Tetrahedron 66 (2010) 7155–7160

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 2-pyranosyl benzothiazoles, benzimidazoles and benzoxazoles via nucleophilic addition reactions of pyranosyl nitrile oxides

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ARTICLE INFO

Article history:
Received 27 April 2010
Received in revised form
15 June 2010
Accepted 28 June 2010
Available online 24 July 2010

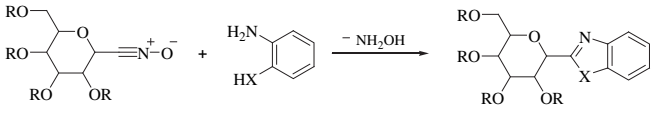
Keywords:
Nitrile oxides
C-Glycosides
Pyranosyl benzimidazoles
Pyranosyl benzoxazoles
Pyranosyl benzothiazoles
X-ray crystallography

ABSTRACT

Reaction of per-*O*-acetylated-β-D-pyranosyl nitrile oxides, generated by dehydrochlorination of the corresponding hydroximoyl chlorides, with 2-aminothiophenol afforded 2-(β-D-pyranosyl)benzothiazoles. 1,2-Diaminobenzene and 2-aminophenol reacted similarly to yield 2-(β-D-pyranosyl)benzimidazoles and 2-(β-D-pyranosyl)benzoxazoles, respectively. The structures of 2-β-D-glucopyranosylbenzimidazole (**17**), 2-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)benzimidazole (**19**) and the xylopyranosyl thiohydroximate **13** were established by X-ray crystallography.

1. Introduction

Nucleoside analogues in which a heterocycle is attached via a carbon atom to the anomeric position of a furanose have been the subject of intensive investigation and useful biological activity has been found for such C-nucleosides.[1] In contrast, less attention has been paid to pyranosyl-substituted heterocyclic systems.[2–14] 2-Pyranosyl benzothiazoles (**1**) have been studied as inhibitors of glycosidase[2] and glycogen phosphorylase,[3,4] and as masked formyl and acyl *C*-glycoside equivalents;[5,6] methods for their synthesis include reaction of 2-aminothiophenol with pyranosyl cyanides,[2,3,7,9] and addition of 2-lithiobenzothiazole to a D-aldonolactone and subsequent deoxygenation of the resulting ketal.[5] Pyranosylbenzimidazoles (**2**) have also been investigated as glycosidase[2] and glycogen phosphorylase inhibitors,[3,4] and recently as potential growth inhibitors of pathogenic yeasts;[10] they have been prepared by the reaction of 1,2-diaminobenzene with pyranosylcarboxylic acids,[9] thioimidates[3] and pyranosylmethanal dimethylacetals.[8] Pyranosyl benzoxazoles (**3**), however, appear to be unknown. We now report that pyranosyl benzothiazoles, benzimidazoles and benzoxazoles can all readily be prepared by reaction of pyranosyl nitrile oxides (**4**) with, respectively, 2-aminothiophenol, 1,2-diaminobenzene and 2-aminophenol. The synthetic route (Scheme 1) is based on the original work of Sasaki et al. who used this approach to prepare the 2-aryl analogues from aryl nitrile oxides.[15]



Scheme 1.

2. Results and discussion

2.1. Generation of pyranosyl nitrile oxides

As nitrile oxides are prone to dimerisation to 1,2,5-oxadiazole-2-oxides (furoxans)[16] they are usually generated in situ, either by base-induced dehydrohalogenation of hydroximoyl halides or by dehydration of nitromethyl compounds.[17] We have previously reported a short and efficient method for the preparation of pyranosyl hydroximoyl chlorides,[13,14,18] and these were therefore used as the precursors of the nitrile oxides required for the present work. The route is illustrated in Scheme 2 for the D-glucose-derived hydroximoyl chloride **5** as a source for the D-glucopyranosyl nitrile oxide **6**. It involves initial addition of nitromethane to D-glucose and acetylation to afford the pyranosylnitromethane derivative **7**, which is then converted to the hydroximoyl chloride **5** by reduction to the pyranosyl oxime[19] and finally reaction with chlorine. Treatment with base then releases the nitrile oxide **6**.

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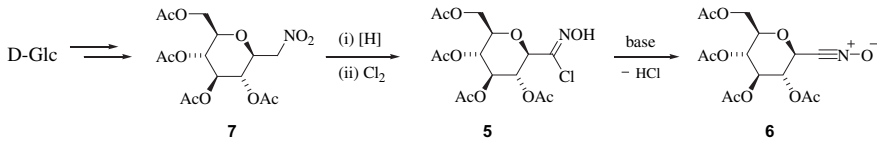
doi:10.1016/j.tet.2010.06.076



Scheme 2.

