The Synthesis of 4-Alkylsulphonyl-5-amino- and 5-Amino-4-phosphono-imidazole Nucleosides as Potential Inhibitors of Purine Biosynthesis

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Conversion of 4(5)-methylthio-5(4)-nitroimidazole (**11**) into its silyl derivative and subsequent condensation with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) in the presence of trimethylsilyl trifluoromethanesulphonate for a short reaction time gave 4-methylthio-5-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**15**) with high regioselectivity; use of longer reaction times gave predominantly the 5-methylthio-4-nitro-isomer (**14**). 5-Amino-4-methylsulphonyl-1-β-D-ribofuranosyl)imidazole (**7**) was obtained from (**15**) in three steps.

Similar chemistry was used to prepare 5-amino-4-[(carboxamido)methyl]sulphonyl-1-β-D-ribofuranosylimidazole (**8**), 5-[(diethylphosphono)methyl]thio-4-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**26**), and 4-{[2,3-bis(methoxycarbonyl)propyl]thio}-5-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**29**).

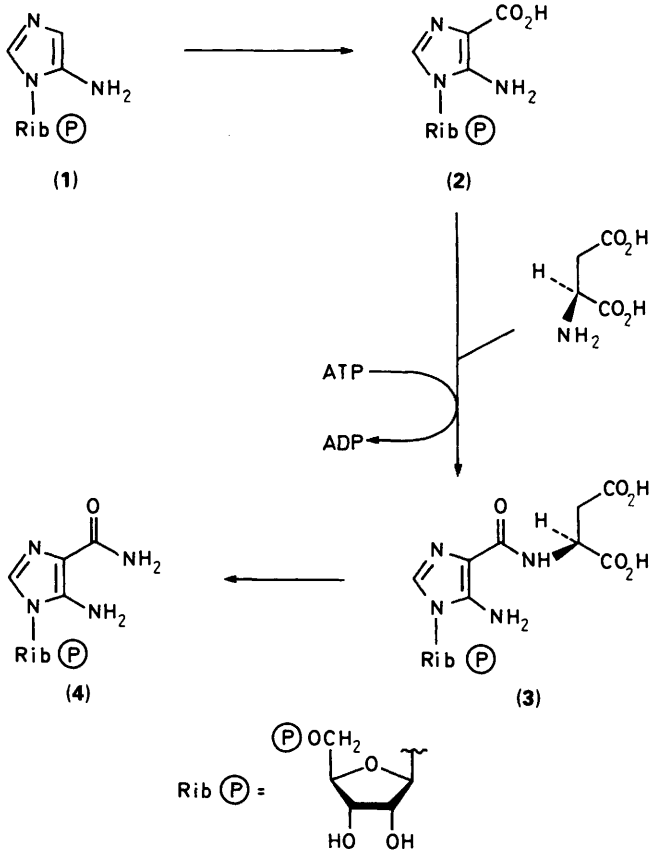
Desulphurization of 3',5'-di-*O*-t-butyldimethylsilyl-β-D-arabinofurano[1',2':4,5]oxazolidine-2- thione (**33**) and subsequent interaction with diethyl α-amino-cyanomethyl phosphonate (**32**) gave, after desilylation, 5-amino-4-diethylphosphono-1-(β-D-arabinofuranosyl)imidazole (**36**).

Of the drugs currently employed in the treatment of cancer, a number are antimetabolites which act by inhibiting the biosynthesis of nucleotides for RNA and DNA synthesis. A fundamental problem in cancer chemotherapy is that of selectivity of a drug between malignant and normal tissues, and one is looking to exploit differences in the anabolic or catabolic processes occurring in tumour cells and in normal cells.

The pathway for the *de novo* biosynthesis of purines has been studied in malignant tissues as well as normal ones. The activity of the pathway is known to be very low in several normal tissues,[1-3] and the rate-limiting enzyme of the pathway, phosphoribosylpyrophosphate (PRPP) amidotransferase, was undetectable in rat skeletal muscle.[4] Malignant tissues, however, appear to be readily capable of *de novo* purine synthesis,[5] and, in studies in Ehrlich ascites cells, a number of enzymes of the pathway show elevated activity relative to appropriate control tissues.[6,7] Thus, rationally designed inhibitors of particular steps in purine biosynthesis may selectively inhibit the growth of malignant cells.

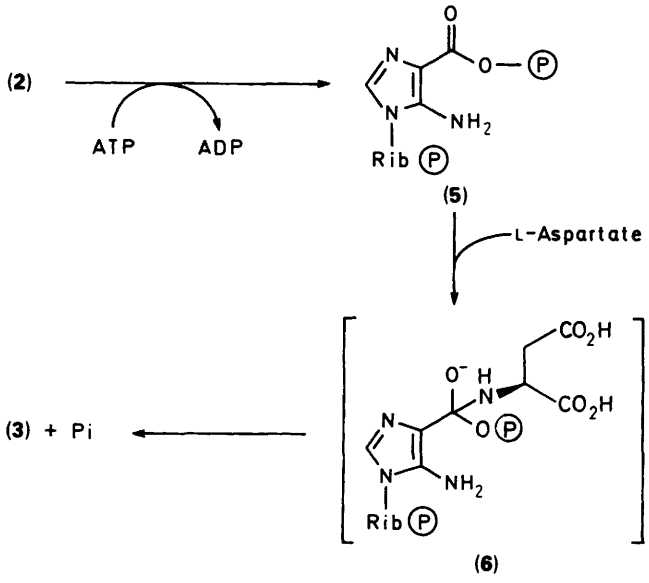
The intermediate stages in purine biosynthesis involve the enzymic carboxylation of 5-amino-1-β-D-ribofuranosylimidazole-5'-phosphate (AIR) (**1**), itself produced from PRPP in a five-step process, to generate the 4-carboxyimidazole (CAIR) (**2**) (Scheme 1). This intermediate is then linked with L-aspartate to give the *N*-succinyl amide (SAICAR) (**3**), which undergoes β-elimination to produce 5-amino-4-carboxamido-1-β-D-ribofuranosylimidazole-5'-phosphate (AICAR) (**4**), and fumarate.

The conversion of CAIR (**2**) into SAICAR (**3**) is catalysed by the enzyme 5'-phosphoribosyl-4-carboxy-5-aminoimidazole:L-aspartate ligase (ADP-forming) (SAICAR synthetase, E.C. 6.3.2.6),[8] and the formation of the amide bond is linked to the hydrolysis of ATP to ADP. Thus one may reasonably assume[9] a mechanism along the lines of Scheme 2, involving an acyl phosphate intermediate (**5**), which interacts with aspartate to give SAICAR (**3**) *via* a tetrahedral intermediate (**6**). Thus SAICAR synthetase may well be susceptible to inhibition by appropriate transition state analogues[10] designed to mimic (**6**), particularly with regard to the tetrahedral geometry at the reaction centre. Previous reports[11] on inhibitors of SAICAR synthetase [purified as an enzyme 'duet' with the carboxylase

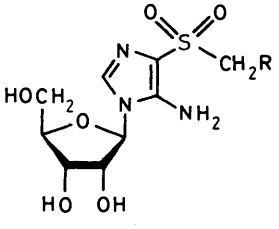


Scheme 1.

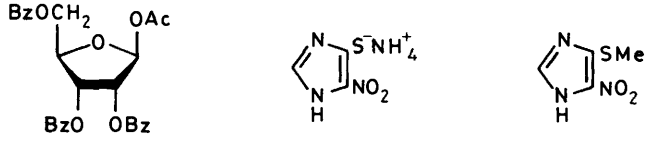
catalysing the conversion of (**1**) into (**2**)],[12] have been concerned with substrate analogues, although more recently 5-amino-4-diazoacetyl-1-β-D-ribofuranosylimidazole has been prepared as an active-site-directed irreversible inhibitor; this compound



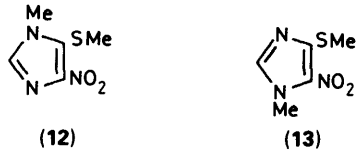
Scheme 2.



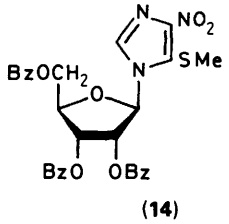
(7) R = H
(8) R = $CONH_2$



(9) (10) (11)



(12) (13)



(14)

showed cytotoxity but its mode of action does not involve inhibition of purine biosynthesis.[13]

In this paper, we report the synthesis of two simple analogues (7) and (8) of (6), where the tetrahedral geometry is ensured by the sulphone grouping. We also describe some chemistry directed towards analogues with more complex side-chains, and an analogue of (6) with 4-co-ordinate phosphorus at the reaction centre.

