Synthesis of *C*-ribosyl imidazo[2,1-*f*][1,2,4]triazines as inhibitors of adenosine and AMP deaminases

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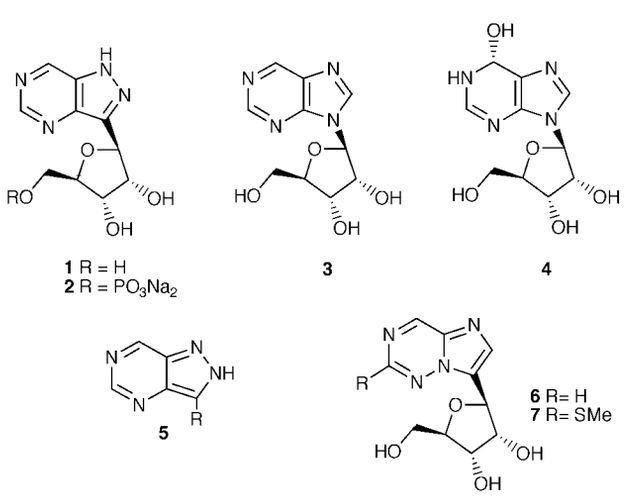
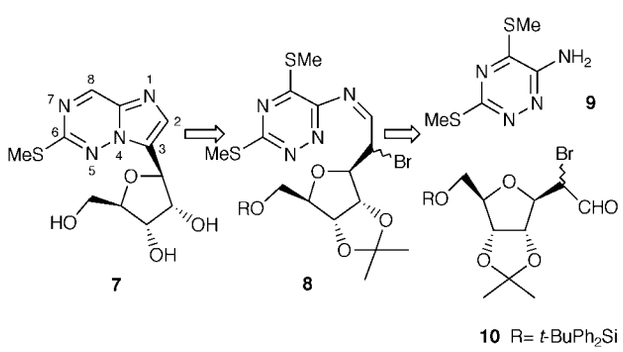
The 3-β-D-ribofuranoside **6** of the new imidazo[2,1-*f*][1,2,4]triazine **27** is isomeric and isoelectronic with the nucleoside deaminoformycin **1** which is a good inhibitor of adenosine deaminase (ADA) while its 5′-monophosphate **2** is a good inhibitor of adenosine 5′-monophosphate deaminase (AMPDA). The 6-methylsulfanyl derivative **7** of **6** is synthesized by condensation of the monocyclic 1,2,4-triazine **9** with bromo aldehyde **10**, which is accompanied by cyclization to give the protected *C*-nucleoside **21**; the 8-methylsulfanyl group of **21** is removed by replacement by hydrazine and oxidation. The 1,2,4-triazine **9** cyclizes similarly with chloroacetaldehyde or its dimethyl acetal to give 6,8-bis(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine **17**, which is converted into the parent heterocycle **27** by two routes, and into mono- and di-substituted derivatives (**19**, **20**, **24**, **25**, **28**–**30**) of the new ring system. Riboside **7** is an inhibitor of mammalian ADA (IC_{50} 40 μM).

Inhibitors of the enzyme adenosine 5′-monophosphate deaminase (AMPDA, EC 3.5.4.6) have potential for use as herbicides[1] and in the treatment of ischaemia.[2] Inhibitors of the related enzyme adenosine deaminase (ADA, EC 3.5.4.4) are of interest as potential fungicides[3] and in cancer and viral chemotherapy.[4] Deaminoformycin **1** and the corresponding 5′-phosphate derivative **2** have recently been shown to be good inhibitors of ADA and AMPDA, respectively.[5] The isomeric ADA inhibitor, purine riboside **3**, binds to the enzyme as the covalent hydrate **4**[6] and it is believed that an analogous hydration also occurs upon binding of **1** and **2** to ADA and AMPDA. Calculation of the heats of formation differences between the N7-H and N8-H tautomers of the pyrazolopyrimidine ring system and their corresponding covalent hydrates indicated that the less stable N8-H tautomer **5** formed the more stable hydrate.[5] Thus, in an effort to improve inhibitory potency we have attempted to design new non-tautomeric heterocycles possessing similar electronic properties to structure **5**. Simple exchange of C-4 and N-8 of the pyrazolopyrimidine ring gives the furanosyl imidazo[2,1-*f*][1,2,4]triazine **6** as a new target molecule. Calculations suggested that this 10π aromatic system would readily undergo covalent hydration as desired for biological activity.[7] This heterocyclic ring system was unknown although various physical chemical properties of some of its derivatives have been calculated,[8] and some related fused benzimidazo derivatives have been reported.[9]



We now describe the synthesis of the imidazo[2,1-*f*]-[1,2,4]triazine ring system, including the parent **27**, and our biological target, the *C*-nucleoside **7**. The presence of the 6-methylsulfanyl group in **7** facilitated the synthesis and, based on the results of studies with substituted purines,[10] should be compatible with achieving inhibition of ADA and AMPDA. Disconnection of the C3–N4 bond of **7**, with introduction of a second methylsulfanyl group for synthetic convenience, leads to the imine **8** which could be constructed from the aminotriazine **9** and the bromo aldehyde **10** (Scheme 1).

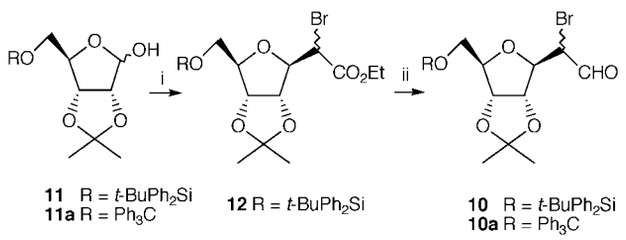


Scheme 1

Results and discussion

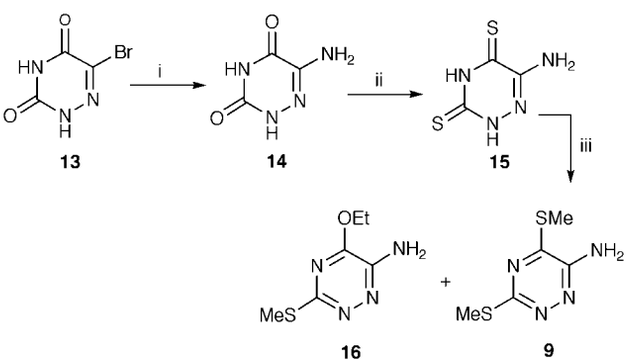
The bromo aldehyde **10** was synthesized from D-ribose by adapting the method used by Clingerman and Secrist in their synthesis of the related compound **10a**.[11] (Scheme 2). We found that whereas tritylation of the acetonide of D-ribose afforded the protected D-ribose **11a** in only modest yield (48%), silylation with *tert*-butyldiphenylsilyl chloride gave **11** in good yield (75%). Wittig reaction of the masked aldehyde **11** with the stabilized phosphorus ylide, ethyl bromo(triphenylphosphoranylidene)acetate,[12] followed by addition of DBU to aid

cyclization of the open-chain compound formed, gave a good yield of the ester **12** (82%). Reduction of this ester with DIBAL-H in dry toluene at low temperature gave the desired bromo aldehyde **10** (58%) (Scheme 2).



Scheme 2 *Reagents and conditions* (*and yields*): (i) $Ph_3P{=}CBrCO_2Et$, reflux, 7 h; then DBU (82%); (ii) DIBAL-H, $PhCH_3$, −100 °C, 15 min (58% **10**).

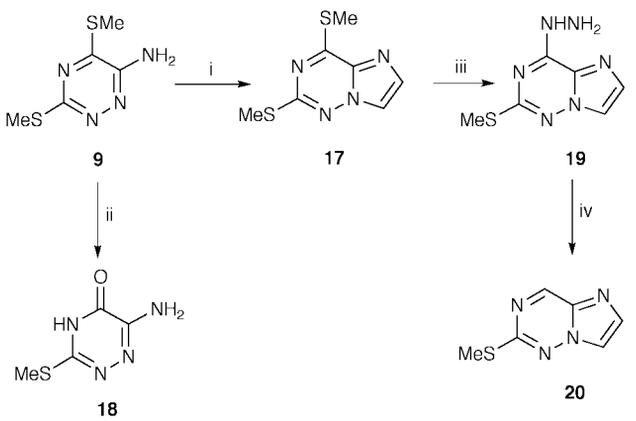
A key feature of this synthesis of the *C*-nucleoside **7** is the availability of aminotriazine **9** in gram quantities by a rapid and reliable method (Scheme 3).[13] 6-Azauracil was brominated in



Scheme 3 *Reagents and conditions* (*and yields*): (i) $NH_{3(l)}$, Cu(0), autoclave, 80 °C 2 d (74%); (ii) P_2S_5, py, S_8, reflux, 5 h; (iii) (a) MeI, 1M NaOH, EtOH, RT (43%) **9**, 7% (**16**), (b) Hünig's base, MeI, DCM, RT, 16 h (52% **9** from **14**).

high yield to give **13**, from which the bromine was displaced by liquid ammonia in an autoclave in the presence of copper powder at 80 °C to give the amine **14** in 74% yield. Attempts to simplify this procedure by working at atmospheric pressure or in a Carius tube, and with ammonium acetate in place of ammonia, all gave much lower yields of **14**. Thiation was accomplished with phosphorus pentasulfide and pyridine in the presence of sulfur, but after extensive purification the dithione **15** was isolated in very low yield. Methylation of **15** with iodomethane and aqueous sodium hydroxide in ethanol gave amine **9** together with a small amount of ethoxy compound **16**, though the latter could be avoided by using Hünig's base in DCM for the methylation reaction. The tedious and wasteful purification of the dithione **15** could be avoided by methylation of the crude material before purification.