2.2. Benzothiazoles

The procedure adopted for the preparation of the pyranosyl benzothiazoles was based on that reported by Sasaki et al. for the aryl analogues.[15] In a typical experiment, a solution of the xylopyranosyl hydroximoyl chloride **8** (0.6 mmol) and 2-aminothiophenol (1.5 mmol) in ethanol (10 mL) was heated at reflux under nitrogen for 5 h. Work-up of the reaction mixture afforded the per-acetylated 2-β-D-xylopyranosylbenzothiazole **9** (90%) as a white crystalline solid (Table 1, entry 1). Under these conditions there was no evidence for the formation of the dipyranosylfuroxan **10**,[13] the dimer of the intermediate nitrile oxide. The per-acetylated β-D-glucopyranosyl benzothiazole **11** (81%) was prepared similarly from the glucose-derived hydroximoyl chloride **5** (Table 1, entry 2). Attempts to achieve these reactions at room temperature, as reported by Sasaki et al.[15] and others[20] for the arene nitrile oxide additions, were not successful. The products **9** and **11** were identified from their spectroscopic properties by comparison with those of similar compounds in the literature.[3,21] In addition to the expected NMR signals for the pyranose and arene rings there were ^{13}C NMR peaks at ~166 ppm, characteristic for C-2 of 2-pyranosyl benzothiazoles. The formation of the benzothiazole is believed to involve initial dehydrochlorination of the hydroximoyl chloride by 1 equiv of the aminothiophenol acting as a base thus generating the nitrile oxide, nucleophilic attack by a second equivalent of the amine to form the amidoxime **14**/**15**, and finally intramolecular nucleophilic displacement of hydroxylamine to yield **9**/**11** (Scheme 3). The possibility of nucleophilic attack on the nitrile oxide by the thiol, rather than the amine, was considered unlikely in view of the observations of Sasaki et al.;[15] presumably the neutral conditions do not favour the formation of the more nucleophilic thiolate anion. We have previously shown that pyranosyl amidoximes are formed on reaction of anilines with pyranosyl nitrile oxides.[18] Furthermore, Risitano et al. have reported the isolation of amidoxime intermediates when studying the corresponding reaction of 1,2-diaminobenzene with arene nitrile oxides.[22] These conclusions are supported by a reaction carried out in the presence of triethylamine as the base to achieve the dehydrochlorination of the hydroximoyl chloride **8**; under these conditions the thiohydroximate **13** (78%) was formed, together with traces of the furoxan **10**.[13] Attempts to convert **13** into the benzothiazole **11** by heating in ethanol under reflux were not successful. The structure of thiohydroximate **13** was confirmed by X-ray crystallography (Fig. 1). In the crystal the thiohydroximate moiety adopts the *Z*-configuration and the S–C=N–O unit is near planar [torsion angle 2.036(4)°]. The formation of the *Z*-product is consistent with the asynchronous concerted process proposed by Hegarty et al.[23] for nucleophilic additions to nitrile oxides.

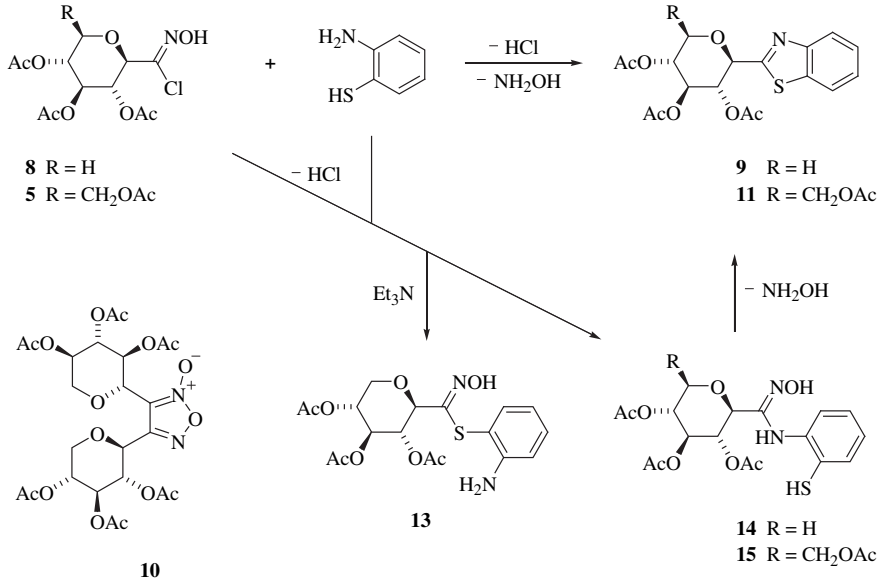
Table 1
2-(β-D-Pyranosyl)benzazoles

Entry	Benzazole	X	2-Substituent	Yield/%
1	**9**	S	Xyl-Ac$_3$	90
2	**11**	S	Glc-Ac$_4$	81
3	**16**	NH	Glc-Ac$_4$	89
4	**19**	NH	Xyl-Ac$_3$	83
5	**21**	NH	Gal-Ac$_4$	62
6	**23**	O	Xyl-Ac$_3$	68
7	**25**	O	Glc-Ac$_4$	71
8	**26**	O	Gal-Ac$_4$	61
9	**17**	NH	Glc	95
10	**20**	NH	Xyl	93
11	**24**	O	Xyl	92

Xyl-Ac$_3$: 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl; Glc-Ac$_4$: 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; Gal-Ac$_4$: 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl; Xyl: Glc: β-D-glucopyranosyl; β-D-xylopyranosyl.

2.3. Benzimidazoles

The approach used to prepare the 2-pyranosylbenzimidazoles (Table 1, entries 3–5) was similar to that described above for the benzothiazoles. Reaction of the D-glucose-derived hydroximoyl chloride **5** with 1,2-diaminobenzene (1:2.5 molar ratio) in ethanol



Scheme 3.

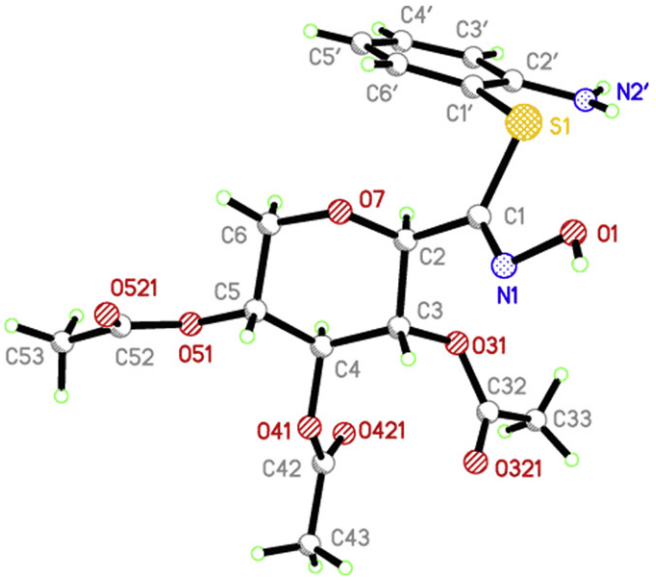
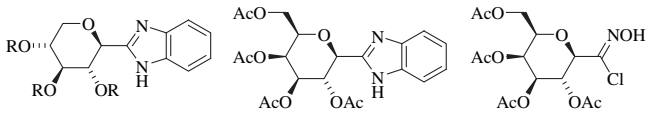


