

# Synthesis of $\beta$ -D-ribofuranosylbenzazoles using nitrile oxide addition chemistry

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## Abstract

A nitrile oxide based route to 2- $\beta$ -D-ribofuranosylbenzazoles has been developed. Tri-*O*-benzoyl- $\beta$ -D-ribofuranosylformonitrile oxide (**14**) was generated from the corresponding carbaldoxime **16** by treatment with NCS/pyridine, followed by base-induced dehydrochlorination of the resulting hydroximoyl chloride. Reaction of the nitrile oxide with 1,2-diaminobenzene afforded 2-(tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)benzimidazole (**21**), from which 2-( $\beta$ -D-ribofuranosyl)benzimidazole (**22**) was prepared by treatment with Et<sub>3</sub>N/MeOH. 2-Aminophenol reacted similarly to yield 2-(tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)benzoxazole (**18**). In the absence of a co-reactant dimerisation of the nitrile oxide afforded 3,4-di(tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)-1,2,5-oxadiazole-2-oxide (**17**). The carbaldoxime starting material **16** was prepared from tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl cyanide by reaction with semicarbazide to form the semicarbazone, followed by transimination with hydroxylamine.

**Keywords:** Nitrile oxides, benzimidazoles, benzoxazoles, C-glycosides, C-nucleosides

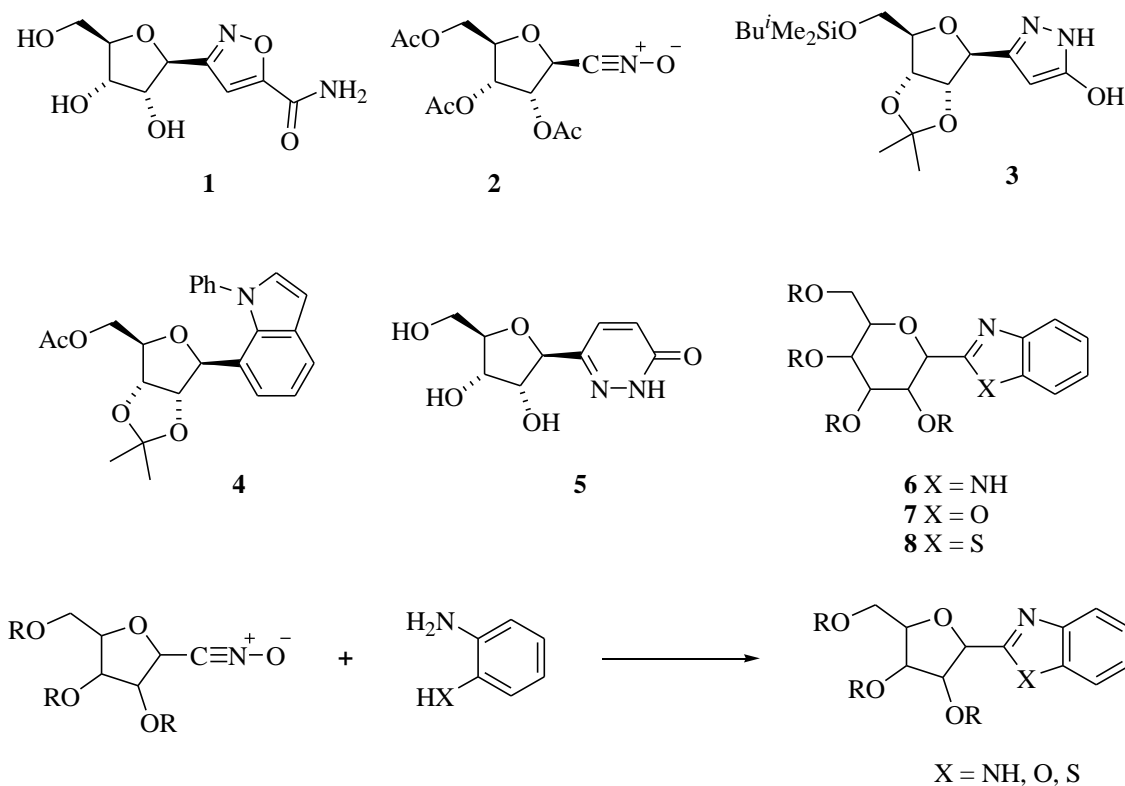
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## Introduction

Nucleoside analogues (*C*-nucleosides) in which the ribose unit is attached to a carbon atom of a heterocycle have attracted much attention, both from a synthetic perspective and on account of their potential biological activities.<sup>1</sup> Two general approaches have been employed for their synthesis: introduction of an intact heterocycle at the anomeric centre of the furanose, and creation of the heterocycle at that position, for example via cycloaddition reactions. Among the latter methods are the 1,3-dipolar cycloaddition reactions of furanosyl nitrile oxides.<sup>2-5</sup> A key step in the preparation by Albrecht, Repke and Moffat of 3-( $\beta$ -D-ribofuranosyl)isoxazole-5-carboxamide (**1**) was the cycloaddition of nitrile oxide **2** to ethyl propiolate.<sup>2</sup> The Kozikowski group used nitrile oxide – isoxazoline chemistry<sup>6</sup> to synthesise various *C*-nucleoside analogues,

e.g. the ribofuranosyl pyrazole **3** and the indole compound **4**,<sup>3,4</sup> and the same method was used by Baraldi et al. for the pyridazinone **5**.<sup>5</sup> Whereas the cycloaddition reactions of nitrile oxides have been extensively used over many years for heterocycle synthesis, their 1,3-nucleophilic addition reactions have received less attention.<sup>7</sup> We have, however, recently established that nitrile oxide addition chemistry can be used to prepare 2-pyranosylbenzazoles (benzimidazoles **6**, benzoxazoles **7**, benzothiazoles **8**),<sup>8</sup> and we anticipated that a similar approach might be used for their furanosyl analogues, as outlined in Scheme 1.

