 g, 0.687 mmol) in acetonitrile (15 cm^3) was added at 0°C, followed by trimethylsilyl trifluoromethanesulfonate (0.19 cm^3, 1.03 mmol). The mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated sodium bicarbonate solution (15 cm^3), and diluted with dichloromethane (15 cm^3). The layers were separated and the aqueous layer extracted with more dichloromethane (2 x 15 cm^3). The combined organic extracts were dried and evaporated to leave a brown foam which was chromatographed on silica with toluene-ethyl acetate (7:1) as eluent to give firstly the *4-nitro-β- compound* **41** (0.22 g, 40%) as an off white amorphous solid, R_F 0.65 (toluene: ethyl acetate, 4:1), $[\alpha]_D$ +48.7 (*c* 1.375, CH_2Cl_2); δ_H 1.06 and 1.19 (each 3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.73 (1H, dd, *J* 17.6 and 4.1, CH_2^a), 2.99 (1H, dd, *J* 17.6 and 4.5, CH_2^b), 4.07 (4H, m, 2 x $CO_2CH_2CH_3$), 4.46(1H, m, CH), 4.60-4.93 (3H, m, 4'-H, 5'-H), 5.78 (1H, dd, *J* 5.4 and 7.3, 3'-H), 5.98 (1H, dd, *J* 2.6 and 5.35, 2'-H), 6.82 (1H, d, *J* 2.6, 1'-H), 7.24-7.60 (9H, m, *m*- and *p*- H of Ph), 7.75-8.13 (7H, m, *o*-H of Ph, 2-H); δ_C 13.7, 13.9 (2 x $CO_2CH_2CH_3$), 37.0 ($CH_2CO_2CH_2CH_3$), 53.4 (CH), 61.4, 62.5, 63.2 (2 x $CO_2CH_2CH_3$, C-5'), 69.7, 75.3 (C-2', C-3'), 80.1 (C-4'), 89.9 (C-1'), 127.9-129.8 (Ph, C-5), 132.1-133.9 (Ph, C-2), 146.6 (C-4), 164.8, 165.5, 166.1 (COPh), 169.7, 170.2 (2 x $CO_2CH_2CH_3$); (Found: C, 55.3; H, 4.5; N, 7.1; S, 4.3. $C_{37}H_{36}N_4O_{15}S$ requires C, 54.94; H, 4.49; N, 6.93; S, 3.96%).

Further elution of the column yielded the 4-nitro-α- isomer **42** (0.17 g, 31%) as a white amorphous solid, R_F 0.61 (toluene-ethyl acetate 4:1), δ_H 1.04 and 1.15 (each 3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.73 (1H, dd, *J* 17.4 and 4.5, CH_2^a), 2.98 (1H, dd, *J* 17.41 and 4.8, CH_2^b), 3.99 (4H, m, 2 x $CO_2CH_2CH_3$), 4.39 (1H, m, CH), 4.60 (1H, dd, $J_{5'a,4'}$ 3.9, J_{gem} 12.4, 5'-H_a), 4.77 (1H, dd, $J_{5'b,4'}$ 3.3, J_{gem} 12.3, 5'-H_b), 5.08 (1H, q, *J* 3.7, 4'-H), 5.97 (1H, dd, *J* 4.2 and 5.4, 3'-H), 6.34 (1H, t, *J* 5.4, 2'-H), 7.03 (1H, d, *J* 5.3, 1'-H), 7.18-7.55 (9H, m, *m*- and *p*-H of Ph), 7.60-8.14 (7H, m, *o*-H of Ph, 2-H); δ_C 13.7, 13.9 (2 x $CO_2CH_2CH_3$), 37.1 ($CH_2CO_2CH_2CH_3$), 53.3 (CH), 61.4, 62.4, 63.8 (2 x $CO_2CH_2CH_3$, C-5'), 71.5, 71.9 (C-2', C-3'), 81.8 (C-4'), 87.3 (C-1'), 127.8-129.6 (Ph, C-5), 133.5-134.5 (Ph, C-2), 146.0 (C-4), 164.3, 165.0, 165.9 (COPh), 169.2, 169.9 (2 x $CO_2CH_2CH_3$).

