Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 13 (2005) 353–361
Bioorganic & Medicinal Chemistry

# Stereoselective synthesis, structural characterization, and properties of 1,2-*O*-isopropylidene-3-*C*-(5-phenyl-1,2,4-oxadiazol-3-yl)-β-D-psicopyranose

Jianxin Yu,[a,*] Suna Zhang,[b] Zhongjun Li,[c] Wenjie Lu[d] and Mengshen Cai[c]

[a]*Advanced Radiological Sciences, Department of Radiology, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75390-9058, USA*
[b]*Department of Chemistry, Xinjiang University, Wulumqi 830046, China*
[c]*National Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking Medical University, Beijing 100083, China*
[d]*Department of Chemistry, Wuyi University, Jiangmen 529020, China*

Received 17 March 2003; revised 7 October 2004; accepted 9 October 2004
Available online 2 November 2004

**Abstract**—1,2:4,5-Di-*O*-isopropylidene-3-*C*-(5-phenyl-1,2,4-oxadiazol-3-yl)-β-D-psicopyranose **14** was synthesized stereoselectively from 1,2:4,5-di-*O*-isopropylidene-3-*C*-amidoximino-3-*O*-benzoyl-β-D-psicopyranose **8** using a novel procedure. Treatment of **8** with acetic anhydride, chloroacetyl chloride, propanic anhydride, or benzoyl chloride causes the 3-*O*-benzoyl group to undergo an intramolecular replacement reaction with neighboring group participation and transfer resulting in a more stable conjugation system of the 1,2,4-oxadiazol ring. A possible mechanism, as well as structural analysis and bioactivity are described.


## 1. Introduction

The synthesis of branched-chain sugars has attracted considerable attention[1] because of their biological importance. In addition, the incorporation of heterocyclic moieties in the carbohydrate framework has gained much importance.[2–4] Recently, a number of oxadiazolines have been reported to possess anti-HIV activity[5] prompting us to synthesize heterocyclic moieties as branched-chain links to carbohydrate fragments.[6] We report here the stereospecific synthesis of 1,2:4,5-di-*O*-isopropylidene-3-*C*-(5-phenyl-1,2,4-oxadiazol-3-yl)-β-D-psicopyranose (**14**) from the key intermediate 1,2:4,5-di-*O*-isopropylidene-3-*C*-amidoximino-3-*O*-benzoyl-β-D-psicopyranose (**8**) using a novel approach, as well as a possible mechanism and the structural confirmation by spectroscopic data and X-ray crystallographic analysis (Scheme 1).

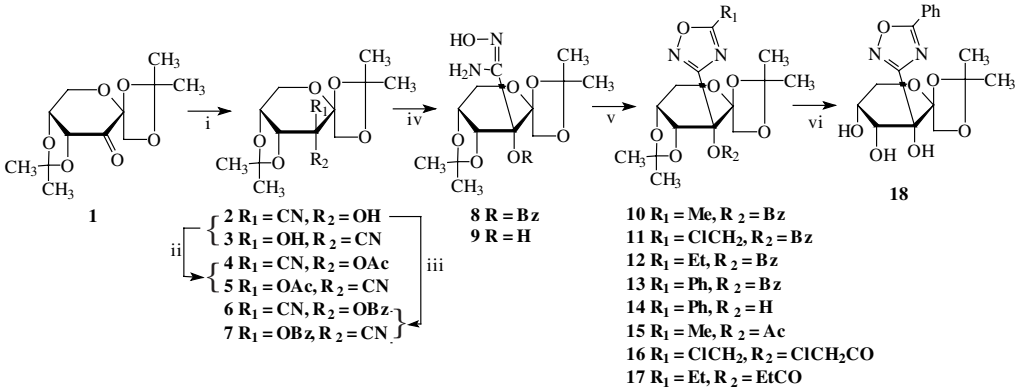
## 2. Results and discussion

Since cyano group can be easily transformed into other functional groups, cyano branched carbohydrates offer useful, versatile intermediates in the syntheses of branched sugars.[7–12] Our syntheses started with the reaction of 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2-hexulopyranose-3-ulose (**1**), which was prepared in two steps with high yields.[13] Application of the phase transfer catalysis method yielded 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-β-D-psicopyranose (**2**) with complete stereoselectivity in nearly quantitative yield.[14]