Such furanosylbenzazoles show a range of useful biological activities. They are of interest as antiviral compounds,<sup>9,10</sup> and have been identified as potential therapeutic agents for the treatment of diseases such as cystic fibrosis.<sup>11</sup> In particular it has been reported that they show excellent agonist potency and selectivity for the P2Y<sub>2</sub> receptor, and that they also have enhanced metabolic stability compared with *N*-linked analogues and the natural ligand ATP.<sup>11</sup> Methods for their synthesis have included addition of 2-lithiated benzimidazoles/benzothiazoles to sugar lactones and deoxygenation of the resulting hemiacetals,<sup>12-14</sup> and reaction of 2-substituted anilines with aldonic acids,<sup>11,15</sup> and with acetimidates/thioacetimidates derived from furanosyl cyanides.<sup>16</sup> Forcing conditions were sometimes required, mixtures of isomers formed and overall yields were variable. Alternative approaches are therefore desirable, particularly for the benzoxazoles and benzimidazoles. We selected nitrile oxide addition chemistry as it had the potential to provide furanosyl benzimidazoles, benzoxazoles and benzothiazoles all from the same source.

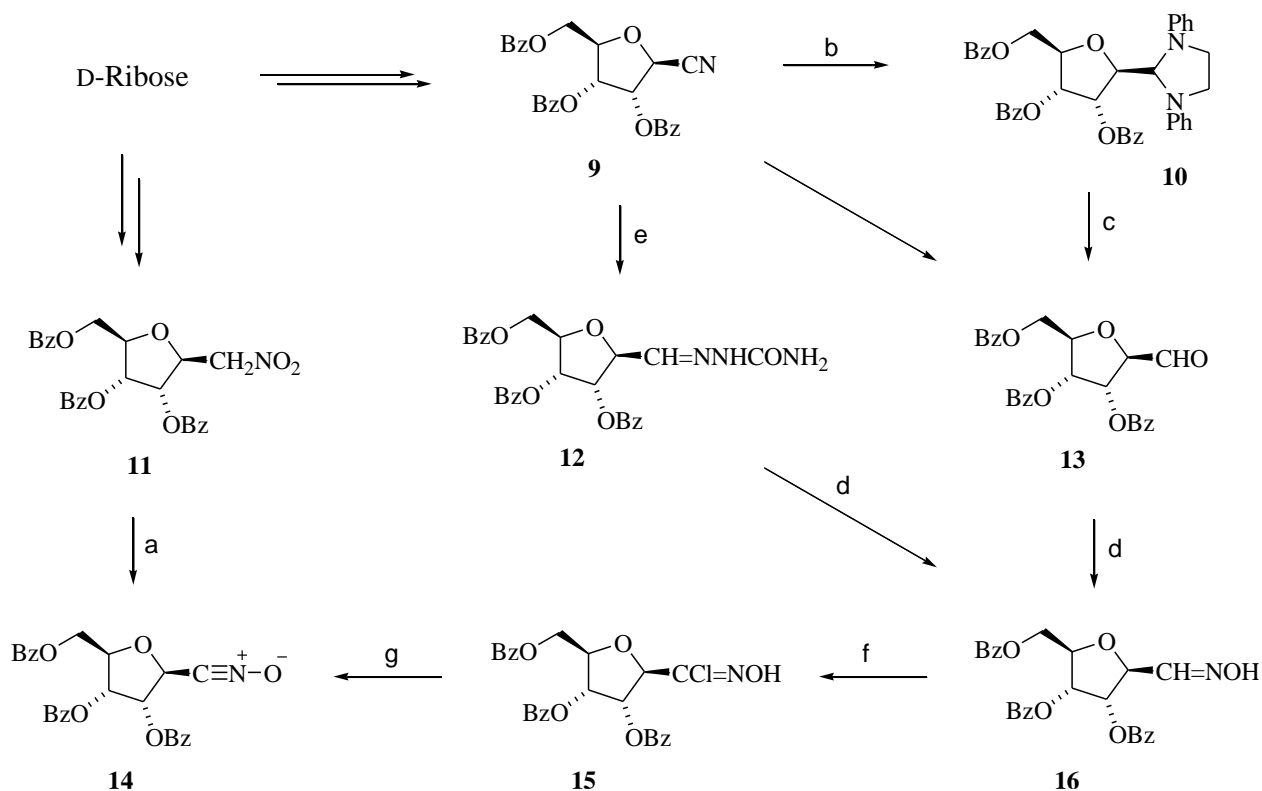


Scheme 1

## Results and Discussion

In order to test the effectiveness of the method we selected the known  $\beta$ -D-ribose-derived nitrile oxide **14**<sup>2</sup> as a representative example that should provide access to a range of benzazole C-nucleoside derivatives. As most nitrile oxides are short-lived compounds that readily dimerise to 1,2,5-oxadiazole *N*-oxides (furoxans), it is common practice in synthetic applications for the nitrile oxides to be generated in situ in the presence of the co-reactant. The two main methods, both of which have been used for carbohydrate synthesis,<sup>17</sup> involve either base-induced dehydrohalogenation of hydroximoyl halides (usually the chloride) or dehydration of nitromethyl compounds.<sup>6,18</sup> In the present case the shortest route is conversion of D-ribose into the nitromethyl compound **11** via initial reaction condensation with nitromethane (the 'Fischer-Sowden reaction'), followed by Mukaiyama-type dehydration of **11** with an isocyanate, e.g. PhNCO<sup>19</sup> or tolylene diisocyanate.<sup>20</sup> However, in our hands and those of others,<sup>21,22</sup> the literature route to the nitromethylribose afforded a mixture of the  $\alpha$ - and  $\beta$ -isomers which were time-consuming to separate and gave only a moderate yield of the target  $\beta$ -product. We therefore turned to the longer but ultimately more reliable route via the cyanide **9**, the oxime **16** and the hydroximoyl chloride **15**, as originally developed by the Moffat group.<sup>2</sup>