Figure 1. Crystal structure of thiohydroximate **13**.

under reflux for 5 h afforded, after work-up, the per-acetylated β-D-glucopyranosylbenzoimidazole **16** in 89% yield. In this case, however, it also proved possible to carry out the reaction at room temperature in similar yield, albeit using longer reaction times (16 h cf. 5 h). In pilot experiments the product was separated from unreacted 1,2-diaminobenzene by chromatography. This time-consuming work-up was greatly improved by diluting the reaction mixture with dichloromethane and washing with 4% aq $CuSO_4$; this step afforded a lilac-coloured precipitate attributable to formation of a copper phenylenediamine complex.[24] Pure product was obtained by filtration through a silica pad and recrystallisation from EtOAc/hexane. The reaction is believed to proceed by nucleophilic addition of one of the amino groups to the pyranosyl nitrile oxide to form the amidoxime **18**, followed by nucleophilic displacement of hydroxylamine by the other amino group as outlined in Scheme 4. Finally, the product was de-acetylated using the conditions reported by Field et al.,[25] involving treatment with powdered 4 Å molecular sieves in warm methanol, to afford 2-β-D-glucopyranosylbenzimidazole (**17**) (84% overall from hydroximoyl chloride **5**). The corresponding reaction of the D-xylose-derived hydroximoyl chloride **8** with 1,2-diaminobenzene yielded the expected xylopyranosylbenzimidazole **19** in 83% yield, from which the de-acetylated analogue **20** (93%) was obtained following treatment with triethylamine in methanol. The D-galactose-derived benzimidazole **21** (62%) was prepared similarly from the hydroximoyl chloride **22**. The products were identified from their spectroscopic properties by comparison with those in the literature.[3,8] Noteworthy features of the NMR spectra in $CDCl_3$ for per-acetylated compound **16** were the single broad ^1H NMR signal for 4-H/7-H and the apparent simplicity of the ^{13}C NMR spectra: the only distinct peaks for the carbons of the benzimidazole moiety were those at 148.8 ppm (C-2) and 123.4 ppm (C-5/C-6); the remaining carbons gave broad signals.

This effect is attributed to rapid exchange between the protons attached to N-1 and N-3 of the imidazole; such prototropic tautomerism is well established for $CDCl_3$ solutions of imidazoles and benzimidazoles.[26] In contrast, the NMR spectra of the deprotected glycosyl benzimidazoles **17** and **20** did not show this effect and had the expected signals for the benzimidazole fragment.



19 R = Ac
20 R = H

21 **22**

The structures of pyranosylbenzimidazoles **17** (Fig. 2) and **19** (Fig. 3) were established by X-ray crystallography. For the D-glucose-derived compound **17** the Cramer and Pople puckering parameters[27] [Q=0.579 Å, θ=1.7°, ϕ=351°] for the six-membered ring comprising O1′, C1′, C2′, C3′, C4′, C5′ show that it adopts the expected $^4C_1$ conformation. In particular the θ value of 1.7° is close the theoretical value for the chair conformation (θ=0°). Similarly for the D-xylo-pyranosylbenzimidazole derivative **19** Q=0.576 Å, θ=6.1° and ϕ=41°. The bond lengths for the heterocyclic ring of the benzimidazole **17** [N1–C2 1.360(2), C2–N3 1.314(2), N3–C4 1.395(2), C4–C9 1.400(2), C9–N1 1.384(2) Å] are similar to those recorded for benzimidazole itself [N1–C2 1.361(7), C2–N3 1.315(8), N3–C4 1.376(8), C4–C9 1.398(7), C9–N1 1.390(7) Å].[28] Of particular note is the dihedral angle (82.7°) between the best plane of the benzimidazole atoms and the plane through C1′–C3′–C5′ of the pyranoid ring.

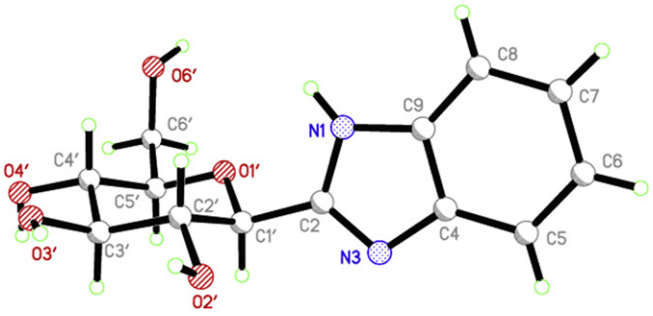
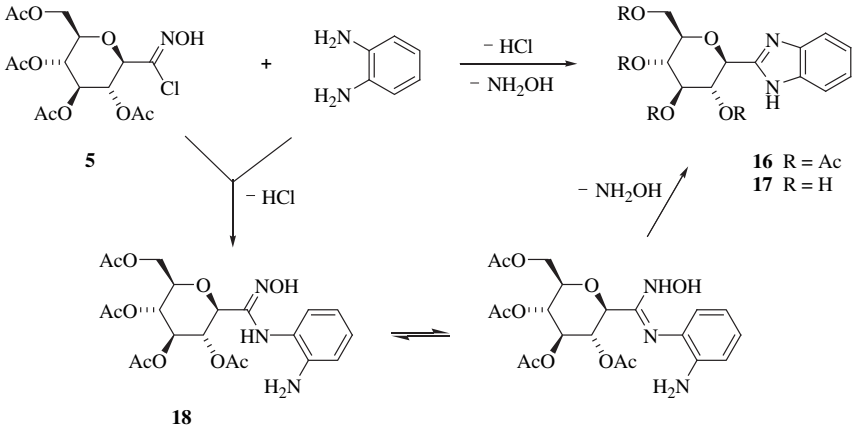


Figure 2. Crystal structure of 2-β-D-glucopyranosylbenzimidazole (**17**).



Scheme 4.