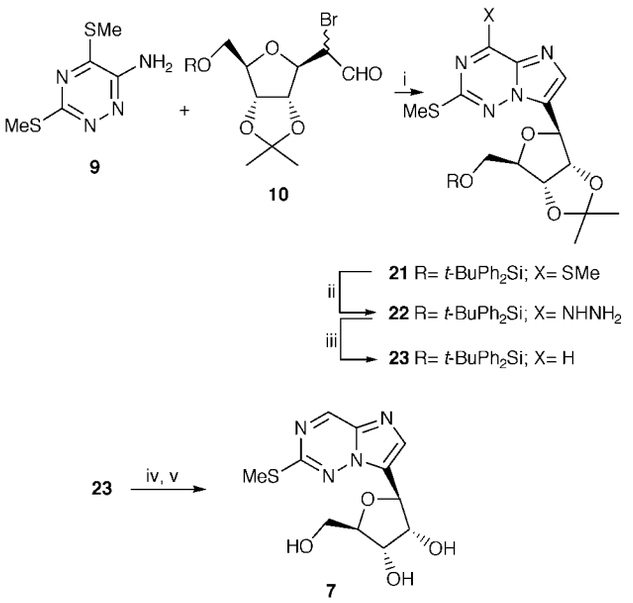
The 1,2,4-triazine **9** was first converted into the heterocyclic aglycone of the *C*-nucleoside target for use in model desulfurization reactions. Treatment of **9** with chloroacetaldehyde and 4 Å molecular sieves at ambient temperature gave 6,8-bis-(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine **17** (65%); chloroacetaldehyde dimethyl acetal in toluene with a catalytic amount of toluene-*p*-sulfonic acid at the same temperature gave a 75% yield. Desulfurization of the bis-sulfide **17** with Raney nickel[14] in boiling ethanol or with nickel boride generated *in situ*[15] failed to give the parent heterocycle **27**. Similar reductive desulfurization of the triazine **9** with Raney nickel in boiling water resulted only in hydrolysis of the 5-methylsulfanyl group to give **18** (62%), presumably as a consequence of the electrophilicity of the triazine 5-position. With the failure of reductive desulfurization we turned to the hydrazine-oxidation method which has been used, for example, in the removal of a phenylthio group from a purine[16] and a methylthio group from a 1,2,4-triazine.[17] With two equiv. of hydrazine monohydrate in refluxing ethanol for 1 h, bis-sulfide **17** gave the monohydrazine **19** in high yield; an excess of hydrazine in refluxing ethanol for 12 h still gave only the monohydrazine. Subsequent experiments showed that conversion of **17** into **19** (89%) required only 1 h at room temperature. The hydrazine group was readily removed by oxidation with yellow mercuric oxide (HgO) in refluxing ethanol for 5 min to give 6-(methylsulfanyl)imidazo[2,1-*f*]-[1,2,4]triazine **20** (66%) (Scheme 4).



Scheme 4 *Reagents and conditions* (*and yields*): (i) $ClCH_2CHO$, 4 Å MS, RT (65%) or $ClCH_2CH(OCH_3)_2$, $PhCH_3$, PTSA, 60 °C, 24 h (75%); (ii) Ra–Ni, H_2O, reflux, 12 h (62%); (iii) $N_2H_4{\cdot}H_2O$, EtOH, RT, 1 h (89%); (iv) HgO, EtOH, reflux, 5 min (66%).

We now planned to apply this removal of the 8-methylsulfanyl group in the synthesis of the *C*-nucleoside **7**, following coupling of the amine **9** with the aldehyde **10**. Condensation of **9** with **10** in toluene in a Dean–Stark apparatus for 24 h was accompanied by spontaneous cyclization to give the protected *C*-nucleoside **21** (56%) in reasonable yield (Scheme 5). The silyl derivative gave a much cleaner reaction than the analogous trityl derivative, but it only worked well on a small scale (up to 200 mg), the yield being much reduced on a 1 g scale. However, with a mixture of toluene and HMPA as solvent at 100 °C a reasonable yield of **21** (62%) was reinstated on the larger scale. The homogeneity of the ^1H and ^{13}C NMR spectra indicated that the condensation reaction gave only the β-isomer of **21**. The ^{13}C data were fully consistent with the assigned stereochemistry and in particular the chemical shifts of the isopropylidene methyl groups and the quaternary carbon (δ_C 26, 28 and 115 ppm, respectively) agreed with the values reported for 1β-substituted ribose derivatives.[18] The ^1H NMR signals, at 270 MHz, for the isopropylidene methyl groups appeared at δ_H 1.37 and 1.62 ($\Delta\delta > 20$ Hz) which also supports β-stereochemistry, and $J_{3',4'}$ was 3.70 Hz (usually about 0 Hz for α-forms). This assignment was subsequently verified by X-ray diffraction analysis of a related derivative **7** (below). Synthesis of the protected *C*-nucleoside **21** was now reproducible on a 1 g scale, and we next studied the removal of the 8-methylsulfanyl group. Treatment of **21** with hydrazine hydrate in refluxing ethanol for 1 h gave the monohydrazine **22** (87%), which was oxidized with yellow mercuric oxide in refluxing ethanol to give the 8-unsubstituted protected *C*-nucleoside **23** (72%). In contrast with the model reactions above, both of these reactions required boiling ethanol and a longer reaction time for completion. The NMR spectra of **22** and **23** were both in agreement with the β-configuration (Scheme 5).

Our first attempt at deprotection of **23** involved simultaneous removal of both protecting groups with aqueous trifluoroacetic acid,[19] which proceeded only in low yield. Better was to remove the silyl group with tetrabutylammonium fluoride (TBAF) in



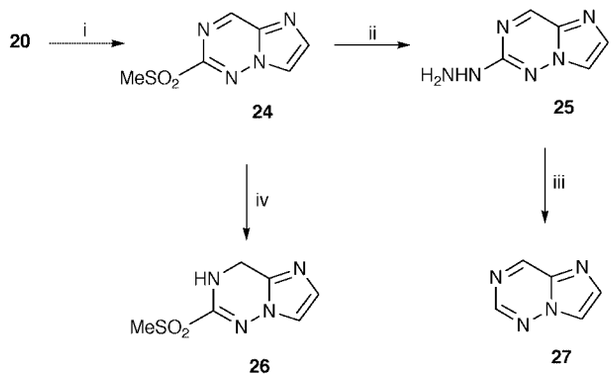
Scheme 5 *Reagents and conditions* (*and yields*): (i) $PhCH_3$, K_2CO_3, Dean–Stark 24 h (56%) or $PhCH_3$, HMPA, 100 °C, 24 h (62%); (ii) $N_2H_4 \cdot H_2O$, EtOH, reflux, 1 h (87%); (iii) HgO, EtOH, reflux, 2 h (72%); (iv) TBAF, THF, RT, 30 min (90%); (v) 60–80% AcOH, RT, 18 h (60%).

THF (90%) followed by hydrolysis (60%) of the acetonide with aqueous acetic acid, both at room temperature, to give the final target **7** (Scheme 5). Fortunately there was no sign of acid-catalyzed addition of water (covalent hydration[20]) at the free 8-position of the imidazotriazine. The β-configuration of *C*-nucleoside **7** was again supported by the ^{1}H NMR spectrum in DMSO-d_6 which showed the H-1′ signal as a doublet at δ_H 5.16 with a coupling constant of 6.23 Hz, similar to that for the related *C*-nucleoside deaminoformycin **1** (δ 5.08, J 7.5 Hz).[5,21] The structure and stereochemistry was subsequently confirmed by single-crystal X-ray diffraction.[22]

Imidazo[2,1-*f*][1,2,4]triazine 27

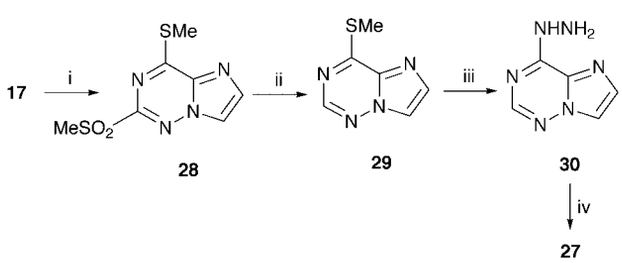
Having synthesized the *C*-nucleoside **7** we wished to remove the remaining methylsulfanyl group, though model studies suggested that this would be difficult. In the hope of providing a better leaving group, sulfide **20** was converted into its sulfone **24** by treatment with either *m*-chloroperbenzoic acid (MCPBA) in DCM or potassium permanganate in acetic acid. Both methods gave similar yields but oxidation with permanganate took only 30 min as opposed to 24 h for the peracid. Nucleophilic displacement of methylsulfonyl by hydrazine was very fast and virtually quantitative, and oxidation of the resulting hydrazine **25** with mercuric oxide gave the parent heterocyclic system, imidazo[2,1-*f*][1,2,4]triazine **27** as a colourless oil in low yield (18%) (Scheme 6). Low yields are sometimes observed in the oxidation of hydrazines which afford products susceptible to covalent hydration since the hydrate can be oxidized by mercuric oxide to give the corresponding keto product, which is sometimes isolated.