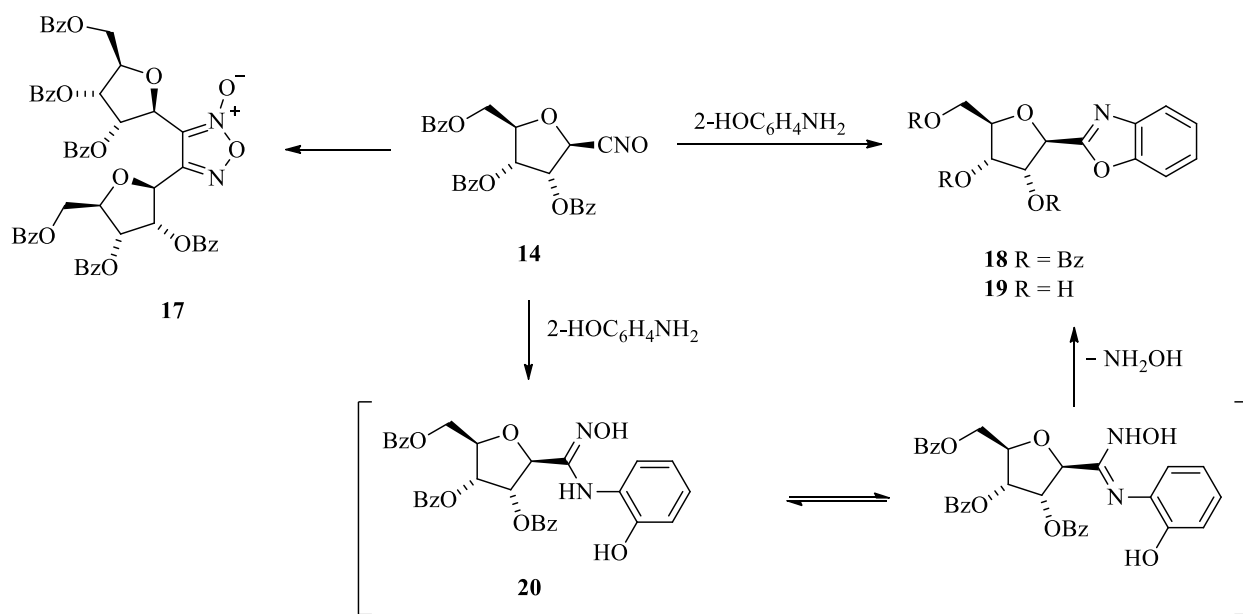
Of the various literature methods for the preparation of the starting material we chose that reported by Morelli et al.,<sup>23</sup> involving reaction of tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl acetate with trimethylsilyl cyanide in the presence of catalytic boron trifluoride etherate, and this afforded the cyanide **9** in 86% yield. As direct hydrolysis of **9** to the aldehyde **13**, and thence the carbaldoxime **16**, was reported to be problematic, the cyanide **9** was first converted into the imidazolidine derivative **10** (59%) by reaction with 1,2-dianilinoethane (Wanzlick's reagent) and sodium hypophosphite in acetic acid and pyridine. Treatment of the product with tosylic acid afforded the crude aldehyde **13**, which was not isolated but reacted immediately with hydroxylamine-pyridine to afford the required aldoxime **16** (45%). Although the oxime had thus been obtained by the Moffat group route, the procedure was not considered satisfactory for larger scale synthesis. Toth and Somsak have reported<sup>24</sup> an alternative method which they used to convert pyranosyl cyanides into pyranosyl aldoximes via the corresponding semicarbazones, and we considered that this approach should also be applicable for their furanosyl counterparts. This proved to be the case. Reaction of the ribofuranosyl cyanide **9** with semicarbazide afforded the semicarbazone **12** (85%), which was then converted to the aldoxime **16** (81%) as a mixture of *E*- and *Z*-isomers by transimination with hydroxylamine. This latter route thus provided the oxime in 69% overall yield from the cyanide, compared with 27% via the imidazolidine.



**Scheme 2.** *Reagents:* (a) RNCO, Et<sub>3</sub>N; (b) PhNHCH<sub>2</sub>CH<sub>2</sub>NHPh, Raney Ni, NaH<sub>2</sub>PO<sub>2</sub>·H<sub>2</sub>O, pyridine, AcOH, H<sub>2</sub>O; (c) TsOH, H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>; (d) NH<sub>2</sub>OH, pyridine; (e) NH<sub>2</sub>NHCONH<sub>2</sub>, Raney Ni, NaH<sub>2</sub>PO<sub>2</sub>·H<sub>2</sub>O, pyridine, AcOH, H<sub>2</sub>O; (f) Cl<sub>2</sub>, Et<sub>2</sub>O or NCS, pyridine, CHCl<sub>3</sub>; (g) Et<sub>3</sub>N.

Attempts to convert the aldoxime **16** into the hydroximoyl chloride **15** with chlorine in diethyl ether, using the technique that we had previously used for pyranosyl hydroximoyl chlorides,<sup>25</sup> were only partially successful and the product was not isolated in pure form. A milder chlorination procedure, originally reported by Larsen and Torssell,<sup>26</sup> employing *N*-chlorosuccinimide in pyridine was therefore investigated. The hydroximoyl chloride was not isolated; instead the nitrile oxide was generated from the crude product by addition of triethylamine. The reaction was first carried out in the absence of a co-reactant in order to provide access to 3,4-di(tri-*O*-benzoyl-β-*D*-ribofuranosyl)furoxan (**17**) (72%), which is of interest both in its own right and is also a likely by-product of reactions involving the nitrile oxide (Scheme 3). The product was identified from its spectroscopic properties. In the <sup>13</sup>C NMR spectrum in CDCl<sub>3</sub> there are, in addition to the expected resonances for the two tri-*O*-benzoylribofuranose units, characteristic peaks at 112.6 (C-3) and 155.0 ppm (C-4) for the carbon atoms of the 1,2,5-oxadiazole ring. These values are typical for unstrained furoxans.<sup>27</sup> In the proton NMR spectrum the two non-equivalent furanosyl substituents give rise to overlapping and only partially resolved signals. There are, however, distinct doublets at 5.46 (H-1) and 5.37 ppm (H-1') for the protons bonded to the carbons adjacent to C-3 and C-4, respectively, of the

furoxan ring; these assignments were made by comparison with data reported for other dialkylfuroxans.<sup>28</sup>