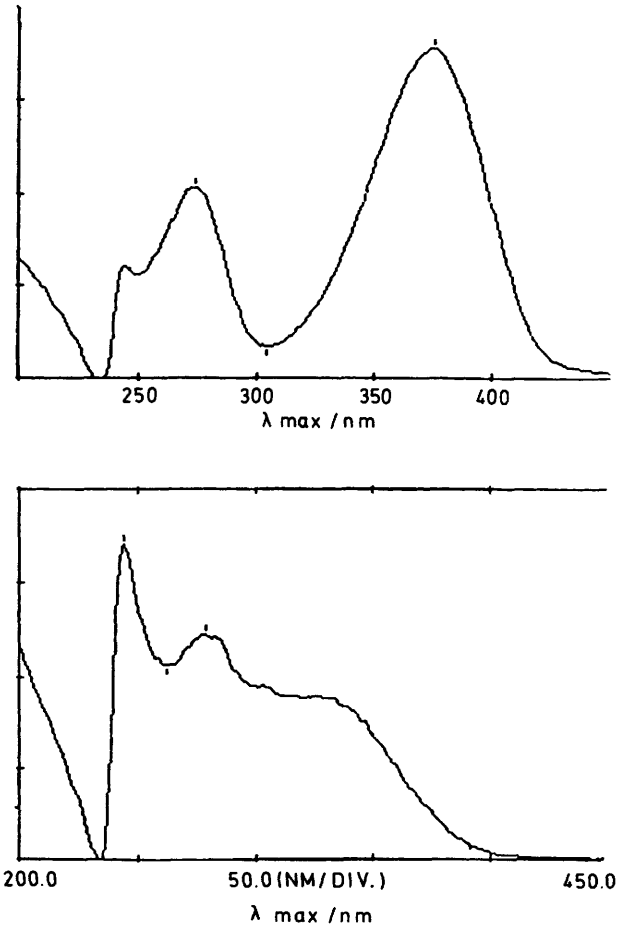
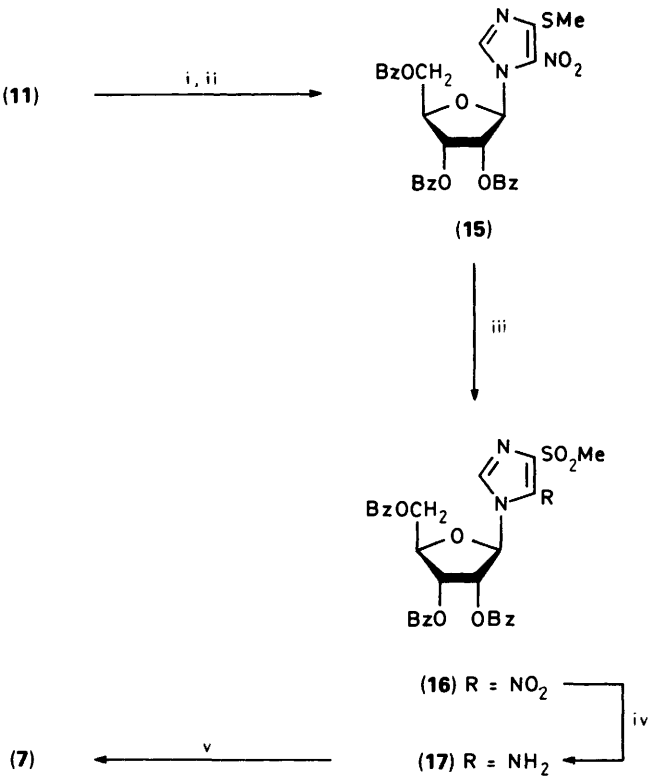


Figure. UV spectra (in chloroform) of: (*top*) 1-methyl-4-methylthio-5-nitroimidazole (**13**), λ_{max} 274 (ε 6 500) and 376 nm (11 100); (bottom) 1-methyl-5-methylthio-4-nitroimidazole (**12**), λ_{max} 244 (ε 9 800), 278 (6 880) and 325sh nm (5 075).

We envisaged that (7), (8), and similar systems could be best approached *via* interaction of suitably substituted imidazoles and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) using mild Lewis acid catalysis, as developed by Vorbrüggen and co-workers for the synthesis of purine and pyrimidine nucleosides,[14] and applied by others to imidazole nucleoside synthesis.[15] Clearly, in such an approach, the question of regiochemistry in the condensation would need to be addressed.

Thus, for the synthesis of (7), the ammonium salt of 4(5)-mercapto-5(4)-nitroimidazole (**10**)[16] was treated with methyl iodide to give 4(5)-methylthio-5(4)-nitroimidazole (**11**).[16] It was found that, if a large excess of reagent was used, an *N*,*S*-dimethyl product was also produced in small amounts. This crystalline material was different from the known[16] 1-methyl-5-methylthio-4-nitroimidazole (**12**), and could therefore be assigned the structure 1-methyl-4-methylthio-5-nitroimidazole (**13**), a conclusion which was supported by the observation that, in its ^1H NMR spectrum, the *N*-methyl group of (**13**) showed a downfield shift of 0.15 ppm compared with that for (**12**). The isolation of (**13**) proved particularly fortuitous when we observed that the UV spectra of (**12**) and (**13**) were very different (Figure); indeed, the yellow colouration of (**13**) was much more pronounced than that of (**12**), as was consistently found in similar pairs of isomers (*vide infra*). Thus it would seem that UV spectroscopy should



Scheme 3. *Reagents and conditions:* i, TMSCl, HMDS, heat; ii, (**9**), TMSOTf, CH_3CN, 3 min; iii, MCPBA, CH_2Cl_2; iv, H_2, Pd/C, EtOAc; v, NH_3, MeOH.

enable ready distinction to be made between regioisomeric nucleosides formed by condensation reactions involving compounds such as (**11**). We also found that oxidation of (**12**) and (**13**) gave sulphones with very similar UV spectra, so that it was clearly preferable to oxidize at sulphur after nucleoside formation, rather than before.

Hence, to form the nucleoside, (**11**) was treated firstly with trimethylsilyl chloride (TMSCl) and hexamethyldisilazane (HMDS) until a homogeneous solution was obtained; the residue after evaporation was treated with the ribose derivative (**9**)[17] in 1,2-dichloroethane in the presence of trimethylsilyl trifluoromethanesulphonate (TMSOTf). After reaction overnight at room temperature, a yellow product could be isolated in 51% yield which was shown by ^{1}H NMR to be a protected β-D-ribofuranosyl nucleoside of (**11**). However, since the UV spectrum of this product was very similar to that of (**12**), it could be assigned as the undesired regioisomer (**14**).

It seemed to us that this result might well represent the thermodynamic product of the reaction, and possibly not the result under conditions of kinetic control. It has also been observed that isomer ratios in similar condensations are dependent on solvent polarity.[18] Indeed we found that, using acetonitrile as solvent, another product could be observed to accumulate at short reaction times, and, after considerable experimentation, this material could be isolated in 80% yield after 3 min reaction time in acetonitrile as solvent and with 1.5 equiv. of TMSOTf present. Under these conditions, only trace amounts of (**14**) were produced (TLC), and these could be separated from the new, darker yellow, product by crystallisation. The new product was also clearly a nucleoside of (**11**), and its UV spectrum was closely similar to that of (**13**). Thus the structure (**15**) was assigned (Scheme 3), supported by the observation that, in the ^{1}H NMR spectra, the signal for 1′-H of (**15**) was shifted 0.31 ppm downfield as compared with the corresponding signal from (**14**). The desired isomer (**15**) also showed downfield shifts (0.25 and 0.11 ppm respectively) for 2-H and the *S*-methyl group, relative to isomer (**14**). The synthesis of (**7**) then proceeded routinely. Oxidation of (**15**) with *m*-chloroperbenzoic acid gave the sulphone (**16**) in 77% yield after chromatography; the structure of (**16**) as the sulphone was supported by IR evidence (ν_{max} 1 320 and 1 135 cm^{-1}), and by the downfield shift of 0.75 ppm shown by the SCH_3 group in the ^{1}H NMR in going from (**15**) to (**16**). Catalytic reduction of (**16**) gave the amine (**17**) in near quantitative yield, and deprotection with methanolic ammonia led to the crystalline amino sulphone (**7**) in 65% yield.

