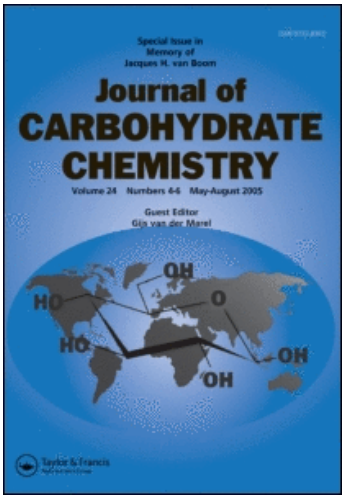


## Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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**To cite this Article** Hashmi, Imran Ali , Feist, Holger , Michalik, Manfred , Reinke, Helmut and Peseke, Klaus(2006) 'Synthesis of "Reversed" Pyrazole-*C*-nucleoside Precursors from Push-pull Activated Monosaccharide Derivatives', Journal of Carbohydrate Chemistry, 25: 1, 19 — 32
**To link to this Article: DOI:** 10.1080/07328300500471770
**URL:** http://dx.doi.org/10.1080/07328300500471770

*Journal of Carbohydrate Chemistry, 25:19–32, 2006*

*ISSN: 0732-8303 print 1532-2327 online*
*DOI: 10.1080/07328300500471770*



# Synthesis of "Reversed" Pyrazole-*C*-nucleoside Precursors from Push-pull Activated Monosaccharide Derivatives

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3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-ulofuranurononitrile (**1**) was reacted with *N*,*N*-dimethylformamide dimethylacetal in tetrahydrofuran to furnish the (*E*)-3-*O*-benzyl-6-deoxy-6-dimethylaminomethylene-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-ulofuranurononitrile (**2**) as a major product. Furthermore, treatment of compound **1** with carbon disulphide and methyl iodide under basic conditions afforded 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-[bis(methylsulfanyl)methylene]-α-D-*xylo*-hept-5-ulofuranurononitrile (**6**). Reaction of **2** and **6** with hydrazines yielded the "reversed" pyrazole-*C*-nucleoside analogs **4, 5a, 5b, 7, 8**, and **9**, respectively.

**Keywords** Deoxyuloses, Nucleoside analogs, Pyrazoles, Push-pull alkenes, Enones, α-Oxoketene-*S*,*S*-acetals

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## INTRODUCTION

The synthesis of "reversed" or "iso-" nucleosides and *C*-nucleosides has been carried out in a search for compounds having anticancer and antiviral activities.[1–3] "Reversed" *C*-nucleosides constitute a class of nucleoside analogs in which the nucleobase is linked by a carbon-carbon bond to a ribose carbon other than C-1. It is anticipated that "reversed" *C*-nucleosides may have increased chemical and enzymatic stability under physiologic conditions. The synthesis of "reversed" *C*-nucleosides has been reported by several laboratories.[4,5]

In recent years, we have reported the preparation of *C*-branched monosaccharides with push-pull functionality that could be used as precursors for the synthesis of "reversed" *C*-nucleoside analogs.[6,7] In this paper, we describe the synthesis of such compounds with a pyrazole moiety starting from D-glucose.

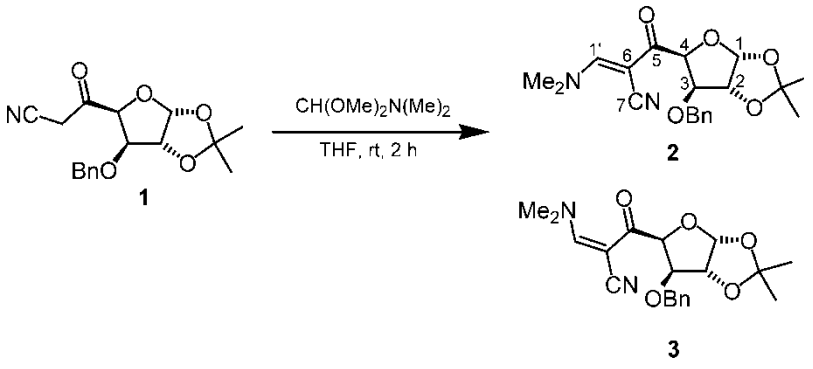


## RESULTS AND DISCUSSION

The 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-ulofuranurononitrile **1** was synthesized starting from D-glucose.[8–13] We have reported the reaction of 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose with acetals of amides to yield the 4,6-*O*-benzylidene-3-deoxy-3-dimethylaminomethylen-α-D-*erythro*-hexopyranosid-2-ulose.[14] Similarly, compound **1** was reacted with *N*,*N*-dimethylformamide dimethylacetal in THF to furnish the crystalline (*E*)-3-*O*-benzyl-6-deoxy-6-dimethylaminomethylene-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-ulofuranurononitrile (**2**) in 72% yield and the noncrystalline (*Z*)-3-*O*-benzyl-6-deoxy-6-dimethylaminomethylene-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-ulofuranurononitrile (**3**) in 5% yield (Sch. 1).

The spectroscopic data of **2** were in accordance with the push-pull character of C,C-double bond.[15] In the $^{13}C$ NMR spectra the signal for C-6 appeared at $\delta = 77.6$ and for C-1′ at $\delta = 157.3$. The CO resonance gave a signal at $\delta = 187.4$, which is shifted upfield compared with this of **1** ($\delta = 196.9$). Similarly, in IR spectrum the CN vibrations could be observed at a lower wave number ($2192\,cm^{-1}$; for **1**: $2257\,cm^{-1}$).

Furthermore, compound **2** was subjected to X-ray analysis at 293 K. The crystallographic data are given below. An ORTEP drawing of compound **2** is shown in Fig. 1 clearly demonstrating the (*E*)-configuration of the double bond. It is known from the literature[15,16] that the bond length of push-pull functionalized double bonds is increased and the single bonds to the donor substituents are shortened. Also in compound **2** this effect can be seen. The bond distance for C6-C8 is 1.38 pm longer than for a noninfluenced C,C-double bond. The interatomic distance C5-C6 (1.46 pm) and C6-C7 (1.41 pm) are shorter than for comparable typical single bonds.