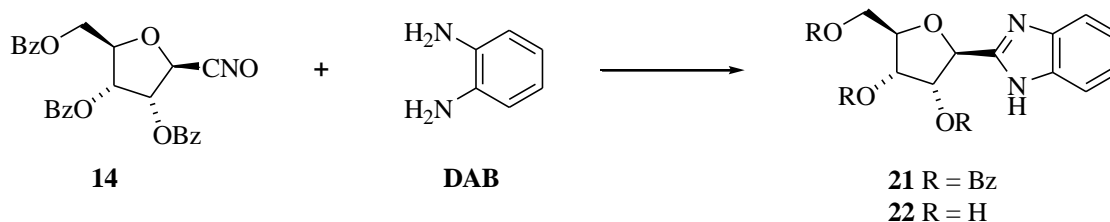


### Scheme 3

Having isolated the furoxan **17** in good yield, and thus established that nitrile oxide **14** could be generated efficiently from the oxime **16** in a one-pot procedure, the synthesis of ribofuranosyl benzoxazoles was investigated. As an efficient route from glycosyl cyanides to glycosyl benzothiazoles is already well established,<sup>29</sup> we concentrated our attention on the benzimidazoles and benzoxazoles. To obtain the benzoxazole **18** nitrile oxide **14** was reacted with 2-aminophenol. A mixture of the oxime **16** (0.30 mmol), *N*-chlorosuccinimide and pyridine in chloroform was heated at 40 °C for 45 minutes and, after cooling and removal of the solvent, 2-aminophenol (0.75 mmol) in ethanol was added and the solution heated at reflux for five hours. From the reaction mixture was isolated 2-(tri-*O*-benzoyl-β-*D*-ribofuranosyl)benzoxazole (**18**) (90%), which was identified from its spectroscopic properties. The carbon NMR spectrum in CDCl<sub>3</sub> showed characteristic signals for the benzoxazole moiety [162.5 (C-2), 152.0 (C-7a), 141.7 (C-3a), 126.9 (C-5), 125.7 (C-6), 121.7 (C-4) and 112.0 ppm (C-7)], which were very similar to those previously reported for 2-pyranosylbenzoxazoles **7**,<sup>8</sup> and are typical of 2-alkyl-substituted benzoxazoles.<sup>30</sup> The presence of the perbenzoylribofuranose unit was evident in both the <sup>13</sup>C and <sup>1</sup>H NMR spectra. The reaction pathway is believed to proceed by initial dehydrochlorination of the hydroximoyl chloride **15** by one equivalent of the 2-aminophenol to generate the nitrile oxide **14**, followed by nucleophilic addition of the anilino group of a second equivalent of 2-aminophenol to form the amidoxime **20**; nucleophilic displacement of hydroxylamine by the phenolic group then leads to the benzoxazole, as illustrated in Scheme 3.

Debenzoylation with NaOMe/MeOH afforded the parent ribofuranosylbenzoxazole **19** as a mixture of  $\alpha$ - and  $\beta$ -anomers.

The approach used to prepare the ribofuranosylbenzimidazole was similar to that described above for the benzoxazole, but using 1,2-diaminobenzene (DAB) instead of 2-aminophenol as the nucleophilic co-reactant. Reaction of the nitrile oxide **14** with DAB (1:2.5 molar ratio) in ethanol at reflux for five hours afforded, after work-up, the per-benzoylated  $\beta$ -D-ribofuranosylbenzimidazole **21** in 92% yield. Work-up of the reaction mixture was aided by washing with 4% aq. CuSO<sub>4</sub>, which removed excess DAB as its copper complex,<sup>31</sup> thus reducing time-consuming chromatographic separations. The <sup>1</sup>H and <sup>13</sup>C NMR spectra in CDCl<sub>3</sub> showed the presence of both the ribofuranose and benzimidazole units. The proton spectrum had the expected benzimidazole peaks at 7.90–7.94 (H-4,7) and 7.23–7.27 ppm (H-5,6). In the carbon spectrum the signals for benzimidazole unit were similar to those reported for the pyranosyl analogues **6**.<sup>8</sup> There were two distinct peaks at 151.3 ppm and 123.2 ppm for C-2 and C-5/6 respectively, with the other carbons giving broad signals. This effect has been reported previously for imidazoles and benzimidazoles,<sup>8,32</sup> and is attributed to rapid proton exchange between N-1 and N-3. Debenzoylation using triethylamine/methanol yielded the parent 2- $\beta$ -D-ribofuranosylbenzimidazole (**22**) (91%). The overall yield from the oxime **16** to the benzimidazole **22** was 82%.



#### Scheme 4

In conclusion, these results also show that nitrile oxide addition chemistry can provide an effective alternative to current synthetic routes to furanosylbenzazoles. For example, 2-( $\beta$ -D-ribofuranosyl)benzimidazole can be prepared in four steps from the corresponding commercially-available cyanide in 58% overall yield. The same approach should also be applicable for the synthesis of 2-furanosylbenzothiazoles. An improved procedure for the conversion of furanosyl cyanides into furanosyl carbaldoximes has also been established.

## Experimental Section

**General.** 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 <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with

Brucker AX250 or Brucker avance spectrometers on solutions in  $\text{CDCl}_3$  (unless otherwise stated) with  $\text{Me}_4\text{Si}$  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<sub>254</sub> (0.2 mm) were used for analytical TLC; detection was by UV or with a staining solution [ $\text{P}_2\text{O}_5$  x 24  $\text{MoO}_3$  x  $x\text{H}_2\text{O}$  (10 g),  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$  (5 g),  $\text{H}_2\text{O}$  (450 mL), and  $\text{H}_2\text{SO}_4$  (50 mL)] and heat. Dry flash chromatography was carried out using Kieselgel GF<sub>254</sub> and eluted under water pump vacuum. 2,3,5-Tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl acetate was purchased from Aldrich and used without further purification.