Diethyl N-*[(4-Amino-1-(2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranosyl)imidazole-5-sulfonyl]-L-aspartate* **(43)** - The nitrocompound **41** (0.10 g, 0.124 mmol) in ethyl acetate (10 cm^3) was hydrogenated and processed as in the preparation of **22** to give the *aminosulfonamide* **43** (0.085 g, 88%) as a white amorphous solid, R_F 0.28 (ethyl acetate), $[\alpha]_D$ +5.1 (*c* 0.58, CH_2Cl_2); δ_H 1.09 and 1,19 (each 3H, t, J 7.1, $CO_2CH_2CH_3$), 2.86 (2H, m, CH_2), 3.90-4.14 (4H, m, 2 x $CO_2CH_2CH_3$), 4.58-4.89 (4H, m, CH, 4'-H, 5'-H_2), 5.89 (1H, t, *J* 5.3, 3'-H), 6.16 (1H, t, *J* 5.3, 2'-H), 6.25 (2H, broad s, exchangeable, NH_2), 6.36 (1H, d, *J* 5.1, 1'-H), 7.23-7.59 (9H, m, *m*- and *p*- H of Ph), 7.82-8.13 (7H, m, *o*-H of Ph and 2-H); δ_C 13.9, 14.0 (2 x $CO_2CH_2CH_3$), 37.5 (CH_2CO_2Et), 52.1(CH), 61.0, 62.2, 63.3 (2 x CO_2CH_2 CH_3, C-5'), 70.7, 73.2 (C-2', C-3'), 80.4 (C-4'), 87.3 (C-1'), 103.0 (C-5), 128.5-130.0 (Ph), 133.4-133.8 (Ph), 135.7 (C-2), 154.0 (C-4), 164.9, 165.2, 166.0 (COPh), 169.9, 170.0 (2 x $CO_2CH_2CH_3$) (Found: C, 57.0; H, 5.2; N, 7.2; S, 4.5. $C_{37}H_{38}N_4O_{13}S$ requires C, 57.05; H, 4.92; N, 7.20; S, 4.11%).

Diethyl N-*[(4-Amino-1-(2,3,5-tri*-O-*benzoyl*-α-D-*ribofuranosyl)imidazole-5-sulfonyl]*-L-*aspartate* **(44)** - The nitrocompound **42** (0.10 g, 0.124 mmol) in ethyl acetate (10 cm^3) was hydrogenated and processed as described above for the preparation of **22** to give the 4-amino-α- product **44** (0.092 g, 95%) as an amorphous solid, R_F 0.25 (ethyl acetate), $[\alpha]_D$ +18.8 (*c* 0.58 in CH_2Cl_2); δ_H 1.07 and 1,15 (each 3H, t, *J* 7.0, $CO_2CH_2CH_3$), 2.71 (1H, dd, *J* 17.0 and 4.9, CH_2^a), 2.80 (1H, dd, *J* 17.0 and 5.0, CH_2^b), 3.86-4.23 (4H, m, 2 x $CO_2CH_2CH_3$), 4.48-4.94 (4H, m, CH, 4'-H, 5'-H_2), 5.92 (1H, t, *J* 5.5, 3'-H), 6.06 (2H, broad s, exchangeable, NH_2), 6.14 (1H, t, *J* 5.3, 2'-H), 6.68 (1H, d, *J* 5.0, 1'-H), 7.20-7.61 (9H, m, *m*- and *p*- H of Ph), 7.25-8.19 (7H, m, *o*-H of Ph and 2-H); δ_C 13.9, 14.0 (2 x $CO_2CH_2CH_3$), 37.1($CH_2CO_2CH_2CH_3$), 52.2 (CH), 61.4, 62.5, 64.0 (2 x $CO_2CH_2CH_3$, C-5'), 71.2, 71.9 (C-2', C-3'), 80.5 (C-4') , 85.3 (C-1'), 108.7 (C-5), 128.7-130.1 (Ph), 133.5-133.9 (Ph), 138.5 (C-2), 143.8 (C-4), 164.4, 165.2 and 166.0 (COPh), 169.6 and 169.9 ($CO_2CH_2CH_3$).