**Scheme 1:** Synthesis of push-pull activated α-D-*xylo*-hept-5-ulofuranurononitriles.



4,6-*O*-Benzylidene-3-deoxy-3-dimethylaminomethylen-α-D-*erythro*-hexo-pyranosid-2-ulose easily reacts with hydrazine to form a pyrazolo anellated pyranoside.[14] The corresponding reaction of the α-dimethylaminomethylene ulofuranurononitrile **2** was performed in ethanol at room temperature using hydrazine hydrate. After 15 min the TLC indicated the absence of starting material. The "reversed" pyrazole-*C*-nucleoside **4** was isolated in a yield of 94% (Sch. 2).

The pyrazole **4** can exist in the tautomeric forms **4a** and **4b** but, due to the fast NH-proton exchange, they were not distinguishable. In the $^{13}C$ NMR spectrum of compound **4**, absence of a carbonyl carbon signal and appearance

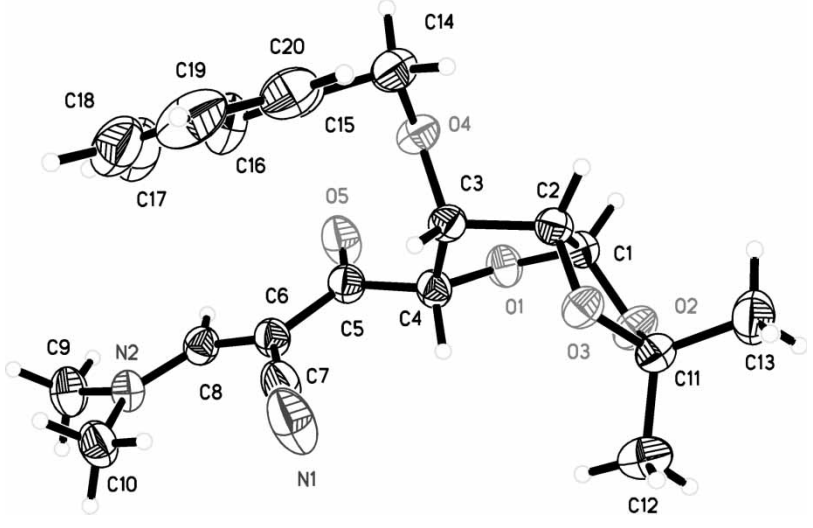
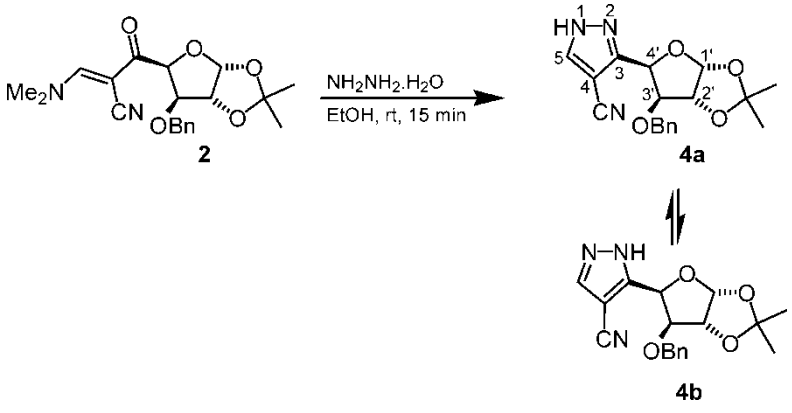



**Figure 1:** ORTEP drawing of compound **2**.




**Scheme 2:** Synthesis of "reversed" pyrazole-*C*-nucleoside.



of two broad singlets of C-5 ($\delta = 139.2$) and C-3 ($\delta = 146.8$) confirmed that cyclization had taken place.

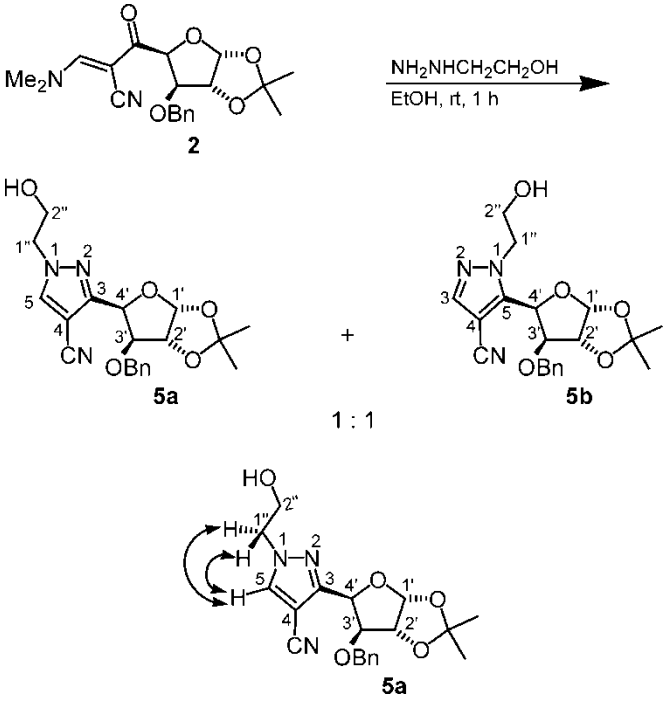
The reaction of compound **2** with 2-hydrazinoethanol in ethanol at room temperature afforded after chromatography the isomeric products **5a** and **5b** in yields of 35% each (Sch. 3). The EI-MS spectra of both compounds supplied an $M^+$ signal at $m/z$ 386. In the $^{13}C$ NMR spectra of both compounds signals of a hydroxyethyl group were visible at $\delta = 54.8$, $\delta = 60.8$, and $\delta = 53.8$, $\delta = 61.4$. All the other spectral data of these two compounds were quite similar and in accordance with the structures of **5a** and **5b**.

By recording a NOESY spectrum, we were able to assign the position of 2-hydroxyethyl group in compound **5a**. Cross peaks between the protons H-5 and H-1″ were observed (Sch. 3), which confirmed the attachment of the 2-hydroxyethyl group at the nitrogen atom in the neighborhood of C-5.