We had hoped to replace the methylsulfonyl group in **24** by hydrogen in one step with $NaBH_4$ following a related literature reaction,[23] but similar treatment of **24** with $NaBH_4$ at room temperature gave the dihydro derivative **26** (Scheme 6) with the methylsulfonyl group intact. This parallels the ready reduction of monocyclic 1,2,4-triazines to their dihydro derivatives.[24] We therefore returned to the bis-sulfide **17** and its oxidation with $KMnO_4$ in acetic acid; this gave only the monosulfone **28** (63%) in agreement with the exclusive oxidation of 3,5-bis(methylsulfanyl)-1,2,4-triazine to the 3-methylsulfone.[25] With both substrates the sulfur which is not oxidized is made less nucleophilic by the electron-withdrawing heteroatoms. Reduction of sulfone



Scheme 6 *Reagents and conditions* (*and yields*): (i) (a) MCPBA, DCM, RT, 24 h (52%) or $KMnO_4$, AcOH, H_2O, RT, 30 min (58%); (ii) $N_2H_4 \cdot H_2O$, EtOH, RT, 1 min (97%); (iii) HgO, EtOH, reflux, 10 min (18%); (iv) $NaBH_4$, EtOH, $CHCl_3$, RT, 10 min (34%).

28 with $NaBH_4$ under the Hitoshi conditions[23] gave the 6-unsubstituted imidazotriazine **29** (79%), no reduction of the heterocyclic ring being observed in the presence of the 8-methylsulfanyl group. This group was then removed with hydrazine hydrate in ethanol to give the hydrazine **30** (76%), followed by oxidation with mercuric oxide, to give the parent imidazotriazine **27**, identical with that described above, but in slightly better yield (27%) (Scheme 7). We hope that the method



Scheme 7 *Reagents and conditions* (*and yields*): (i) $KMnO_4$, AcOH, H_2O, RT, 30 min (63%); (ii) $NaBH_4$, EtOH, $CHCl_3$, RT, 5 min (79%); (iii) $N_2H_4 \cdot H_2O$, EtOH, RT, 2 h (76%); (iv) HgO, EtOH, reflux, 10 min (27%).

developed for the synthesis of **27** will be applied to the synthesis of ribofuranoside **6** in the future.

In the course of this work the new ring system, imidazo[2,1-*f*]-[1,2,4]triazine **27**, has been prepared, together with several of its mono-, di- and tri-substituted derivatives including the ribofuranoside **7**. Preliminary biochemical studies indicate that **7** is an inhibitor of mammalian ADA (IC_{50} 40 μM). Further details concerning biological activity will be published elsewhere.

Experimental

Tetrahydrofuran (THF) and toluene were used freshly distilled from sodium wire with benzophenone under nitrogen. All reactions were protected from moisture by calcium chloride drying tubes, unless carried out under a dry nitrogen atmosphere. Anhydrous magnesium sulfate was used for drying organic extracts, and volatiles were removed under reduced pressure. Ether refers to diethyl ether and light petroleum had boiling range 60–80 °C. All reactions and chromatography column eluents were monitored by TLC using commercial aluminium-backed thin-layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 350 nm. Flash column chromatography refers to the technique described by Still[26] using medium pressure generated by a hand bellows or a small air compressor and was used throughout. Dry flash chromatography was carried out with suction using a water pump according to the technique described by Harwood.[27] Mps were determined using a Reichert

Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710FT spectrometer and strong, medium and weak peaks are represented by s, m or w respectively. ^{1}H NMR spectra were recorded on JEOL GSX 270 (at 270 MHz) and Bruker AM300WB (at 300 MHz) machines. ^{13}C NMR spectra were recorded on JEOL GSX 270 (at 68 MHz) and Bruker AM300WB (at 76 MHz) machines. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Mass spectra were recorded on a VG Micromass 7070E or a VG Autospec "Q" mass spectrometer. FAB spectra were obtained using a glycerol matrix, and CI measurements were carried out using ammonia for ionization. Microanalyses were carried out on a Perkin-Elmer 2400 CHN Analyzer.

2,3-*O*-Isopropylidene-D-ribose[28]

A solution of D-ribose (50 g, 0.33 mol) in dry acetone (800 ml) containing conc. hydrochloric acid (0.8 ml) and copper(II) sulfate monohydrate (45 g) was stirred overnight at 37 °C. The solution was neutralized by stirring with calcium hydroxide. The inorganic salts were filtered off and washed with dry acetone. The combined organic phase was concentrated *in vacuo* to give the crude product as pale yellow oil. Purification of the crude product by flash chromatography on silica gel (gradient elution; 20–30% ethyl acetate in light petroleum) gave the acetonide (55.1 g, 87%) as a colourless oil; ν_{max} (NaCl/film)/cm^{-1} 3391s, (OH), 1462w, 1383s, 1327s, 1274s, 1243s, 1212s, 1116s, 1068s, 997w, 925w, 871s; δ_H(270 MHz; $CDCl_3$) 5.52 (1H, d, *J* 6.2 Hz, *H*-1), 5.38 (1H, s, O*H*), 4.77 (1H, d, *J* 5.8 Hz, *H*-2 or *H*-3), 4.54 (1H, d, *J* 6.0 Hz, *H*-3 or *H*-2), 4.35 (1H, m, *H*-4), 4.19 (1H, s, O*H*), 3.67 (2H, m, *H*-5), 1.45 (3H, s, CH_3), 1.29 (3H, s, CH_3); δ_C(76 MHz; $CDCl_3$) 112.19 (*C*CH_3), 102.75 (*C*-1), 87.66 (*C*-4), 86.72 (*C*-2), 81.51 (*C*-3), 63.49 (*C*-5), 26.35 (*C*H_3), 24.70 (*C*H_3); *m*/*z* (CI, NH_3) 208 (MNH_4^+, 50%), 190 ($MNH_4^+ - H_2O$, 100), 175 ($M^+ - CH_3$, 22), 173 ($M^+ - H_2O$, 20), 68 (30) (Found: MNH_4^+, 208.1189. Calc. for $C_8H_{18}NO_5$: *M*NH_4, 208.1185).

5-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-isopropylidene-D-ribofuranose 11

A solution of 2,3-*O*-isopropylidene-D-ribose (4.19 g, 22.1 mmol) and imidazole (1.65 g, 24.3 mmol) in DCM (40 ml) at 0 °C was treated with *tert*-butyldiphenylsilyl chloride (6.67 g, 24.3 mmol). The reaction mixture was allowed to warm to 25 °C and was stirred for 24 h. After dilution with ether (120 ml) the reaction mixture was washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (gradient elution; 5–10% ethyl acetate in light petroleum) to give the epimeric alcohols **11** (7.08 g, 75%) as a colourless oily 2:1 mixture; ν_{max}(NaCl/film)/cm^{-1} 3431br s (OH), 3072w, 3050w, 2935s, 1590s, 1568w, 1488s, 1473w, 1429w, 1383w, 1313w, 1212w, 1212w, 1075s, 990w, 872w, 798w, 742w, 703s; δ_H(270 MHz; $CDCl_3$) 7.63–7.70 (4H, m, Ar*H*), 7.39–7.48 (6H, m, Ar*H*), 5.36 (1H, d, *J* 10.2 Hz, O*H*), 4.65–4.80 (2H, m, *H*-2 and *H*-3), 4.61 (1H, d, *J* 6.01 Hz, *H*-1), 4.27–4.30 (1H, m, *H*-4, major), 4.15–4.16 (1H, m, *H*-4, minor), 3.79–3.89 (1H, m, *H*-5a), 3.61–3.69 (1H, m, *H*-5b), 1.57 (3H, s, CH_3, minor), 1.40 (3H, s, CH_3, major), 1.48 (3H, s, CH_3, minor), 1.32 (3H, s, CH_3, major), 1.10 (9H, s, ^{t}Bu); δ_C(76 MHz; $CDCl_3$) [135.76, 135.58, 130.44, 130.25, 128.13, 128.07, 127.92, 127.73] (Ar *C*), [113.04, 112.15] (*C*CH_3), [103.44, 98.04] (*C*-1), [87.36, 87.11] (*C*-4), [81.99, 81.68] (*C*-2), [81.30, 79.54] (*C*-3), [66.09, 65.53] (*C*-5), [26.92, 26.89] [*C*$(CH_3)_3$], [26.60, 24.71] (*C*H_3), [26.50, 25.00] (*C*H_3), [26.19, 19.16] [C(*C*$H_3)_3$]; *m*/*z* (CI, NH_3) 446 (MNH_4^+, 12%), 428 ($MNH_4^+ - H_2O$, 6), 411 ($MH^+ - H_2O$, 10), 371 ($M^+ - {}^t$Bu, 2), 353 (10), 274 ($M^+ - 2$Ph), 241 (8), 221 (15), 216 (25), 199 (28), 181 (13), 161 ($M^+ - OSiPh_2Bu^t$, 100), 91 (28), 78 (30), 58 (24) (Found: C, 67.0; H, 7.7. $C_{24}H_{32}O_5Si$ requires C, 67.3; H, 7.5%).