Initially, we assumed that reaction of **1** with NaCN in $CH_2Cl_2$–$H_2O$ in the presence of tetrabutylammonium bromide (TBAB) as catalyst possibly would give **2** and its epimer 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-β-D-fructopyranose (**3**). We expected one of epimer be predominant due to the attack of cyanide anion on the carbonyl group from the less hindered side of the asymmetric 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose (**1**). However, the $^{13}C$ NMR spectrum showed a single isomer (**2** or **3**) was formed in the synthesis of the cyano branched sugar,

*Keywords*: Branched-chain sugars; Oxadiazoles; Synthesis; X-ray; Bioactivity.
* Corresponding author. Tel.: +1 214 648 8872; fax: +1 214 648 4538; e-mail: jian-xin.yu@utsouthwestern.edu

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.10.023




**Scheme 1.** Reagents and conditions: (i) NaCN, TBAB, rt, $CH_2Cl_2$–$H_2O$; (ii) $Ac_2O$–Py, rt; (iii) BzCl–Py, 0 °C–rt; (iv) $NH_2OH$–$CH_3OH$, reflux; (v) $Ac_2O$, $ClCH_2COCl$, $(CH_3CH_2CO)_2O$ or benzoyl chloride, respectively, $N_2$, 80 or 120–130 °C; (vi) $CF_3CO_2H$ (90%)–$CH_2Cl_2$, reflux, 24 h, 80%.

which indicates that the new asymmetric center was formed with total stereoselectivity.

Configuration of **2** or **3** was confirmed by comparison of the reduced derivative with a known compound.[14] Because **2** or **3** were key intermediates for further syntheses of heterocyclic branched carbohydrates, an absolute determination of its structure was deemed to be of value. At first, we intended to determine the specific configuration of **2** or **3** through the NOESY spectrum of the acetylated derivative **4** or **5** by use of the correlations between H-1,1′ or H-4, H-5, H-6, H-6′ and the methyl protons of acetyl group. Molecular modeling studies of **4** and **5** showed that the distances between H-1,1′ or H-4, H-5, H-6, H-6′ and the methyl protons of acetyl group are all above 2.5 Å, rendering the NOESY approach impractical. Fortunately, we obtained suitable crystals of **4** or **5** from AcOEt–cyclohexane (1:1) for X-ray crystallographic analysis. X-ray diffraction clearly indicated that the specific configuration of the 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-hex-2-ulopyranose is the structure **2**. The pyranoid ring adopts a $_4C^1$ chair conformation. Crystallographic data, and details on data collection and structure refinement are summarized in Table 1. The coordinates of the nonhydrogen atoms are listed in Table 2. The bond lengths and bond angles are listed in Tables 3 and 4, respectively. The ORTEP plot for compound **4** is shown in Figure 1, and the packing arrangement of the molecules is shown in Figure 2. The stereoselectivity is probably because the steric hindrance by the 4,5-*O*-isopropylidene group limits the approaching cyanide anion from the upper face of the pyranose ring, and the addition reaction of NaCN to **1** proceeds in kinetic control manner.[15–17]

Treatment of **2** with benzoyl chloride in pyridine from 0 °C to room temperature overnight gave 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-psicopyranose (**6**) in a yield of 60% and 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-fructopyranose (**7**) in a yield of 30%. Perez-Perez et al.[18] have demonstrated that cyanohydrins could be epimerized to the thermodynamically more stable forms by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene in acetonitrile. But, there is no previous report so far of this phenomenon during acylation in pyridine. Furthermore, the results are very different from those of **2** in acetylation and benzoylation. Presumably this happened by pyridine-promoted formation of **1** followed by attack of the cyanide anion onto the carbonyl carbon under thermodynamic control affording **3**, which was then benzoylated to form **7**. The structures of **2**, **4**, **6**, and **7** were based on analytical and spectroscopic data, the IR spectrum of **2** has absorption for the –OH group at 3389.5 $cm^{-1}$ and **4**, **6** and **7** have absorption for the carbonyl groups at ~1740 $cm^{-1}$, but none had a band for the C≡N group in accord with those reported previously for cyano branched-chain sugars and glycosyl cyanides.[14,19] The presence of the C≡N group was confirmed by the crystallographic data and supported by the $^{13}C$ resonances at 115–118 ppm. Epimerization of **6** to **7** caused the

