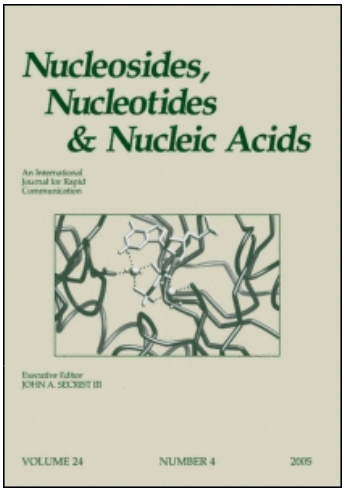

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The Synthesis of Ribosides of Asymmetrically-Substituted Aminohalogenobenzimidazoles

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THE SYNTHESIS OF RIBOSIDES OF ASYMMETRICALLY-SUBSTITUTED AMINOHALOGENOBENZIMIDAZOLES

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ABSTRACT. A series of ribosides of asymmetrically-substituted aminohalogenobenzimidazoles has been prepared by reaction of a suitably protected ribose with 6(5)-fluoro-5(6)-formylaminobenzimidazole (1), 5-amino-4-chloro-6-fluorobenzimidazole(2), 5-acetylamino-4,7-dichlorobenzimidazole(13), 5(6)-amino-6(5)-fluoro-2-methylbenzimidazole(20) and 6(5)-fluoro-5(6)-formylamino-2-methylbenzimidazole(21).

The β-linked ribofuranosides of halogenated benzimidazoles are highly active inhibitors of cell RNA synthesis[1,2]. 5,6-Dichloro-1-β-D-ribofuranosyl benzimidazole has been the most extensively studied compound. This appears to act by interfering with the incorporation of adenosine into RNA[2]. The high inhibitory activity of N-glycosides of halogenated benzimidazoles on influenza virus multiplication depends on both on the halogen and carbohydrate substituents. For the highest inhibitory activity the carbohydrate must not only be ribose but specifically ribofuranose in the β-configuration.

As a part of our programme designed to establish structure-activity relationships amongst asymmetrically-substituted aminohalogenobenzimidazoles and their asymmetrically-substituted nucleosides, we report here the synthesis of the ribofuranosyl nucleosides of 5-formylamino-6-fluorobenzimidazole (1), 5-amino-4-chloro-6-fluoro benzimidazole (2), 5-acetylamino-4,7-dichlorobenzimidazole (13) and 5-amino-6-fluoro-2-methylbenzimidazole (20). The synthesis of these benzimidazoles has been previously reported by us[3].

Glycosylation of the benzimidazole derivatives 1,2,13,20 and 21 was first attempted by the fusion[4] and Vorbrüggen[5] procedures but both

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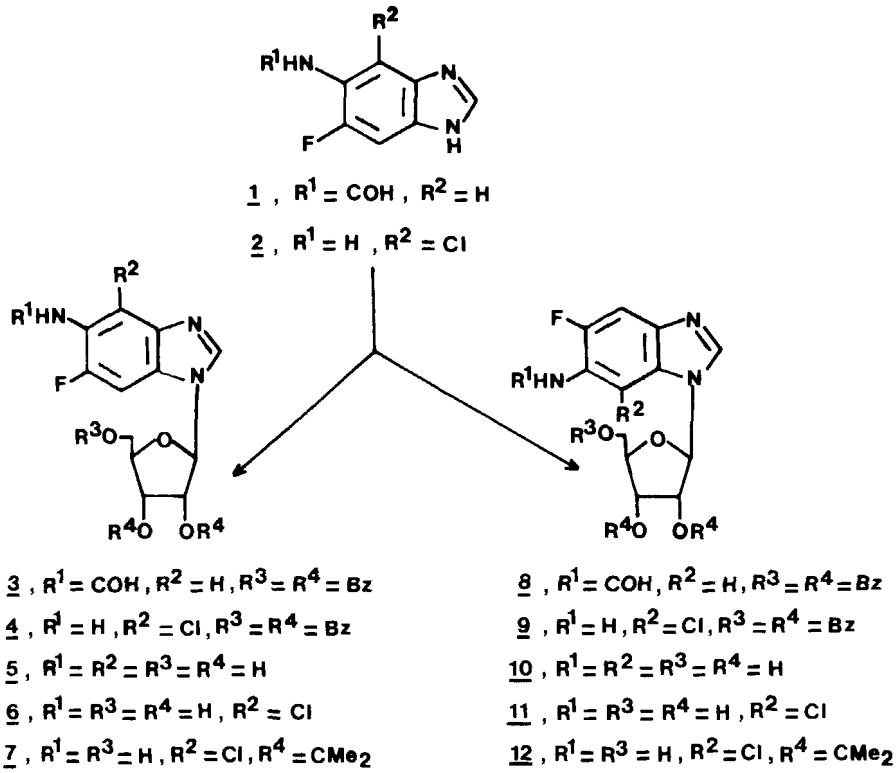
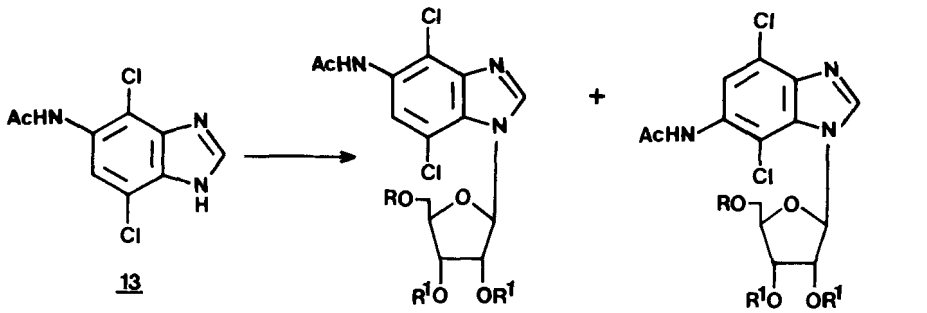