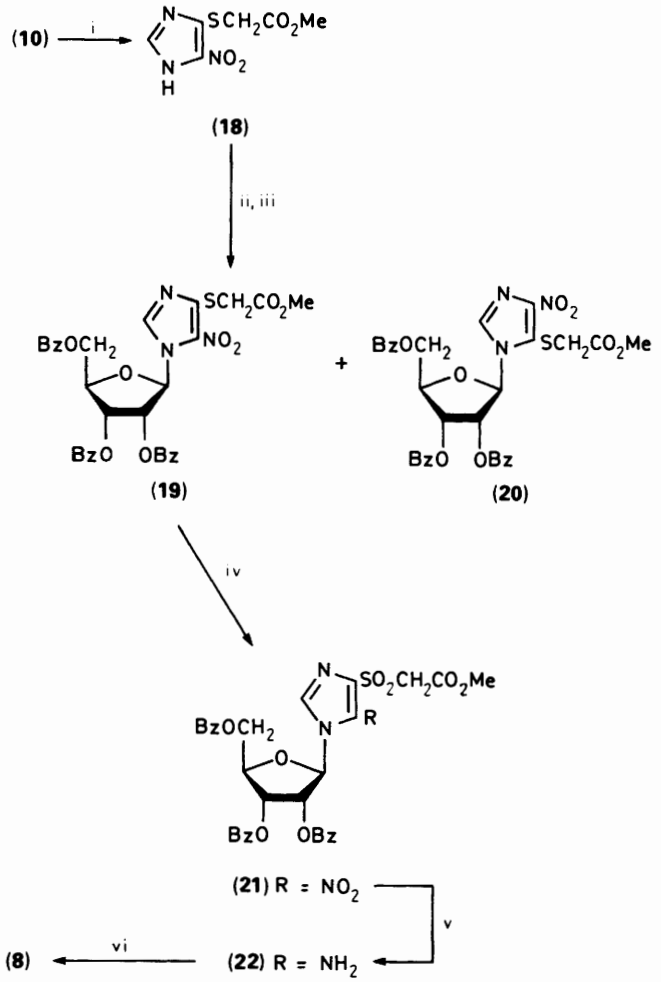
As an example of an analogue of (**6**) with a more complex polar side-chain we have also prepared the carboxamide (**8**) by a similar sequence (Scheme 4). The ammonium salt (**10**)[16] was thus alkylated with methyl bromoacetate to yield 4(5)-methoxycarbonylmethylthio-5(4)-nitroimidazole (**18**) in high yield. The heterocycle was then silylated, and the silyl derivative allowed to interact in acetonitrile with the ribose derivative (**9**) in the presence of TMSOTf for 90 s. Quenching the reaction after this time led to the isolation of a major product by crystallisation in 70% yield; chromatography of the mother liquors permitted the isolation of a minor product (0.8%). Both materials were, by NMR, clearly regioisomeric nucleosides, and it was possible to assign structures (**19**) and (**20**) to major and minor isomers respectively by virtue of their UV spectra which followed the established pattern of the Figure. However, the complementary evidence based on the chemical shift of 1′-H was less conclusive than for the *S*-methyl compounds. Although (**19**) showed 1′-H at lower field than did (**20**), the difference was only small (Δδ 0.05 ppm); indeed, the values of the chemical shifts [δ 6.83 for (**19**) and δ 6.78 for (**20**)] were both comparable with that shown by (**15**) (δ 6.85). It thus seems that, in isomer (**20**), the methoxycarbonyl group is exerting a deshielding effect on 1′-H similar to that of the nitro group in (**15**) and (**19**). However, the downfield shifts of 2-H and the *S*-CH_2 protons (Δδ 0.16 and 0.14 respectively) in (**19**), as compared to (**20**), is in accordance with the similar findings for (**15**) and (**14**) noted above.

Since (**19**) was highly crystalline, an X-ray determination was carried out on it,[19] to establish conclusively the regiochemistry of such nucleosides. Full details will be published elsewhere, but we note here that the crystal structure indicates approximate coplanarity between the imidazole ring, all three atoms of the nitro group, and both the sulphur and attached methylene carbon. Thus a long wavelength UV absorption might be expected. Presumably, in compounds such as (**14**) and (**20**), steric effects would force the *S*-CH_2 or *S*-CH_3 bond out of the plane of the heterocycle, thus leading to a reduction in p-orbital overlap.

Conversion of (**19**) to (**8**) could be carried out in three steps (Scheme 4). Oxidation of (**19**) with *m*-chloroperbenzoic acid proceeded more slowly than for *S*-methyl compound (**15**), but good yields of (**21**) could be obtained. Shorter reaction times led to the detection of the intermediate sulphoxide. Reduction of nitro sulphone (**21**) catalytically gave the amino sulphone (**22**) in high yield, which upon ammonolysis gave the deprotected nucleoside (**8**).

The target systems (**7**) and (**8**) were both evaluated for toxicity against Walker, L1210, and V.79 cell lines, *in vitro*, by continuous exposure. Since 5-amino-4-carboxamido-1-β-D-ribofuranosylimidazole can be phosphorylated to its 5′-phosphate AICAR (**4**) by adenosine kinase,[20] it seemed reasonable to assume that (**7**) and (**8**) might also be phosphorylated enzymically within the cells. However, neither (**7**) nor (**8**) showed significant cytotoxicity. Studies on the enzymic phosphorylation[21] of (**7**) and (**8**), and their effects on SAICAR synthetase[11,12] will be reported elsewhere.

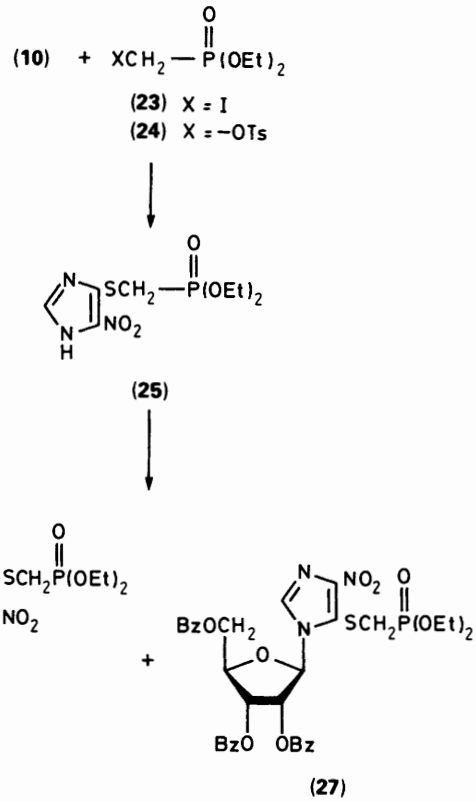
We were also interested in devising routes to more complex



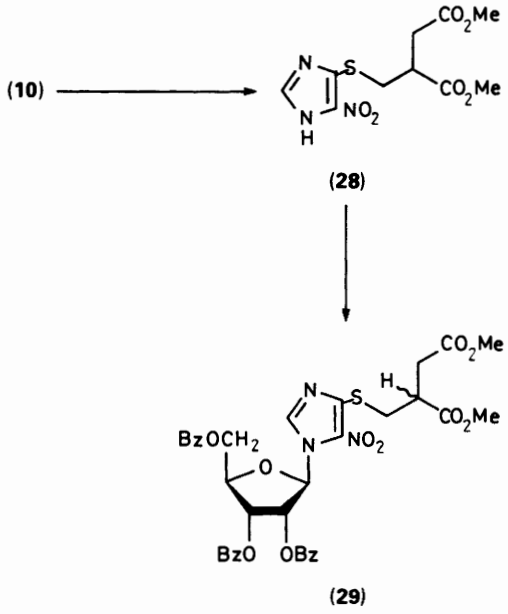
Scheme 4. *Reagents and conditions:* i, $BrCH_2CO_2Me$, heat; ii, TMSCl, HMDS, xylene, 130 °C; iii, (**9**) TMSOTf, CH_3CN, 1.5 min; iv, MCPBA, CH_2Cl_2; v, H_2, Pd/C, EtOAc; vi, NH_3, MeOH.

analogues of the intermediate (**6**), in which either or both of the phosphoryl and aspartyl units might be incorporated in stabilized form. A frequently used, hydrolytically stable analogue of a phosphate ester is the corresponding phosphonate. Thus, in a route towards such an analogue of (**6**), the thiolate (**10**) gave, on reaction with either diethyl iodomethylphosphonate (**23**) or diethyl toluene-*p*-sulphonyloxymethanephosphonate (**24**),[22,23] the phosphonate (**25**) (Scheme 5); reaction with the former reagent was somewhat higher yielding, but led also to the formation of 4(5)-ethylthio-5(4)-nitroimidazole as a by-product. When (**25**) was silylated and condensed with (**9**) as in the previous cases, nucleoside formation proceeded more slowly than before; the reaction was terminated when appreciable amounts of a second product became evident by TLC, but even so, the overall yield was less satisfactory, and the second product was present at more than trace quantities. The major and minor products could be assigned as (**26**) and (**27**) respectively by UV spectroscopy, and the NMR correlations noted above also applied. With three pairs of regioisomeric nucleosides to hand, a further NMR correlation could be observed; the desired regioisomers (**15**), (**19**), and (**26**) all showed the coupling constant $J_{1'\text{-}H,2'\text{-}H}$ in the range 3.41–3.53 Hz, whilst the unwanted regioisomers (**14**), (**20**), and (**27**) had the equivalent coupling constant in the range 5.40–5.73 Hz.