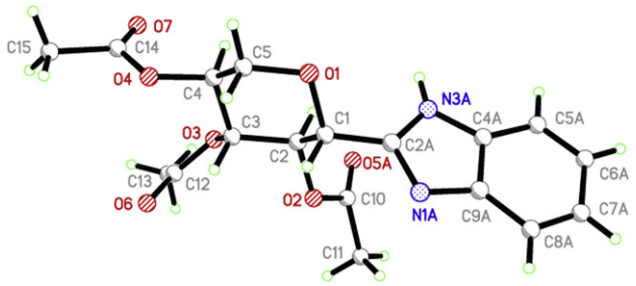
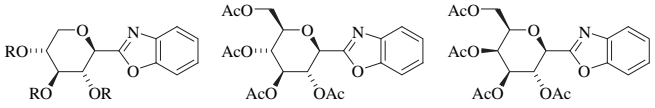


Figure 3. Crystal structure of 2-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)benzimidazole (**19**).

2.4. Benzoxazoles

In contrast to the 2-pyranosyl benzothiazoles and benzimidazoles described above, there have been no reports, to the best of our knowledge, of 2-pyranosyl benzoxazoles. It was therefore of interest to see if the nitrile oxide addition approach, using 2-aminophenol instead of 2-aminothiophenol as the nucleophile, would prove successful. A solution of the D-xylose-derived hydroximoyl chloride **8** (0.6 mmol) and 2-aminophenol (1.5 mmol) in ethanol was therefore heated at reflux for 5 h. After work-up of the reaction mixture the target benzoxazole **23** was obtained in 68% yield. The reaction was also found to proceed at room temperature (16 h) with no reduction in yield. Subsequent treatment with triethylamine/methanol afforded 2-β-D-xylopyranosyl benzoxazole (**24**) (92%). The D-glucose and D-galactose analogues **25** and **26** were prepared similarly (Table 1, entries 6–8). The products were identified from their characteristic spectroscopic properties. Their ^{1}H and ^{13}C NMR data are all consistent with the presence of the pyranose and benzoxazole units in the proposed structures. In particular, the δ_C values for C-2 (159–163 ppm), C-3a (140–141 ppm) and C-7a (150–151 ppm) are typical of 2-alkyl benzoxazoles.[29]



23 R = Ac
24 R = H

25 **26**

In conclusion, 2-pyranosyl benzothiazoles, benzimidazoles and benzoxazoles can all be prepared in good to excellent yields from pyranosyl hydroximoyl chlorides by reaction with the appropriate 2-substituted aniline. These reactions are believed to involve initial dehydrochlorination of the hydroximoyl chloride to generate the pyranosyl nitrile oxide, followed by nucleophilic addition of the aniline and, finally, intramolecular displacement of hydroxylamine. The key addition–cyclisation reactions proceed under mild and neutral conditions and do not require robust protecting groups and chromatographic purification is largely avoided. Whereas pyranosyl-substituted benzothiazoles and benzimidazoles have been previously reported, these are believed to be the first examples of pyranosyl benzoxazoles. This nitrile oxide approach therefore offers an effective alternative to current methods that proceed, for example, via the corresponding nitrile. For example, in five steps D-xylose can be converted to 2-β-D-xylopyranosylbenzimidazole in 30% overall yield.

3. Experimental

3.1. General methods

Melting points were measured on a Gallenkamp capillary apparatus and are uncorrected. Optical rotations were measured at 21 °C on an Optical Activity Polaar 20 polarimeter using 2 ml of filtered solution. The ^{1}H and ^{13}C NMR spectra were recorded with Brucker WP200SY, AX250, WH360 or Varian VXR600 spectrometers on solutions in $CDCl_3$ (unless otherwise stated) with Me_4Si as internal standard. Positive-ion FAB and high resolution mass spectra were obtained on a Kratos MS50TC instrument using either glycerol or thioglycerol matrices. Merck aluminium-backed plates coated with Kieselgel GF_{254} (0.2 mm) were used for analytical TLC; detection was by UV or with a staining solution [$P_2O_5\times24MoO_3\times xH_2O$ (10 g), $(NH_4)_2Ce(NO_3)_6$ (5 g), H_2 (450 mL), and H_2SO_4 (50 mL)] and heat. Dry flash chromatography was carried out using Kieselgel GF_{254} and eluted under water pump vacuum.

3.2. Pyranosyl hydroximoyl chlorides (2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-alditols)

The D-glucose-derived hydroximoyl chloride **5** was prepared, as previously reported,[14] by passing dry chlorine gas through a solution of tetra-*O*-acetyl-β-D-glucopyranosylformaldoxime[19] in dry dichloromethane at −78 °C until the colour changed from blue to green. On warming to room temperature the colour faded and the product was isolated as solid by removing the solvent in vacuo and trituration with ice-cold Et_2O. The D-xylose and D-galactose hydroximoyl chlorides **8** and **22** were prepared similarly.

*3.2.1. 3,4,5-Tri-O-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-gluco-hexitol (**8**).* White powder (98%); mp 147–149 °C; δ_H (250 MHz, $CDCl_3$) 1.92, 1.95, 1.98 (9H, 3×s, $COCH_3$), 3.34 (1H, dd, *J*=11.3, 10.8 Hz, 6a-H), 4.12 (1H, dd, *J*=11.3, 6.1 Hz, 6e-H), 4.17 (1H, d, *J*=9.3 Hz, 2-H), 5.01 (1H, ddd, *J*=10.8, 8.0, 6.1 Hz, 5-H), 5.15 (1H, dd, *J*=9.3, 9.2 Hz, 3-H), 5.22 (1H, dd, *J*=9.2, 8.0 Hz, 4-H), 8.80 (1H, br s, NOH); δ_C (63 MHz, $CDCl_3$) 20.4, 20.6 (3×$COCH_3$), 66.5 (C-6), 68.5, 68.9, 73.1, 78.8 (C-2,3,4,5), 136.5 (C-1) 169.3, 169.9, 170.5 ($COCH_3$). HRMS (FAB): MH^+, found 338.06427. $C_{12}H_{16}{}^{35}ClNO_8$ requires 338.06442.