**Table 1.** Crystal data and structure refinement for **4**

| | |
|---|---|
| Empirical formula | $C_{15}H_{21}NO_7$ |
| Formula weight | 327.13 |
| Temperature | 296(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions | $a$ = 7.879(1) Å, $\alpha$ = 90°<br>$b$ = 14.111(1) Å, $\beta$ = 90°<br>$c$ = 15.256(1) Å, $\chi$ = 90° |
| Volume, $Z$ | 1696.2(3) $Å^3$, 4 |
| $D_{calcd}$ | 1.282 $mg/m^3$ |
| Absorption coefficient | 0.096 $mm^{-1}$ |
| F(000) | 888 |
| Crystal size | 0.10 × 0.20 × 0.20 mm |
| $\theta$ Range for data collection | 0–180.0° |
| Limiting indices | $0 \leqslant h \leqslant 11$, $0 \leqslant k \leqslant 13$,<br>$-1 \leqslant l \leqslant 24$ |
| Reflections collected | 1712 |
| Independent reflections | 2570 ($R_{int}$ = 0.0092) |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 2570/0/277 |
| Goodness-of-fit on $F^2$ | 3.506 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R^1$ = 0.0700, $WR^2$ = 0.0640 |
| $R$ indices | $R^1$ = 0.0490, $WR^2$ = 0.0780 |
| Absolute structure parameter | −1.9(12) |
| Extinction coefficient | 0.089(10) |
| Largest diff. peak and hole | 0.270 and −0.240 e $Å^{-3}$ |

**Table 2.** Fractional atomic coordinates ($\times 10^4$) and equivalent thermal parameters of **4**

| Atom | *x* | *y* | *z* | *U*(equiv) × 10 |
|---|---|---|---|---|
| O-1 | 1679(6) | 6524(3) | 4715(2) | 4.9(2) |
| O-2 | 1478 (4) | 6003(2) | 3298(2) | 3.3(1) |
| O-3 | −3339(5) | 5977(3) | 1822(2) | 3.9(1) |
| O-4 | −1278(5) | 6796(3) | 1092(2) | 4.4(2) |
| O-5 | −1414(5) | 6108(2) | 3668(2) | 3.6(1) |
| O-6 | −1839(6) | 7708(3) | 2646(3) | 4.9(2) |
| O-7 | −677(5) | 8934(3) | 3425(3) | 4.6(2) |
| N-1 | 2411(7) | 8098(3) | 2088(4) | 5.2(3) |
| C-1 | 80(7) | 6609(3) | 3452(3) | 3.2(2) |
| C-2 | −279(6) | 7144(3) | 2576(3) | 2.9(2) |
| C-3 | −523(7) | 6375(4) | 1844(3) | 3.2(2) |
| C-4 | −1757(7) | 5592(3) | 2116(3) | 3.5(2) |
| C-5 | −1754(8) | 5329(4) | 3086(4) | 4.1(2) |
| C-6 | 618(8) | 7187(4) | 4258(3) | 4.2(2) |
| C-7 | 2565(8) | 5987(4) | 4077(3) | 4.1(2) |
| C-8 | 4240(8) | 6454(5) | 3818(4) | 5.4(3) |
| C-9 | 2761(10) | 4983(5) | 4397(4) | 5.8(3) |
| C-10 | −2964(8) | 6361(5) | 976(4) | 4.6(3) |
| C-11 | −2816(10) | 5604(6) | 265(4) | 6.4(4) |
| C-12 | −4235(10) | 7132(6) | 758(4) | 6.3(4) |
| C-13 | −1909(7) | 8577(3) | 3083(3) | 3.4(1) |
| C-14 | −3642(8) | 9021(4) | 3089(4) | 4.4(3) |
| C-15 | 1232(7) | 7727(4) | 2319(3) | 3.7(2) |

**Table 3.** The bond lengths (Å) for **4**

| | | | |
|---|---|---|---|
| O(1)–C(6) | 1.435(7) | O(4)–C(10) | 1.474(7) |
| O(1)–C(7) | 1.418(7) | O(5)–C(1) | 1.412(6) |
| O(2)–C(1) | 1.414(6) | O(5)–C(5) | 1.438(7) |
| O(2)–C(7) | 1.464(6) | O(6)–C(2) | 1.469(6) |
| O(3)–C(4) | 1.431(7) | O(6)–C(13) | 1.396(6) |
| O(3)–C(10) | 1.431(7) | O(7)–C(13) | 1.212(7) |
| O(4)–C(3) | 1.423(6) | N(1)–C(15) | 1.123(8) |
| C(1)–C(2) | 1.561(7) | C(7)–C(8) | 1.527(9) |
| C(1)–C(6) | 1.534(7) | C(7)–C(9) | 1.506(9) |
| C(2)–C(3) | 1.568(7) | C(10)–C(11) | 1.526(9) |
| C(2)–C(15) | 1.500(7) | C(10)–C(12) | 1.516(9) |
| C(3)–C(4) | 1.529(7) | C(13)–C(14) | 1.502(8) |
| C(4)–C(5) | 1.526(8) | | |