As a route towards an analogue incorporating the aspartyl unit of (**6**), the ammonium salt (**10**) was treated with dimethyl itaconate to give the Michael adduct (**28**) in moderate yield



Scheme 5.

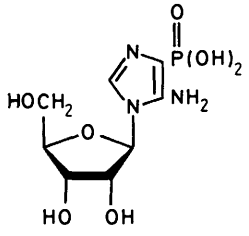


Scheme 6.

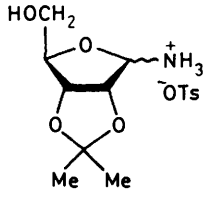
(Scheme 6). Silylation of (**28**), followed by TMSOTf-catalysed condensation with ribose derivative (**9**) for a short reaction time, gave the protected nucleoside (**29**) in 63% yield, with no sign of the regioisomer. The regiochemistry of (**29**) was evident, as in the previous similar cases, from its UV spectrum, supported by ^1H NMR data; the proton spectrum also provided evidence, in the apparent doubling of some signals, that (**29**) was the expected mixture of two diastereoisomers.

We were also interested in developing routes to analogues of (**6**) with tetrahedral phosphorus at the reaction centre, as typified by the simple aminophosphonic acid (**30**). Any possible

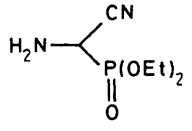
investigation of the synthesis of (**30**) by heterocycle–sugar condensation was thwarted by the failure of several projected routes to 4(5)-dialkylphosphono-5(4)-nitroimidazoles. We therefore considered a route to (**30**) involving condensation of the ribofuranosylamine derivative (**31**)[24] with the α-aminophosphonate (**32**)[25] and a C-1 unit such as triethyl orthoformate, as developed by Shaw and co-workers for the synthesis of CAIR (**2**) and related aminoimidazole nucleosides and nucleotides.[24,26] However, under a variety of conditions,[24,26] no nucleoside products could be isolated from such condensations involving (**32**).



(**30**)

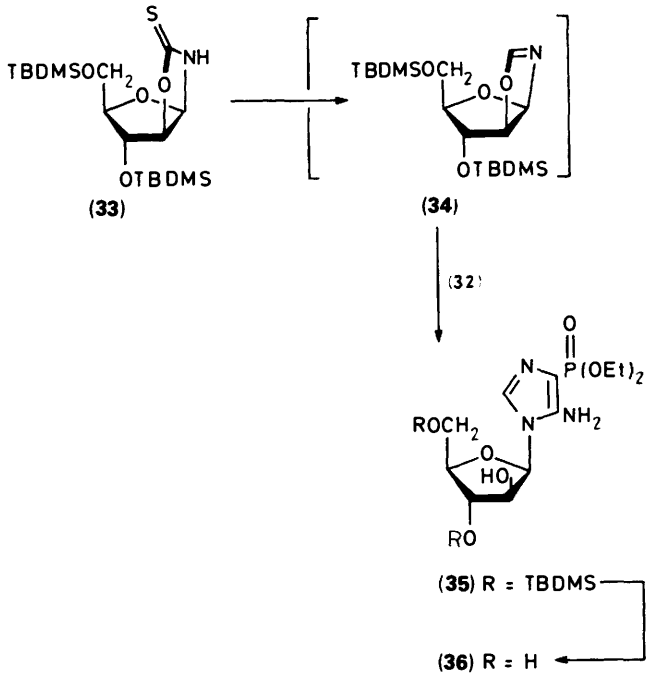


(**31**)



(**32**)

Shaw and co-workers have shown that β-D-arabinofuranosyl nucleotides related to the intermediates (**1**)–(**4**) in purine biosynthesis can display substrate or inhibitory activity towards the enzyme 'duet' of AIR carboxylase and SAICAR synthetase.[11] Imbach's group have developed a good route to β-D-arabinofuranosyl nucleosides of this type,[27] which has been extended by others to the synthesis of 5-amino-1-β-D-fructofuranosyl imidazole-4-carboxamide.[28] We thus investigated the applicability of this methodology to the synthesis of 4-phosphonoimidazoles, with a view to synthesis of both β-D-arabinofuranosyl, and, by inversion at C-2′, β-D-ribofuranosyl systems (Scheme 7). The oxazolidine-2-thione (**33**) was therefore prepared by the reported procedure,[27] and reduced with Raney nickel to (**34**), which was directly condensed with diethyl α-amino-α-cyanophosphonate (**32**)[25] to yield the crystalline β-D-arabinofuranosyl nucleoside (**35**) in 31% yield. The low yield seemed to be due in part to over-reduction in the first stage, since examination of (**34**) by mass spectrometry and NMR revealed the dihydro derivative to be present also. Treatment of (**35**) with fluoride ion led to the triol (**36**) in high yield.



Scheme 7.

Experimental

IR spectra were recorded on a Perkin-Elmer 580 spectrophotometer; UV spectra were obtained on a Shimadzu 160 spectrophotometer. Mass spectrometry was performed using VG updated MS 9 and VG ZAB-E high resolution EI/CI/FAB instruments. NMR spectra were recorded on Perkin-Elmer R12B, Bruker WP 200 SY and WH 360 spectrometers with $CDCl_3$ as solvent unless otherwise stated. Specific rotations were measured at room temperature using a Bendix-NPL 143D automatic polarimeter (path length 1 cm). M.p.s were determined using an Electrothermal MK II melting point apparatus and are uncorrected.

Reactions were monitored by TLC on pre-coated aluminium-backed plates [Kieselgel HF_{254} type 60 (Merck)]. Column chromatography was carried out using Kieselgel H type 60 (Merck 7734); an external pressure was applied to the top of the columns. Light petroleum refers to material of boiling range 40–60 °C. Organic extracts were dried over anhydrous sodium sulphate.

1-Methyl-4-methylthio-5-nitroimidazole (**13**) *and* 4(5)-*Methylthio-5(4)-nitroimidazole* (**11**).—To a solution of the ammonium salt (**10**) (0.6 g, 3.7 mmol) in methanol (20 ml) was added methyl iodide (0.74 ml, 11.9 mmol). The resultant mixture was heated under reflux, with stirring, for 30 min to give a clear yellow solution. The solvent was evaporated and the residue pre-adsorbed on silica gel using acetone and applied to the top of a column of silica gel. The column was eluted with ethyl acetate–ether (4:1) to yield firstly the *dialkylated product* (**13**) (0.024 g, 3.7%) as a yellow solid, m.p. 166–167 °C; $\lambda_{max}(CHCl_3)$ 274 (ε 6 500) and 376 (11 100) nm; ν_{max}(KBr) 1 500 and 1 360 (NO_2), 1 425 (NMe), and 1 315 cm^{-1} (SMe); δ_H[60 MHz; $(CD_3)_2SO$] 2.5 (3 H, s, SMe), 3.9 (3 H, s, NMe), and 8.05 (1 H, s, 2-H); δ_C[50 MHz; $(CD_3)_2SO$] 12.9 (SMe), 35.2 (NMe), 133.6 (C-4), 142.8 (C-2) and 147.4 (C-5); *m/z* 173 ($M^{+\cdot}$) and 126 (M − SMe)$^{+\cdot}$ (Found: C, 34.1; H, 3.9; N, 24.3; S, 18.9. $C_5H_7N_3O_2S$ requires C, 34.7; H, 4.0; N, 24.3; S, 18.5%).