*3.2.2. 3,4,5,7-Tetra-O-acetyl-2,6-anhydro-1-deoxy-1-chloro-1-hydroxyimino-D-glycero-L-manno-heptitol (**22**).* White solid (99%); mp 169–171 °C; δ_H (250 MHz, $CDCl_3$) 1.93, 1.95, 2.00, 2.13 (12H, 4×s, $COCH_3$), 3.96 (1H, t, 5-H), 4.07–4.10 (2H, m, 7a-H, 7b-H), 4.20 (2H, d, *J*=9.8 Hz, 2-H), 5.04 (1H, dd, 4-H), 5.39 (1H, dd, 5-H), 5.47 (1H, dd, *J*=10.1, 9.8 Hz, 3-H), 9.07 (s, OH); δ_C (63 MHz, $CDCl_3$) 21.0, 21.0, 21.1, 21.1 ($COCH_3$), 61.9 (C-7), 66.6, 67.6, 72.1, 74.7, 79.2 (C-2,3,4,5,6), 137.1 (C-1), 169.9, 170.7, 170.8, 171.1 ($COCH_3$); *m*/*z* (FAB) 410 (MH^+); HRMS (FAB): MH^+, found 410.08537. $C_{15}H_{20}{}^{35}ClNO_{10}$ requires 410.08540.

3.3. Benzothiazoles

3.3.1. General procedure for the synthesis of the benzothiazoles. A solution of the pyranosyl hydroximoyl chloride (0.6 mmol, 1 equiv) and 2-aminothiophenol (1.5 mmol, 2.5 equiv) in ethanol (10 mL) was heated at reflux under an atmosphere of nitrogen for 5 h. The products were usually found to crystallise from the solution on cooling, although the following alternative work-up was also employed. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 0.1 aq M HCl (50 mL), the aqueous layer was further extracted with CH_2Cl_2 (2×50 mL), and the combined organic layers dried ($MgSO_4$). Removal of the solvent in vacuo afforded the crude product, which was purified by dry flash chromatography (silica, hexane/Et_2O, gradient elution).

*3.3.1.1. 2-(2,3,4-Tri-O-acetyl-β-D-xylopyranosyl)benzothiazole (**9**)*[7]. White solid (90%); mp 160–161 °C (lit.[7] 161–162 °C); $[\alpha]_D^{20}$ −36 (*c* 0.6, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.91, 1.97, 2.00 (9H, 3×s, $COCH_3$), 3.48 (1H, dd, *J*=11.2, 10.5 Hz, 5′axial-H), 4.28 (1H, dd, *J*=11.2, 5.5 Hz, 5′equatorial-H), 4.76 (1H, d, *J*=9.5 Hz, 1′-H), 5.06 (1H, ddd, *J*=10.5, 9.3,

5.5 Hz, 4′-H), 5.19 (1H, dd, *J*=9.5, 9.4 Hz, 2′-H), 5.34 (1H, dd, *J*=9.4, 9.3 Hz, 3′-H), 7.36–7.44 (2H, m, Ar), 7.81–7.96 (2H, m, Ar); δ_C (63 MHz, $CDCl_3$) 20.5 ($COCH_3$), 66.9 (C-5′), 68.8, 71.4, 72.8, 77.9 (C-1′,2′,3′,4′), 121.8, 123.2, 125.4, 126.1 (C-4,5,6,7), 134.7 (C-7a), 152.5 (C-3a), 166.6 (C-2), 169.3, 169.7, 170.1 ($COCH_3$); *m*/*z* (FAB) 393 (MH^+); HRMS (FAB): MH^+ found 393.09568. $C_{18}H_{20}NO_7S$ requires 393.09605.

*3.3.1.2. 2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)benzothiazole (**11**)*[3,21]. White solid (81%); mp 128–129 °C (lit.[3] 128–129 °C, lit.[21] 129–130 °C); $[\alpha]_D^{20}$ −24 (*c* 1, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.99, 2.05, 2.10, 2.14 (12H, 4×s, $COCH_3$), 3.99 (1H, ddd, *J*=9.4, 4.7, 2.5 Hz, 5′-H), 4.28 (1H, dd, *J*=12.4, 2.5 Hz, 6′b-H), 4.37 (1H, dd, *J*=12.4, 4.7 Hz, 6′a-H), 4.97 (1H, d, *J*=9.5 Hz, 1′-H), 5.30 (1H, dd, *J*=9.5, 9.2 Hz, 2′-H), 5.37 (1H, dd, *J*=9.5, 9.4 Hz, 4′-H), 5.47 (1H, dd, *J*=9.5, 9.3 Hz, 3′-H), 7.39–7.54 (2H, m, Ar), 7.89–8.56 (2H, m, Ar); δ_C (63 MHz, $CDCl_3$) 20.2, 20.3, 20.4 ($COCH_3$), 61.7 (C-6′), 67.9, 71.1, 73.3, 76.1, 76.4 (C-1′,2′,3′,4′,5′), 121.6, 123.1, 125.3, 125.9 (C-4,5,6,7), 134.6 (C-7a), 152.4 (C-3a), 166.2 (C-2), 168.9, 169.1, 169.9, 170.3 ($COCH_3$); *m*/*z* (FAB) 466 (MH^+); HRMS (FAB): MH^+ found 466.11680. $C_{21}H_{24}NO_9S$ requires 466.11718.

3.4. Benzimidazoles

3.4.1. General procedure for the synthesis of the benzimidazoles. A solution of the pyranosyl hydroximoyl chloride (0.6 mmol, 1 equiv) and 1,2-diaminobenzene (1.5 mmol, 2.5 equiv) in ethanol was stirred under an atmosphere of nitrogen, either at reflux for 5 h or at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 4% aq $CuSO_4$ solution (50 mL); the aqueous layer was further extracted with CH_2Cl_2 (2×50 mL), and the combined organic layers dried ($MgSO_4$). Removal of the solvent in vacuo afforded the crude product, which was purified by filtration through a silica pad and trituration with ice-cold Et_2O.