**Table 4.** The bond angles (°) for **4**

| | | | |
|---|---|---|---|
| C(6)–O(1)–C(7) | 107.5(4) | O(3)–C(10)–C(11) | 113.1(5) |
| C(1)–O(2)–C(7) | 109.2(4) | O(3)–C(10)–C(12) | 109.4(5) |
| C(4)–O(3)–C(10) | 104.3(4) | O(4)–C(10)–C(11) | 107.9(5) |
| C(3)–O(4)–C(10) | 107.5(4) | O(3)–C(10)–C(12) | 108.8(5) |
| C(1)–O(5)–C(5) | 113.2(4) | C(11)–C(10)–C(12) | 113.4(5) |
| C(2)–O(6)–C(13) | 122.9(4) | C(3)–C(4)–C(5) | 115.9(4) |
| O(2)–C(1)–O(5) | 112.7(4) | O(5)–C(5)–C(4) | 114.4(5) |
| O(2)–C(1)–C(2) | 106.9(4) | O(1)–C(6)–C(1) | 101.8(4) |
| O(2)–C(1)–C(6) | 103.9(4) | O(1)–C(7)–O(2) | 105.2(4) |
| O(5)–C(1)–C(2) | 106.9(4) | O(1)–C(7)–C(8) | 111.9(5) |
| O(5)–C(1)–C(6) | 108.1(4) | O(6)–C(13)–O(7) | 122.7(4) |
| C(2)–C(1)–C(6) | 118.6(4) | O(6)–C(13)–C(14) | 113.9(5) |
| O(6)–C(2)–C(1) | 110.6(4) | O(7)–C(13)–C(14) | 123.5(5) |
| O(6)–C(2)–C(3) | 108.9(4) | N(1)–C(15)–C(2) | 174.1(6) |
| O(6)–C(2)–C(15) | 112.7(4) | O(3)–C(4)–C(3) | 101.2(4) |
| C(1)–C(2)–C(3) | 107.3(4) | O(3)–C(4)–C(5) | 113.4(4) |
| C(1)–C(2)–C(15) | 110.2(4) | O(1)–C(7)–C(9) | 109.3(5) |
| C(3)–C(2)–C(15) | 106.9(4) | O(2)–C(7)–C(8) | 106.8(4) |
| O(4)–C(3)–C(2) | 109.7(4) | O(2)–C(7)–C(9) | 109.7(5) |
| O(4)–C(3)–C(4) | 104.7(4) | C(8)–C(7)–C(9) | 113.6(5) |
| C(2)–C(3)–C(4) | 112.6(4) | O(3)–C(10)–O(4) | 103.6(5) |