Ethyl 3,6-anhydro-2-bromo-7-*O*-*tert*-butyldiphenylsilyl-2-deoxy-4,5-*O*-isopropylidene-D-*glycero*-D-*allo*- and -D-*altro*-heptonate 12

To a solution of 5-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-D-ribofuranose **11** (3.20 g, 7.48 mmol) in dry benzene (10 ml) was added ethyl bromo(triphenylphosphoranylidene)-acetate[12] (4.47 g, 10.5 mmol) and the solution was heated to reflux. After 7 h, TLC indicated the disappearance of starting material **11** and the appearance of 3 new products. The reaction mixture was cooled to room temperature and DBU (1 drop) was added. After the mixture was stirred for 1 min at room temperature, TLC indicated only 2 compounds. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (gradient elution; 10–15% ether in light petroleum) to furnish a mixture of esters **12** (3.54 g, 82%) as a colourless oil; ν_{max}(NaCl/film)/cm^{-1} 3072w, 3050w, 1746s (C=O, ester), 1590w, 1473s, 1429s, 1382s, 1372s, 1338w, 1264s, 1213s, 1185w, 1156s, 1114s, 1080s, 1028s, 966w, 864w, 742w, 703s; δ_H(270 MHz; $CDCl_3$) 7.68–7.74 (4H, m, Ar IH), 7.38–7.47 (6H, m, Ar*H*), 4.73–4.83 (2H, m, *H*-4 and *H*-5), 4.54, 4.50 (1H, each d, *J* 3.00, 3.23 Hz, *H*-2), 4.39–4.42 (1H, m, *H*-3), 4.24–4.32 (3H, m, *H*-6 and $CO_2CH_2CH_3$), 3.64–3.81 (2H, m, H_2-7), 1.59 (3H, s, CH_3, major), 1.40 (3H, s, CH_3, minor), 1.57 (3H, s, CH_3, major), 1.38 (3H, s, CH_3, minor), 1.30 (3H, t, *J* 7.16 Hz, $CO_2CH_2CH_3$), 1.11 (9H, s, ^{t}Bu); δ_C(76 MHz; $CDCl_3$) 168.28 (*C*=O, ester), [135.70(×3), 132.68, 130.04, 129.92, 127.94, 127.84] (Ar *C*), 113.59 (*C*CH_3), 86.05 (*C*-6), 85.91 (*C*-4), 84.29 (*C*-3 or *C*-5), 82.35 (*C*-5 or *C*-3), 64.90 (*C*-7), 62.12 ($CO_2CH_2CH_3$), 44.59 (*C*HBr), 27.31 (*C*H_3), 27.01 [*C*$(CH_3)_3$], 25.51 (*C*H_3), 19.24 [C(*C*$H_3)_3$], 13.92 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 596, 594 (MNH_4^+, 85%), 520 ($M^+ - {}^t$Bu, 30), 516 (MNH_4^+ − Br, 100), 497 (M^+ − Br, 5), 441 (42), 421 (35), 383 (8), 295 (18), 274 (16), 216 (45), 196 (28), 169 (18), 91 (18), 58 (30) (Found: C, 58.9; H, 6.1. $C_{28}H_{37}BrO_6Si$ requires C, 58.2; H, 6.5%; Found: MNH_4^+, 594.1893. $C_{28}H_{41}BrNO_6Si$ requires *M*NH_4, 594.1887).

3,6-Anhydro-2-bromo-7-*O*-*tert*-butyldiphenylsilyl-2-deoxy-4,5-*O*-isopropylidene-D-*glycero*-D-*allo*- and -D-*altro*-heptose 10

A solution of bromo ester **12** (1.14 g, 1.98 mmol) in dry toluene (10 ml) at −100 °C was treated with DIBAL-H (1.5 M in toluene; 2.63 ml, 3.95 mmol) added *via* a cannula and stirred at −100 °C for 15 min. The reaction was quenched with dry methanol (5 ml) and the resulting mixture was allowed to warm to 25 °C. A thick gelatinous mass was formed. This was filtered off (Celite pad) and washed with ether. The resulting filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution; 20–30% ether in light petroleum) to furnish the bromo aldehyde **10** (0.61 g, 58%) as a colourless oil; ν_{max}(NaCl/film)/cm^{-1} 3072w, 3050w, 1732s (C=O, aldehyde), 1590w, 1568w, 1473s, 1463s, 1429s, 1383s, 1244w, 1214s, 1157s, 1114s, 1078s, 1008w, 999w, 971w, 920w, 824w, 742s, 703s; δ_H(270 MHz; $CDCl_3$) 9.50 (1H, d, *J* 2.77 Hz, C*H*O, major), 9.41 (1H, d, *J* 3.69 Hz, C*H*O, minor), 7.68–7.75 (4H, m, Ar*H*), 7.40–7.48 (6H, m, Ar*H*), 4.68–4.85 (2H, m, *H*-4 and *H*-5), 4.36–4.50 (2H, m, *H*-3 and *H*-2), 4.26–4.29 (1H, m, *H*-6), 3.70–3.88 (2H, m, H_2-7), 1.59, 1.41 (6H, each s, CH_3, minor), 1.57, 1.39 (6H, each s, CH_3, major), 1.12, 1.10 (9H, each s, ^{t}Bu); δ_C(76 MHz; $CDCl_3$) [192.07, 190.66] (*C*HO), [135.72, 135.64, 132.66, 130.10, 130.02, 129.91, 129.84, 127.99] (Ar *C*), [114.73, 113.98] (*C*CH_3), [86.19, 85.34] (*C*-6), [84.29, 84.22] (*C*-4), [82.89, 82.73] (*C*-3 or *C*-5), [82.02, 81.44] (*C*-5 or *C*-3), [64.67, 63.95] (*C*-7), [55.95, 52.60] (*C*HBr), [27.51, 25.60] (*C*H_3), [27.38, 25.48] (*C*H_3), [27.05, 26.95] [*C*$(CH_3)_3$], 19.29 [C(*C*$H_3)_3$]; *m*/*z* (CI, NH_3) 552, 550 (MNH_4^+, 3%), 472 (MNH_4^+ − Br, 12), 397 (2), 377 (2), 295 (6), 241 (2), 199 (9), 181 (6), 161 (58), 129 (22), 108 (45), 91 (100), 73 (26), 61 (50), 44 (20) (Found: MNH_4^+, 550.1631. $C_{26}H_{37}BrNO_5Si$ requires *M*NH_4, 550.1624).

6-Bromo-1,2,4-triazine-3,5(2*H*,4*H*)-dione 13

A mixture of 6-azauracil (25 g, 221 mmol), bromine (25 ml) and water (400 ml) was stirred at 25 °C for 27 h. The colourless crystalline precipitate was collected by filtration. More product was obtained by concentrating the filtrate. Recrystallization of the combined product from water gave 6-bromo-1,2,4-triazine-3,5(2*H*,4*H*)-dione **13** (35 g, 82%) as crystals, mp 235–236 °C (lit.,[13] 232–234 °C); ν_{max}(NaCl/Nujol)/cm^{-1} 3262br w, 3162br w (NH), 1694s (C=O, amide), 1566s, 1464s, 1269w, 1136w, 1087w, 994w, 845w, 753w, 721w; δ_H(270 MHz; DMSO-d_6) 12.58 (1H, br s, N*H*), 12.32 (1H, br s, N*H*); δ_C(76 MHz; DMSO-d_6) 154.19 (*C*-5), 149.58 (*C*-3), 129.62 (*C*-6); *m*/*z* (EI) 192, 191 (M^+, 100%), [150, 148] ($M^+ - NCO$, 49), [122, 120] (47), 103 (9), 94 (13), 69 (24), 57 (12), 44 (51) (Found: M^+, 190.9312. Calc. for $C_3H_2BrN_3O_2$: *M*, 190.9330).