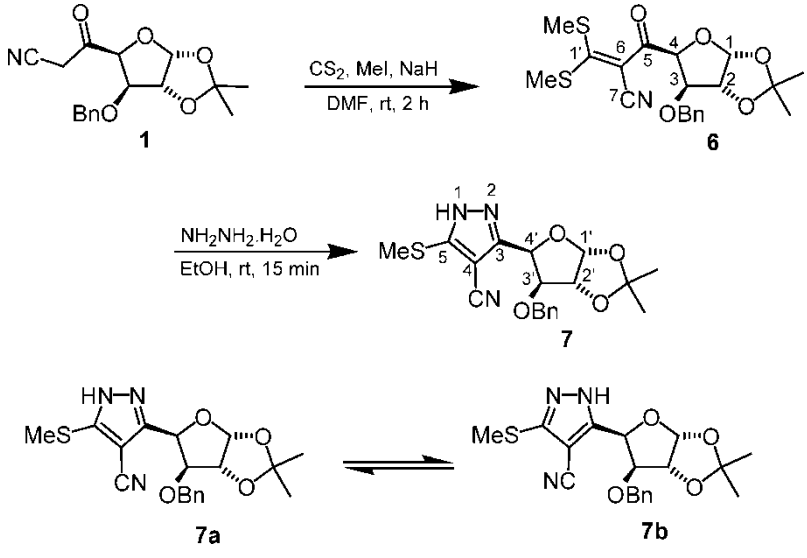
As it is well known, $\alpha$-oxoketene dithioacetals can be prepared by the reaction of cyclic or acyclic ketones with carbon disulphide in the presence of a base and an alkylating agent.[17–19] To synthesize the first type of furanosyl substituted push-pull activated ketene-S,S-acetal, compound **1** was reacted with carbon disulphide and methyl iodide in the presence of sodium hydride in dimethylformamide to give **6** as a yellow syrup in 52% yield (Sch. 4).

The $^1H$ NMR spectrum of compound **6** shows two sharp S-methyl signals at $\delta = 2.46$ and $\delta = 2.62$. In the $^{13}C$ NMR spectrum, S-methyl signals appeared at $\delta = 19.7$ and $\delta = 20.8$, the CO signal was shifted upfield to $\delta = 186.3$ (for **2**: $\delta = 187.4$), and C-1′ gave a strong downfield shift signal at $\delta = 183.7$. The IR spectrum showed CN and CO vibrations at 2201 $cm^{-1}$ and 1683 $cm^{-1}$, respectively. All these spectroscopic data indicate the formation of required compound **6**.

$\alpha$-Oxoketene dithioacetals react easily with hydrazines to form pyrazoles.[6,17,18] To prove the suitability of the $\alpha$-oxoketene dithioacetal **6** for this




**Scheme 3:** Synthesis of "reversed" hydroxyethyl-pyrazole-*C*-nucleosides.



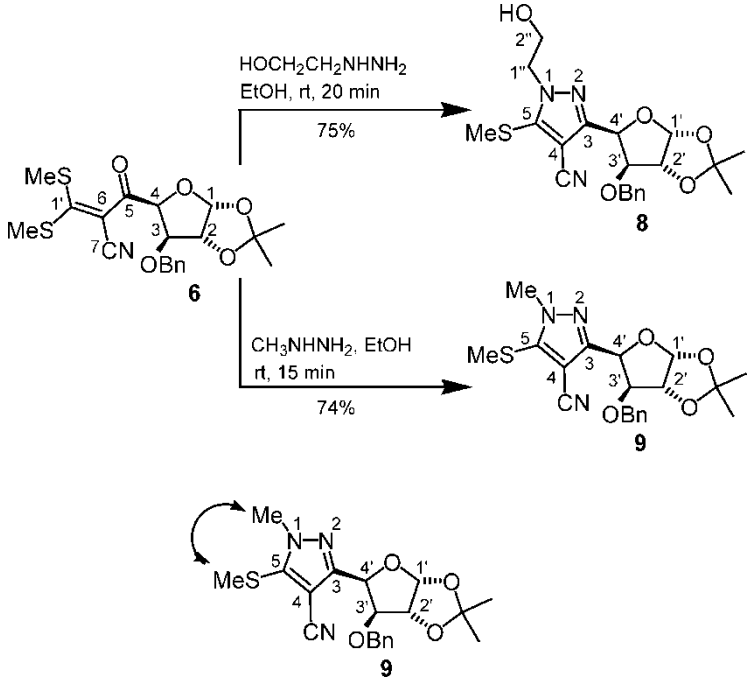

**Scheme 4:** Synthesis of a push-pull activated bis(methylsulfanyl)methylene-α-D-*xylo*-hept-5-ulofuranurononitrile and of "reversed" pyrazole-*C*-nucleoside.

transformation, we studied its reaction with hydrazine hydrate in ethanol. In a simple way the pyrazole **7** was obtained in 87% yield (Sch. 4).

The spectroscopic data confirmed the proposed structure, but it was not possible to determine which of the two tautomers had been formed. As already mentioned for compound **4**, 1*H*-pyrazoles normally constitute an equilibrium of the two possible tautomeric forms in solution (Sch. 4).

Treatment of compound **6** with 2-hydrazinoethanol and methylhydrazine, in ethanol resulted in formation of the substituted 2-hydroxyethylpyrazole **8** and the methylpyrazole **9**, respectively, in good yields (Sch. 5). Always, in these reactions only one main product was obtained in contrast to the reaction of enaminoketone **2** with hydrazinoethanol (Sch. 3) in which two isomers were obtained. Generally, the reactions of such push-pull alkenes **2** and **6**, respectively, proceed according to an addition-elimination mechanism. It seems the reaction of compound **6** afforded a higher nucleophility as **2** and, therefore, 2-hydrazinoethanol and methylhydrazine attack the C-1′ stereoselectively with the substituted N-atom.

The HRMS of compound **8** showed the expected molecular ion peak at $m/z$ 431.15298. The $^{13}C$ NMR displayed resonances for three $CH_2$-groups at $\delta = 51.6$, $\delta = 61.0$, and $\delta = 72.1$. Two $CH_2$ groups belong to 2-hydroxyethyl




**Scheme 5:** Reactions bis(methylsulfanyl)methylene-α-D-*xylo*-hept-5-ulofuranurononitrile **6** with hydrazine derivatives.

and one to benzyl. Two signals at $\delta = 144.0$ (C-3) and $\delta = 151.0$ (C-5) correspond to a pyrazole ring formation.