Diethyl N-*[(4-nitro-1-(2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranosyl)imidazole-5-sulfonyl]*-L-*aspartate* **(41)** *and diethyl* N-*[(5-nitro-1-(2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranosyl)imidazole-5-sulfonyl]*-L-*aspartate* **(45)** - The imidazole **40** (1.0 g, 2.748 mmol), chlorotrimethylsilane (0.352 cm^3, 2.748 mmol), hexamethyldisilazane (3 cm^3), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **11** (1.38 g, 2.748 mmol) and trimethylsilyl trifluoromethanesulphonate (0.76 cm^3, 4.12 mmol) were allowed to react as in the preparation of **41** and **42** above, but

with a reaction time of 3 min. Chromatography over silica with toluene-ethyl acetate (7:1) as eluent yielded firstly the *4-nitro-β-nucleoside* **41** (0.85 g, 38%) as an amorphous solid, R_F 0.65 (toluene-ethyl acetate 4:1), with properties as reported above.

Further elution of the column yielded the *5-nitro-β- isomer* **45** (0.65 g, 29%) as a white amorphous solid, R_F 0.35 (toluene-ethyl acetate 4:1), $[\alpha]_D$+45.2 (*c* 1.15 in CH_2Cl_2); δ_H 1.11 and 1.18 (each 3H, t, *J* 7.1, $CO_2CH_2C\underline{H}_3$), 2.85 (1H, dd, *J* 17.2 and 4.5, CH_2^a), 3.02 (1H, dd, *J* 17.2 and 4.3, CH_2^b), 3.90-4.14 (4H, m, 2 x $CO_2C\underline{H}_2CH_3$), 4.42 (1H, m, CH), 4.65-4.92 (3H, m, 4'-H, 5'-H_2), 5.89 (1H, t, *J* 5.7, 3'-H), 5.97 (1H, dd, *J* 3.3 and 5.46, 2'-H), 6.54 (1H, broad s, exchangeable, NH), 6.79 (1H, d, *J* 3.3, 1'-H), 7.20-7.61 (9H, m, *m*- and *p*-H of Ph), 7.74-8.15 (7H, m, *o*-H of Ph, 2-H); δ_C 13.8 and 14.0 ($CO_2CH_2\underline{C}H_3$), 37.8 ($\underline{C}H_2CO_2Et$), 53.0 (CH), 61.3, 62.2 and 62.8 (2 x $CO_2\underline{C}H_2CH_3$, C-5'), 69.9, 75.9 (C-2', C-3'), 81.1 (C-4'), 90.3 (C-1'), 128.2-129.9 (Ph,C-4), 133.4-135.0 (Ph, C-2), 142.1 (C-5), 164.6, 165.0, 166.0 ($\underline{C}OPh$), 169.6 and 170.1 ($\underline{C}O_2CH_2CH_3$) (Found: C, 54.7; H, 4.5; N, 7.2; S, 4.4. $C_{37}H_{36}N_4O_{15}S$ requires C, 54.94; H, 4.49; N, 6.93; S, 3.96%).