**2,3,5-Tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl cyanide (9).**<sup>23</sup> To a stirred solution of 2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl acetate (450 mg, 1 mmol), trimethylsilyl cyanide (0.5 mL, 4 mmol) and dry acetonitrile (15 mL) a few drops (0.2 mL) of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  were added. The reaction mixture was stirred under argon at room temperature for 10 minutes. After quenching with aq.  $\text{NaHCO}_3$  (10 mL), the mixture extracted with  $\text{Et}_2\text{O}$  (3 x 30 mL) and the organic layers dried over  $\text{MgSO}_4$ . The solvent was removed *in vacuo* and the resultant oil purified by chromatography (silica, 25%  $\text{EtOAc}$  in hexane) to afford the title compound as a white solid (360 mg, 86%).

**1,3-Diphenyl-2-(2',3',5'-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)imidazoline (10).** Raney nickel (2 g) was added to a vigorously stirred solution of pyridine (8 mL), glacial acetic acid (6 mL) and water (6 mL).  $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$  (1 g) was then added, along with 1,2-dianilinoethane (550 mg, 2.6 mmol) and the D-ribose-derived cyanide **9** (550 mg, 2.5 mmol). After stirring for 16 hour, the resulting mixture was filtered through a pad of celite and the filter cake washed thoroughly with  $\text{CH}_2\text{Cl}_2$ . The filtrate was washed with water (~200 mL), extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 50 mL) and the combined organic layers were dried over  $\text{MgSO}_4$ . The solvent was co-evaporated with water (to remove residual pyridine) to yield a gum. The gum was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL), acetic anhydride (4.72 mL) and triethylamine (8.3 mL) and the mixture stirred for 16 hours. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and stirred with water (20 mL) for 20 minutes before extracting with  $\text{CH}_2\text{Cl}_2$  (2 x 10 mL). The combined organic layers were washed with aq.  $\text{NaHCO}_3$  (20 mL) and dried over  $\text{MgSO}_4$ . Dry-flash chromatography (silica, hexane/ $\text{Et}_2\text{O}$  gradient elution) afforded the product as a colourless oil, which solidified on addition of methanol (295 mg, 59%).  $[\alpha]_{\text{D}}^{20}$  10 ( $c = 0.1$ ,  $\text{CHCl}_3$ ) (lit.<sup>33</sup>  $[\alpha]_{\text{D}}^{23}$  11.2 ( $c = 0.1$ ,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.62–3.77 (2H, m,  $\text{NCH}_2$ ), 3.81–3.96 (2H, m,  $\text{NCH}_2$ ), 4.48 (1H, dd,  $^3J_{5a-4}$  4.7 Hz,  $^2J_{5a-5b}$  11.6 Hz, H-5a), 4.57–4.61 (1H, m, H-4), 4.66 (1H, dd,  $^3J_{5b-4}$  3.2 Hz,  $^2J_{5b-5a}$  11.6 Hz, H-5b), 4.92 (1H, d,  $^3J_{1-2}$  5.4 Hz, H-1), 5.61 (1H, dd,  $^3J_{3-4}$  5.8 Hz,  $^3J_{3-2}$  5.7 Hz, H-3), 5.81 (1H, dd,  $^3J_{2-3}$  5.7 Hz,  $^3J_{2-1}$  5.4 Hz, H-2), 5.97 (1H, s, CHN), 6.79–6.97 (4H, m, ArH), 7.26–7.68 (15H, m, ArH), 7.82–8.06 (6H, m, ArH);  $^{13}\text{C}$  NMR (93 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  48.0 ( $\text{NCH}_2$ ), 48.4 ( $\text{NCH}_2$ ), 65.3 (C-5), 73.4, 73.8, 74.4, (C-2, C-3, C-4), 80.6 (C-1), 84.2 (CHN), 114.2, 114.6, 119.1, 128.5, 130.85 (ArCH), 134.1, 134.4, 134.5 (ArC), 166.5, 166.6, 167.2 (3 x C=O); MS (ES):  $m/z$  483 ( $\text{MH}^+$ ).

**2,5-Anhydro-3,4,6-tri-O-benzoyl- $\beta$ -D-allose semicarbazone (12).** Raney nickel (3.75 g) was added to a vigorously stirred solution of pyridine (10 mL), glacial acetic acid (9 mL) and water (5 mL).  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$  (1.85 g) was added, followed by semicarbazide hydrochloride (550 mg) and KOH (285 mg) in water (5 mL) and the D-ribose-derived cyanide **9** (1.05 g, 2.41 mmol) in pyridine (5 mL). The reaction was heated to 40 °C for 4 hours. The resultant mixture was filtered through a pad of celite and the filter cake was washed thoroughly with  $\text{CH}_2\text{Cl}_2$ . The filtrate was washed with water (~200 mL), extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 50 mL) and the combined organic layers were dried over  $\text{MgSO}_4$ . The solvent was co-evaporated with water (to remove residual pyridine) to yield a gum. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (50 mL) and washed with 1 M HCl (2 x 30 mL),  $\text{NaHCO}_3$  (2 x 30 mL) and dried over  $\text{MgSO}_4$ . Removal of the solvent *in vacuo* afforded crude semicarbazone **12** as a brown foam (1.09 g, 85%).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  4.43 (1H, dd,  $^3J_{5a-4}$  3.6 Hz,  $^2J_{5a-5b}$  11.4 Hz, H-5a), 4.51–4.64 (2H, m, H-4, H-5b), 4.76 (1H, dd,  $^3J_{1-2}$  5.7 Hz,  $^3J_{1-1'}$  4.8 Hz, H-1), 5.69 (1H, dd,  $^3J_{3-2}$  5.2 Hz,  $^3J_{3-4}$  4.7 Hz, H-3), 5.87 (1H, dd,  $^3J_{2-1}$  5.7 Hz,  $^3J_{2-3}$  5.2 Hz, H-2), 7.13 (1H, d,  $^3J_{1-1'}$  4.8 Hz,  $\text{HC}=\text{NNHCONH}_2$ ), 7.22–7.49 (9H, m, ArH), 7.82–8.03 (6H, m, ArH), 9.85 (1H, brs, NH);  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  63.8 (C-5), 67.7, 72.6, 72.8, (C-2, C-3, C-4), 79.9 (C-1), 128.2, 128.3, 128.8, 129.2, 129.5 (ArCH), 133.1, 133.3, 133.6 (ArC), 138.6 ( $\text{HC}=\text{NNHCONH}_2$ ), 157.4 ( $\text{HC}=\text{NNHCONH}_2$ ), 165.1, 165.2, 166.0 (3 x CPh); MS (ES):  $m/z$  532 ( $\text{MH}^+$ ).