Further elution of the column with the same solvent gave 4(5)-*methylthio-5(4)-nitroimidazole* (**11**) (0.54 g, 92%), m.p. 187–190° (lit.,[16] 187–189 °C). This material could be obtained without chromatography by use of the literature preparation.[16]

5-Methylthio-4-nitro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazole (**14**).—A mixture of the sulphide (**11**) (0.447 g, 2.8 mmol), TMSCl (0.36 ml, 2.8 mmol), and HMDS (3.54 ml) were stirred and heated at 130 °C. After *ca.* 1 h 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 in 1,2-dichloroethane (2 ml). A solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) (1.446 g, 2.8 mmol) in

1,2-dichloroethane (14 ml) was added, and after cooling to 0 °C, TMSOTf (0.63 ml, 2.8 mmol) was added dropwise with stirring. This solution was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (14 ml) and filtered through Celite–sand which was washed thoroughly with 1,2-dichloroethane. The organic layer was dried and evaporated to give a residue which was pre-adsorbed on silica gel using acetone and applied to the top of a column of silica gel. The column was eluted with hexane–ether (3:2) to yield the *title compound* (**14**) (0.857 g, 51%) as a pale yellow amorphous solid, R_F 0.39 (ether–hexane, 4:1), $[\alpha]_D$ −95.0° (*c* 0.895 in $CHCl_3$); $\lambda_{max}(CHCl_3)$ 243 (ε 23 818), 278 (10 854) and 330sh nm (4 824); λ_{max}(KBr) 1 730 (C=O), 1 535, and 1 350 (NO_2), 1 320 (SMe), and 1 270 cm^{-1} (C–O); δ_H(360 MHz) 2.50 (3 H, s, Me), 4.70 (1 H, dd, *J* 12.3 and 3.5 Hz, 5$_b$′-H), 4.82 (1 H, m, 4′-H), 4.88 (1 H, dd, *J* 12.3 and 2.8 Hz, 5$_a$′-H), 5.93 (2 H, m, 2′-H, 3′-H), 6.5 (1 H, d, *J* 5.4 Hz, 1′-H), 7.36–7.63 (9 H, m, Ph), 7.81 (1 H, s, 2-H), and 7.9–8.1 (6 H, m, Ph) (Found: C, 59.5; H, 3.9; N, 6.7; S, 5.4. $C_{30}H_{25}N_3O_9S$ requires C, 59.7; H, 4.2; N, 7.0; S, 5.3%).

4-*Methylthio*-5-*nitro*-1-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**15**).—A mixture of the sulphide (**11**) (1.35 g, 8.49 mmol), TMSCl (1.07 ml, 8.49 mmol), HMDS (10.7 ml), and xylene (8 ml) were stirred and heated at 130 °C. Ammonium chloride sublimed into the condenser and after *ca.* 1 h a clear brown solution was obtained. Evaporation under reduced pressure gave a brown residue to which was added a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) (4.28 g, 8.49 mmol) in acetonitrile (45 ml). The resultant solution was cooled to 0 °C, and TMSOTf (2.4 ml, 12.7 mmol) was added with stirring. After 3 min, with the cooling bath removed, the reaction was quenched by pouring the mixture into saturated aqueous sodium hydrogen carbonate (45 ml) and diluting it with dichloromethane (25 ml). After this, the mixture was filtered through Celite–sand and the aqueous layer was extracted with dichloromethane (2 × 15 ml). The combined organic extracts were dried and evaporated to give a yellow foam which was crystallised from acetone–hexane to give the *nucleoside* (**15**) (4.1 g, 80%), m.p. 144–145 °C, R_F 0.57 (ether–hexane, 4:1), $[\alpha]_D$ + 2.7° (*c* 0.74 in $CHCl_3$); $\lambda_{max}(CHCl_3)$ 242 (ε 33 889), 276 (13 145), and 377 nm (16 160); ν_{max}(KBr) 1 730 (C=O) and 710 cm^{-1} (aromatic); δ_H(360 MHz) 2.61 (3 H, s, Me), 4.72 (1 H, dd, *J* 13.06 and 4.6 Hz, 5$_a$′-H), 4.80–4.85 (2 H, m, 4′-H, 5$_b$′-H), 5.86 (1 H, app. t, *J* 5.78 Hz, 3′-H), 5.91 (1 H, dd, *J* 3.56 and 5.54 Hz, 2′-H), 6.85 (1 H, d, *J* 3.53 Hz, 1′-H), 7.31–7.61 (9 H, m, Ph), 7.86–8.08 (6 H, m, Ph), and 8.06 (1 H, s, 2-H), (Found: C, 59.6; H, 4.2; N, 7.0; S, 5.3. $C_{30}H_{25}N_3O_9S$ requires C, 59.7; H, 4.2; N, 7.0; S, 5.3%).

4-*Methylsulphonyl*-5-*nitro*-1-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**16**).—A solution of the nucleoside (**15**) (1.219 g, 2.02 mmol) and *m*-chloroperbenzoic acid (1.095 g, 6.36 mmol) in dichloromethane (23 ml) were stirred at 20 °C for 1.5 h. The solution was filtered and washed with saturated aqueous sodium hydrogen carbonate (20 ml) followed by water (20 ml). The dried organic layer was evaporated with silica gel. The resultant silica gel was applied to the top of a column of more silica and the column eluted with ether–hexane (3:2) and then ether to yield the *sulphone* (**16**) (0.99 g, 77%), m.p. (acetone–hexane) 147–148 °C, $[\alpha]_D$ +16.1° (*c* 0.93 in $CHCl_3$); ν_{max}(KBr) 1 730 (C=O), 1 540 (NO_2), 1 320, and 1 135 (SO_2), and 710 cm^{-1} (aromatic); δ_H(360 MHz) 3.36 (3 H, s, Me), 4.75 (1 H, dd, *J* 13.16 and 4.35 Hz, 5$_b$′-H), 4.84–4.88 (2 H, m, 4′-H, 5$_a$′-H), 5.86–5.91 (2 H, m, 2′-H, 3′-H), 6.75 (1 H, d, *J* 3.57 Hz, 1′-H), 7.34–7.63 (9 H, m, Ph), 7.88–8.07 (6 H, m, Ph), and 8.12 (1 H, s, 2-H) (Found: C, 56.9; H, 4.1; N, 6.7; S, 4.9. $C_{30}H_{25}N_3O_{11}S$ requires C, 56.7; H, 3.9; N, 6.6; S, 5.0%).

5-*Amino*-4-*methylsulphonyl*-1-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**17**).—To a solution of the sulphone (**16**) (0.99 g, 1.56 mmol) in ethyl acetate (120 ml) was added Pd/C (5%; 0.1 g) and the resultant suspension was stirred under an atmosphere of H_2 at 20 °C. The reaction was monitored by TLC. After the nitro group had been completely reduced the reaction mixture was filtered and evaporated to yield the *amine* (**17**) as a white amorphous solid (0.93 g, 99%), $[\alpha]_D$ −31.7° (*c* 1.04 in $CHCl_3$); ν_{max}(KBr) 3 430 and 3 340 (NH_2), 1 730 (C=O), 1 320 and 1 120 (SO_2), and 710 cm^{-1} (aromatic); δ_H(200 MHz) 3.11 (3 H, s, Me), 4.82 (3 H, m, 4′-H, 5$_a$′-H, 5$_b$′-H), 5.24 (2 H, s, disappears on D_2O shake, NH_2), 5.79 (1 H, app. t, *J* 5.4 Hz, 3′-H), 5.88 (1 H, t, *J* ~4.8 Hz, 2′-H), 5.93 (1 H, d, *J* 4.5 Hz, 1′-H), 7.4–7.7 (10 H, m, Ph, 2-H), and 7.9–8.1 (6 H, m, Ph) (Found: C, 59.1; H, 4.6: N, 6.7; S, 4.9; $C_{30}H_{27}N_3O_9S$ requires C, 59.5; H, 4.5; N, 6.9; S, 5.3%) (Found: M^+, 605.1476; $C_{30}H_{27}N_3O_9S$ requires 605.1468).