Diethyl N-*[(5-Amino-1-(2,3,5-tri-*O*-benzoyl-*β*-*D*-ribofuranosyl)imidazole-4-sulfonyl]*-L-*aspartate* (**46**) - The nitrocompound **45** (0.55 g, 0.682 mmol) in ethyl acetate (50 cm^3) was hydrogenated as described above in the preparation of **22**. Chromatography on silica with ethyl acetate as eluent afforded the *aminosulfonamide* (0.51 g, 96%) as a white amorphous solid, R_F 0.12 (ethyl acetate), $[\alpha]_D$ -12.4 (*c* 0.96 in CH_2Cl_2); δ_H 1.17 (6H, 2 t, $CO_2CH_2C\underline{H}_3$), 2.88 (1H, dd, *J* 17.0 and 4.9, $CH_{2,a}$), 2.93 (1H, dd, *J* 17.0 and 4.5, $CH_{2,b}$), 3.98-4.16 (4H, m, 2x$CO_2C\underline{H}_2CH_3$), 4.28-4.40 (1H, m, CH), 4.78 (3H, m, 4'-H, 5'-H_2), 5.10 (2H, broad s, exchangeable, NH_2), 5.79 (2H, m, collapses to 1H, m, on D_2O shake, 3'-H, NH), 5.89 (1H, t, *J* 5.1, 2'-H), 5.95 (1H, d, *J* 4.8, 1'-H), 7.30-7.62 (9H, m, *m*- and *p*- H of Ph), 7.89-8.14 (7H, m, *o*-H of Ph and 2-H); δ_C 13.9 and 14.0 ($CO_2CH_2\underline{C}H_3$), 37.9 ($\underline{C}H_2CO_2Et$), 52.4 (CH), 60.9 , 62.0, 63.1 (2 x $CO_2\underline{C}H_2CH_3$, C-5'), 70.3, 73.2 (C-2', C-3'), 80.6 (C-4') , 87.3 (C-1'), 117.7 (C-4), 128.1-129.8 (Ph, C-2), 133.7-134.1 (Ph), 140.7 (C-5), 165.1, 165.4, 166.1 ($\underline{C}OPh$), 170.1 (2 x $\underline{C}O_2Et$) (Found: C, 56.8; H, 5.1; N, 7.3; S, 4.5. $C_{37}H_{38}N_4O_{13}S$ requires C, 57.05; H, 4.92; N, 7.20; S, 4.11%).

N-*[5-Amino-1-(β-D-ribofuranosyl)imidazole-4-sulfonyl]*-L-*aspartic acid* (**8**) - A catalytic amount of sodium methoxide was added to a solution of the tri-*O*-benzoyl compound **46** (0.30 g, 0.386 mmol) in methanol (30 cm^3). After 16 hours at 20°C the mixture was neutralised with resin (Amberlite IRC-50, H^+), filtered and evaporated. The resultant off-white residue was dissolved in water (30 cm^3) which was extracted with ether (4 x 30 cm^3). The aqueous layer was evaporated to dryness and the residue was stirred in sodium hydroxide solution (1M, 40 cm^3) for 2 hours at 20°C. The solution was acidified to pH 5.5 with resin (Amberlite IRC-50, H^+), filtered and evaporated under reduced pressure to give an off-white solid. Precipitation from methanol - diethyl ether gave the *nucleoside* **8** (0.05 g, 31%) as a colourless solid, $[\alpha]_D$ +20.9 (*c* 0.67, H_2O); δ_H (400 MHz, D_2O) 2.48 (1H, dd, *J* 15.7 and 7.85, CH_2^a), 2.58 (1H, dd, *J* 15.7 and 4.6, CH_2^b), 3.75 (1H, dd, *J* 12.6 and 3.7, 5'-H^a), 3.81 (1H, dd, *J* 12.7 and 2.9, 5'-H^b), 3.87 (1H, dd, *J* 4.85 and 7.7, CH), 4.17 (1H, m, 4'-H), 4.28 (1H, t, *J* 4.6, 3'-H), 4.54 (1H, m, 2'-H), 5.61(1H, d, *J* 6.0, 1'-H), 7.51 (1H, s, 2-H); δ_C (100 MHz, D_2O). 40.5 (CH_2), 49.7(CH), 61.7 (C-5'), 70.9, 73.7 (C-2', C-3'), 86.1 (C-4'), 89.0 (C-1'), 114.3 (C-4), 132.3 (C-2), 143.0 (C-5), 177.6, 178.0 (CO_2H) (Found: MH^+ 425.0977. $C_{13}H_{21}N_4O_{10}S$ requires 425.0978).