SCHEME – 1

methods failed to produce the required nucleosides. The desired reaction was achieved, however, by the mercuric cyanide-nitromethane method[6] for compounds 1, 13 and 21, or by a modification of this method for compounds 2 and 20.

Reaction of 1 with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride[7] gave a mixture of N-1 and N-3 ribofuranosylnucleosides 3 and 8, in 36 and 38% yield respectively. Due to the insolubility of compound 2 in organic solvents and to avoid the possibility of linkage of the sugar to the exocyclic NH_2 group during the glycosylation reaction, this group was previously silylated. The use of trimethylsilyl as the protecting group in the glycosylation reaction has the advantage that it gives nucleosides with the amino group deprotected.

Reaction of 2 with hexamethyldisilazane/ammonium sulphate and subsequent ribosylation of the silylated base according to "mercuric cyanide" method[6] afforded the ribonucleosides 4 and 9 in 26 and 19% yield respectively (SCHEME-1). Similarly reaction of 13 with the chlorosugar[7] gave compounds 14 and 17 in 22 and 18% yield respectively (SCHEME-2).



14 , R = R¹ = Bz
15 , R = R¹ = H
16 , R = H , R¹ = CMe₂

17 , R = R¹ = Bz
18 , R = R¹ = H
19 , R = H , R¹ = CMe₂

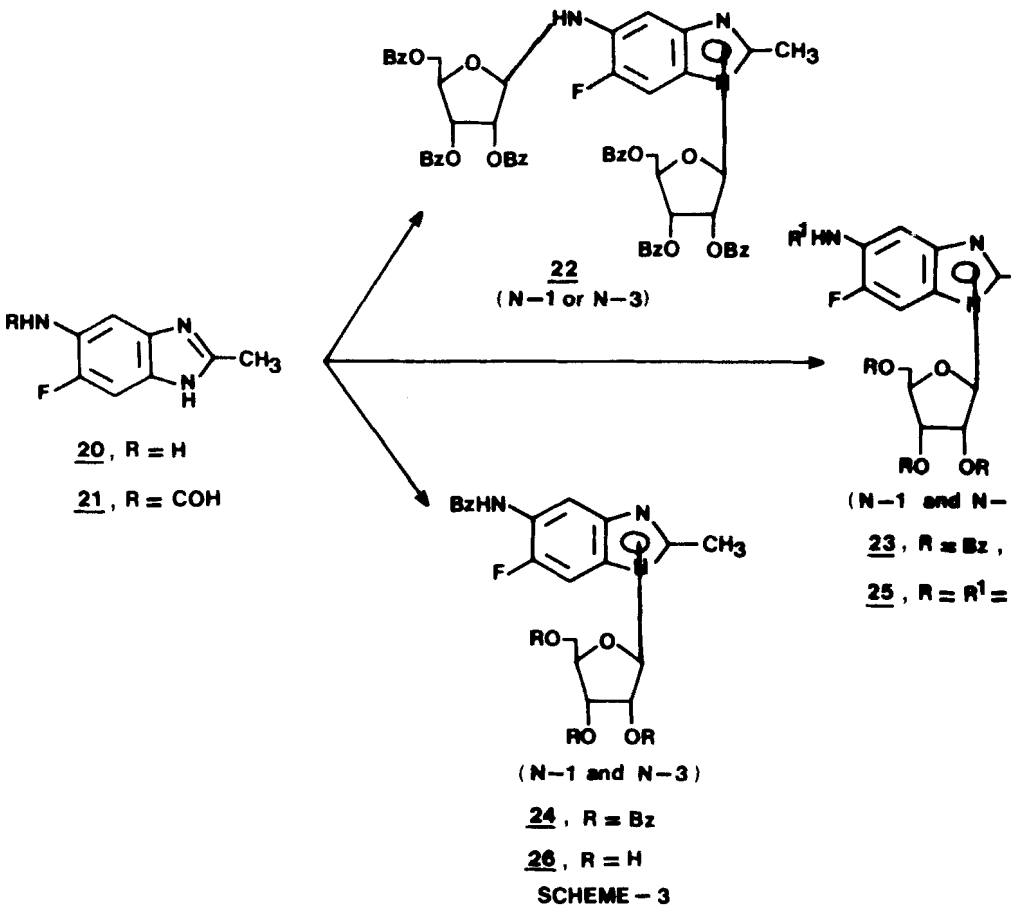
SCHEME - 2

Finally, ribosylation of either 20 or 21 gave a complex mixture of compounds in which the diriboside 22 and the monoribosides 23 and 24 (SCHEME-3) were detected by n.m.r. and mass spectroscopy. The latter were found to be a mixture of the N-1 and N-3 ribosylated nucleosides in each case.