*3.4.1.1. 2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)benzimidazole (**16**).* White solid (89%); mp 171–172 °C; $[\alpha]_D^{20}$ −20 (*c* 1, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 2.14, 2.21, 2.25 (12H, 4×s, $COCH_3$), 4.12 (1H, ddd, *J*=10.2, 5.2, 2.0 Hz 5′-H), 4.33 (1H, dd, *J*=12.5, 2.0 Hz, 6′b-H), 4.51 (1H, dd, *J*=12.5, 5.2 Hz, 6′a-H), 5.04 (1H, d, *J*=9.7 Hz, 1′-H), 5.36 (1H, dd, *J*=9.7, 9.5 Hz, 2′-H), 5.50 (1H, dd, *J*=10.1, 9.1 Hz, 4′-H), 5.61 (1H, dd, *J*=9.5, 9.1 Hz, 3′-H), 7.41–7.48 (2H, m, Ar), 7.76 (2H, br s, Ar); δ_C (63 MHz, $CDCl_3$) 20.9, 21.0, 21.0, 21.1 ($COCH_3$), 62.5 (C-6′), 66.2, 68.7, 70.9, 73.8, 75.1 (C-1′,2′,3′,4′), 123.4 (C-4,5,6,7), 134.6 (C-3a), 148.8 (C-7a), 152.4 (C-2), 170.0, 170.5, 169.9, 171.1, 171.2 ($COCH_3$); *m*/*z* (FAB) 449 (MH^+); HRMS (FAB): MH^+ 449.15606. $C_{21}H_{24}N_2O_9$ requires 449.15601.

*3.4.1.2. 2-(2,3,4-Tri-O-acetyl-β-D-xylopyranosyl)benzimidazole (**19**).* White solid (83%); mp 152–153 °C; $[\alpha]_D^{20}$ −78 (*c* 1, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.89, 1.98, 2.01 (9H, 3×s, $COCH_3$), 3.46 (1H, dd, *J*=11.3, 10.4 Hz, 5′axial-H), 4.18 (1H, dd, *J*=11.3, 5.6 Hz, 5′equatorial-H), 4.70 (1H, d, *J*=9.7 Hz, 1′-H), 5.03 (1H, ddd, *J*=10.4, 9.6, 5.6 Hz, 4′-H), 5.21 (1H, dd, *J*=9.7, 9.4 Hz, 2′-H), 5.35 (1H, dd, *J*=9.6, 9.4 Hz, 3′-H), 7.08–7.75 (2H, m, Ar), 7.50 (2H, br s, Ar); δ_C (63 MHz, $CDCl_3$) 20.5, 20.5, 20.6 ($COCH_3$), 67.0 (C-5′), 68.9, 70.6, 72.7, 75.1 (C-1′,2′,3′,4′), 122.9 (C-4,5,6,7), 134.7 (C-3a), 148.6 (C-7a),152.5 (C-2), 169.8, 169.9, 170.0 ($COCH_3$); *m*/*z* (FAB) 377 (MH^+); HRMS (FAB): MH^+ 377.13424. $C_{18}H_{21}N_2O_7$ requires MH^+ 377.13488.

*3.4.1.3. 2-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)benzimidazole (**21**).* White solid (62%); mp 211–213 °C; $[\alpha]_D^{20}$ −2 (*c* 0.5, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.92, 1.93, 1.98, 2.06 (12H, 4×s, $COCH_3$), 4.03–4.23 (3H, m, 5′-H, 6′a-H, 6′b-H), 4.77 (1H, d, *J*=9.9 Hz, 1′-H), 5.19 (1H, dd, *J*=10.3, 3.3 Hz, 3′-H), 5.42 (1H, dd, *J*=10.3, 9.9 Hz, 2′-H), 5.49 (1H, m, 4′-H), 7.17–7.20 (2H, m, 5-H, 6-H), 7.38––7.65 (2H, m, 4-H, 7-H), 10.14 (1H, s, 1-H); δ_C (63 MHz, $CDCl_3$) 21.0, 21.0, 21.1, 21.1 ($COCH_3$), 62.0 (C-6′), 68.0, 68.2, 71.9, 75.5, 75.6 (C-1′,2′,3′,4′,5′), 123.5, 123.5 (C-5, C-6), 149.0 (C-2), 170.2, 170.5, 170.5, 170.9 ($COCH_3$); *m*/*z* (FAB) 449 (MH^+); HRMS (FAB): MH^+ 449.15617. $C_{21}H_{24}N_2O_9$ requires 449.15601.

3.5. Benzoxazoles

3.5.1. General procedure for the synthesis of the benzoxazoles. A solution of the pyranosyl hydroximoyl chloride (0.6 mmol, 1 equiv) and 2-aminophenol (1.5 mmol, 2.5 equiv) in ethanol was stirred under an atmosphere of nitrogen either at reflux for 5 h or at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 0.1 M aq HCl (50 mL); the aqueous layer was extracted with CH_2Cl_2 (2×50 mL), and the combined organic layers dried ($MgSO_4$). Removal of the solvent in vacuo afforded the crude product, which was purified by filtration through a silica pad.

*3.5.1.1. 2-(2,3,4-Tri-O-acetyl-β-D-xylopyranosyl)benzoxazole (**23**).* White solid (68%); mp 155–156 °C; $[\alpha]_D^{20}$ −74 (*c* 1, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.84, 1.97, 2.00 (9H, 3×s, $COCH_3$), 3.47 (1H, dd, *J*=11.3, 10.3 Hz, 5′axial-H), 4.26 (1H, dd, *J*=11.3, 5.5 Hz, 5′equatorial-H), 4.68 (1H, d, *J*=10.2 Hz, 1′-H), 5.08 (1H, ddd, *J*=10.3, 9.2, 5.5 Hz, 4′-H), 5.31 (1H, dd, *J*=10.2, 9.1 Hz, 2′-H), 5.43 (1H, dd, *J*=9.2, 9.1 Hz, 3′-H), 7.27–7.32 (2H, m, Ar), 7.47–7.51 (1H, m, Ar), 7.64–7.68 (1H, m, Ar); δ_C (63 MHz, $CDCl_3$) 20.5, 20.6 ($COCH_3$), 66.9 (C-5′), 68.5, 69.9, 72.6, 73.9 (C-1′,2′,3′,4′), 110.8, 120.4, 124.6, 125.8 (C-4,5,6,7), 140.2 (C-3a), 150.6 (C-7a), 159.9 (C-2), 169.1, 169.6, 170.1 ($COCH_3$); *m*/*z* (FAB) 378 (MH^+); HRMS (FAB): MH^+ 378.11935. $C_{18}H_{20}NO_8$ requires 378.11889.