Similarly, the spectroscopic data proved the structure of pyrazole **9**. Compound **9** showed a molecular ion peak at $m/z$ 401.14177 in the HRMS. The $^{13}$C NMR spectrum displayed a signal at $\delta = 37.2$, which was in agreement with a methyl group attached to an electron-withdrawing nitrogen atom. Two signals at $\delta = 143.0$ (C-3) and $\delta = 150.6$ (C-5) confirmed the pyrazole ring formation.

Furthermore, we were able to check by NOESY experiments which nitrogen atom is carrying the methyl group. Cross peaks were observed between the N-methyl and S-methyl protons in compound **9** (Sch. 5), indicating their vicinal arrangement. With this result in mind and in accordance with the identical chemical shifts for the C-3 and C-5 in the compounds **8**, **9**, also in pyrazole **8**, the 2-hydroxy ethyl group should be linked at the same nitrogen atom.

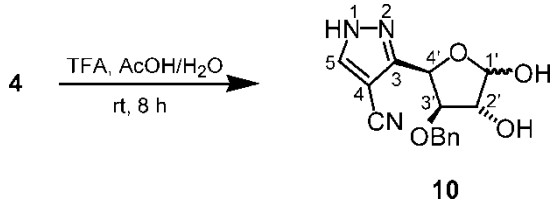
For the deprotection of isopropylidene group of compound **4** (Sch. 6), we used a mixture of acetic acid and water with a few drops of trifloroacetic acid. The reaction mixture was stirred at room temperature for 8 h. The deprotected compound **10** was obtained in a yield of 68%. The $^1$H and $^{13}$C NMR spectra of compound **10** proved the existence of a mixture of two isomers having the $\alpha$-D-*xylo*- and $\beta$-D-*xylo*-configuration in a ratio of 2 : 1.



## EXPERIMENTAL

### General Procedures

Melting points were determined with a Boëtius melting point apparatus and are corrected. Optical rotations were measured with a Polar LμP (IBZ Meßtechnik) polarimeter. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. $^1$H and $^{13}$C NMR spectra were recorded with Bruker spectrometers AC 250 (250.13 MHz and 62.9 MHz, respectively), ARX 300 (300.13 MHz and 75.5 MHz, respectively), and AVANCE 500 (500.13 MHz and 125.8 MHz, respectively). The calibration of spectra was carried out by




**10**

**Scheme 6:** Deisopropylidenation of "reversed" pyrazole-*C*-nucleoside **4**.

means of solvent signals ($CDCl_3$: $\delta$ $^1H = 7.25$, $\delta$ $^{13}C = 77.0$; acetone-$d_6$: $\delta$ $^1H = 2.05$, $\delta$ $^{13}C = 29.8$). For the assignment of $^1H$ and $^{13}C$ NMR signals, DEPT and two-dimensional $^1H$, $^1H$ COSY, and NOESY as well as $^1H$, $^{13}C$ correlation spectra were recorded. Mass spectra were obtained with an AMD 402/3 spectrometer (AMD Intectra GmbH). Elemental analyses were performed with a Leco CHNS-932. Column chromatography was carried out on silica gel 60 (230-400 μm, Merck). Thin-layer chromatography (TLC) was performed on silica gel 60 $GF_{254}$ foils (Merck) with detection by UV–light and by charring with sulphuric acid. Solvents and liquid reagents were purified and dried according to recommended procedures.

**3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-ulofuranurononi-trile (1).** 3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-*α*-D-*gluco*-heptfuranurononitrile (1.824 g, 5.68 mmol) was added to a suspension of PCC (3.59 g, 17.04 mmol) with molecular sieves 0.3 nm (5.68 g) in dichloromethane (35 mL). The mixture was stirred for 3 h and the reaction followed by TLC. When the oxidation was completed, the reaction mixture was diluted with diethylether and filtered through a glass filter filled with silica gel (silicagel 40, Merck Darmstadt). Removal of the solvent gave slightly impure compound **1**, which was purified by column chromatography (toluene/EtOAc 9 : 1) to obtain **1** as a colorless syrup. Yield: 1.19 g (65.7%, colorless syrup); $R_f$ 0.51 (toluene/ethyl acetate 9 : 1); $[\alpha]_D^{22}$ −116 ($c = 1.0$, $CHCl_3$); IR (capillary), $\nu$ ($cm^{-1}$): 1739 (C=O), 2257 (CN); $^1H$ NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.32, 1.45 (2s, 6H, $CMe_2$), 3.74 (s, 2H, $CH_2CN$), 4.29 (d, 1H, $J_{3,4} = 3.8$ Hz, H-3), 4.46 (d, 1H, $J_{CH(a),CH(b)} = 11.6$ Hz, CH*H*Ph), 4.58 (d, 1H, C*H*HPh), 4.61 (d, 1H, $J_{1,2} = 3.5$ Hz, H-2), 4.70 (d, 1H, H-4), 6.06 (d, 1H, H-1), 7.14–7.35 (m, 5H, Ph); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$ 26.2, 26.8 (C*Me*$_2$), 31.1 (*C*$H_2$CN), 72.8 (*C*$H_2$Ph), 81.5 (C-2), 83.7 (C-3), 84.5 (C-4), 106.2 (C-1), 112.9 (*C*$Me_2$), 113.4 (CN), 128.1, 128.4, 129.6 (Ph), 136.0 (*i*-Ph), 196.9 (CO); MS, (EI), $m/z$ (%): 317 $[M]^+$.

Anal. Calcd for $C_{17}H_{19}NO_5$(317.339): C, 64.34; H, 6.03; N, 4.41. Found: C, 64.21; H, 5.92; N, 4.33.

**(*E*)-3-*O*-Benzyl-6-deoxy-6-dimethylaminomethylene-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-ulofuranurononitrile (2) and (*Z*)-3-*O*-Benzyl-6-deoxy-6-dimethylaminomethylene-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-ulofuranurononi-trile (3).** **1** (100 mg, 0.32 mmol) and *N,N*-dimethylformamide dimethylacetal (0.1 mL, 0.64 mmol) in anhydrous THF (5 mL) were stirred at rt for 2 h. After completion of the reaction (monitored by TLC), the solvent was evaporated in vacuo and the residue purified by column chromatography (100% ethyl acetate) to furnish the crystalline **2** and the noncrystalline **3**.