Separation of the two positional isomers could not be achieved by chromatographic procedures or by fractional crystallization (see experimental). Compounds 3, 4, 8, 9, 14 and 17 were debenzoylated with NaOMe/MeOH or with Amberlyst A-26(OH)/MeOH[8], to give the free ribonucleosides 5, 6, 10, 11, 15 and 18 respectively.

Glycosilation positions were assigned by ^{1}H-n.m.r. and ^{13}C-n.m.r. The criteria followed for the assignment of structures between the isomers 3 and 8, and 5 and 10 were: (a) Due to the deshielding effect of the adjacent acetamido group, H-4 in compound 3(δ8.36) appeared at lower field than in compound 8(δ7.78-7.30) while H-7 in compound 8(δ8.55) appeared at lower field than in compound 3(δ7.82). (b) Because of the deshielding effect of the adjacent sugar the signal of the proton adjacent to the fluorine group appeared at lower field for 3(δ7.82) and 5(δ7.50) than for 8(δ7.78-7.30) and 10(δ7.28). This latter criterion was used initially to assign the ribosylation site of compounds 4 or 6 and 9 or 11 as N-1 and N-3 respectively, (H-7 for 4 and 6 were δ7.96 and δ7.70 respectively; H-4 for 9 and 11 were δ7.78 and δ7.62 respectively). This assignment was further confirmed by the ^{13}C-n.m.r. data of the deblocked nucleosides 6 and 11.

TABLE-1 shows the ^{13}C-chemical shifts of the anion of the base 2 and of its ribosides 6 and 11. Assignments of the ^{13}C chemical shifts of the base anion 2 were based on the general rules of ^{13}C-n.m.r.[9,10] and on a



SCHEME - 3

comparison with the related benzimidazole anion[11]. Assignment of the carbon atoms in ribosides 6 and 11 were based on the theoretical ^{13}C-shieldings reported in parentheses in TABLE-1 which were calculated using a substitution shift parameter of 7ppm upfield for the carbons in the α position to the substituted nitrogen, and a downfield shift of 2 ppm for carbons in the β position[12].

^{1}H-n.m.r. data for the benzenic protons of compounds 14, 15, 17 and 18 showed no significative differences which would allow one to establish the ribosylation site of these compounds. Therefore, compounds 14 or 15 and 17 or 18 were established as N-1 and N-3 respectively, by comparing the ^{13}C chemical shift of the anion of the base 13 with those of the unprotected ribosides 15 and 18, following the ^{13}C-n.m.r. criterion[12] mentioned above (TABLE-1).

The anomeric configuration of the ribonucleosides reported so far (3 to 6, 8 to 11 and 14, 15, 17 and 18) could not be unequivocally establishe

TABLE-1. ^{13}C Chemical Shifts of the base anions 2 and 13 and their nucleosides 6, 11, 15 and 18 at 75 MHz in DMSO with TMS as internal reference

Carbon	Compound					
nº	2	6	11	13	15	18
1'	--	89.14	89.11	--	89.97	89.06
2'	--	85.70	85.58	--	84.80	84.76
3'	--	73.94	73.46	--	75.15	75.14
4'	--	70.02	70.03	--	69.24	69.19
5'	--	61.13	61.16	--	60.38	60.34
2	152.36	143.21 (145.36)	142.43 (145.36)	153.53	143.95 (146.53)	143.71 (146.53)
4	129.96	126.25	129.52	114.59	113.47	121.70
5	100.41	97.85	96.89	125.14	130.33	131.55
6	101.46	99.27	98.19	116.47	122.67	121.13
7	125.06	127.14 (127.06)	123.55	117.66	127.71	121.13
8	136.3	127.8 (129.3)	137.86 (138.3)	140.71	130.33 (133.71)	143.71 (142.89)
9	136.99	137.90 (138.90)	130.39 (129.9)	142.89	142.53 (144.89)	139.63 (135.89)
C=O				170.05	168.96	168.88
CH_3				22.80	23.04	23.03

Values in parentheses are theoretical chemical shifts using α- and β-substitution parameters of +7 and -2 ppm respectively.

by ^1H-n.m.r., since the coupling constant values $J_{1',2'}$ were not less than 1 Hz[13] (see experimental). However, they were tentatively assigned as β on the basis of the mechanism for the glycosylation by the "mercuric cyanide method"[14]. The anomeric configuration of compounds 3 to 6, 8, to 11 and 14, 15, 17 and 18 was unequivocally ascertained following their conversion to the corresponding 2',3'-O-isopropylidene derivatives[15] 7, 12, 16 and 19, whose ^1H-n.m.r. spectra showed a difference of chemical shift for the isopropylidene methyl groups of 0.20 ppm for 7, 0.19 ppm for 12, 0.18 ppm for 16 and 0.19 ppm for 19, only consistent with a β configuration.[16]

The compounds described above have been tested for antiviral activity against herpes simplex virus types 1 and 2, vaccinia virus, vesicular stomatitis virus, coxsackie virus B-4 and polio virus-1, but none of them showed any significant activity nor toxicity. Further tests of these compounds in other biological systems are in progress.