*3.5.1.2. 2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)benzoxazole (**25**).* White solid (71%); mp 174–175 °C; $[\alpha]_D^{20}$ −36 (*c* 1, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.81, 1.97, 1.99, 2.01 (12H, 4×s, $COCH_3$), 3.86 (1H, ddd, *J*=9.9, 4.8, 2.2 Hz, 5′-H), 4.09 (1H, dd, *J*=12.6, 2.2 Hz, 6′b-H), 4.25 (1H, dd, *J*=12.6, 4.8 Hz, 6′a-H), 4.76 (1H, d, *J*=10.0 Hz, 1′-H), 5.19 (1H, dd, *J*=10.0, 9.5 Hz, 2′-H), 5.33 (1H, dd, *J*=9.9, 9.3 Hz, 4′-H), 5.51 (1H, dd, *J*=9.5, 9.3 Hz, 3′-H) 7.28–7.33 (2H, m, Ar), 7.49–7.52 (1H, m, Ar), 7.65–7.69 (1H, m, Ar); δ_C (63 MHz, $CDCl_3$) 20.7, 20.9, 21.0, 21.1 ($COCH_3$), 62.3 (C-6′), 68.3, 69.5, 70.2, 73.9, 76.9 (C-1′,2′,3′,4′), 111.5, 120.9, 125.1, 126.4 (C-4,5,6,7), 140.7 (C-3a), 151.2 (C-7a), 159.9 (C-2), 169.3, 169.7, 170.6, 171.0 ($COCH_3$); *m*/*z* (FAB) 450 (MH^+); HRMS (FAB): MH^+ 450.14098. $C_{21}H_{24}NO_{10}$ requires 450.14002.

*3.5.1.3. 2-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)benzoxazole (**26**).* White solid (61%); mp 84–86 °C; $[\alpha]_D^{20}$ −6 (*c* 0.5, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.83, 1.93, 1.95, 2.16 (12H, 4×s, $COCH_3$), 4.07–4.18 (3H, m, 5′-H, 6′a-H, 6′b-H), 4.72 (1H, d, *J*=9.9 Hz, 1′-H), 5.17 (1H, dd, *J*=10.2, 3.3 Hz, 3′-H), 5.49 (1H, m, 4′-H), 5.65 (1H, dd, *J*=10.2, 9.9 Hz, 2′-H), 7.28–7.33 (2H, m, 5′-H, 6′-H), 7.52 (1H, dd, 4-H), 7.68 (1H, dd, 7-H); δ_C (63 MHz, $CDCl_3$) 20.9, 21.0, 21.1, 21.1 ($COCH_3$), 62.0 (C-6′), 67.6, 67.7, 72.0, 74.7, 75.6 (C-1′,2′,3′,4′,5′), 111.5, 121.0, 125.1, 126.4 (C-4,5,6,7), 140.8 (C-7a), 150.7 (C-3a), 160.2 (C-2), 169.5, 170.5, 170.7, 170.8 ($COCH_3$); *m*/*z* (FAB) 450 (MH^+); HRMS (FAB): MH^+ 450.13982. $C_{21}H_{23}NO_{10}$ requires 450.14002.

3.6. Deprotection reactions

3.6.1. General procedures. Method A: A modified version of the procedure described by Bazin et al.[30] The benzazole (0.3 mmol) was dissolved in MeOH (5 ml) and the stirred with triethylamine (0.36 mmol) at room temperature under nitrogen for 36 h. Removal of the solvent in vacuo afforded the crude product as a white solid.

Method B: A modified version of the procedure described by Field et al.[25] A mixture of the benzimidazole (0.4 mmol) and powdered, activated 4 Å molecular sieves (equal in weight to that of the sugar) in HPLC grade methanol (5 mL) was stirred at room temperature. On completion of the reaction (monitored by TLC) the

mixture was filtered through Celite and the solvent removed in vacuo to afford the crude product as a white solid.

*3.6.1.1. 2-β-D-Glucopyranosylbenzimidazole (**17**)*[3,8]. White solid (95%) (method B); mp 253–254 °C (lit.[3] syrup, lit.[8] 267–268 °C); $[\alpha]_D^{20}$ 21 (*c* 1, MeOH); δ_H (360 MHz, DMSO) 3.24 (1H, ddd, *J*=9.3, 9.0 Hz, 4′-H), 3.33 (1H, ddd, *J*=9.3, 9.2 Hz, 3′-H), 3.37 (1H, m, *J*=9.0, 5.8, 1.4 Hz, 5′-H), 3.49 (1H, ddd, *J*=11.9, 5.8 Hz, 6′b-H), 3.67 (1H, ddd, *J*=9.8, 9.2 Hz, 2′-H), 3.75 (1H, ddd, *J*=11.9, 1.4 Hz, 6′a-H), 4.37 (1H, d, *J*=9.8 Hz, 1′-H), 4.58 (1H, t, OH), 5.12 (1H, d, OH), 5.16 (1H, d, OH), 5.19 (1H, d, OH), 7.12–7.26 (2H, m, Ar), 7.46–7.65 (2H, m, Ar); δ_C (93 MHz, DMSO); 62.9 (C-6′), 71.6, 74.3, 77.5, 79.3 (C-2′,3′,4′,5′), 83 (C-1′), 112.8, 120.2, 122.6, 123.7 (C-4,5,6,7), 135.5 (C-3a), 144.0 (C-7a), 154.0 (C-2); *m*/*z* (FAB) 281 (MH^+); HRMS (FAB): MH^+ 281.11362. $C_{13}H_{17}N_2O_5$ requires 281.11375.