*5-Ethoxymethyleneamino-4-ethoxymethyleneaminosulfonyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazole* (**48**) - A solution of the aminosulfonamide **30** (0.5 g, 0.825 mmol) in triethyl orthoformate (30 cm^3) was heated at 120°C for 4 h. After cooling, the solvent was evaporated. Chromatography of the residue on silica, with toluene-ethyl acetate (1:1) as eluent, afforded the *bis(ethoxymethylene) compound* **48** (0.45 g, 76%) as an amorphous solid, R_F 0.8 (ethyl acetate), $[\alpha]_D$ -23.4 (*c* 0.77, CH_2Cl_2); δ_H 1.2-1.3 (6H, m, 2 x $OCH_2C\underline{H}_3$), 4.28 (4H, m, $OC\underline{H}_2CH_3$), 4.74 (3H, m, 4'-H, 5'-H_2), 5.85 (1H, t, *J* 5.3, 3'-H), 5.94 (1H, t, *J* 5.1, 2'-H), 6.11 (1H, d, *J* 4.7, 1'-H), 7.23 - 7.59 (9H, m, *m*- and *p*- H of Ph), 7.82 - 8.06 (7H, m, *o*-H of Ph and 2-H), 8.20 (1H, s, CH=N), 8.44 (1H, s, CH=N); δ_C 13.8 and 13.9 ($OCH_2\underline{C}H_3$), 63.3, 63.8, 65.7 (2 x $O\underline{C}H_2CH_3$, C-5'), 70.9, 74.6 (C-2', C-3'), 80.1 (C-4'), 86.7 (C-1'), 124.4 (C-4), 129.4 - 129.8 (Ph), 131.5 (C-2), 133.5 - 133.8 (Ph), 139.4 (C-5), 163.1, 167.1 (2 x CH), 164.7, 165.1 and 166.0 ($\underline{C}OPh$) (Found: MH^+ 719.1990. $C_{35}H_{35}N_4O_{11}S$ requires 719.2023).

5-(β-D-Ribofuranosyl)-imidazo[4,5-e]-1,2,4-thiadiazine-1,1-dioxide (**9**) - The bis-ethoxymethylene compound **48** (0.3 g, 0.418 mmol) was dissolved in methanol (10 cm^3) and the solution was brought to pH8 by the addition of sodium hydroxide (1M). The solution was stirred at 20°C for 2 h after which the pH was adjusted to 10 by addition of a further quantity of sodium hydroxide (1M). After a further 2 h at 20 °C, the solution was neutralised with acetic acid (1M) and evaporated to dryness. Chromatography on silica with ethyl acetate-methanol (7:1) as eluent yielded the *imidazothiadiazine dioxide* **9** (0.09 g, 71%) as an amorphous white solid, R_F 0.15 (ethyl acetate - methanol, 4:1), $[\alpha]_D$ -60.0 (*c* 0.30, H_2O); λ_{max} [NaOH(aq), pH 8] 228.2, 272.8 nm; δ_H (D_2O) 3.79 (1H, dd, *J* 12.7 and 3.0, 5'-H_a), 3.84 (1H, dd, *J* 12.7 and 2.6, 5'-H_b), 4.22 (1H, q, *J* ~2.8, 4'-H), 4.32 (1H, dd, *J* 2.9 and 5.2, 3'-H), 4.52 (1H, dd, *J* 5.2 and 6.3, 2'-H), 5.85 (1H, d, *J* 6.4, 1'-H), 7.63 (1H, s, 6-H), 7.96 (1H, s, 3-H); δ_C [$(CD_3)_2SO$] 62.2 (C-5'), 71.7, 74.8 (C-2', C-3'), 87.2 (C-4'), 90.2 (C-1'), 120.9 (C-7a), 134.3 (C-4a), 135.8 (C-6), 145.9 (C-3) (Found: MH^+ (FAB) 305.0561. $C_9H_{13}N_4O_6S$ requires 305.0558).

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