6-Amino-1,2,4-triazine-3,5(2*H*,4*H*)-dione 14

6-Bromo-1,2,4-triazine-3,5-dione **13** (3.75 g, 19.5 mmol), copper powder (2 mg) and liquid ammonia (30 ml) were heated in an autoclave at 80 °C for 48 h. After the mixture was cooled, excess of ammonia was vented off and the residual solid was dissolved in hot water (30 ml). The cool, blue solution was carefully acidified to pH 4 with conc. HCl and the resulting precipitate collected by filtration. The crude product was suspended in distilled water (35 ml) and dissolved by the dropwise addition of conc. NH_4OH. The solution was filtered and the colourless filtrate was acidified to pH 4 with conc. HCl. The white precipitate formed was collected by filtration, washed with distilled water (2 × 5 ml) and air-dried to furnish 6-amino-1,2,4-triazine-3,5(2*H*,4*H*)-dione **14** (1.85 g, 74%), mp >300 °C (lit.,[12] 310–315 °C) (from water); δ_H(270 MHz; DMSO-d_6) 11.60 (1H, br s, N*H*), 10.91 (1H, br s, N*H*), 5.98 (2H, br s, NH_2); δ_C(76 MHz; DMSO-d_6) 155.04 (*C*-5), 149.51 (*C*-3), 144.22 (*C*-6); *m*/*z* (EI) 128 (M^+, 100%), 85 (8), 70 (6), 57 (80), 43 (30) (Found: M^+, 128.0329. Calc. for $C_3H_4N_4O_2$: *M*, 128.0334).

6-Amino-1,2,4-triazine-3,5(2*H*,4*H*)-dithione 15

Phosphorus pentasulfide (8.89 g, 40 mmol) was added to a stirred, warm solution of the amino compound **14** (2.56 g, 20 mmol) and elemental sulfur (1.28 g, 5 mmol) in dry pyridine (180 ml). The mixture was heated to reflux for 5 h. The reaction mixture was allowed to cool and to stand at 25 °C for 16 h. The clear, reddish-brown supernatant liquid was decanted and the pyridine removed *in vacuo*. The resulting residue was covered with water (50 ml), boiled for 10 min and allowed to stand at 4 °C for 18 h. The precipitate was collected, washed with water and air-dried to give the crude dithione **15** (3.2 g); *m*/*z* (CI, NH_3) 161 (MH^+, 100%) (Found: MH^+, 160.9983. Calc. for $C_3H_5N_4S_2$: *M*H, 160.9956).

6-Amino-3,5-bis(methylsulfanyl)-1,2,4-triazine 9

Method A. A solution of the above crude dithione **15** (3.2 g, 20 mmol) was suspended in DCM (150 ml) and treated with Hünig's base (20.9 ml, 120 mmol) and iodomethane (6.25 g, 2.73 ml, 44 mmol). The mixture was stirred at 25 °C for 24 h. Excess of solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution; 5–15% ethyl acetate in light petroleum) to give the triazine **9** (1.96 g, 52%) as pale yellow crystals, mp 173–174 °C (lit.,[12] 171–173 °C) (from DCM–light petroleum); ν_{max}(NaCl/film)/cm^{-1} [3424br w, 3275br w, 3115br w] (NH), 1693w, 1636s, 1579w, 1523s, 1489s, 1462s, 1420s, 1325s, 1244s, 1202w, 1121s, 1074s, 972w, 891s, 720w; δ_H(270 MHz; $CDCl_3$) 4.79 (2H, br s, NH_2), 2.61 (3H, s, SCH_3), 2.59 (3H, s, SCH_3); δ_C(76 MHz; DMSO-d_6) [159.18, 153.99, 153.36] (Het *C*), 13.87 (SCH_3), 12.04 (SCH_3); *m*/*z* (EI) 188 (M^+, 68%), 173 ($M^+ - CH_3$, 30), 150 (2), 136 (4), 102 (12), 87 (98), 72 (100), 69 (52), 45 (50) (Found: M^+, 188.0197. Calc. for $C_5H_8N_4S_2$: *M*, 188.0190).

Method B. Crude dithione **15** (2.80 g, 17.5 mmol) was suspended in absolute EtOH (400 ml) and treated with 1M NaOH (50 ml) at 40 °C. The solution was allowed to cool to 25 °C and iodomethane (10.90 g, 4.78 ml, 76.8 mmol) was added. The reaction mixture was stirred at 25 °C for 30 min. Excess of solvent was removed *in vacuo* and the residue was dissolved in water (100 ml). The aqueous solution was extracted with ethyl acetate (3 × 100 ml) and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a dark residue, which was purified by flash chromatography on silica gel (gradient elution; 5–15% ethyl acetate in light petroleum) to afford the bis-sulfide **9** (1.62 g, 43%) as pale yellow crystals, mp 173–174 °C (lit.,[12] 171–173 °C); and **16** (260 mg, 10%) as crystals, mp 128–130 °C; δ_H(300 MHz; $CDCl_3$) 5.12 (2H, br s, NH_2), 4.49 (2H, q, *J* 7.08 Hz, OCH_2CH_3), 2.58 (3H, s, SCH_3), 1.43 (3H, t, *J* 7.05 Hz, OCH_2CH_3); *m*/*z* (EI) 186 (M^+, 100%), 157 ($M^+ - Et$, 35), 131 (3), 116 (10), 98 (3), 86 (6), 74 (32), 69 (25), 57 (60), 43 (26).

6,8-Bis(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 17

Method A. A mixture of amine **9** (1.20 g, 6.38 mmol), chloroacetaldehyde (12 ml; ≈50 wt.-% solution in water) and 4 Å molecular sieves was stirred at 25 °C for 2 days. The molecular sieves were removed (Celite pad), and washed with DCM. The filtrate was washed successively with water and brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification of the residue by flash chromatography on silica gel (gradient elution; 20–30% ether in light petroleum) gave the *title compound* **17** (0.88 g, 65%) as a white solid, mp 120–122 °C (from DCM–light petroleum); ν_{max}(NaCl/film)/cm^{-1} 3442w, 3304w, 3051w, 1693, 1628w, 1560w, 1519w, 1451s, 1428s, 1355s, 1316s, 1292s, 1266s, 1169s, 1156s, 1145s, 1063w, 1019w, 968w, 928w, 880s, 759s, 739s; δ_H(300 MHz; $CDCl_3$) 7.74 (1H, d, *J* 0.97 Hz, *H*-2 or *H*-3), 7.60 (1H, d, *J* 0.96 Hz, *H*-3 or *H*-2), 2.65 (3H, s, SCH_3), 2.56 (3H, s, SCH_3); δ_C(76 MHz; $CDCl_3$) [163.36, 161.41, 132.66(×2), 117.24] (Het *C*), 14.15 (SCH_3), 11.88 (SCH_3); *m*/*z* (EI) 212 (M^+, 100%), 197 (15), 165 (35), 152 (10), 139 (20), 103 (25), 93 (60), 84 (35), 57 (39), 47 (14), 43 (38) (Found: C, 39.7; H, 3.6; N, 26.7. $C_7H_8N_4S_2$ requires C, 39.6; H, 3.8; N, 26.4%).

Method B. To a stirred solution of amine **9** (500 mg, 2.66 mmol) in dry toluene (6 ml) were added chloroacetaldehyde dimethyl acetal (8 ml) and toluene-*p*-sulfonic acid (PTSA, 80 mg). The reaction mixture was stirred at 60 °C for 24 h and then allowed to cool to 25 °C. Excess of solvent was removed *in vacuo* and the residue was diluted with chloroform. The organic solvent was washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a dark residue. This was purified by flash chromatography on silica gel (gradient elution; 20–30% ether in light petroleum) to give the title compound **17** (423 mg, 75%) which was identical to that described above.

Attempted desulfurization of triazine 9: 6-amino-3-methylsulfanyl-1,2,4-triazine-5(4*H*)-one 18

To a stirred solution of aminotriazine **9** (100 mg, 0.53 mmol) in water (8 ml) was added Raney nickel (≈80 mg). The reaction mixture was stirred vigorously at 40 °C for 12 h and the Raney nickel was then removed (Celite pad). The mixture was concentrated *in vacuo* and the crude product was purified by recrystallization from ethanol to afford the *aminotriazinone* **18** (52 mg, 62%) as a solid, mp >280 °C (from ethanol); ν_{max}(NaCl/Nujol)/cm^{-1} 3326s (NH), 1675s (C=O, amide), 1651s, 1588s, 1568s, 1539s, 1521s, 1249w, 1214w, 1079w, 991w, 949w, 794w, 722w; δ_H(300 MHz; DMSO-d_6) 6.48 (2H, br s, NH_2), 2.50 (3H, s, SCH_3); δ_C(76 MHz; DMSO-d_6) [157.66, 157.62, 150.24] (Het *C*), 13.25 (SCH_3); *m*/*z* (EI) 158 (M^+, 100%), 116 ($M^+ - NCO$, 10), 111 ($M^+ - SCH_3$, 8), 91 (3), 86 (5), 74 (17), 69 (90), 57 (12),

48 (30), 43 (54) (Found: M^+, 158.0280. $C_4H_6N_4OS$ requires *M*, 158.0262).