*3.6.1.2. 2-β-D-Xylopyranosylbenzimidazole (**20**).* White solid (93%) (methods A and B); mp 232–233 °C; $[\alpha]_D^{20}$ −17 (*c* 1, MeOH); δ_H (360 MHz, DMSO) 3.20 (1H, dd, *J*=10.9, 10.7 Hz, 5′axial-H), 3.25 (1H, dd, *J*=9.1, 8.7 Hz, 3′-H), 3.42 (1H, ddd, *J*=10.7, 9.1, 5.2 Hz, 4′-H), 3.59 (1H, dd, *J*=9.7, 8.7 Hz, 2′-H), 3.81 (1H, dd, *J*=10.9, 5.2 Hz, 5′equatorial-H), 4.25 (1H, d, *J*=9.7 Hz, 1′-H), 5.12 (3H, br s, OH), 7.09–7.13 (2H, m, Ar), 7.45–7.49 (2H, m, Ar); δ_C (93 MHz, DMSO) 69.4 (C-3′), 70.0 (C-5′), 72.6 (C-2′), 76.8 (C-1′), 77.8 (C-4′), 111.2, 118.6, 121.0, 122.0 (C-4,5,6,7), 134.6 (C-3a), 142.2 (C-7a), 152.2 (C-2); *m*/*z* (FAB) 251 (MH^+); HRMS (FAB): MH^+ 251.10372. $C_{12}H_{15}N_2O_4$ requires 251.10318.

*3.6.1.3. 2-β-D-Xylopyranosylbenzoxazole (**24**).* White solid (92%) (method A); mp 192–194 °C; $[\alpha]_D^{20}$ −26 (*c* 1, MeOH); δ_H (360 MHz, DMSO) 3.22 (1H, dd, 5′axial-H), 3.24 (1H, ddd, 3′-H), 3.39 (1H, m, 4′-H), 3.60 (1H, ddd, *J*=9.8, 8.6 Hz, 2′-H), 3.78 (1H, dd, 5′equatorial-H), 4.32 (1H, d, *J*=9.8 Hz, 1′-H), 5.09 (1H, d, OH), 5.12 (1H, d, OH), 5.29 (1H, d, OH), 7.29–7.40 (2H, m, Ar), 7.62–7.71 (2H, m, Ar); δ_C (93 MHz, DMSO) 69.3 (C-3′), 70.0 (C-5′), 71.9 (C-2′), 75.8 (C-1′), 77.5 (C-4′), 110.8, 119.8, 124.4, 125.4 (C-4,5,6,7), 140.1 (C-7a), 149.9 (C-3a), 162.8 (C-2); *m*/*z* (FAB) 252 (MH^+); HRMS (FAB): MH^+ 252.08679. $C_{12}H_{14}NO_5$ requires 252.08720.

3.7. X-ray crystal structures of compounds 13, 17 and 19

Diffraction data were collected with graphite-monochromated Mo Kα radiation (λ=0.71073 Å) on a Bruker Smart Apex CCD diffractometer equipped with an Oxford Cryosystems low temperature device operating at 150 K. The structures were solved by direct methods and refined by full-matrix least squares against F^2 (using Shelxtl).[31] All hydrogen atoms were placed geometrically and allowed to ride on their host atom, except for those attached to heteroatoms in compounds **13** and **19**; for compound **17** some disorder exists, and this was treated by using two components, each with 50% occupancy. The crystallographic data are summarised below; these data can be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB12 1EZ, UK. (fax: +44 1223 336033, email: deposit@ccdc.cam.ac.uk via www.ccdc.cam.ac.uk).

*3.7.1. Compound **13**.* $C_{18}H_{22}N_2O_8S$, *M* 426.44, colourless block, crystal dimensions 0.46×0.40×0.31 mm, orthorhombic, space group $P2_12_12_1$, *a*=9.1358(5) Å, *b*=13.3082(7) Å, *c*=17.5321(9) Å, α=90°, β=90°, γ=90°, *V*=2131.6(2) Å^3, D_c=1.329 mg m^{-3}, *Z*=4, 19,133 reflections collected, 5175 independent reflections [*R*(int)=0.0256], giving R_1=0.0380 [4960 data] [$F>4\sigma(F)$] and wR_2=0.0964 for all data (CCDC 660865).

*3.7.2. Compound **17**.* $C_{13}H_{16}N_2O_5$, *M* 280.28, colourless block, crystal dimensions 0.40×0.27×0.16 mm, monoclinic, space group $P2_1$, *a*=6.2177 (2) Å, *b*=9.6686(3) Å, *c*=10.6720(3) Å, α=90°, β=92.6769(10)°, γ=90°, *V*=680.86(3) Å^3, D_c=1.452 mg m^{-3}, *Z*=2, 18,479 reflections collected, 1680 independent reflections [*R*(int)=0.0328], giving R_1=0.0330 [1604 data] [$F>2\sigma(F)$] and wR_2=0.0842 for all data (CCDC 773870).

*3.7.3. Compound **19**.* $C_{18}H_{18}N_2O_7$, *M* 464.46, colourless block, crystal dimensions 0.97×0.66×0.24 mm, hexaganol, space group $P6_5$, *a*=12.1781(2) Å, *b*=12.1781(2) Å, *c*=28.1631(6) Å, α=90°, β=90°, γ=120°, *V*=3617.18(11) Å^3, D_c=1.279 mg m^{-3}, *Z*=6, 21,712 reflections collected, 2060 independent reflections [*R*(int)=0.0673], giving R_1=1049 [1710 data] [$F>4\sigma F$] and wR_2=0.2658 for all data (CCDC 773869).

Acknowledgements

We thank S. Wharton for help with NMR spectra, R. Smith for mass spectrometry work, and H. McNab and S. Moggach for helpful discussions. We are grateful to the EPSRC for financial support.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.06.076.

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