EXPERIMENTAL

Melting points were measured on a electrothermal m.p. apparatus or on a Kofler block and are uncorrected. N.m.r. spectra were measured at 300 MHz on a Varian XL-300 spectrometer, at 100 MHz on a Varian XL-100 or at 90 MHz on a Varian EM-390 with $(CD_3)_2SO$ as solvent, ^{13}C-n.m.r. spectra were measured at 75 MHz on a Varian XL-300 spectrometer using TMS as internal reference. The anion of the benzimidazoles 2 and 13 were formed by neutralization with lithium hydroxide in $(CD_3)_2SO$.

Mass spectra were obtained on a Kratos MS 80 RF mass spectrometer and uv absorption spectra were recorded on a Perkin-Elmer 552 spectrophotometer. Analytical t.l.c. was performed on silica gel 60 F_{254} (Merck), and column chromatography on Kiesegel 60, 70-230 mesh ASTM type 7734 (Merck).

General procedure for the glycosylation of the benzimidazoles

Method A:

To a mixture of 2,3,5,-tri-O-benzoyl-ribofuranosyl chloride[7] (prepared from 1g(2 mmol) of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose), mercuric cyanide (3 mmol) and 4Å molecular sieves (0.5 g), a solution of the benzimidazole derivative (1.6 mmol) in dry nitromethane (50 ml) was added. The resulting mixture was boiled under reflux, under anhydrous conditions, for 4 to 8 hours. It was then filtered while still hot, the insoluble residue washed with hot nitromethane, and the filtrate evaporated to dryness under reduced pressure. The residue thus obtained was treated with chloroform and filtered. The filtrate was washed successively with 30% aqueous potassium iodide, water, and dried over anhydrous sodium sulphate. The solvent was evaporated to dryness and the residue was chromatographed on silica gel. The specific solvents for each case and the properties of the products obtained are described below.

Method B:

The benzimidazole derivative (5 mmol) was boiled under reflux in hexamethyldisilazane (46 ml), to which ammonium sulphate (100 mg) had been added, until the solution became clear (30 min to 2 hours). The excess of HMDS was removed by distillation under reduced pressure. The solid residue thus obtained was dissolved in dry nitromethane (90 ml) to which mercuric cyanide (9 mmol) and 4Å molecular sieves (1 g) were added. To the refluxing solution, 2,3,5-tri-O-benzoyl-ribofuranosyl chloride[7] (prepared from 4 g (8 mmol) of 1-O-acetyl-2,3,5-tri-O-benzoyl-ribofuranose) dissolved in dry nitromethane (30 ml) was added. The solution was boiled under reflux for 6 to 8 hours. At this point the work-up was similar to the previously described in method A.

6-Fluoro-5-formylamino-1(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (3) and 5-fluoro-6-formylamino-1(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (8)

Method A was followed with 6(5)-fluoro-5(6)-formylaminobenzimidazole (1)[3]. The yellow foam obtained was purified by column chromatography using ethyl acetate-hexane (2:1) as the eluant. From the faster-moving fractions, compound 8 (0.39 g, 38% yield) was obtained as a yelow foam.
(Found: C, 65.6; H, 4.5; N, 6.5. $C_{34}H_{26}FN_3O_8$ requires C, 65.49; H, 4.17; N, 6.74%); n.m.r. (100 MHz): δ4.68-5.00(3H, 2 overlapping m, H-4', 2H-5'), 5.88-6.24(2H, 2 overlapping m, H-2', H-3'), 6.69(1H, d, H-1', $J_{1',2'}$= 6Hz), 7.30-7.78(10H, m, OBz, H-4), 7.84-8.12(6H, m, OBz), 8.27(1H, d, HCO, $J_{H,NH}$= 3 Hz, collapses to a singlet on D_2O shake), 8.55(1H, d, H-7, $J_{F,H}$= 8Hz), 8.62(1H, s, H-2), 10.05(1H, bs, NH); m/z 623(M^+, 7%), 595(2), 501(4), 446 (30), 445(98), 341(1), 323(6), 283(5), 269(5), 255(49), 201(6), 179(10), 161(5), 151(12), 134(3), 122(30), 105(100), 94(4), 77(40), 51(7).

The slower moving fractions afforded compound 3 (0.37 g, 36% yield) as a yellow foam.
(Found: C, 65.7; H, 4.3; N, 6.4. $C_{34}H_{26}FN_3O_8$ requires C, 65.49; H, 4.17; N, 6.74%); n.m.r. (100 MHz): δ4.72-5.02(3H, 2 overlapping m, H-4', 2H-5') 5.94-6.26(2H,2 overlapping m, H-2', H-3'), 6.67(1H, d, H-1', $J_{1',2'}$= 6 Hz), 7.40-7.74(9H, m, OBz), 7.82(1H, d, H-7, $J_{F,H}$=12 Hz), 7.74-8.16(6H, m, OBz), 8.34(1H, d, HCO, $J_{H,NH}$= 2 Hz, collapses to a singlet on D_2O shake), 8.36 (1H, d, H-4, $J_{F,H}$= 8 Hz), 8.61(1H, s, H-2), 10.04(1H, bs, NH); m/z 624 (M^++1, 5%), 623(12), 595(5), 501(6), 486(2), 473(2), 445(100), 359(2), 345(2), 335(1), 323(4), 283(3), 255(90), 201(99), 179(9), 151(12), 122(31), 105(100), 97(3), 77(42), 51(10).