Compound **2**: Yield: 85 mg (72%, colorless crystals); mp 128°C; $R_f$ 0.48 (ethyl acetate); $[\alpha]_D^{21}$ −86 ($c = 0.2$, $CHCl_3$); IR (capillary), $\nu$ ($cm^{-1}$): 1681

(C═O), 2192 (CN); $^1$H NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.32, 1.49 (2s, 6H, $CMe_2$), 3.20, 3.30 (2s, 6H, $NMe_2$), 4.52 (d, 1H, $J_{CH(a),CH(b)} = 12.2$ Hz, CH*H*Ph), 4.61 (d, 1H, $J_{3,4} = 3.8$ Hz, H-3), 4.63 (d, 1H, $J_{1,2} = 3.5$ Hz, H-2), 4.67 (d, 1H, C*H*HPh), 5.22 (d, 1H, H-4), 6.11 (d, 1H, H-1), 7.28 (m, 5H, Ph), 7.83 (s, 1H, H-1′); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 26.2, 26.8 (C*Me*$_2$), 38.6, 47.8 (N*Me*$_2$), 71.9 (*C*$H_2$Ph), 77.6 (C-6), 82.5, 82.7 (C-2, C-3), 82.9 (C-4), 105.0 (C-1), 112.0 (*C*$Me_2$), 118.8 (CN), 127.4, 127.6, 127.9 (Ph), 137.1 (*i*-Ph), 157.3 (C-1′), 187.4 (CO); MS (EI), $m/z$ (%): 372 $[M]^+$.

Anal. Calcd for $C_{20}H_{24}N_2O_5$ (372.415): C, 64.50; H, 6.50; N, 7.52; Found: C, 64.91; H, 6.68; N, 7.45.

Compound **3:** Yield: 6 mg (5%, colorless syrup); $R_f$ 0.46 (ethyl acetate); $^1$H NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.30, 1.48 (2s, 6H, $CMe_2$), 3.25, 3.43 (2s, 6H, $NMe_2$), 4.62 (d, 1H, $J_{2,3} = 2.0$ Hz, H-3), 4.64 (d, 1H, $J_{1,2} = 4.0$ Hz, H-2), 4.70 (center of $q_{AB}$, 2H, $J_{CH(a),CH(b)} = 11.5$ Hz, C*H*$_2$Ph), 5.01 (d, 1H, H-4), 6.03 (d, 1H, H-1), 7.25–7.41 (m, 5H, Ph), 7.93 (s, 1H, H-1′); $^{13}$C NMR (62.9 MHz, $CDCl_3$): $\delta$ 25.9, 26.3 (C*Me*$_2$), 38.9, 48.1 (N*Me*$_2$), 72.4 (*C*$H_2$Ph), 78.7 (C-6), 83.8, 84.0 (C-2, C-3), 87.2 (C-4), 106.6 (C-1), 113.1 (*C*$Me_2$), 118.9 (CN), 127.8, 127.8, 128.4 (Ph), 137.3 (*i*-Ph), 158.2 (C-1′), 189.7 (CO); MS(EI), $m/z$ (%): 372 $[M]^+$.



## X-ray Structure Determination of 2

The data collection was performed on a Bruker P4 four-circle diffractometer with Mo-$K_\alpha$ radiation ($\lambda = 0.71073$ Å) and a graphite monochromator in routine $\omega$-scan after checking the crystal quality by a rotational photo and determining a reasonable reduced cell. Further data: Temperature: 293(2) K; Crystal system: Orthorhombic; Space group: $P2_12_12_1$; Unit cell dimensions: $a = 9.913(4)$ Å, $\alpha = 90^\circ$, $b = 10.735(4)$ Å, $\beta = 90^\circ$, $c = 18.848(6)$ Å, $\gamma = 90^\circ$; Volume: 2005.7(13) Å$^3$; Z: 4; Density (calculated): 1.233 Mg/m$^3$; Absorption coefficient: 0.089 mm$^{-1}$; F(000): 792; Crystal size: $0.78 \times 0.76 \times 0.42$ mm$^3$; $\Theta$ range for data collection: 2.18 to 23.01°; Index ranges: $-10 \le h \le 10$, $-11 \le k \le 11$, $-20 \le l \le 20$; Reflections collected: 3218; Independent reflections: 2781 [R(int) = 0.0237]; Completeness to $\Theta = 23.01^\circ$: 99.4%; Absorption correction: None; Data/restraints/parameters: 2781/0/245; Goodness of fit on $F^2$: 1.028: Final R indices $[I > 2\sigma(I)]$: R1 = 0.0360, wR2 = 0.0943; R indices (all data): R1 = 0.0435, wR2 = 0.0993; Absolute structure parameter: 0.6(14); Extinction coefficient: 0.029(3); Largest diff. peak and hole: 0.153 and $-0.125$ e · Å$^{-3}$. The weighting scheme was calculated according to $w^{-1} = \sigma^2(F_o^2) + (0.0558\,P)^2 + 0.1523\,P$ with $P = (F_o^2 + 2\,F_c^2)/3$. The structure was solved by direct methods (Bruker SHELXTL) and refined by the full matrix least-squares method of the Bruker SHELXTL software package. All nonhydrogen atoms were refined anisotropically with the hydrogen atoms introduced into theoretical positions and refined according to the riding model. CCDC 252045 contains the supplementary crystallographic data for

this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

**3-(3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-1*H*-pyrazole-4-carbonitrile (4).** To a solution of **2** (100 mg, 0.26 mmol) in MeOH (2 mL) was added hydrazine hydrate (0.03 mL, 0.62 mmol) at rt. The resulting mixture was stirred for 15 min. After completion of the reaction (monitored by TLC), the solvent was evaporated in vacuo and the residue purified by column chromatography (toluene/EtOAc 9 : 1) to obtain **4** as a colorless syrup. Yield: 86 mg (94%, colorless syrup); $R_f$ 0.48 (toluene/EtOAc 8 : 2); $[\alpha]_D^{22}$ −80 ($c = 1.0$, $CHCl_3$); IR (capillary), $\nu$ ($cm^{-1}$): 3357 (NH), 2235 (CN); $^1$H NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.36, 1.56 (2s, 6H, $CMe_2$), 4.31 (d, 1H, $J_{3',4'} = 3.3$ Hz, H-3′), 4.37 (d, 1H, $J_{CH(a),CH(b)} = 11.6$ Hz, CH*H*Ph), 4.50 (d, 1H, C*H*HPh), 4.73 (d, 1H, $J_{1',2'} = 3.8$ Hz, H-2′), 5.50 (d, 1H, H-4′), 6.06 (d, 1H, H-1′), 7.01–7.07 (m, 2H, *o*-Ph), 7.21–7.28 (m, 3H, *m*-, *p*-Ph), 7.91 (s, 1H, H-5), 12.40 (br, 1H, NH); $^{13}$C NMR (62.9 MHz, $CDCl_3$): $\delta$ 26.1, 26.8 ($CMe_2$), 72.6 ($CH_2$Ph), 75.5 (C-4′), 82.2, 82.6 (C-2′, C-3′), 90.2 (C-4), 104.8 (C-1′), 112.7 ($CMe_2$), 113.1 (CN), 127.7, 128.1, 128.4 (Ph), 136.4 (*i*-Ph), 139.2 (C-5), 146.8 (C-3); MS(EI), $m/z$ (%): 341 $[M]^+$.