5-*Amino*-4-*methylsulphonyl*-1-(β-D-*ribofuranosyl*)*imidazole* (**7**).—A solution of (**17**) (0.744 g, 1.23 mmol) in methanolic ammonia (50 ml) was stirred overnight at room temperature. After evaporation, the residue was dissolved in water (30 ml) and extracted with ether (2 × 20 ml). The aqueous layer was filtered and the solvent was evaporated. Crystallisation from ethanol–ether gave the *triol* (**7**) (0.2328 g, 65%), m.p. 171–172 °C, $[\alpha]_D$ − 51.1° (*c* 0.685 in H_2O); $\lambda_{max}(H_2O)$ 235 nm (ε 7 237); ν_{max}(KBr) 3 430, 3 300, and 1 635 (NH_2), 3 600–3 000 (OH), and 1 325 and 1 120 cm^{-1} (SO_2); δ_H(200 MHz; CD_3OD) 3.05 (3 H, s, Me), 3.74 (2 H, m, 5$_a$′-H, 5$_b$′-H), 4.07 (1 H, q, *J* 2.59 Hz, 4′-H), 4.21 (1 H, dd, *J* 2.56 and 5.63 Hz, 3′-H), 4.48 (1 H, dd, *J* 6.81 and 5.47 Hz, 2′-H), 5.56 (1 H, d, *J* 6.79 Hz, 1-H′), and 7.49 (1 H, s, 2-H); *m/z* (FAB) 294 $(M + H)^+$ and 277 $(M - Me)^+$ (Found: C, 36.8; H, 4.8; N, 13.7; S, 10.8. $C_9H_{15}N_3O_6S$ requires C, 36.8; H, 5.1; N, 14.3; S, 10.9%).

4(5)-[(*Methoxycarbonyl*)*methyl*]*thio*-5(4)-*nitroimidazole* (**18**).—Methyl bromoacetate (1.94 ml, 23 mmol) was added to a solution of ammonium salt (**10**) (3.41 g, 21 mmol) in hot methanol, and the mixture was heated under reflux, with stirring, for 4 h. The solvent was evaporated and the residue washed with water (10 ml). The dried yellow solid obtained was crystallised from methanol to afford the sulphide (**18**) (3.99 g. 87%), m.p. 135–136 °C; ν_{max}(KBr) 1 740 (C=O), 1 525 and 1 350 cm^{-1} (NO_2); δ_H [60 MHz; $(CD_3)_2SO$] 3.7 (3 H, s, OMe), 4.15 (2 H, s, CH_2), and 8.0 (1 H, s, 2-H); δ_C[50 MHz; $(CD_3)_2SO$] 33.4 (Me), 52.5 (CH_2), 133.9 (C-4 or -5), 137.1 (C-2), 140.5 (C-5 or -4), and 168.7 (C=O): *m/z* 217 (M^+), 184, and 154 (Found: C, 33.6; H, 3.3; N, 19.3. $C_6H_7N_3O_4S$ requires C, 33.2; H, 3.2; N, 19.3%).

4-[(*Methoxycarbonyl*)*methyl*]*thio*-5-*nitro*-1-(2,3,5-tri-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**19**) *and* 5-[(*Methoxycarbonyl*)*methyl*]*thio*-4-*nitro*-1-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**20**).—A mixture of the sulphide (**18**) (1.0 g, 4.6 mmol), TMSCl (0.58 ml, 4.6 mmol), HMDS (5.8 ml), and xylene (5 ml) were stirred and heated at 130 °C. Ammonium chloride sublimed into the condenser and a clear brown solution was obtained after *ca.* 10 min. Evaporation gave an oily residue, to which was added a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) (2.32 g, 4.6 mmol) in acetonitrile (20 ml). This mixture was cooled to 0 °C and TMSOTf, (1.34 ml, 6.9 mmol) was added. The reaction mixture was stirred for 90 s with the cooling bath removed, quenched with saturated aqueous sodium hydrogen carbonate (10 ml) and diluted with dichloromethane (10 ml). The organic layer was extracted with saturated aqueous sodium hydrogen carbonate (2 × 5 ml) followed by water (5 ml). The dried organic extracts were evaporated to yield a yellow foam. Crystallisation from acetone–hexane afforded the yellow *nucleoside* (**19**) (2.14 g, 70%), m.p.

132–133 °C; R_F 0.49 (ether–hexane, 4:1); $[\alpha]_D$ −13.4° (*c* 1.12 in $CHCl_3$); $\lambda_{max}(CHCl_3)$ 245 (ε 16 176), 273 (12 096), and 366 nm (15 156); ν_{max}(KBr) 1 735 and 1 720 (C=O) and 710 cm^{-1} (aromatic); δ_H(360 MHz) 3.74 (3 H, s, Me), 3.99 (2 H, s, CH_2), 4.72 (1 H, dd, *J* 13.12 and 4.68 Hz, 5$_a$′-H), 4.79–4.84 (2 H, m, 4′-H, 5$_b$′-H), 5.85 (1 H, app. t, *J* 5.6 Hz, 3′-H), 5.89 (1 H, dd, *J* 3.49 and 5.52 Hz, 2′-H), 6.83 (1 H, d, *J* 3.41 Hz, 1′-H), 7.31–7.62 (9 H, m, Ph), 7.86–8.07 (6 H, m, Ph), and 8.04 (1 H, s, 2-H) (Found: C, 57.9; H, 3.9; N, 6.3; S, 4.3. $C_{32}H_{27}N_3O_{11}S$ requires C, 58.1; H, 4.1; N, 6.3; S, 4.8%).

The filtrate from the crystallisation was evaporated to dryness with silica gel. The resultant silica gel was applied to the top of a column of more silica and the column eluted with light petroleum–ether (3:2) to yield more (**19**) (0.071 g, 2.3%), as well as the *regioisomer* (**20**) (0.026 g, 0.8%) as a glass, R_F 0.37 (ether–hexane, 4:1); $[\alpha]_D$ −70.5° (*c* 0.78 in $CHCl_3$); $\lambda_{max}(CHCl_3)$ 244 (ε 4 731), 277 (2 738) and 320sh nm (1 416); δ_H(200 MHz) 3.57 (3 H, s, Me), 3.70 (1 H, d, *J* 16.46 Hz, 1 H of CH_2), 3.92 (1 H, d, *J* 16.46 Hz, 1 H of CH_2), 4.51–4.92 (3 H, m, 4′-H, 5$_a$′-H, 5$_b$′-H), 5.85–5.99 (2 H, m, 2′-H, 3′-H), 6.78 (1 H, d, *J* 5.42 Hz, 1′-H), 7.36–7.66 (9 H, m, Ph), 7.88 (1 H, s, 2-H) and 7.91–8.10 (6 H, m, Ph).

4-[(*Methoxycarbonyl*)*methyl*]*sulphonyl*-5-*nitro*-1-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**21**).—To a solution of the nucleoside (**19**) (0.8576 g, 1.3 mmol) in dichloromethane (15 ml) was added *m*-chloroperbenzoic acid (0.668 g, 3.88 mmol). The resultant solution was stirred at 20 °C for 19 h, filtered, and washed with saturated aqueous sodium hydrogen carbonate (2 × 10 ml) and water (10 ml). The dried organic layer was evaporated to dryness with silica gel, which was applied to the top of a column of more silica and the column eluted with ether–hexane (4:1) to yield the *sulphone* (**21**) (0.654 g, 73%) as an amorphous white solid, $[\alpha]_D$ +19.7° (*c* 0.3 in $CHCl_3$); δ_H(200 MHz) 3.72 (3 H, s, Me), 4.54 (2 H, s, CH_2), 4.74 (1 H, dd, *J* 13.07 and 4.23 Hz, 5$_a$′-H), 4.83–4.89 (2 H, m, 4′-H, 5$_b$′-H), 5.85–5.90 (2 H, m, 2′-H, 3′-H), 6.74 (1 H, d, *J* 3.31 Hz, 1′-H), 7.25–7.65 (9 H, m, Ph), 7.87–8.07 (6 H, m, Ph), and 8.16 (1 H, s, 2-H) (Found: C, 55.2; H, 3.9; N, 5.9; S, 4.3. $C_{32}H_{27}N_3O_{13}S$ requires C, 55.4; H, 3.9; N, 6.1; S, 4.6%).

5-*Amino*-4-[(*methoxycarbonyl*)*methyl*]*sulphonyl*-1-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**22**).—To a solution of the sulphone (**21**) (0.192 g, 0.277 mmol) in ethyl acetate (25 ml) was added Pd/C (5%, 25 mg) and the resultant suspension stirred under an atmosphere of H_2 at 20 °C. The reaction was monitored by TLC. When the nitro group had been completely reduced the catalyst was removed by filtration and the solvent was evaporated. The glass obtained was dissolved in acetone and water was added. Removal of both solvents under reduced pressure yielded the amine (**22**) (0.178 g, 97%) as a white amorphous solid, $[\alpha]_D$ −24.8° (*c* 1.25 in $CHCl_3$); ν_{max}(KBr) 3 445 and 3 355 (NH_2), 1 730 (C=O), and 710 cm^{-1} (aromatic); δ_H(360 MHz) 3.71 (3 H, s, Me), 4.18 (2 H, s, CH_2), 4.81 (3 H, m, 4′-H, 5$_a$′-H, 5$_b$′-H), 5.32 (2 H, br s, disappears on D_2O shake, NH_2), 5.78 (1 H, app. t, *J* 5.5 Hz, 3′-H), 5.87 (1 H, dd, *J* 4.44 and 5.53 Hz, 2′-H), 5.93 (1 H, d, *J* 4.41 Hz, 1′-H), 7.38–7.63 (10 H, m, 2-H, Ph) and 7.94–8.07 (6 H, m, Ph); *m/z* (FAB) 664 (*M* + H)$^+$; [Found: (*M* + H)$^+$ 664.1624. $C_{32}H_{30}N_3O_{11}S$ requires 664.1601].