5-Amino-6-fluoro-1(β-D-ribofuranosyl)benzimidazole (5)

The protected nucleoside 3(0.33 g) was treated with 0.2M-NaOMe/MeOH (4 ml). After standing at room temperature overnight, the solution was heated at 50-60°C for five hours. The reaction mixture was neutralized with acetic acid and then evaporated to dryness. The residue thus obtained was dissolved in water (15 ml) and extracted with ether (4 x 15 ml). The aqueous phase was evaporated to dryness to give a syrup which was purified by column chromatography using ethyl acetate-ethanol (5:1) as the eluant, to afford compound 5(0.11 g, 69% yield) as a yellow foam.
(Found: M^+, 283.0970. $C_{12}H_{14}FN_3O_4$ requires M, 283.0968); u.v.: λ_{max} (0.1M-NaOH), 297nm(ε, 3600), 245nm(ε, 5100); λ_{max} (0.1M-HCl), 299nm(ε, 3200), 279nm(ε, 3900); n.m.r. (100 MHz): δ3.62(2H, m, 2H-5'), 3.96(1H, m, H-4'), 4.12(1H, m, H-3'), 4.30(1H, m, H-2'), 4.60-5.20(3H, m, OH-2', OH-3', OH-5'),

5.70(1H, d, H-1', $J_{1',2'}$= 5 Hz), 6.99(1H, d, H-4, $J_{F,H}$= 8 Hz), 7.50(1H, d, H-7, $J_{F,H}$= 12 Hz), 8.18(1H, s, H-2), 10.03(2H, bs, NH_2); m/z 283(M^+, 71%), 265(16), 256(17), 242(24), 229(98), 201(70), 179(6), 151(100), 123(14), 97(16), 70(9), 57(8).

6-Amino-5-fluoro-1(β-D-ribofuranosyl)benzimidazole (10)

The protected nucleoside 8(0.58 g) was deprotected with 0.2M-NaOMe/MeOH (8 ml), according to the procedure described for 5, to give the product (0.17 g, 59% yield) as a yellow foam.
(Found: M^+, 283.0975. $C_{12}H_{14}FN_3O_4$ requires M, 283.0969). u.v.: λ_{max} (0.1M-NaOH) 295 nm(ε, 6300), 255nm(ε, 5400); λ_{max} (0.1M-HCl) 299nm (ε, 6700), 280nm(ε, 7500), 274nm(ε, 6800); n.m.r. (100 MHz): δ4.61(2H, m, 2H-5'), 4.96(1H, t, H-4'), 5.11(1H, t, H-3'), 5.33(1H, t, H-2'), 5.02(3H, m, OH-2', OH-3', OH-5'), 5.67(1H, d, H-1', $J_{1',2'}$= 5 Hz), 6.94(1H, d, H-7, $J_{F,H}$= 8Hz), 7.28(1H, d, H-4, $J_{F,H}$= 12 Hz), 8.20(1H, s, H-2), 10.20(2H, bs, NH_2); m/z 283(M^+, 48%), 265(77), 245(34), 231(98), 229(92), 217(43), 201(86), 151(100), 123(15), 97(18), (81)6, 70(9), 57(7).

5-Amino-4-chloro-6-fluoro-1(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl) benzimidazole (4) and 6-amino-7-chloro-5-fluoro-1(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (9)

Glycosylation of compound 2[3] (1 g) following method B gave a dark foam. This was purified by column chromatography using ethyl acetate-hexane (1:1) as the eluant and finally by preparative t.l.c. using chloroform-acetone (20:1) as the eluant. The plates were developped several times. The faster moving band gave compound 4(0.88 g, 26% yield) as a white foam.
(Found: C, 63.28; H, 4.20; N, 6.20. $C_{33}H_{25}ClFN_3O_7$ requires C, 62.90; H, 3.97; N, 6.67%); n.m.r. (90 MHz): δ4.56(2H, m, 2H-5'), 4.82(1H, m, H-4'), 5.85(1H, m, H-3'), 6.04(1H, m, H-2'), 6.65(1H, d, H-1', $J_{1',2'}$= 6 Hz), 7.96(1H, d, H-7, $J_{F,H}$= 12 Hz), 7.30-8.13(15H, 2 overlapping m, OBz), 8.60 (1H, s, H-2); m/z 631(M^++2, 38%), 629(M^+, 1), 445(98), 322(9), 289(2), 254 (6), 201(98), 185(8), 183(3), 122(59), 105(100), 77(18).