**2,5-Anhydro-3,4,6-tri-O-benzoyl- $\beta$ -D-allose oxime (16).** This compound was prepared by two methods:

**Method A.** Tosylic acid (212 mg, 1.1 mmol) was added to a solution of the imidazoline **10** (220 mg, 0.45 mmol) in  $\text{CH}_2\text{Cl}_2$  (4.5 mL), and the mixture stirred at room temperature under nitrogen for 45 minutes. The resultant mixture was filtered and the filter cake washed with  $\text{CH}_2\text{Cl}_2$ , before concentrating the filtrate *in vacuo* (the water bath temperature did not exceed 30 °C). The residue was dissolved in ethanol (2.5 mL) and pyridine (2.25 mL), hydroxylamine hydrochloride (160 mg) was added, and the mixture heated to 95 °C under reflux for 2.5 hours. On cooling, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (50 mL) and washed with aq.  $\text{NHCO}_3$  (50 mL), water (50 mL) and 1 M HCl (50 mL), and the organic layer dried over  $\text{MgSO}_4$ . Dry-flash chromatography (silica, hexane/ $\text{Et}_2\text{O}$  gradient elution) afforded the title compound as a colourless oil (100 mg, 45%).

**Method B.** Hydroxylamine hydrochloride (278 mg) was added to a solution of the semicarbazone **12** (300 mg, 0.6 mmol) in acetonitrile (12.5 mL) and pyridine (4.2 mL), and the resulting mixture was stirred at room temperature under argon for 16 hours. The mixture was diluted with ethyl acetate (30 mL) and washed with 1 M HCl (3 x 30 mL), aq.  $\text{NaHCO}_3$  (3 x 30 mL) and brine (30 mL), before drying the organic layer over  $\text{MgSO}_4$ . Wet-flash chromatography (silica, 25% ethyl acetate in hexane) afforded the title compound as a colourless oil (236 mg, 81%).

$[\alpha]_{\text{D}}^{20}$  14 (c = 0.2, MeOH) (lit.<sup>2</sup>  $[\alpha]_{\text{D}}^{23}$  12.9 (c = 0.2, MeOH));  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  4.61 (1H, dd,  $^3J_{5a-4}$  4.3 Hz,  $^2J_{5a-5b}$  11.7 Hz, H-5a), 4.66–4.71 (m, 1H, H-4), 4.77 (1H, dd,  $^3J_{5b-4}$  3.2 Hz,  $^2J_{5b-5a}$  11.7 Hz, H-5b), 4.95 (1H, dd,  $^3J_{1-2}$  5.5 Hz,  $^3J_{1-\text{CH}=\text{N}}$  5.3 Hz, H-1(E)), 5.53 (1H, dd,



$^3J_{1-\text{CH}=\text{N}}$  5.0 Hz,  $^3J_{1-2}$  4.7 Hz, H-1(Z)), 5.75 (1H,  $^3J_{3-2}$  5.5 Hz,  $^3J_{3-4}$  5.2 Hz, H-3(Z)), 5.80–5.84 (2H, m, H-3(E), H-2(E)), 5.92 (1H, dd,  $^3J_{2-1}$  4.7 Hz,  $^3J_{2-3}$  5.2 Hz, H-2(Z)), 6.99 (1H, d,  $^3J_{\text{CH}=\text{N}-1}$  5.0 Hz, HC=NOH(Z)), 7.31–8.22 (16H, m, HC=NOH, ArH), 8.88 (1H, brs, OH);  $^{13}\text{C}$  NMR (93 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  64.9 (C-5(Z)), 65.2 (C-5(E)), 73.4, 73.6, 74.6, 75.1, 78.5, 79.6, (C-2, C-3, C-4 (E and Z)), 80.2 (C-1(Z)), 80.4 (C-1(E)), 129.5, 129.6, 129.9, 130.1, 130.4, 130.5, 130.8, 130.9, 131.2 (ArCH), 134.4, 134.6, 134.7 (ArC), 148.8 (C=N), 166.3, 166.4, 166.5, 167.4 (6 x COPh); MS (ES):  $m/z$  490 ( $\text{MH}^+$ ).

**3,4-Di(2',3',5'-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)-1,2,5-oxadiazole-2-oxide (17).** A stirred mixture of ribose derived oxime **16** (150 mg, 0.3 mmol), *N*-chlorosuccinimide (41 mg, 0.30 mmol), pyridine (0.01 mL) and chloroform (2.5 mL) was heated to 40 °C under nitrogen for 45 minutes. On cooling, triethylamine (0.3 mL) was added and the mixture stirred for 1 hour. The solution was diluted with  $\text{CH}_2\text{Cl}_2$  (40 mL), 1 M HCl (40 mL) and dried over  $\text{MgSO}_4$ . Dry-flash chromatography (silica, hexane/ $\text{Et}_2\text{O}$  gradient elution) afforded the title compound as a colourless gum (107 mg, 72%).  $[\alpha]_{\text{D}}^{20}$  -7.4 ( $c = 5.65$ ,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  4.45–4.63 (6H, m, H-5a, H-5b, H-5a', H-5b', H-4, H-4'), 5.37 (1H,  $^3J_{1-2}$  5.4 Hz, H-1), 5.46 (2H, d,  $^3J_{1-2}$  4.7 Hz, H-1'), 5.73–5.77 (2H, m, H-3, H-3'), 6.03 (1H, dd,  $^3J_{2-1}$  5.4 Hz,  $^3J_{2-3}$  6.0 Hz, H-2), 6.15 (1H, dd,  $^3J_{2-1}$  4.7 Hz,  $^3J_{2-3}$  5.6 Hz, H-2'), 7.21–7.45 (15H, m, ArH), 7.81–8.18 (m, 12H, ArH);  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  63.6 (C-5), 63.8 (C-5'), 71.9, 72.4, 72.6, 73.9, 74.4, 76.0 (C-2, C-2', C-3, C-3', C-4, C-4'), 80.6 (C-1), 80.3 (C-1') 112.6 (C=N), 128.9, 129.1, 129.2, 129.7, 129.8, 130.0, 130.2 (ArCH), 133.7, 134.1 (ArC), 155.0 (C=N<sup>+</sup>), 165.6, 165.8, 166.4, 166.6 (6 x CPh); HRMS (FAB): Calcd. for  $\text{C}_{54}\text{H}_{42}\text{N}_2\text{O}_{16}$ :  $[\text{M}+\text{H}]$  975.2613. Found:  $m/z$  975.2602.