Anal. Calcd for $C_{18}H_{19}N_3O_4$(341.361): C, 63.33; H, 5.61; N, 12.31; Found: C, 63.51; H, 5.46; N, 12.01.

**3-(3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-1-(2-hydroxyethyl)-1*H*-pyrazole-4-carbonitrile (5a) and 5-(3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-1-(2-hydroxyethyl)-1*H*-pyrazole-4-carbonitrile (5b).** To a solution of **2** (122 mg, 0.323 mmol) in MeOH (2 mL) was added 2-hydrazinoethanol (0.065 mL, 0.97 mmol) at rt. The resulting mixture was stirred for 1 h. After completion of the reaction (monitored by TLC) the solvent was evaporated in vacuo and the residue purified by column chromatography (toluene/EtOAc 9 : 1) gave the isomeric products **5a** and **5b**.

Compound **5a**: Yield: 44 mg (35%, colorless syrup); $R_f$ 0.51 (ethyl acetate); $[\alpha]_D^{24}$ −49 ($c = 1.0$, $CHCl_3$); IR (capillary), $\nu$ ($cm^{-1}$): 3463 (OH), 2235 (CN); $^1$H NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.35, 1.53 (2s, 6H, $CMe_2$), 2.76 (br, 1H, OH), 3.92 (“t”, 2H, H-2″), 4.16 (d, 1H, $J_{3',4'} = 3.5$ Hz, H-3′), 4.20 (“t”, 2H, H-1″), 4.34 (d, 1H, $J_{CH(a),CH(b)} = 12.5$ Hz, CH*H*Ph), 4.50 (d, 1H, C*H*HPh), 4.72 (d, 1H, $J_{1',2'} = 3.8$ Hz, H-2′), 5.43 (d, 1H, H-4′), 6.16 (d, 1H, H-1′), 7.08–7.10 (m, 2H, *o*-Ph), 7.22–7.28 (m, 3H, *m*-, *p*-Ph), 7.86 (s, 1H, H-5); $^{13}$C NMR (62.9 MHz, $CDCl_3$): $\delta$ 26.3, 26.9 ($CMe_2$), 54.8 (C-1″), 60.8 (C-2″), 72.1 ($CH_2$Ph), 77.3 (C-4′), 82.9, 83.1 (C-2′, C-3′), 92.3 (C-4), 105.2 (C-1′), 112.2 ($CMe_2$), 113.3 (CN), 127.2, 127.7, 128.2 (Ph), 136.6 (C-5), 137.2 (*i*-Ph), 151.0 (C-3); MS(EI), $m/z$ (%): 385 $[M]^+$.

Anal. Calcd for $C_{20}H_{23}N_3O_5$(385.417): C, 62.33; H, 6.01; N, 10.90; Found: C, 62.01; H, 5.91; N, 11.01.

Compound **5b**: Yield: 44 mg (35%, colorless syrup); $R_f$ 0.53 (ethyl acetate); IR (capillary), $\nu$ ($cm^{-1}$): 3353 (OH), 2186 (CN); $^1H$ NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.37, 1.55 (2s, 6H, $CMe_2$), 2.90 (br, 1H, OH), 3.85 (t, 2H, $J = 4.5$ Hz, H-2″), 4.18 (d, 1H, $J_{3',4'} = 3.3$ Hz, H-3′), 4.22–4.40 (m, 3H, H-1″, CH*H*Ph), 4.53 (d, 1H, $J_{CH(a),CH(b)} = 11.6$ Hz, C*H*HPh), 4.74 (d, 1H, $J_{1',2'} = 3.6$ Hz, H-2′), 5.54 (d, 1H, H-4′), 6.11 (d, 1H, H-1′), 6.94–7.01 (m, 2H, *o*-Ph), 7.24–7.30 (m, 3H, *m*-, *p*-Ph), 7.79 (s, 1H, H-3); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$ 26.2, 26.9 ($CMe_2$), 53.8 (C-1″), 61.4 (C-2″), 72.5 ($CH_2Ph$), 75.4 (C-4′), 82.4, 82.8 (C-2′, C-3′), 92.5 (C-4), 105.0 (C-1′), 112.8 ($CMe_2$), 112.9 (CN), 127.8, 128.4, 128.6 (Ph), 136.2 (*i*-Ph), 141.6 (C-3), 142.7 (C-5); MS(EI), $m/z$ (%): 385 $[M]^+$.