The slower moving band gave compound 9 (0.65 g, 19% yield) as a white foam.
(Found: C, 63.14; H, 4.15; N, 6.41. $C_{33}H_{25}ClFN_3O_7$ requires C, 62.90; H, 3.97; N, 6.67%); n.m.r. (300 MHz): δ4.80(3H, m, H-4', 2H-5'), 5.07(2H, bs, NH_2), 6.04(2H, m, H-2', H-3'), 6.59(1H, d, H-1', $J_{1',2'}$= 5 Hz), 7.35-8.12 (15H, 2 overlapping m, OBz), 7.78(1H, d, H-4, $J_{F,H}$= 12 Hz), 8.47(1H, s, H-2); m/z 631(M^++2, 9%), 629(28), 456(5), 446(30), 445(98), 364(4), 322(90), 294(26), 281(30), 269(3), 245(5), 227(5), 218(10), 201(20), 195(13), 185 (14), 162(4), 122(27), 105(100), 77(24), 51(7).

5-Amino-4-chloro-6-fluoro-1-β-D-ribofuranosylbenzimidazole (6)

The blocked nucleoside 4(0.7 g) was stirred in methanol (20 ml) at room temperature with Amberlyst A-26(OH^-)[8a](150 mg) for 72 hours. Filtration and evaporation of the filtrate gave a white foam which was triturated with hexane (to remove methyl benzoate) to afford pure compound 6 (0.29 g, 85% yield), as a white solid. m.p. 120°C.
(Found: C, 45.40; H, 4.20; N, 13.45. $C_{12}H_{13}ClFN_3O_4$ requires C, 45.35; H, 4.09; N, 13.22%); u.v.: λ_{max} (0.1M-NaOH), 292nm(ε, 3300), 255nm(ε, 4800); λ_{max} (0.1M-CHl); 303nm(ε, 4000); n.m.r. (90 MHz): δ3.63(3H, m, H-4', 2H-5'), 4.05(1H, m, H-3'), 4.29(1H, m, H-2'), 4.60-5.40(3H, 3 overlapping m, OH-2', OH-3', OH-5'), 5.79(1H, d, H-1', $J_{1',2'}$= 5 Hz), 7.70(1H, d, H-7, $J_{F,H}$= 12 Hz), 8.40(1H, s, H-2); m/z 319(M^++2, 5%), 317(M^+, 14), 269(5), 268(8), 266(98), 264(32), 246(1), 228(32), 227(13), 215(4), 198(3), 187(32), 186(11), 185(100), 184(20), 136(8), 131(6), 130(7), 123(7), 122(7), 105(2), 96(2), 95(31), 92(13), 86(17), 77(20).

6-Amino-7-chloro-5-fluoro-1-β-D-ribofuranosylbenzimidazole (11)

Compound 9(0.65 g) was deprotected with Amberlyst A-26(OH^-)/MeOH[8a] according to the procedure described for 6, to give the product (0.26g, 81% yield) as a white solid. m.p. 198-200°C (dec.).
(Found: C, 45.70; H, 4.20; N, 13.60. $C_{12}H_{13}ClFN_3O_4$ requires C, 45.35; H, 4.09; N, 13.22%); u.v.: λ_{max} (0.1M-NaOH), 298nm (ε, 4300), 252nm (ε, 6300); λ_{max} (0.1M-HCl), 304nm (ε, 6000), 250 sh; n.m.r. (90 MHz): δ3.63(2H, m, 2H-5'), 3.96(1H, m, H-4'), 4.12(1H, m, H-3'), 4.30(1H, m, H-2'), 4.96(1H, m, OH-5'), 5.12(1H, m, OH-3'), 5.39(1H, d, OH-2'), 5.75(1H, d, H-1', $J_{1',2'}$= 6 Hz), 7.62(1H, d, H-4, $J_{F,H}$= 12 Hz), 8.30(1H, s, H-2); m/z 319(M^++2, 3%), 317(8), 299(0.1), 297(0.3), 268(2), 229(2), 227(5), 187(60), 185(100), 159 (8), 157(19), 150(25), 122(30), 96(12).

5-Acetylamino-4,7-dichloro-1(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl) benzimidazole (14) and 6-acetylamino-4,7-dichloro-1(2',3',5'-tri-O-benzoyl-β-D-ribofuranosyl)benzimidazole (17).

Glycosylation method A was followed using the acetylaminodichlorobenzimidazole (13)[3] (1g). After the work-up, the yellow foam obtained was purified by column chromatography using ethyl acetate-hexane (1:1) as the eluant, and finally by preparative t.l.c. using chloroform-acetone (20:1) as the eluant. The plates were developped several times. From the faster moving band the riboside 17(0.5 g, 18% yield) was isolated as a pale yellow foam.

(Found: M^+, 687.1230. $C_{35}H_{27}Cl_2N_3O_8$ requires M, 687.1175), (M^+-Cl peak; Found: M^+-Cl, 652.1481. $C_{35}H_{27}ClN_3O_8$ requires M-Cl, 652.1487); n.m.r. (300 MHz): δ2.04(3H, s, NAc), 4.78(2H, m, 2H-5'), 4.92(1H, m, H-4'), 6.02(1H, t, H-3'), 6.20(1H, t, H-2'), 7.19(1H, d, H-1', $J_{1',2'}$= 4.5 Hz), 7.48(9H, m, OBz), 7.63(1H, s, H-5), 7.94(6H, m, OBz), 8.82(1H, s, H-2), 9.76(1H, bs, NH); m/z 691(M^++4, 5%), 689(15), 687(28), 654(40), 652(98), 594(6), 592(13), 567(3), 565(8), 532(22), 530(54), 445(90), 322(2), 270(3), 243(6), 201(8), 166(1), 122(18), 105(100), 77(38).