**2-(2',3',5'-Tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)benzoxazole (18).** A stirred mixture of D-ribose-derived oxime **16** (150 mg, 0.30 mmol), *N*-chlorosuccinimide (41 mg, 0.30 mmol), pyridine (0.01 mL) and chloroform (2.5 mL) was heated to 40 °C under nitrogen for 45 minutes. The solvent was removed *in vacuo* before ethanol (10 mL) and 2-aminophenol (85 mg, 0.75 mmol) were added, and the mixture heated at reflux for 5 hours. On cooling, the solvent was removed *in vacuo* and  $\text{CH}_2\text{Cl}_2$  added to precipitate out excess 2-aminophenol. After filtration, the solution was washed with 1 M HCl (20 mL) and dried over  $\text{MgSO}_4$ . Dry-flash chromatography (silica, hexane/ $\text{Et}_2\text{O}$  gradient elution) afforded the title compound as a colourless gum (155 mg, 92%).  $[\alpha]_{\text{D}}^{20}$  -125 ( $c = 2.9$ ,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  4.66 (1H, dd,  $^3J_{5a-4}$  3.0 Hz,  $^2J_{5a-5b}$  11.5 Hz, H-5a), 4.83–4.92 (2H, m, H-4, H-5b), 5.62 (1H, d,  $^3J_{1-2}$  4.6 Hz, H-1), 6.11 (1H, dd,  $^3J_{3-4}$  5.4 Hz,  $^3J_{3-2}$  4.9 Hz, H-3), 6.28 (1H, dd,  $^3J_{2-3}$  4.9 Hz,  $^3J_{2-1}$  4.6 Hz, H-2), 7.30–7.41 (10H, m, ArH), 7.53–7.58 (3H, m, ArH), 7.72–7.74 (1H, m, ArH), 7.98–8.12 (5H, m, ArH);  $^{13}\text{C}$  NMR (93 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  61.4 (C-5), 64.6, 73.6, 75.7, (C-2, C-3, C-4), 81.6 (C-1), 112.0 (C-7), 121.7 (ArC-4), 125.7 (ArC-6), 126.9 (ArC-5), 129.4, 129.5, 129.8, 129.9, 130.6, 130.9 (ArCH), 131.0, 134.2, 134.6 (ArC), 141.7 (ArC-3a), 152.0 (ArC-7a), 162.5 (ArC-2), 166.2, 166.3, 167.2 (3 x CPh); MS (FAB):  $m/z$  564 ( $\text{MH}^+$ ); HRMS (FAB): Calcd. for  $\text{C}_{33}\text{H}_{25}\text{NO}_8$ :  $[\text{M}+\text{H}]$  564.1658. Found:  $m/z$  564.1666.

**2-(D-Ribofuranosyl)benzoxazole (19).** A solution of 2-(2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)benzoxazole (169 mg, 0.3 mmol) in methanol (8 mL) was stirred at room temperature. Freshly prepared 1 M NaOMe (7 mL) solution was added, and the reaction stirred for 16 hours. Amberlite 120(H<sup>+</sup>) resin was added in portions until the solution was neutral to pH paper. After filtration the resulting solution was concentrated *in vacuo* to afford a residue. Following wet-flash chromatography (silica, 10% methanol in ethyl acetate), 2-( $\beta$ -D-ribofuranosyl)benzoxazole was obtained as an inseparable mixture of anomers ( $\beta$ : $\alpha$ , 62:38) (colourless foam, 65 mg, 87%). <sup>1</sup>H NMR (360 MHz, D<sub>2</sub>O): furanose signals:  $\delta$ <sub>H</sub>  $\beta$ -anomer: 3.74 (1H, dd, <sup>3</sup>J<sub>5a-4</sub> 4.1 Hz, <sup>2</sup>J<sub>5a-5b</sub> 12.7 Hz, H-5a), 3.89 (1H, dd, <sup>3</sup>J<sub>5b-4</sub> 2.9 Hz, <sup>2</sup>J<sub>5b-5a</sub> 12.7 Hz, H-5b), 4.07 (1H, m, H-4), 4.14 (1H, m, H-3), 4.34 (1H, dd, <sup>3</sup>J<sub>2-3</sub> 4.6 Hz, <sup>3</sup>J<sub>2-1</sub> 3.3 Hz, H-2), 4.47 (1H, d, <sup>3</sup>J<sub>1-2</sub> 3.3 Hz, H-1);  $\alpha$ -anomer: 3.71 (1H, dd, <sup>3</sup>J<sub>5a-4</sub> 5.3 Hz, <sup>2</sup>J<sub>5a-5b</sub> 12.6 Hz, H-5a), 3.82 (1H, dd, <sup>3</sup>J<sub>5b-4</sub> 3.4 Hz, <sup>2</sup>J<sub>5b-5a</sub> 12.6 Hz, H-5b), 4.14 (1H, m, H-4), 4.26 (1H, dd, <sup>3</sup>J<sub>3-2</sub> 5.2 Hz, <sup>3</sup>J<sub>3-4</sub> 5.2 Hz, H-3), 4.53 (1H, dd, <sup>3</sup>J<sub>2-1</sub> 5.3 Hz, <sup>3</sup>J<sub>2-3</sub> 5.2 Hz, H-2), 5.08 (1H, d, <sup>3</sup>J<sub>1-2</sub> 5.3 Hz, H-1); aromatic signals:  $\delta$ <sub>H</sub> 6.92–6.96 (m, 2H, ArH), 7.12–7.14 (m, 1H, ArH), 7.38–7.44 (m, 3H, ArH), 7.59–7.67 (m, 2H, ArH); <sup>13</sup>C NMR (63 MHz, D<sub>2</sub>O):  $\delta$ <sub>C</sub> 60.6, 61.8 (C-5 $\alpha$ , C-5 $\beta$ ), 70.5, 71.5, 74.8, 74.9, 78.0, 83.3, 83.4, 85.1 (C-1 $\alpha$ , C-2 $\alpha$ , C-3 $\alpha$ , C-4 $\alpha$ , C-1 $\beta$ , C-2 $\beta$ , C-3 $\beta$ , C-4 $\beta$ ), 111.5, 116.6, 119.8, 120.9, 123.4, 125.5, 126.5, 128.3 (ArCH), 139.6, 149.3, 150.8 (ArC), 164.1 (C=N); *m/z* (FAB) 252 (MH<sup>+</sup>); HRMS (FAB): Calcd. for C<sub>12</sub>H<sub>14</sub>NO<sub>5</sub>: [M+H] 252.08720. Found: *m/z* 252.08755.