5-*Amino*-4-[(*carboxamido*)*methyl*]*sulphonyl*-1-(β-D-*ribofuranosyl*)*imidazole* (**8**).—A solution of the amine (**22**) (0.11 g, 0.167 mmol) in saturated methanolic ammonia (8 ml) was stirred at 20 °C for 20 h. The solution was evaporated to dryness with silica gel which was applied to the top of a column of more silica. The column was eluted with ether followed by a gradient of acetone in ether. Crystallisation of the residue after evaporation from methanol–ether gave the *amide* (**8**) (0.02 g, 36%), m.p. 186–188 °C; $[\alpha]_D$ +17.4° (*c* 0.115 in water); $\lambda_{max}(H_2O)$ 239 (ε 20 361) nm; ν_{max}(KBr) 3 420, 3 405, and 3 310 (amide and amine), 1 680 (C=O), 1 635 (NH), and 1 300 cm^{-1} (C–OH); δ_H(200 MHz; CD_3OD) 3.76 (2 H, m, 5$_a$′-H, 5$_b$′-H), 4.07 (1 H, q, *J* 2.49 Hz, 4′-H), 4.21 (1 H, dd, *J* 2.68 and 5.45 Hz, 3′-H), 4.47 (1 H, dd, *J* 5.47 and 6.58 Hz, 2′-H), 5.55 (1 H, d, *J* 6.66 Hz, 1′-H), and 7.49 (1 H, s, 2-H); *m/z* (FAB) 359 (*M* + Na)$^+$ and 337 (*M* + H)$^+$ [Found: (*M* + H)$^+$. 337.0835. $C_{10}H_{17}N_4O_7S$ requires 337.0818].

4(5)-[(*Diethylphosphono*)*methyl*]*thio*-5(4)-*nitroimidazole* (**25**).—(a) To a solution of sodium (0.182 g, 7.9 mmol) in ethanol (36 ml) were added the ammonium salt (**10**) (1.285 g, 7.9 mmol) and diethyl iodomethyl phosphonate (**23**) (2.43 g, 8.74 mmol). The resultant solution was heated under reflux for 41 h then evaporated to dryness with silica gel. This silica gel was applied to the top of a column of more silica and the column was eluted with ethyl acetate–hexane (3:2) to afford firstly 4(5)-ethylthio-5(4)-nitroimidazole as a yellow solid, m.p. 194–196 °C (lit.,[16] 196–198 °C); δ_H(200 MHz; CD_3OD) 1.36 (3 H, t, *J* 7.37 Hz, Me), 3.12 (2 H, q, *J* 7.36 Hz, CH_2), and 7.74 (1 H, s, 2-H).

Further elution of the column with ethyl acetate yielded the *phosphonate* (**25**) (1.28 g, 55%) as a dark orange syrup; δ_H(200 MHz) 1.39 (6 H, t, *J* 7.06 Hz, Me), 3.14 (2 H, d, *J* 11.18 Hz, SCH_2), 4.26 (4 H, quintet, *J* 7.3 Hz, OCH_2), and 7.55 (1 H, s, 2-H); δ_C(50 MHz) 16.25 (d, *J* 5.7 Hz, OCH_2CH_3), 26.5 (d, *J* 151 Hz, SCH_2), 64.05 (d, *J* 7 Hz, OCH_2CH_3), and 135.4 (C-2); *m/z* 295 ($^{+\bullet}$) and 249 (*M* − NO_2)$^{+\bullet}$ [Found (*M*H)$^+$ 296.0495. $C_8H_{15}N_3O_5PS$ requires 296.0470].

(b) To a solution of the ammonium salt (**10**) (0.25 g, 1.54 mmol) in methanol (10 ml) was added diethyl toluene-*p*-sulphonyloxymethanephosphonate (**24**) (0.547 g, 1.7 mmol) in methanol (2 ml). The resultant mixture was heated under reflux for 11 h and then stirred at room temperature for 4 days. The orange solid was removed by filtration and identified as unchanged ammonium salt (0.065 g). The filtrate was evaporated to dryness under reduced pressure with silica gel. The resultant silica gel was added to the top of a column of more silica and the column eluted with ether–ethyl acetate (3:2) to afford the phosphonate (**25**) (0.205 g, 45%) as a dark orange syrup, spectroscopically identical with the product from method (a).

4-[(*Diethylphosphono*)*methyl*]*thio*-5-*nitro*-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**26**) *and* 5-[(*Diethylphosphono*)*methyl*]*thio*-4-*nitro*-1-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**27**).—A mixture of the sulphide (**25**) (0.686 g, 2.3 mmol), TMSCl (0.3 ml, 2.3 mmol), HMDS (3 ml), and xylene (3 ml) were stirred and heated at 130 °C. Ammonium chloride sublimed into the condenser and a clear brown solution was formed after *ca.* 10 minutes. Evaporation under reduced pressure gave an oily residue to which was added a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) (1.17 g, 2.3 mmol) in acetonitrile (14 ml). The mixture was cooled to 0 °C, and TMSOTf (0.67 ml, 3.47 mmol) was added with stirring. The reaction mixture was stirred at room temperature for 42 min, quenched with saturated aqueous sodium hydrogen carbonate (10 ml) and diluted with dichloromethane (10 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (2 × 5 ml) followed by water (5 ml) and dried. The residue after evaporation was pre-adsorbed on silica with acetone and applied to the top of a column of more silica gel. The column was eluted with ether, followed by ether–ethyl acetate (4:1) to afford the *regioisomer* (**27**) (0.127 g, 7.4%) as an orange oil, R_F 0.62 (ethyl acetate), $[\alpha]_D$ −98.3° (*c* 1.73 in $CHCl_3$); $\lambda_{max}(CHCl_3)$ 250 (ε 14 279), 281 (6 232) and 335sh (3 721); δ_H(200 MHz) 1.15 (6 H,

dt, *J* 1.43 and 7.02 Hz, 2 × Me), 3.07 (1 H, dd, *J* 14.06 and 15.28 Hz, 1 H of CH_2P), 3.45 (1 H, dd, *J* 9.94 and 15.3 Hz, 1 H of CH_2P), 3.94 [4 H, m, $(OCH_2)_2$], 4.68–4.92 (3 H, m, 4′-H, 5_a′-H, 5_b′-H) 5.80 (1 H, app. t, *J* 5.73 Hz, 3′-H), 5.92 (1 H, dd, *J* 4.02 and 5.69 Hz, 2′-H), 6.78 (1 H, d, *J* 5.73 Hz, 1′-H), 7.3–7.6 (9 H, m, Ph), 7.92 (1 H, s, 2-H), and 7.95–8.2 (6 H, m, Ph) (Found: C, 55.2; H, 5.0; N, 5.5; P, 3.9; S, 3.6. $C_{34}H_{34}N_3O_{12}PS$ requires C, 55.2; H, 4.6; N, 5.7; P, 4.2; S, 4.3%).

Further elution of the column with ether–ethyl acetate (4:1) yielded *compound* (**26**) (0.329 g, 19%) as an orange amorphous solid, R_F 0.56 (ethyl acetate), $[\alpha]_D$ −54.5° (*c* 1.01 in $CHCl_3$); $\lambda_{max}(CHCl_3)$ 246 (ε 9 261), 275 (7 632) and 365 nm (5 184); δ_H(360 MHz) 1.31 (6 H, t, *J* 7.1 Hz, 2 × Me), 3.62 (2 H, 2 dd, *J* 14.1 and 15.1 Hz, CH_2P), 4.15 (4 H, m, OCH_2), 4.72 (1 H, dd, *J* 4.64 and 13.19 Hz, 5_a′-H), 4.83 (2 H, m, 4′-H, 5_b′-H), 5.85 (1 H, app. t, *J* 5.7 Hz, 3′-H), 5.89 (1 H, dd, *J* 3.49 and 5.51 Hz, 2′-H), 6.83 (1 H, d, *J* 3.41 Hz, 1′-H), 7.31–7.62 (9 H, m, Ph), 7.8–8.1 (6 H, m, Ph), and 8.06 (1 H, s, 2-H); *m/z* (FAB) 762 $(M + Na)^{+\bullet}$ and 693 $(M - NO_2)^{+\bullet}$ [Found: $(MH)^{+\bullet}$ 740.1692. $C_{34}H_{35}N_3O_{12}PS$ requires 740.1679].