The slower moving band afforded compound 14 (0.64 g, 22% yield) as a pale yellow foam.
(Found: M^+, 687.1180. $C_{35}H_{27}Cl_2N_3O_8$ requires M, 687.1175); n.m.r. (90 MHz): δ2.02(3H, s, NAc), 4.80(3H, m, H-4', 2H-5'), 6.00(1H, m, H-3'), 6.20(1H, m, H-2'), 7.03(1H, d, H-1', $J_{1',2'}$= 4 Hz), 7.27-7.79(9H, m, OBz), 7.65 (1H, s, H-6), 7.76-8.06(6H, m, OBz), 8.83(1H, s, H-2), 9.70(1H, bs, NH); m/z 691(M^++4, 9%), 689(M^++2,30), 687(M^+,58), 654(46), 652(98), 614(8), 473(8), 456(13), 449(10), 447(30), 445(98), 429(7), 407(9), 281(4), 270(4), 253(5), 243(9), 208(42), 201(98), 149(34), 105(100), 94(80), 77(48).

5-Acetylamino-4,7-dichloro-1-β-D-ribofuranosylbenzimidazole (15)

The blocked riboside 14(0.6 g) was deblocked with Amberlyst A-26(OH^-)[8a] (150 mg), following a procedure similar to that described for compounds 6 and 10. The product (15) was obtained as a white solid (0.31 g, 94% yield), m.p. 150-152°C.
(Found: C, 45.01; H, 4.10; N, 11.40. $C_{14}H_{15}Cl_2N_3O_5$ requires C, 44.68; H, 3.98; N, 11.17%); u.v.: λ_{max} (0.1M-NaOH), 288nm (ε, 2400), 257 nm (ε, 11900), λ_{max} (0.1M-HCl), 261nm (ε, 10400); n.m.r. (90 MHz): δ2.10(3H, s, NAc), 3.67(2H, m, 2H-5'), 4.00-4.13(3H, 2 overlapping m, H-3', H-4', OH-4'), 4.36(1H, m, H-2'), 5.17(1H, m, OH-3'), 5.58(1H, m, OH-2'), 6.43(1H, d, H-1', $J_{1',2'}$ = 4 Hz), 7.59(1H, s, H-6), 8.79(1H, s, H-2), 9.68(1H, s, NH); m/z 379(M^++4 ,3%), 377(M^++2 ,20), 375(M^+, 67), 322(21), 320(35), 297(33), 295(44), 281(98), 247(1), 245(7), 243(8), 210(10), 208(30), 203(63), 201 (100), 173(7), 167(9).

6-Acetylamino-4,7-dichloro-1-β-D-ribofuranosylbenzimidazole (18)

The riboside 17 (0.5 g) was deprotected according to the procedure described for 6 and 10. The product (18) was obtained as a white solid (0.25 g, 93% yield), m.p. 230-231°C.
(Found: C, 44.38; H, 3.99; N, 11.00. $C_{14}H_{15}Cl_2N_3O_5$ requires C, 44.68; H, 3.98; N, 11.17%); u.v.: λ_{max} (0.1M-NaOH), 264nm (ε, 4920). λ_{max} (0.1M-CHl) 264nm(ε, 8400), 201nm(ε, 18250); n.m.r. (90 MHz): δ 2.06(3H, s, NAc), 3.66

(2H, m, 2H-5'), 3.96(1H, m, H-4'), 4.14(1H, t, H-3'), 4.37(1H, t, H-2'), 5.15(2H, m, OH-3', OH-4'), 5.56(1H, m, OH-2'), 6.53(1H, d, H-1', $J_{1',2'}$= 4 Hz), 7.56(1H, s, H-5), 8.80(1H, s, H-2), 9.69(1H, bs, NH); m/z 379(M^++4, 0.5%), 377(M^++2, 1), 375(6), 281(30), 252(42), 247(1), 245(8), 243(10), 242 (10), 210(1), 208(32), 205(10), 203(61), 201(100), 173(3), 139(7), 103(7).

Reaction of 5-amino-6-fluoro-2-methylbenzimidazole (20) and 5-formylamino-6-fluoro-2-methylbenzimidazole (21) with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride

(a) Method B was followed with 5-amino-6-fluoro-2-methylbenzimidazole (20)[3] (1.2 g), the crude reaction product was purified several times by column chromatography using ethyl acetate-hexane (1:1) as the eluant, and finally by preparative t.l.c. using ethyl acetate-hexane (1:1) as the eluant. From the faster moving band a yellow foam was obtained. This was identified as the diriboside 22 (0.34 g, 4% yield). n.m.r. (90 MHz): δ 2.83 (3H, s, CH_3), 4.40(1H, m, H-4'), 4.60(1H, m, H-4"), 4.92(4H, m, 2H-5', 2H-5"), 5.90 and 6.06(5H, 2 overlapping m, H-1', H-2', H-2", H-3', H-3"), 6.90 (1H, m, H-1"), 7.20-8.03(32H, m, OBz, H-4, H-7).