8-Hydrazino-6-(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 19

To a solution of bis-sulfide **17** (100 mg, 0.47 mmol) in ethanol (4 ml) was added hydrazine monohydrate (47.2 mg, 0.046 ml, 0.94 mmol) and the mixture was stirred at 25 °C for 1 h. A white precipitate was collected, and washed with ethyl acetate. The precipitate was recrystallized from ethanol to give the *title compound* **19** (82 mg, 89%) as white crystals, mp 225–226 °C (from EtOH); ν_{max}(NaCl/Nujol)/cm^{-1} 3442br w (NH), 3328w (NH), 3134w, 1694w, 1627w, 1604s, 1568w, 1498w, 1451s, 1404s, 1347s, 1314w, 1279w, 1215s, 1179w, 1142w, 1124w, 1098w, 971w, 922s, 867w, 754s, 739s, 722w; δ_H(300 MHz; $CDCl_3$) 10.26 (1H, br s, N*H*), 7.94 (1H, s, *H*-2 or *H*-3), 7.46 (1H, s, *H*-3 or *H*-2), 4.88 (2H, br s, NH_2), 2.50 (3H, s, SCH_3); δ_C(76 MHz; $CDCl_3$) [162.06, 149.94, 130.62, 126.49, 117.90] (Het *C*), 13.84 (SCH_3); *m*/*z* (EI) 196 (M^+, 46%), 181 (12), 150 (2), 133 (5), 119 (2), 109 (8), 103 (2), 94 (40), 89 (26), 84 (7), 73 (25), 68 (7), 45 (100) (Found: C, 37.6; H, 3.8; N, 42.2%; M^+, 196.0536. $C_6H_8N_6S$ requires C, 36.7; H, 4.1; N, 42.8%; *M*, 196.0531).

6-(Methylsulfanyl)imidazo[2,1-f][1,2,4]triazine 20]

To a stirred solution of the hydrazine **19** (36 mg, 0.18 mmol) in ethanol (4 ml) was added yellow mercury(II) oxide (120 mg, 0.55 mmol) at 25 °C. The reaction mixture was heated to reflux for 5 min, cooled and the inorganic residue was removed (Celite pad), washed with ethanol and the filtrate was evaporated *in vacuo* to give a pale yellow solid. Purification of the solid by flash chromatography on silica gel (gradient elution; 30–40% ether in light petroleum) afforded the *title compound* **20** (20 mg, 66%) as crystals, mp 129–130 °C (from DCM–light petroleum); ν_{max}(NaCl/Nujol)/cm^{-1} 1694w, 1629w, 1584w, 1316w, 1290w, 1116w, 910w, 755w, 740w, 662w; δ_H(300 MHz; $CDCl_3$) 9.02 (1H, s, *H*-8), 7.93 (1H, s, *H*-2 or *H*-3), 7.84 (1H, s, *H*-3 or *H*-2), 2.61 (1H, s, SCH_3); δ_C(76 MHz; $CDCl_3$) [163.42, 149.38, 135.41, 134.19, 117.52] (Het *C*), 14.22 (SCH_3); *m*/*z* (CI, NH_3) 184 (MNH_4^+, 3%), 167 (MH^+, 100), 153 (2), 138 (3), 121 (6), 96 (7), 69 (4), 45 (2) (Found: C, 43.7; H, 3.3; N, 33.6. $C_6H_6N_4S$ requires C, 43.4; H, 3.6; N, 33.7%).

3-(5′-*O*-*tert*-Butyldiphenylsilyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-6,8-bis(methylsulfanyl)imidazo[2,1-*f*][1,2,4]-triazine 21

Method A. A mixture of bromo aldehyde **10** (664 mg, 1.25 mmol), amine **9** (234 mg, 1.25 mmol) and anhydrous K_2CO_3 (208 mg, 1.50 mmol) in dry toluene (80 ml) was stirred at reflux with azeotropic removal of water (Dean–Stark trap) for 24 h. After the solution was cooled to 25 °C, excess of solvent was removed *in vacuo* to give a dark residue. This was purified by flash chromatography on silica gel (gradient elution; 10–15% ether in light petroleum) to furnish the title compound **21** (434 mg, 56%) as pale yellow foam; ν_{max}(NaCl/film)/cm^{-1} 3071w, 1694w, 1631w, 1574w, 1516w, 1441s, 1372w, 1352w, 1214w, 1154s, 1114s, 1080s, 952w, 863w, 704s; δ_H(270 MHz; $CDCl_3$) 7.63–7.69 (4H, m, Ar*H*), 7.60 (1H, s, *H*-2), 7.32–7.43 (6H, m, Ar*H*), 5.39 (1H, d, *J* 4.9 Hz, *H*-1′), 4.97 (1H, dd, *J* 6.58, 4.85 Hz, *H*-2′), 4.82 (1H, dd, *J* 6.47, 3.70 Hz, *H*-3′), 4.24–4.27 (1H, m, *H*-4′), 3.84–3.86 (2H, m, H_2-5′), 2.67 (3H, s, SCH_3), 2.52 (3H, s, SCH_3), 1.62 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.05 (9H, s, ^{t}Bu); δ_C(76 MHz; $CDCl_3$) [163.47, 161.46, 135.63, 129.79 127.74] (Het *C*), [135.63, 133.15, 131.42, 127.70] (Ar *C*), 114.58 (CCH_3), 84.87 (*C*-4′), 83.97 (*C*-3′), 82.14 (*C*-2′), 77.27 (*C*-1′), 64.07 (*C*-5′), 27.62 (CH_3), 26.86 [$C(CH_3)_3$], 25.62 (CH_3), 19.28 [$C(CH_3)_3$], 14.20 (SCH_3), 11.83 (SCH_3); *m*/*z* (FAB, NBA) 623 (MH^+, 100%), 507 (7), 295 (25), 267 (4), 237 (6), 225 (12), 197 (19), 135 (42), 120 (6), 105 (7), 91 (14), 69 (17), 57 (29) (Found: C, 58.6; H, 5.5; N, 8.05. $C_{31}H_{38}N_4O_4S_2Si$ requires C, 59.8; H, 6.15; N, 9.0%. Found: MH^+, 623.2182. $C_{31}H_{39}N_4O_4S_2Si$ requires *M*H, 623.2111).

Method B. To a stirred solution of amine **9** (1.20 g, 6.38 mmol) in HMPA (6 ml) was added a solution of aldehyde **10** (3.40 g, 6.38 mmol) in dry toluene (16 ml). The reaction mixture was stirred at 100 °C for 18 h under nitrogen and then allowed cool to 25 °C. Excess of solvent was removed *in vacuo* to give a dark residue. This was dissolved in water and the aqueous solution was extracted with ethyl acetate (3 × 40 ml). The combined organic extract was washed successively with water and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product. The residue was purified by flash chromatography on silica gel (gradient elution; 10–15% ether in light petroleum) to afford the title compound **21** (2.46 g, 62%) which was identical to that described above.

3-(5′-*O*-*tert*-Butyldiphenylsilyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-8-hydrazino-6-(methylsulfanyl)imidazo[2,1-*f*]-[1,2,4]triazine 22

To a solution of bis-sulfide **21** (50.9 mg, 0.08 mmol) in ethanol (2 ml) was added hydrazine monohydrate (0.02 ml, 0.70 mmol). The solution was stirred and heated under reflux for 1 h. The reaction mixture was allowed to cool to 25 °C and concentrated *in vacuo*. The residue was dissolved in DCM (6 ml), washed with water, dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography on silica gel (ether as eluent) to furnish the title compound **22** (43.1 mg, 87%) as a colourless foam; ν_{max}(NaCl/film)/cm^{-1} 3442br s (NH), 2931w, 2858w, 1694s, 1631s, 1603s, 1443s, 1428s, 1353s, 1265s, 1113s, 1079s, 863w, 703s; δ_H(270 MHz; $CDCl_3$) 7.63–7.69 (4H, m, Ar*H*), 7.54 (1H, s, *H*-2), 7.31–7.40 (6H, m, Ar*H*), 5.35 (1H, d, *J* 4.85 Hz, *H*-1′), 5.02 (1H, dd, *J* 6.47, 4.85 Hz, *H*-2′), 4.82 (1H, dd, *J* 6.47, 3.69 Hz, *H*-3′), 4.24–4.25 (1H, m, *H*-4′), 3.84–3.86 (2H, m, H_2-5′), 2.48 (3H, s, SCH_3), 1.62 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.05 (9H, s, ^{t}Bu); δ_C(76 MHz; $CDCl_3$) [162.60, 151.39, 135.59, 133.23, 129.70] (Het *C*), [135.59, 133.23, 127.65, 126.75] (Ar *C*), 114.46 (CCH_3), 84.75 (*C*-4′), 83.83 (*C*-3′), 82.20 (*C*-2′), 77.24 (*C*-1′), 64.11 (*C*-5′), 27.57 (CH_3), 26.81 [$C(CH_3)_3$], 25.59 (CH_3), 19.23 [$C(CH_3)_3$], 13.99 (SCH_3); *m*/*z* (FAB, NBA) 607 (MH^+, 100%), 577 (4), 491 (4), 279 (15), 264 (4), 197 (22), 183 (4), 163 (12), 135 (54), 121 (12), 95 (18), 57 (58) (Found: MH^+, 607.2537. $C_{30}H_{39}N_6O_4SSi$ requires *M*H, 607.2523).