4(5)-{[2,3-*Bis*(*methoxycarbonyl*)*propyl*]*thio*}-5(4)-*nitroimidazole* (**28**).—To a solution of the ammonium salt (**10**) (0.79 g, 4.88 mmol) in methanol (40 ml) was added dimethyl itaconate (1.54 g, 9.75 mmol). The resultant mixture was heated under reflux for 22 h and stirred at room temperature for 14 h. The solution was filtered to remove unchanged starting material (**10**) (0.41 g) and then evaporated to dryness with silica gel. The resultant silica gel was applied to the top of a column of more silica. The column was eluted initially with ether and then with ethyl acetate to give a yellow solid which was crystallised from methanol to yield the *sulphide* (**28**) (0.396 g, 27%), m.p. 115–117 °C; δ_H(200 MHz) 2.76 (2 H, m, CH_2CO_2), 3.13 (1 H, m, CH), 3.27 (1 H, dd, *J* 4.59 and 14.3 Hz, 1 H of SCH_2), 3.42 (1 H, dd, *J* 8.39 and 14.29, 1 H of SCH_2), 3.67 and 3.69 (each 3 H, s, OMe) and 7.80 (1 H, s, 2-H); δ_C(50 MHz) 32.4 (SCH_2 or CH_2CO_2), 34.7 (CH_2CO_2 or SCH_2), 41.5 (CH), 52.5 (2 × OMe), 136.0 (C-2), and 172.6 and 173.0 (2 × C=O); *m/z* 303 $(M^{+\bullet})$ and 271 $(M - MeOH)^{+\bullet}$ (Found: C, 39.4; H, 4.3; N, 13.9; S. 10.6. $C_{10}H_{13}N_3O_6S$ requires C, 39.6; H, 4.3; N, 13.9; S, 10.6%).

4-{[2,3-*Bis-methoxycarbonyl*)*propyl*]*thio*}-5-*nitro*-1-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazole* (**29**).—The sulphide (**28**) (0.298 g, 0.98 mmol), TMSCl (0.125 ml, 0.98 mmol), HMDS (1.24 ml), and xylene (1 ml) were stirred and heated at 130 °C. Ammonium chloride sublimed into the condenser and a clear brown solution was obtained after *ca.* 10 min. Evaporation gave a yellow residue, to which was added a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) (0.494 g, 0.98 mmol) in acetonitrile (3 ml). To the resultant mixture at 0 °C was added TMSOTf (0.285 ml, 1.47 mmol) and the reaction mixture was stirred for 90 s while being warmed to room temperature. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (5 ml) and diluted with dichloromethane (10 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2 × 5 ml), followed by water (5 ml). The residue after evaporation was pre-adsorbed on silica with acetone. The resultant silica gel was applied to the top of a column of more silica and the column eluted with ether–light petroleum (1:1) to afford the *nucleoside* (**29**) (0.46 g, 63%) as an amorphous yellow solid; $\lambda_{max}(CHCl_3)$ 245 (ε 16 758), 274 (14 840), and 372 nm (16 882); ν_{max}(KBr) 1 730 (C=O), 1 270 (C–O), and 710 cm^{-1} (aromatic); δ_H(360 MHz) 2.77 (2 H, m, CH_2CO_2), 3.35 (2 H, m, SCH_2), 3.65 (3 H, s, CO_2Me), 3.70 (1 H, m, CH), 3.73 (3 H, 2 × s, CO_2Me), 4.72 (1 H, dd, *J* 13.09 and 4.75 Hz, 5_a′-H), 4.81–4.84 (2 H, m, 4′-H, 5_b′-H), 5.85 (1 H, app. t, *J* 5.86 Hz, 3′-H), 5.91 (1 H, m, 2′-H), 6.82 (1 H, app. t, *J* 2.9 Hz, 1′-H), 7.31–7.63 (9 H, m, Ph), 7.85–8.08 (6 H, m, Ph), and 8.06 (1 H, s, 2-H); *m/z* (FAB) 770 $(M\text{Na})^+$ and 748 $(MH)^+$ [Found: $(MH)^+$ 748.1801. $C_{36}H_{34}N_3O_{13}S$ requires 748.1812].

5-*Amino*-4-*diethylphosphono*-1-(3′,5′-*di*-O-*t*-*butyldimethylsilyl*-β-D-*arabinofuranosyl*)*imidazole* (**35**).—To a solution of the protected thione (**33**)[27] (0.4 g, 0.955 mmol) in anhydrous dioxane (5 ml) was added Raney nickel (1.2 g). The resultant mixture was heated under reflux and monitored by TLC. After 30 min, when the UV-active thione was no longer evident, the catalyst was removed by filtration and washed with copious amounts of dioxane. The solvent was removed under reduced pressure to yield a pale yellow oil to which was added a solution of the tosylate salt[25] of the amine (**32**) (0.242 g, 0.665) in ethanol (7 ml) containing sodium (15.3 mg, 0.665 mmol). The resultant solution was heated under reflux with stirring for 7.5 h, and then stirred at room temperature for 14 h. The solution was filtered and evaporated to dryness with silica gel. The resultant silica gel was applied to the top of a column of more silica and the column was eluted with ethyl acetate–light petroleum (3:2) to give a yellow solid. Crystallisation from ether–light petroleum yielded the *imidazole* (**35**) (0.169 g, 31%), m.p. 166.5–167.5 °C, $[\alpha]_D$ 0° (*c* 0.91 in $CHCl_3$); ν_{max}(Nujol mull) 3 430, 3 300 and 1 570 (NH_2), 1 255 (P=O) and 1 030 cm^{-1} (P–O); δ_H(360 MHz) 0.09, 0.111, 0.114, 0.14 (12 H, 4 × s, 2 × $SiMe_2$), 0.893, 0.896 (18 H, 2 × s, 2 × CMe_3), 1.31 (6 H, t, *J* 7.06 Hz, 2 × Me), 3.78 (1 H, dd, *J* 2.36 and 11.94 Hz, 5_a′-H), 3.91–3.95 (2 H, m, 4′-H, 5_b′-H), 4.10 (4 H, m, OCH_2), 4.20 (1 H, m, 3′-H), 4.29 (1 H, app. t, *J* 3.0 Hz, 2′-H), 4.65 (1 H, br d, *J* 10.9 Hz, OH), 5.14 (2 H, br s, NH_2), 5.68 (1 H, d, *J* 3.78 Hz, 1′-H) and 7.76 (1 H, br s, 2-H); *m/z* 580 $(MH)^+$ and 522 $(M - Bu^t)^+$ (Found: C, 49.3; H, 8.9; N, 7.1; P, 5.7. $C_{24}H_{50}N_3O_7PSi_2$ requires C, 49.7; H, 8.6; N, 7.2; P, 5.4%).

5-*Amino*-4-*diethylphosphono*-1-(β-D-*arabinofuranosyl*)*imidazole* (**36**).—The amino nucleoside (**35**) (0.268 g, 0.46 mmol) and tetrabutylammonium fluoride (1M solution in THF; 2.7 ml) were stirred together at room temperature for 2 h. The solution was evaporated to dryness with silica gel. The resultant silica gel was applied to the top of a column of more silica gel and the column was eluted with acetone to afford the *title compound* (**36**) (0.143 g, 88%) as a pale yellow syrup, $[\alpha]_D$ +7.74° (*c* 0.77 in MeOH); δ_H(200 MHz; CD_3OD) 1.28 (6 H, t, *J* 7.37 Hz, 2 × Me), 3.73–4.26 (9 H, m, 2′-H, 3′-H, 4′-H, 5_a′-H, 5_b′-H, OCH_2), 5.83 (1 H, d, *J* 4.47 Hz, 1′-H), and 7.68 (1 H, d, *J* 3.22 Hz, 2-H); *m/z* (FAB) 374 $(M\text{Na})^+$ and 352 $(MH)^+$ [Found: $(MH)^+$ 352.1256. $C_{12}H_{23}N_3O_7P$ requires 352.1273].

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