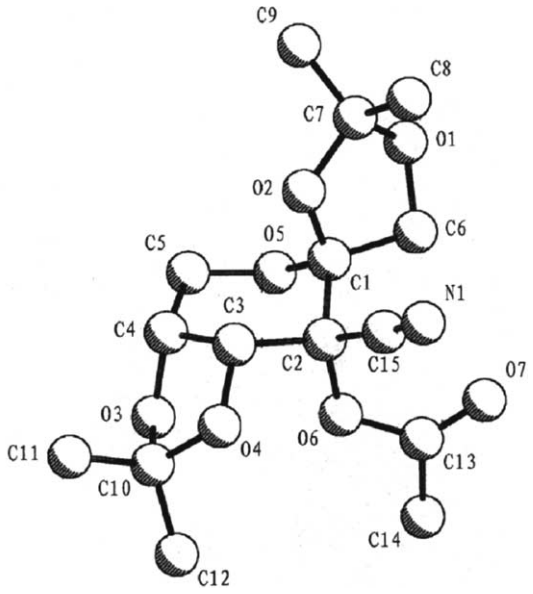



**Figure 1.** The ORTEP plot for structure **4**.

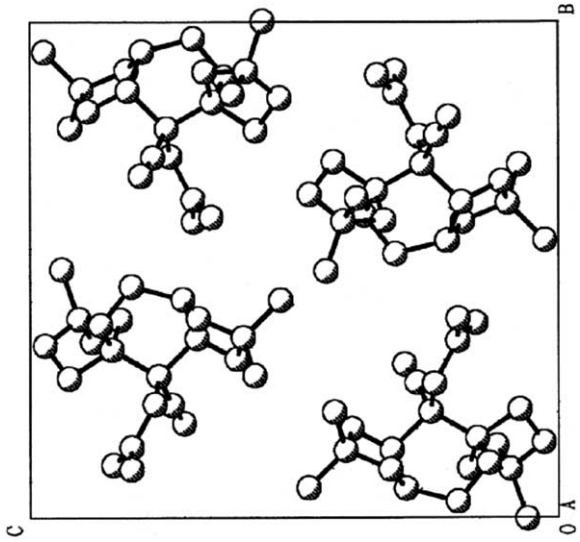



**Figure 2.** The arrangement of the molecules in the unit cell.

neighboring H-4 chemical shift to move from $\delta_{H\text{-}4}$ = 5.09 ppm in **6** to $\delta_{H\text{-}4}$ = 4.64 ppm in **7**, almost overlaping with H-5,6 due to the benzoyl group linked to the C-3 from the above of sugar ring providing a shielding effect.

Moffatt and co-workers[20] reported that the reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide with hydroxylamine in methanol at 50 °C produced 2,5-anhydro-3,4,6-tri-*O*-benzoyl-β-D-allonamidoxime in only 34% yield, and presumed the rather low yield was due to the several more polar by-products arising from partial debenzoylation. Dong and co-workers[21,22] found that the yields of amidoximes through the condensation of nitriles with hydroxylamine were dependent on the pH of the reaction mixtures. By controlling the pH between 7 and 8, the best result, 48% yield of the key

intermediate amidoxime **8** was obtained through refluxing of **6** with hydroxylamine in anhydrous methanol, but unsuccessful through refluxing of **4** under the same reaction conditions because the reaction proceeded in a more-complex manner to give the key intermediate amidoxime **8** in very low yield (<5%). Comparing the product **9** from the condensation of **2** and hydroxylamine or debenzoylation of **8** with the several more polar unseparated by-products by TLC, we verified that **9** and the more polar by-products are different from each other, so the low yield of amidoxime seems not only due to the debenzoylation.

The identities of **8**, **9** were established unequivocally from their analytical and spectroscopic data, both of them showed the strong characteristic IR absorptions of $-NH_2$ and –OH functions at $\sim$3400 $cm^{-1}$ and the expected quasimolecular ion at *m/z* 445 [M+Na], 341 [M+Na] in the FAB-MS. The $-NH_2$, –OH groups of **8**, **9** were also found with characteristics in the $^1H$ NMR spectra. On the other hand, in the $^{13}C$ NMR spectra displayed the absence of the cyano signal at 115–118 ppm instead of the formed C=N signal at $\sim$152 ppm.

The amidoxime **8** was then treated with acetic anhydride, propanoic anhydride, chloroacetyl chloride, and benzoyl chloride expectantly giving the 1,2,4-oxadiazole derivatives **10**, **11**, **12**, and **13**, respectively. First, it was treated with acetic anhydride at 80 °C under nitrogen atmosphere for 18 h, presumably giving 1,2:4,5-di-*O*-isopropylidene-3-*C*-(5-methyl-1,2,4-oxadiazol-3-yl)-3-*O*-benzoyl-β-D-psicopyranose **10**. The FAB-MS and ESI-MS at *m/z* 427 $[M+Na]^+$, 443 $[M+K]^+$, and 405 $[M+1]^+$ with the elemental analysis indicated the molecular formula to be $C_{20}H_{24}N_2O_7$ (**14**) but not $C_{22}H_{26}N_2O_8$ as the substituted 1,2,4-oxadiazole derivative **10** we desired. The characteristics from the NMR spectra by comparison of 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-β-D-psicopyranose, 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-3-*O*-acetyl-β-D-psicopyranose, 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-psicopyranose, 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-fructopyranose with 1,2:4,5-di-*O*-isopropylidene-3-*C*-amidoximino-3-*O*-benzoyl-β-D-psicopyranose **1** showed that the 1,2:4,5-di-*O*-isopropylidene-D-pyranose fragment still remained in **14**. Another remainder was $C_8H_6N_2O_2$, in which two parts composed as 5-phenyl-1,2,4-oxadiazol-3-yl [$C_8H_5N_2O$] on the basis of NMR spectral data, and hydroxyl group –OH at 3397.0 $cm^{-1}$. We tried to determine the configuration of C-3 by NOESY, but there were no correlations between HO-3 or the benzene hydrogens and H-2, -4, -5, and -6 of sugar ring. However, the crystals of **14** from acetone–cyclohexane (1:1) were suitable for X-ray crystallographic analysis.