3-(5′-*O*-*tert*-Butyldiphenylsilyl-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-6-(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 23

A solution of the hydrazine **22** (1.04 g, 1.72 mmol) in ethanol (60 ml) at room temperature was treated with yellow mercury(II) oxide (1.12 g, 5.15 mmol). The dark solution was heated to reflux for 2 h. After being cooled to 25 °C, the inorganic residue was removed through a pad of Celite and washed with ethanol, and the combined solution concentrated *in vacuo* to give the crude product as a yellow foam. This was purified by flash chromatography on silica gel (gradient elution; 5–10% ether in light petroleum) to furnish the title compound **23** (712 mg, 72%) as a colourless foam; δ_H(300 MHz; $CDCl_3$) 9.00 (1H, s, *H*-8), 7.80 (1H, s, *H*-2), 7.64–7.70 (4H, m, Ar*H*), 7.33–7.44 (6H, m, Ar*H*), 5.46 (1H, d, *J* 4.99 Hz, *H*-1′), 4.98 (1H, dd, *J* 6.38, 5.10 Hz, *H*-2′), 4.86 (1H, dd, *J* 6.10, 3.59 Hz, *H*-3′), 4.30–4.31 (1H, m, *H*-4′), 3.87–3.89 (2H, m, H_2-5′), 2.56 (3H, s, SCH_3), 1.65 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.07 (9H, s, ^{t}Bu); δ_C(76 MHz; $CDCl_3$) [163.56, 149.36, 135.62, 129.85, 127.73] (Het *C*), [134.67, 134.13, 132.89, 128.00] (Ar *C*), 114.67 (CCH_3), 84.92 (*C*-4′), 83.94 (*C*-3′), 82.12 (*C*-2′), 77.25 (*C*-1′), 64.08 (*C*-5′), 27.62 (CH_3), 26.86 [$C(CH_3)_3$], 25.60 (CH_3), 19.29 [$C(CH_3)_3$], 14.27 (SCH_3); *m*/*z* (FAB, NBA) 577 (MH^+, 100%), 549 (3), 519 (4), 461 (7), 369 (6), 313 (2), 290 (5), 273 (4), 249 (25), 221 (4), 197 (17), 150 (18), 135 (52), 120 (20), 105 (18),

91 (36), 77 (40), 69 (74), 55 (68) (Found: MH^+, 577.2321. $C_{30}H_{37}N_4O_4SSi$ requires *M*H, 577.2305).

3-(2′,3′-*O*-Isopropylidene-β-D-ribofuranosyl)-6-(methylsulfanyl)-imidazo[2,1-*f*][1,2,4]triazine

A solution of silyloxy compound **23** (211 mg, 0.37 mmol) in dry THF (12 ml) was treated with *n*-Bu_4NF (TBAF; 0.73 ml of a 1 M solution in THF, 0.73 mmol) and stirred at 25 °C for 30 min. After dilution of the mixture with ether (20 ml), water (20 ml) was added. The organic layer was separated, washed with brine (10 ml), dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (gradient elution; 60–70% ether in light petroleum) to give the title compound (111 mg, 90%) as a white solid, mp 92–93 °C (from DCM–light petroleum); ν_{max}(NaCl/film)/cm^{-1} 3441w (OH), 2935w, 2876w, 1694w, 1628w, 1591s, 1531s, 1471s, 1422s, 1382s, 1342s, 1304s, 1274w, 1214s, 1157w, 1122s, 1078s, 921w, 862w, 763w, 735w, 662w; δ_H(270 MHz; $CDCl_3$) 8.99 (1H, s, *H*-8), 7.82 (1H, s, *H*-2), 5.31 (1H, d, *J* 5.54 Hz, *H*-1′), 5.16 (1H, dd, *J* 6.58, 5.54 Hz, *H*-2′), 4.96 (1H, dd, *J* 6.59, 3.70 Hz, *H*-3′), 4.25–4.27 (1H, m, *H*-4′), 3.89–3.90 (2H, m, H_2-5′), 2.91–3.22 (1H, m, O*H*), 2.62 (3H, s, SCH_3), 1.62 (3H, s, CH_3), 1.37 (3H, s, CH_3); δ_C(68 MHz; $CDCl_3$) [163.89, 149.65, 135.13, 135.05, 126.73] (Het *C*), 114.95 (*C*CH_3), 84.78 (*C*-4′), 82.51 (*C*-3′), 81.68 (*C*-2′), 77.72 (*C*-1′), 62.61 (*C*-5′), 27.54 (*C*H_3), 25.43 (*C*H_3), 14.25 (S*C*H_3); *m*/*z* (FAB, NBA) 339 (MH^+, 20%), 282 (24), 242 (100), 197 (6), 135 (22), 121 (15), 91 (50), 69 (42), 55 (48) (Found: MH^+, 339.1144. $C_{14}H_{19}N_4O_4S$ requires *M*H, 339.1127).

6-Methylsulfanyl-3-β-D-ribofuranosylimidazo[2,1-*f*][1,2,4]-triazine 7

A solution of 3-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-6-(methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine (50.9 mg, 0.15 mmol) in a mixture of glacial acetic acid (2 ml) and water (1 ml) was stirred at 25 °C for 18 h. The solvent was removed *in vacuo* to dryness. The residue was recrystallized from ethanol to yield the *title compound* **7** (27 mg, 60%) as white crystals, mp 227–228 °C (from EtOH); ν_{max}(NaCl/Nujol)/cm^{-1} 3441 (OH), 3202 (OH), 1693w, 1630w, 1595s, 1529w, 1311s, 1225s, 1172w, 1116s, 1069w, 1040w, 985w, 957w, 931w, 774w; δ_H(270 MHz; DMSO-d_6 + D_2O) 9.14 (1H, s, *H*-8), 7.97 (1H, s, *H*-2), 5.16 (1H, d, *J* 6.23 Hz, *H*-1′), 4.42 (1H, dd, *J* 6.00, 5.55 Hz, *H*-2′), 4.00–4.08 (1H, m, *H*-3′), 3.90–3.91 (1H, m, *H*-4′), 3.52–3.58 (2H, m, H_2-5′), 2.60 (3H, s, SCH_3); δ_C(76 MHz; DMSO-d_6) [163.29, 150.31, 135.37, 135.03, 129.26] (Het *C*), 85.20 (*C*-4′), 74.95 (*C*-1′), 73.79 (*C*-2′), 71.68 (*C*-3′), 62.19 (*C*-5′), 14.45 (S*C*H_3); *m*/*z* (FAB, NBA) 299 (MH^+, 40%), 273 (5), 242 (6), 192 (22), 165 (18), 150 (40), 133 (65), 124 (28), 120 (45), 105 (32), 89 (90), 77 (100), 69 (20), 63 (52), 51 (55) (Found: C, 44.3; H, 4.5; N, 18.7. $C_{11}H_{14}N_4O_4S$ requires C, 44.3; H, 4.7; N, 18.8%. Found: MH^+, 299.0809. $C_{11}H_{15}N_4O_4S$ requires *M*H, 299.0814).

6-(Methylsulfonyl)imidazo[2,1-*f*][1,2,4]triazine 24

Method A. A solution of sulfide **20** (50 mg, 0.30 mmol) in glacial acetic acid (1 ml) was added to a stirred solution of $KMnO_4$ (95 mg, 0.60 mmol) in a mixture of glacial acetic acid (0.5 ml) and water (0.5 ml) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred vigorously for 30 min. The dark solution was extracted with ethyl acetate (3 × 10 ml) and the combined organic extract was washed successively with 1 M NaOH and brine. After drying ($MgSO_4$) and evaporation of volatiles *in vacuo*, the residue was purified by flash chromatography on silica gel (gradient elution; 30–40% ethyl acetate in light petroleum) to give the sulfone **24** (35 mg, 58%) as pale yellow crystals, mp 185–190 °C (from DCM–light petroleum); ν_{max}(NaCl/Nujol)/cm^{-1} 1695s, 1591w, 1307s, 1264w, 1139s (SO_2), 1113w, 1074w, 899s, 779s, 750w; δ_H(300 MHz; $CDCl_3$) 9.41 (1H, s, *H*-8), 8.31 (1H, s, *H*-2 or *H*-3), 8.25 (1H, d, *J* 0.91 Hz, *H*-3 or *H*-2), 3.45 (3H, s, SO_2CH_3); δ_C(76 MHz; $CDCl_3$) [157.78, 151.07, 139.69, 135.11, 119.35] (Het *C*), 40.26 (SO_2CH_3); *m*/*z* (CI, NH_3) 216 (MNH_4^+, 100%), 199 (MH^+, 98), 183 ($M^+ - CH_3$, 2), 138 (10), 130 (15), 121 (48), 96 (4), 88 (6), 69 (4) (Found: MH^+, 199.0296. $C_6H_7N_4O_2S$ requires *M*H,199.0290).

Method B. A solution of the sulfide **20** (36 mg, 0.22 mmol) in DCM (1 ml) was added to a stirred suspension of MCPBA (172 mg of a 50% mixture with *m*-chlorobenzoic acid, 0.5 mmol) in DCM (2 ml) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred vigorously for 24 h. The organic mixture was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution; 20–30% ethyl acetate in light petroleum) to give the sulfone **24** (22 mg, 52%) which was identical to that described above.