The slower moving band afforded a white foam (0.2 g, 3% yield), which was identified as a mixture of two isomers 24, from the mass spectra. The n.m.r. spectrum showed that it was a mixture (74%: 26%) of two nucleosides (N-1 and N-3).

(Found: M^+, 713.2210. $C_{41}H_{32}FN_3O_8$ requires M, 713.2173). n.m.r. (300 MHz): δ2.55(3H, s, CH_3), 2.6(3H, s, CH_3), 6.48(1H, d, H-1', $J_{1'2'}$= 6 Hz), 6.58 (1H, d, H-1", $J_{1"2"}$= 6 Hz), 7.30-8.10(41H, m, 6 OBz, 2 NBz, H-orto to F), 8.14(1H, d, H-meta to F, $J_{F,H}$= 9 Hz), 8.28(1H, d, H-orto to F, $J_{F,H}$= 13 Hz), 8.38(1H, d, H-meta to F, $J_{F,H}$= 9 Hz), 9.97(1H, bs, NH), 10.02(1H, bs, NH); m/z 714(M^++1, 46%), 713(80), 673(7), 651(22), 635(11), 610(13), 609(31), 591(4), 469(86), 445(40), 365(6), 269(B^+, 90), 201(75), 164(2), 122(22), 105(100), 94(6), 77(40).

(b) Method A was followed with 5-formylamino-6-fluoro-2-methyl-benzimidazole (21)[3] (1.3 g). The syrup obtained was purified by column chromatography several times using ethyl acetate-hexane (1:1) as the eluant and finally by preparative t.l.c. using ethyl acetate-hexane (1:1) as the eluant. From the faster-moving band, a white foam was isolated (0.2 g, 4% yield). The mass spectrum indicated that it was a mixture of the two isomers, 23. The n.m.r. spectrum indicated that was a mixture (64% : 36%) of two nucleosides.

n.m.r. (300 MHz): δ2.55(3H, s, CH_3), 2.60(3H, s, CH_3), 6.50(1H, d, H-1', $J_{1'2'}$= 4 Hz), 6.62(1H, d, H-1", $J_{1"2"}$= 4 Hz), 7.33-8.06(34H, m, 6 OBz, 2

H-ortho to F, 2 H-meta to F), 8.38(1H, d, HCON, collapses to a singlet on D_2O shake), 8.50(1H, d, HCON, collapses to a singlet on D_2O shake), 10.02 (1H, bs, NH), 10.04(1H, bs, NH); m/z 638(M^++1, 2%), 637(6), 610(32), 609 (73), 506(32), 505(98), 487(13), 445(97), 401(4), 341(90), 269(23), 193 (B^++1, 7), 165(38), 122(34), 105(100), 77(71).

From the slower moving band a yellow foam was obtained (0.3 g, 5% yield). From the mass spectrum it was identified as 24, identical to the compounds isolated from the ribosylation of compound 20.

Deprotection of the ribosides 23.

The blocked ribosides 23 were deblocked with Amberlyst A-26(OH^-)[8a], as previously described for compounds 6 and 11. To give a white foam. This was identified as a mixture of isomers, 25.

n.m.r. (90 MHz): δ2.41 (3H, s, CH_3), 2.42(3H, s, CH_3), 5.66(1H, d, H-1', $J_{1'2'}$= 6 Hz), 5.74(1H, d, H-1", $J_{1"2"}$= 6 Hz), 6.92(1H, d, H-meta to F, $J_{F,H}$= 8 Hz), 6.97(1H, d, H-meta to F, $J_{F,H}$= 8 Hz), 7.23(1H, d, H-ortho to F, $J_{F,H}$= 12 Hz), 7.72(1H, d, H-ortho to F, $J_{F,H}$= 12 Hz); m/z 297(M^+, 8%), 245(12), 215(20), 166(10), 165(100), 114(15), 96(4), 74(6).

Deprotection of the ribosides 24.

(a) The blocked ribosides 24 were deprotected with Amberlyst A-26(OH^-)[8a], as previously described, to give a yellow foam. This was identified as the mixture of isomers 26.

n.m.r. (90 MHz): δ2.50(3H, s, CH_3), 2.56(3H, s, CH_3), 5.64(1H, d, H-1', $J_{1'2'}$= 6 Hz), 5.77(1H, d, H-1", $J_{1"2"}$= 6 Hz), 6.92(1H, d, H-meta to F, $J_{F,H}$= 8 Hz), 7.00(1H, d, H-meta to F, $J_{F,H}$= 8 Hz), 7.41(1H, H-ortho to F, $J_{F,H}$= 11 Hz), 7.53(10H, m, 2NBz), 7.63(1H, d, H-ortho to F, $J_{F,H}$= 12Hz). m/z 403(M^+ +2, 0.6%) 402(M^+ +1, 4), 401(M^+, 17), 297(55), 269(45), 165(100), 73(24), 105(22).

(b) Deprotection of the mixture of the isomers 24 with Amberlyst A-26 (OH^-)[8a] heating under reflux, gave a yellow foam. This was identified as the mixture of isomers 25, identical to the compounds isolated from the deprotection of the mixture of isomers 23.

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