Crystallographic data, and details on data collection and structure refinement are summarized in Table 5. The coordinates of the non-hydrogen atoms are listed in Table 6. The bond lengths and bond angles are listed in Tables 7 and 8, respectively. The ORTEP plot for compound **14** is shown in Figure 3 together with the numbering scheme, and the packing arrangement of the molecules is shown in Figure 4. The pyranoid ring

**Table 5.** Crystal data and structure refinement for **14**

| | |
|---|---|
| Empirical formula | $C_{20}H_{24}N_2O_7$ |
| Formula weight | 404.41 |
| Temperature | 291(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhomic |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions | $a$ = 10.309(1) Å, $\alpha$ = 90° |
| | $b$ = 10.474(1) Å, $\beta$ = 90° |
| | $c$ = 18.646(3) Å, $\chi$ = 90° |
| Volume, $Z$ | 2013.3(4) $Å^3$, 4 |
| $D_{calcd}$ | 1.334 $mg/m^3$ |
| Absorption coefficient | 0.102 $mm^{-1}$ |
| F(000) | 856 |
| Crystal size | 0.56 × 0.50 × 0.42 mm |
| $\theta$ range for data collection | 2.18–26.99° |
| Limiting indices | $0 \leqslant h \leqslant 13$, $0 \leqslant k \leqslant 13$, $1 \leqslant l \leqslant 23$ |
| Reflections collected | 2766 |
| Independent reflections | 2625 ($R_{int}$ = 0.0180) |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 2625/0/268 |
| Goodness-of-fit on $F^2$ | 0.914 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R^1$ = 0.0334, $WR^2$ = 0.0662 |
| $R$ indices | $R^1$ = 0.0526, $WR^2$ = 0.0711 |
| Absolute structure parameter | 2.0(11) |
| Extinction coefficient | 0.0283(13) |
| Largest diff. peak and hole | 0.147 and 0.137 e$Å^{-3}$ |

**Table 6.** Fractional atomic coordinates (× $10^4$) and equivalent thermal parameters of **14**

| Atom | $x$ | $y$ | $z$ | $U$(equiv) × 10 |
|---|---|---|---|---|
| O-1 | 1189(2) | 2036(1) | 287(1) | 52(1) |
| O-2 | 2332(1) | 1450(1) | 1262(1) | 43(1) |
| O-3 | 4526(1) | 4018(1) | 802(1) | 43(1) |
| O-4 | 5169(1) | 3804(1) | 2248(1) | 50(1) |
| O-5 | 6471(1) | 2452(2) | 1620(1) | 52(1) |
| O-6 | 4311(2) | 1385(1) | 638(1) | 46(1) |
| O-7 | 1023(2) | 5103(2) | 1974(1) | 61(1) |
| N-1 | 2061(2) | 4232(2) | 2059(1) | 59(1) |
| N-2 | 1986(2) | 4946(2) | 926(1) | 40(1) |
| C-1 | 2480(2) | 2403(2) | 136(1) | 47(1) |
| C-2 | 3212(2) | 2123(2) | 828(1) | 39(1) |
| C-3 | 3693(2) | 3302(2) | 1253(1) | 35(1) |
| C-4 | 4373(2) | 2835(2) | 1943(1) | 39(1) |
| C-5 | 5328(2) | 1758(2) | 1809(1) | 46(1) |
| C-6 | 4974(2) | 830(2) | 1233(1) | 52(1) |
| C-7 | 1234(2) | 1083(2) | 828(1) | 45(1) |
| C-8 | 1461(2) | 218(2) | 503(1) | 58(1) |
| C-9 | 34(2) | 1181(3) | 1273(2) | 68(1) |
| C-10 | 2573(2) | 4178(2) | 1426(1) | 38(1) |
| C-11 | 1059(2) | 5475(2) | 1287(1) | 40(1) |
| C-12 | 85(2) | 6396(2) | 1037(1) | 41(1) |
| C-13 | 650(2) | 7115(2) | 1509(1) | 49(1) |
| C-14 | 1539(2) | 7985(2) | 1253(1) | 57(1) |
| C-15 | 1693(2) | 8144(2) | 528(2) | 60(1) |
| C-16 | 974(2) | 7432(3) | 55(1) | 60(1) |
| C-17 | 89(2) | 6553(2) | 308(1) | 51(1) |
| C-18 | 6508(2) | 3502(2) | 2099(1) | 57(1) |
| C-19 | 7175(3) | 3129(3) | 2789(2) | 91(1) |
| C-20 | 7151(3) | 4612(3) | 1739(2) | 88(1) |