**3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-6-[bis(methylsulfanyl)methylene]-α-D-*xylo*-hept-5-ulofuranurononitrile (6).** Sodium hydride (60%, 0.3 g, 6.6 mmol) was stirred for 10 min in heptane (3 mL). The solvent was decanted after the sodium hydride had settled. Then toluene (3 mL) was added and stirring continued for another 5 min. A solution of **1** (1 g, 3.18 mmol), carbon disulphide (0.41 mL, 6.6 mmol), and methyl iodide (0.81 mL, 13 mmol) in dimethylformamide (10 mL) was added. The mixture was stirred for 1 h, then poured into ice water and extracted with chloroform. The residue was purified by column chromatography (toluene/ethyl acetate 8 : 2) to obtain **6** as a yellow syrup. Yield: 690 mg (52%, yellow syrup); $R_f$ 0.54 (toluene/ethyl acetate 8 : 2); $[\alpha]_D^{22}$ +10 ($c = 1.0$, $CHCl_3$); IR (capillary), $\nu$ ($cm^{-1}$): 1683 (C═O), 2201 (CN); $^1H$ NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.35, 1.51 (2s, 6H, $CMe_2$), 2.46, 2.62 (2s, 6H, 2 × SMe), 4.47 (d, 1H, $J_{CH(a),CH(b)} = 12.0$ Hz, CH*H*Ph), 4.67 (m, 2H, H-2, H-3), 4.68 (d, 1H, C*H*HPh), 5.33 (d, 1H, $J_{3,4} = 4.5$ Hz, H-4), 6.17 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1), 7.16–7.31 (m, 5H, Ph); $^{13}C$ NMR (75.5 MHz, $CDCl_3$): $\delta$ 19.7, 20.8 (2 × SMe), 26.6, 27.2 ($CMe_2$), 72.3 ($CH_2Ph$), 82.7, 83.4, 83.9 (C-2,3,4), 102.6 (C-6), 105.6 (C-1), 112.6 ($CMe_2$), 117.1 (CN), 127.7, 127.9, 128.3 (Ph), 136.8 (*i*-Ph), 183.7 (C-1′), 186.3 (CO); MS(EI), $m/z$ (%): 421 $[M]^+$.

HRMS Calcd for $C_{20}H_{23}NO_5S_2$: 421.10178. Found: 421.10121.

**3-(3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-1-(5-methylsulfanyl)-1*H*-pyrazole-4-carbonitrile (7).** To a solution of **6** (100 mg, 0.23 mmol) in EtOH (2 mL) was added hydrazine hydrate (0.03 mL, 0.62 mmol) at rt. The resulting mixture was stirred for 15 min. After completion of the reaction (monitored by TLC) the solvent was evaporated in vacuo and the residue purified by column chromatography (toluene/EtOAc 8 : 2) to obtain **7** as a yellow syrup. Yield: 80 mg (87%, yellow syrup); $R_f$ 0.51 (toluene/EtOAc 7 : 3); $[\alpha]_D^{22}$ −101 ($c = 0.8$, $CHCl_3$); IR (capillary), $\nu$ ($cm^{-1}$): 3248 (NH), 2230 (CN); $^1H$ NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.33, 1.53 (2s, 6H, $CMe_2$), 2.58 (s, 3H, SMe), 4.22 (d, 1H, $J_{3',4'} = 3.2$ Hz, H-3′), 4.35 (d, 1H, $J_{CH(a),CH(b)} = 11.6$ Hz, CH*H*Ph), 4.52

(d, 1H, C*H*HPh), 4.69 (d, 1H, $J_{1',2'} = 3.7$ Hz, H-2′), 5.38 (d, 1H, H-4′), 6.01 (d, 1H, H-1′), 7.02–7.05 (m, 2H, *o*-Ph), 7.26–7.30 (m, 3H, *m*-, *p*-Ph), 10.83 (br, 1H, NH); $^{13}$C NMR (62.9 MHz, $CDCl_3$): $\delta$ 14.2 (SMe), 25.1, 25.8 ($CMe_2$), 71.8 ($CH_2Ph$), 73.5 (C-4′), 81.1, 81.6 (C-2′, C-3′), 89.7 (C-4), 103.9 (C-1′), 111.8 (*C*$Me_2$), 111.2 (CN), 126.8, 127.4, 127.6 (Ph), 135.0 (*i*-Ph), 144.9 (C-3), 150.1 (C-5); MS(EI), $m/z$ (%): 387 $[M]^+$.

HRMS Calcd for $C_{19}H_{21}N_3O_4S$: 387.12527. Found: 387.12949.

**3-(3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-1-(2-hydroxyethyl)-5-methylsulfanyl-1*H*-pyrazole-4-carbonitrile (8).** To a solution of **6** (100 mg, 0.23 mmol) in EtOH (2 mL) was added 2-hydrazinoethanol (0.047 mL, 0.71 mmol) at rt. The resulting mixture was stirred for 20 min. After completion of the reaction (monitored by TLC) the solvent was evaporated in vacuo and the residue purified by column chromatography (toluene/EtOAc 8 : 2) to obtain **8** as a colorless syrup. Yield: 75 mg (73.5%, colorless syrup); $R_f$ 0.58 (toluene/EtOAc 7 : 3); $[\alpha]_D^{25}$ −28 ($c = 1.0$, $CHCl_3$); IR (capillary), $\nu$ ($cm^{-1}$): 3480 (OH), 2150 (CN); $^1$H NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.34, 1.51 (2s, 6H, $CMe_2$), 2.48 (s, 3H, SMe), 2.59 (br s, 1H, OH), 3.94 (br m, 2H, H-2″), 4.14 (d, 1H, $J_{3',4'} = 3.5$ Hz, H-3′), 4.21–4.39 (m, 3H, H-1″, CH*H*Ph), 4.53 (d, 1H, $J_{CH(a),CH(b)} = 12.3$ Hz, C*H*HPh), 4.72 (d, 1H, $J_{1',2'} = 3.7$ Hz, H-2′), 5.38 (d, 1H, H-4′), 6.14 (d, 1H, H-1′), 7.05–7.10 (m, 2H, *o*-Ph), 7.20–7.26 (m, 3H, *m*-, *p*-Ph); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 18.4 (SMe), 26.3, 26.9 ($CMe_2$), 51.6 (C-1″), 61.0 (C-2″), 72.1 (*C*$H_2$Ph), 77.4 (C-4′), 82.8, 83.1 (C-2′, C-3′), 97.2 (C-4), 105.3 (C-1′), 112.2 (*C*$Me_2$), 113.1 (CN), 127.2, 127.7, 128.2 (Ph), 137.1 (*i*-Ph), 144.0 (C-3), 151.0 (C-5); MS(EI), $m/z$ (%): 431 $[M]^+$.

HRMS Calcd for $C_{21}H_{25}N_3O_5S$: 431.15149. Found: 431.15298.