**2-(2',3',5'-Tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)benzimidazole (21).** A stirred mixture of D-ribose-derived oxime **16** (150 mg, 0.30 mmol), *N*-chlorosuccinimide (41 mg, 0.30 mmol), pyridine (0.01 mL) and chloroform (2.5 mL) was heated to 40 °C under nitrogen for 45 minutes. The solvent was removed *in vacuo* before adding ethanol (10 mL) and *o*-phenylenediamine (85 mg, 0.75 mmol) and the mixture was heated to reflux for 5 hours. On cooling, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with 4% aq. CuSO<sub>4</sub> solution (50 mL), the aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 mL), and the combined organic layers dried (MgSO<sub>4</sub>). Dry-flash chromatography (silica, hexane/Et<sub>2</sub>O gradient elution) afforded the title compound as a colourless gum (152 mg, 90%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -106 (c = 3.65, CHCl<sub>3</sub>); <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>):  $\delta$ <sub>H</sub> 4.78–4.88 (3H, m, H-5a, H-4, H-5b), 5.72 (1H, d, <sup>3</sup>J<sub>1-2</sub> 4.4 Hz, H-1), 5.80 (1H, dd, <sup>3</sup>J<sub>3-4</sub> 5.3 Hz, <sup>3</sup>J<sub>3-2</sub> 4.8 Hz, H-3), 6.09 (1H, dd, <sup>3</sup>J<sub>2-3</sub> 4.8 Hz, <sup>3</sup>J<sub>2-1</sub> 4.4 Hz, H-2), 7.23–7.27 (2H, m, ArH), 7.33–7.59 (11H, m, ArH), 7.90–7.94 (2H, m, ArH), 8.03–8.08 (4H, m, ArH); <sup>13</sup>C NMR (93 MHz, CDCl<sub>3</sub>):  $\delta$ <sub>C</sub> 64.6 (C-5), 72.6, 76.5, 78.9 (C-2, C-3, C-4), 80.9 (C-1), 114.2–118.7 (bs, C-4, C-7), 123.2 (C-5, C-6), 128.9, 129.0, 129.2, 129.3, 129.6, 130.2 (ArCH), 130.3, 133.9 (ArC), 151.3 (ArC-2), 165.7, 167.2 (3 x C<sub>6</sub>H<sub>5</sub>); MS (FAB): *m/z* 563 (MH<sup>+</sup>); HRMS (FAB): Calcd. for C<sub>33</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>: [M+H] 563.1818. Found: *m/z* 563.1811.

**2-( $\beta$ -D-Ribofuranosyl)benzimidazole (22).** A mixture of the tri-*O*-benzoyl- $\beta$ -D-ribofuranosyl)benzimidazole (**21**) (90 mg, 0.16 mmol), methanol (5 mL) and triethylamine (0.8 mL, 5.7 mmol) was heated at 50°C for 4 days. On cooling, the product was purified by wet-flash chromatography (silica, 10% MeOH in EtOAc) to afford the title compound as a colourless foam (43 mg, 91%). <sup>1</sup>H NMR (250 MHz, D<sub>2</sub>O):  $\delta$ <sub>H</sub> 3.61 (1H, dd, <sup>3</sup>J<sub>5a-4</sub> 3.8 Hz, <sup>2</sup>J<sub>5a-5b</sub> 12.3 Hz,

H-5a), 3.76 (1H, dd,  $^3J_{5b-4}$  2.0 Hz,  $^2J_{5b-5a}$  12.3 Hz, H-5b), 3.98–4.05 (2H, m, H-3', H-4'), 4.21 (1H, dd,  $^3J_{2-1}$  5.3 Hz,  $^3J_{2-3}$  4.4 Hz, H-2), 4.92 (1H, d,  $^3J_{1-2}$  5.3 Hz, H-1), 7.07–7.10 (2H, m, ArH), 7.35–7.41 (2H, m, ArH);  $^{13}\text{C}$  NMR (63 MHz,  $\text{D}_2\text{O}$ ):  $\delta_{\text{C}}$  61.7 (C-5), 71.2, 75.7, 78.9, 84.7 (C-1, C-2, C-3, C-4), 115.3 (broad) (ArC-4, ArC-7), 123.2 (ArC-5, ArC-6), 152.9 (ArC-2); MS (FAB):  $m/z$  251 ( $\text{MH}^+$ ); HRMS (FAB): Calcd. for  $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_4$ :  $[\text{M}+\text{H}]$  251.1032. Found:  $m/z$  251.1032.

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