**Table 7.** The bond lengths (Å) for **14**

| | | | |
|---|---|---|---|
| O(1)–C(1) | 1.414(3) | C(2)–C(3) | 1.549(3) |
| O(1)–C(7) | 1.420(2) | C(3)–C(10) | 1.510(3) |
| O(2)–C(2) | 1.405(2) | C(3)–C(4) | 1.544(3) |
| O(2)–C(7) | 1.443(2) | C(4)–C(5) | 1.518(3) |
| O(3)–C(3) | 1.417(2) | C(5)–C(6) | 1.493(3) |
| O(4)–C(4) | 1.424(2) | C(11)–C(12) | 1.468(3) |
| O(4)–C(18) | 1.444(3) | C(12)–C(17) | 1.381(3) |
| O(5)–C(18) | 1.417(3) | C(12)–C(13) | 1.385(3) |
| O(5)–C(5) | 1.430(3) | C(13)–C(14) | 1.378(3) |
| O(6)–C(2) | 1.416(2) | C(14)–C(15) | 1.372(3) |
| O(6)–C(6) | 1.427(3) | C(15)–C(16) | 1.372(3) |
| O(7)–C(11) | 1.339(2) | C(16)–C(17) | 1.379(3) |
| O(7)–N(1) | 1.415(2) | C(7)–C(9) | 1.492(3) |
| N(1)–C(10) | 1.293(3) | C(7)–C(8) | 1.510(3) |
| N(2)–C(11) | 1.293(3) | C(18)–C(20) | 1.497(4) |
| N(2)–C(10) | 1.372(3) | C(18)–C(19) | 1.511(4) |
| C(1)–C(2) | 1.525(3) | | |

**Table 8.** The bond angles (°) for **14**

| | | | |
|---|---|---|---|
| C(2)–O(6)–C(6) | 114.21(16) | O(1)–C(1)–C(2) | 104.15(18) |
| C(1)–O(1)–C(7) | 107.59(16) | O(2)–C(2)–O(6) | 112.79(16) |
| C(2)–O(2)–C(7) | 108.57(15) | O(2)–C(2)–C(1) | 105.30(16) |
| C(4)–O(4)–C(18) | 108.53(16) | O(6)–C(2)–C(1) | 106.76(17) |
| C(18)–O(5)–C(5) | 105.15(17) | O(2)–C(2)–C(3) | 108.22(16) |
| C(11)–O(7)–N(1) | 105.81(16) | O(6)–C(2)–C(3) | 107.91(15) |
| C(10)–N(1)–O(7) | 103.64(17) | C(1)–C(2)–C(3) | 116.00(17) |
| C(11)–N(2)–C(10) | 102.94(17) | O(3)–C(3)–C(10) | 105.60(15) |
| O(3)–C(3)–C(4) | 112.80(16) | N(1)–C(10)–C(3) | 122.26(19) |
| C(10)–C(3)–C(4) | 111.21(16) | N(2)–C(10)–C(3) | 123.29(18) |
| O(3)–C(3)–C(2) | 108.18(15) | N(2)–C(11)–O(7) | 113.19(19) |
| C(10)–C(3)–C(2) | 110.40(16) | N(2)–C(11)–C(12) | 128.40(2) |
| C(4)–C(3)–C(2) | 108.58(15) | O(7)–C(11)–C(12) | 118.42(19) |
| O(4)–C(4)–C(5) | 102.82(16) | C(17)–C(12)–C(13) | 119.40(2) |
| O(4)–C(4)–C(3) | 111.63(16) | C(17)–C(12)–C(11) | 118.70(2) |
| C(5)–C(4)–C(3) | 113.11(17) | C(13)–C(12)–C(11) | 121.90(2) |
| O(5)–C(5)–C(6) | 110.81(19) | C(14)–C(13)–C(12) | 120.20(2) |
| O(5)–C(5)–C(4) | 101.38(16) | C(15)–C(14)–C(13) | 120.00(2) |
| C(6)–C(5)–C(4) | 116.31(18) | C(14)–C(15)–C(16) | 120.30(2) |
| O(6)–C(6)–C(5) | 114.31(18) | C(15)–C(16)–C(17) | 120.10(2) |
| N(1)–C(10)–N(2) | 114.42(19) | C(16)–C(17)–C(12) | 120.10(2) |
| O(1)–C(7)–O(2) | 103.69(16) | O(5)–C(18)–O(4) | 105.43(17) |
| O(1)–C(7)–C(9) | 108.60(2) | O(5)–C(18)–C(20) | 109.40(2) |
| O(2)–C(7)–C(9) | 108.70(17) | O(4)–C(18)–C(20) | 109.90(2) |
| O(1)–C(7)–C(8) | 110.73(18) | O(5)–C(18)–C(19) | 110.40(2) |
| O(2)–C(7)–C(8) | 110.13(19) | O(4)–C(18)–C(19) | 109.10(2) |
| C(9)–C(7)–C(8) | 114.40(2) | C(20)–C(18)–C(19) | 112.40(2) |