**3-(3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-1-methyl-5-methylsulfanyl-1*H*-pyrazole-4-carbonitrile (9).** To a solution of **6** (100 mg, 0.23 mmol) in EtOH (2 mL) was added methylhydrazine (0.04 mL, 0.71 mmol) at rt. The resulting mixture was stirred for 15 min. After completion of the reaction (monitored by TLC) the solvent was evaporated in vacuo and the residue purified by column chromatography (toluene/EtOAc 8 : 2) to obtain **9** as a yellow syrup. Yield: 70 mg (74%, yellow syrup); $R_f$ 0.58 (toluene/EtOAc 8 : 2); $[\alpha]_D^{22}$ −29 ($c = 1.0$, $CHCl_3$); IR (capillary), $\nu$ ($cm^{-1}$): 2233 (CN); $^1$H NMR (250.1 MHz, $CDCl_3$): $\delta$ 1.34, 1.51 (2s, 6H, $CMe_2$), 2.49 (s, 3H, SMe), 3.86 (NMe), 4.14 (d, 1H, $J_{3',4'} = 3.5$ Hz, H-3′), 4.32 (d, 1H, $J_{CH(a),CH(b)} = 12.2$ Hz, CH*H*Ph), 4.53 (d, 1H, C*H*HPh), 4.70 (d, 1H, $J_{1',2'} = 3.6$ Hz, H-2′), 5.36 (d, 1H, H-4′), 6.14 (d, 1H, H-1′), 7.06–7.11 (m, 2H, *o*-Ph), 7.20–7.26 (m, 3H, *m*-, *p*-Ph); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta$ 18.0 (SMe), 26.3, 27.0 ($CMe_2$), 37.2 (NMe), 72.2 (*C*$H_2$Ph), 77.5 (C-4′), 83.0, 83.4 (C-2′, C-3′), 96.9 (C-4), 105.3 (C-1′), 112.1 (*C*$Me_2$), 113.1 (CN), 127.3, 127.6, 128.2 (Ph), 137.3 (*i*-Ph), 143.0 (C-3), 150.6 (C-5); MS(EI), $m/z$ (%): 401 $[M]^+$.

HRMS Calcd for $C_{20}H_{23}N_3O_4S$: 401.14093. Found: 401.14177.

**3-(3-*O*-Benzyl-α,*β*-D-*xylo*-tetrofuranos-4-yl)-1*H*-pyrazole-4-carbonitrile (10).** To a solution of **4** (100 mg, 0.29 mmol) in AcOH (2 mL)/$H_2O$ (0.5 mL) was added a few drops of trifloroacetic acid at 0°C. The resulting mixture was stirred for 8 h at rt. After completion of the reaction (monitored by TLC) the solvent was evaporated in vacuo and the residue purified by column chromatography (toluene/EtOAc 6 : 4) to obtain **10** as a colorless syrup. Yield 60 mg (68%, colorless syrup); $R_f$ 0.45 (toluene/EtOAc 6 : 4); $[\alpha]_D^{22}$ −120 ($c = 1.0$, $CHCl_3$); IR (capillary), $\nu$ ($cm^{-1}$): 3347 (NH, OH), 2230 (CN); $^1$H NMR (500.1 MHz, acetone-$d_6$): $\delta$ 3.90 (dd, 1H, $^3J_{2',3'} = 8.0$ Hz, $^3J_{3',4'} = 6.5$ Hz, H-3′$_{(\beta)}$), 4.12 (dd, 1H, $^3J_{2',3'} = 9.5$ Hz, $^3J_{3',4'} = 6.5$ Hz, H-3′$_{(\alpha)}$), 4.16 (dd, 1H, $^3J_{1',2'} = 3.5$ Hz, $^3J_{2',3'} = 9.5$ Hz, H-2′$_{(\alpha)}$), 4.18 (dd, 1H, $^3J_{1',2'} = 5.5$ Hz, $^3J_{2',3'} = 8.0$ Hz, H-2′$_{(\beta)}$), 4.75 (d, 1H, OH$_{(2'\alpha)}$), 4.91–5.00 (m, 2H$_{(CH2)}$, 1H$_{(\alpha)}$, $CH_2$, H-4′$_{(\alpha)}$), 5.08 (d, 1H, $^3J_{3',4'} = 6.5$ Hz, H-4′$_{(\beta)}$), 5.25 (br, 1H, OH$_{(2'\beta)}$), 5.55 (d, 1H, $^3J_{1',2'} = 5.5$ Hz, H-1′$_{(\beta)}$), 5.79 (d, 1H, $^3J_{1',2'} = 3.5$ Hz, H-1′$_{(\alpha)}$), 6.20 (d, 1H, OH$_{(1'\beta)}$), 6.50 (br, 1H, OH$_{(1'\alpha)}$), 7.26–7.31 (m, 1H, *p*-Ph), 7.33–7.37 (m, 2H, *m*-Ph), 7.45–7.48 (m, 2H, *o*-Ph), 7.93 (s, 1H, H-5$_{(\alpha)}$), 7.94 (s, 1H, H-5$_{(\beta)}$); $^{13}$C NMR (125.8 MHz, acetone-$d_6$): $\delta$ 67.0 (C-4′$_{(\beta)}$), 68.1 (C-4′$_{(\alpha)}$), 70.9 (C-2′$_{(\alpha)}$), 73.4 (C-2′$_{(\beta)}$), 74.6 (CH$_{2(\beta)}$), 74.9 (CH$_{2(\alpha)}$), 80.4 (C-3′$_{(\alpha)}$), 81.7 (C-3′$_{(\beta)}$), 81.7 (C-1′$_{(\alpha)}$), 85.3 (C-1′$_{(\beta)}$), 91.4 (C-4$_{(\beta)}$), 91.8 (C-4$_{(\alpha)}$), 113.8 (CN$_{(\alpha)}$), 113.9 (CN$_{(\beta)}$), 128.2 (*p*-Ph$_{(\alpha)}$), 128.2 (*p*-Ph$_{(\beta)}$), 128.7, 128.9 (*o*-Ph$_{(\beta)}$, *m*-Ph$_{(\beta)}$), 128.6, 129.0 (*o*-Ph$_{(\alpha)}$, *m*-Ph$_{(\alpha)}$), 139.4 (*i*-Ph$_{(\beta)}$), 139.9 (*i*-Ph$_{(\alpha)}$), 144.0 (C-5$_{(\beta)}$), 144.2 (C-5$_{(\alpha)}$), 146.9 (C-3$_{(\beta)}$), 147.8 (C-3$_{(\alpha)}$); MS(EI), $m/z$ (%): 301 $[M]^+$.

Anal. Calcd for $C_{15}H_{15}N_3O_4$(301.30): C, 59.80; H, 5.02; N, 13.95. Found: C, 60.21; H, 4.96; N, 13.71.



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