6-Hydrazinoimidazo[2,1-*f*][1,2,4]triazine 25

To a stirred solution of sulfone **24** (20 mg, 0.10 mmol) in ethanol (0.5 ml) was added hydrazine monohydrate (6 mg, 0.10 mmol) at 25 °C. The reaction mixture was stirred for 1 min and excess of solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient elution; 2–5% MeOH in DCM) followed by recrystallization from EtOH to afford the *hydrazine* **25** (52 mg, 97%) as a white solid; ν_{max}(NaCl/film)/cm^{-1} 3303br s (NH_2), 1667s, 1652s, 1623s, 1538w, 1481w, 1376w, 1142w, 993w, 761w; *m*/*z* (EI) 150 (M^+, 100%), 135 (40), 121 (40), 93 (38), 80 (30), 67 (42), 43 (22) (Found: M^+, 150.0647. $C_5H_6N_6$ requires *M*, 150.0654).

6-Methylsulfonyl-7,8-dihydroimidazo[2,1-*f*][1,2,4]triazine 26

A solution of sulfone **24** (30 mg, 0.15 mmol) in a mixture of chloroform (0.5 ml) and EtOH (0.5 ml) at 25 °C was treated with $NaBH_4$ (8.63 mg, 0.23 mmol) in small portions. The reaction mixture was stirred for 10 min and then quenched with water (0.1 ml). Excess of solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution; 2–5% MeOH in DCM) to afford the *dihydro sulfone* **26** (10 mg, 34%) as a white solid, δ_H(270 MHz; $CDCl_3$) 7.25 (1H, d, *J* 1.62 Hz, *H*-2 or *H*-3), 7.01 (1H, d, *J* 1.61 Hz, *H*-3 or *H*-2), 4.79 (2H, s, H_2-8), 3.31 (3H, s, SO_2CH_3); *m*/*z* 200 (M^+, 76%), 165 (8), 151 (8), 121 ($M^+ - SO_2CH_3$, 20), 111 (35), 97 (52), 81 (95), 69 (78), 57 (100), 43 (82) (Found: M^+, 200.0383. $C_6H_8N_4O_2S$ requires *M*, 200.0368).

8-Methylsulfanyl-6-(methylsulfonyl)imidazo[2,1-*f*][1,2,4]-triazine 28

A solution of bis-sulfide **17** (166 mg, 0.78 mmol) in glacial acetic acid (1 ml) was added to a stirred solution of $KMnO_4$ (248 mg, 1.57 mmol) in a mixture of glacial acetic acid (1 ml) and water (8 ml) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred vigorously for 30 min. The dark solution was extracted with ethyl acetate (3 × 20 ml) and the combined organic extract was washed successively with 1M NaOH and brine. After drying ($MgSO_4$) and evaporation of solvent *in vacuo*, the residue was purified by flash chromatography on silica gel (gradient elution; 30–40% ethyl acetate in light petroleum) to give the *sulfone* **28** (120 mg, 63%) as pale yellow crystals, mp 202–203 °C (from DCM–light petroleum); ν_{max}(NaCl/Nujol)/cm^{-1} 3020w, 2927w, 1693s, 1607w, 1566w, 1538w, 1467w, 1427s, 1406s, 1354w, 1315s, 1268w, 1190w, 1133s (SO_2), 1070w, 1041w, 967w, 883w, 665w; δ_H(270 MHz; $CDCl_3$) 8.04 (1H, d, *J* 1.15 Hz, *H*-2 or *H*-3), 7.90 (1H, d, *J* 0.92 Hz, *H*-3 or *H*-2), 3.39 (3H, s, SO_2CH_3), 2.80 (3H, s, SCH_3); δ_C(76 MHz; $CDCl_3$) [165.02, 153.78, 133.29, 131.11, 116.46] (Het *C*), 37.52 (SO_2CH_3), 9.99 (S*C*H_3); *m*/*z* (EI) 244 (M^+, 45%), 165 ($M^+ - SO_2CH_3$, 100), 151 (2), 138 (7), 123 (60), 119 (25), 94 (30), 93 (45), 69 (15), 47 (8) (Found: C, 34.75; H, 3.0; N, 22.6%;

M^+, 244.0086. $C_7H_8N_4O_2S_2$ requires C, 34.4; H, 3.3; N, 22.9%; *M*, 244.0089).

8-(Methylsulfanyl)imidazo[2,1-*f*][1,2,4]triazine 29

A solution of sulfone **28** (36 mg, 0.15 mmol) in a mixture of chloroform (0.6 ml) and EtOH (0.6 ml) at room temperature was treated with $NaBH_4$ (11 mg, 0.30 mmol) in small portions. The reaction mixture was stirred for 5 min and then quenched with water (0.2 ml). Excess of solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient elution; 5–15% ethyl acetate in light petroleum) to afford the *sulfide* **29** (19.5 mg, 79%) as a pale yellow solid, mp 114–116 °C (from DCM–light petroleum); ν_{max}(NaCl/Nujol)/cm^{-1} 1692s, 1607w, 1579w, 1538w, 1482w, 1430s, 1410s, 1370s, 1340w, 1314w, 1142w, 908w, 864w, 748w; δ_H(270 MHz; $CDCl_3$) 8.45 (1H, s, *H*-6), 7.88 (1H, d, *J* 1.15 Hz, *H*-2 or *H*-3), 7.74 (1H, d, *J* 0.93 Hz, *H*-3 or *H*-2), 2.70 (3H, s, SCH_3); δ_C(76 MHz, $CDCl_3$) [164.90, 146.92, 133.35, 132.69, 117.49] (Het *C*), 11.83 (SCH_3); *m*/*z* (EI) 166 (M^+, 85%), 139 (10), 112 (10), 95 (30), 94 (60), 93 (100), 70 (55), 65 (20), 45 (22) (Found: M^+, 166.0317. $C_6H_6N_4S$ requires *M*, 166.0313).

8-Hydrazinoimidazo[2,1-*f*][1,2,4]triazine 30

To a stirred solution of sulfide **29** (60 mg, 0.36 mmol) in ethanol (1 ml) was added hydrazine monohydrate (22 mg, 0.43 mmol) at 25 °C. The reaction was stirred for 2 h and excess of solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (gradient elution; 2–5% MeOH in DCM) followed by recrystallization from EtOH to afford the hydrazine **30** (41 mg, 76%) as a white solid, mp 205–210 °C (decomp); ν_{max}(NaCl/Nujol)/cm^{-1} 3289w, 3116w, 3103 (NH), 1682w, 1682w, 1661w, 1608w, 1505w, 1417w, 1349s, 1274w, 1140w, 1089w, 1041w, 920w, 773w, 646s; δ_H(270 MHz; DMSO-d_6) 10.08 (1H, br s, N*H*), 8.12 (1H, s, *H*-6), 8.02 (1H, s, *H*-2 or *H*-3), 7.53 (1H, d, *J* 0.70 Hz, *H*-3 or *H*-2), 4.95 (2H, br s, NH_2); δ_C(76 MHz; DMSO-d_6) [151.56, 149.23, 130.92, 128.09, 118.07] (Het *C*); *m*/*z* (EI) 150 (M^+, 70%), 121 (65), 105 (35), 94 (100), 77 (20), 67 (40), 53 (50), 43 (45).

Imidazo[2,1-*f*][1,2,4]triazine 27

Method A. A solution of the hydrazine **25** (50 mg, 0.33 mmol) in ethanol (1 ml) at room temperature was treated with yellow mercury(II) oxide (214 mg, 0.99 mmol). The dark solution was heated gently for 10 min. After being cooled to 25 °C, the inorganic residue was removed through a pad of Celite, washed with ethanol and the combined solution concentrated *in vacuo* to give the crude product as a yellow oil. This was purified by flash chromatography on silica gel (ether as eluent) to furnish the *title compound* **27** (7 mg, 18%) as an oil; ν_{max}(NaCl/film)/cm^{-1} 1691s, 1608w, 1580w, 1482w, 1370s, 1314w, 1142w, 863w, 752w; δ_H(270 MHz; $CDCl_3$) 9.10 (1H, s, *H*-8), 8.52 (1H, s, *H*-6), 7.80 (1H, d, *J* 1.10 Hz, *H*-2 or *H*-3), 7.73 (1H, d, *J* 0.96 Hz, *H*-3 or *H*-2); *m*/*z* (EI) 120 (M^+, 25%), 93 (100), 70 (32), 45 (22) (Found: M^+, 120.1608. $C_5H_4N_4$ requires *M*, 120.1616).

Method B. A solution of the hydrazine **30** (35 mg, 0.23 mmol) in ethanol (1 ml) at room temperature was treated with yellow mercury(II) oxide (150 mg, 0.69 mmol). The dark solution was heated gently for 10 min. After being cooled to 25 °C, the inorganic residue was removed through a pad of Celite and washed with ethanol, and the combined solution concentrated *in vacuo* to give the crude product as a yellow oil. This was purified by flash chromatography on silica gel (ether as eluent) to furnish the *title compound* **27** (8 mg, 27%) as an oil which was identical with that described above.

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