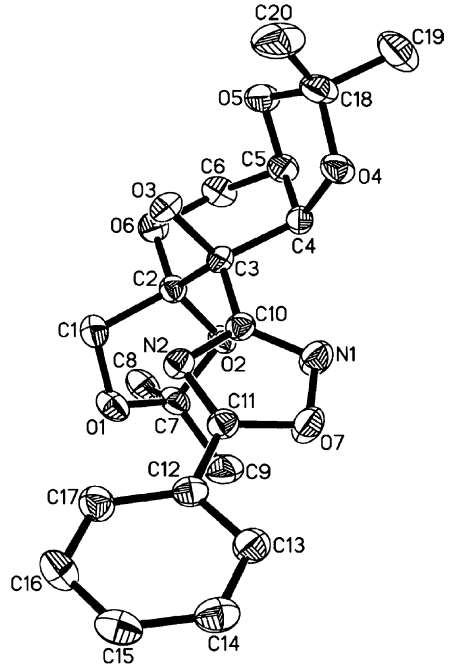



**Figure 3.** The ORTEP plot for compound **14**.

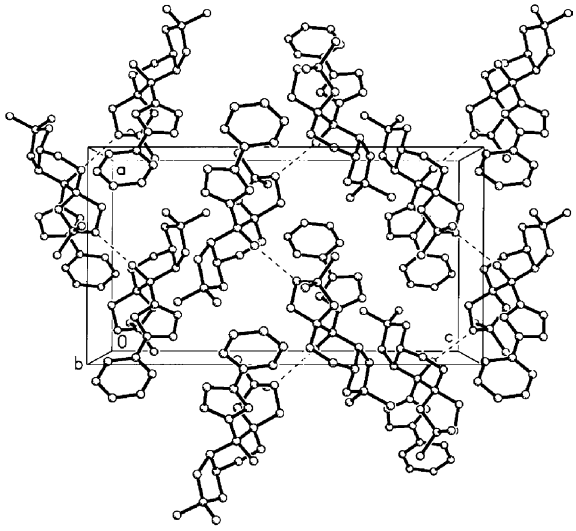
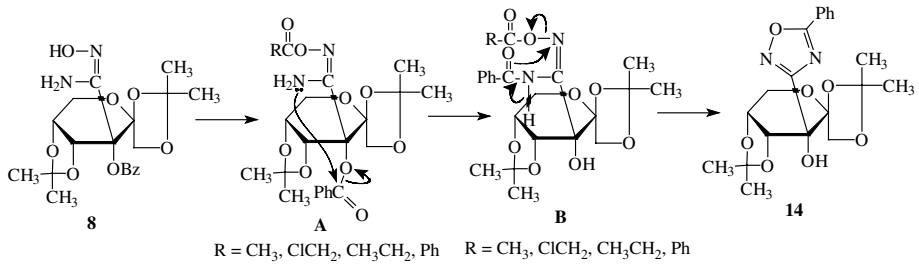



**Figure 4.** The arrangement of the molecules in the unit cell.

retains a $_4C^1$ chair conformation, 5-phenyl-1,2,4-oxadiazole and 3-OH groups are bonded to C-3 in equatorial and axial positions, respectively. The X-ray diffraction analysis also indicates that the crystal has molecular stacking along a one-dimensional chain. Figure 4 exhibits the interaction among the molecules in the columnar stacking. The molecules assemble through 3-OH···O-1 intermolecular hydrogen bonds (2.88 Å; 157.1°).

In order to confirm the unexpected reaction and study the mechanism, we explored the reactions of **8** with chloroacetyl chloride, propanic anhydride, or benzoyl chloride instead of acetic anhydride, at 120–130 °C under nitrogen for 22 h. Only one product, the 5-phenyloxadiazole **14**, but not **11**–**13**, was obtained in yields 81–83% from each of the above three reactions. The products were homogeneous by TLC and had the same sharp melting point as well as the elemental analyses, IR, MS, and $^1$H, $^{13}$C NMR spectral data.

Taking these facts into account, we believe that the 3-*O*-benzoyl group undergoes an intramolecular replacement reaction through neighbor participation and a more stable conjugation system is formed in compound **14** during the cyclization of **8** with acetic anhydride, chloroacetyl chloride, propanic anhydride, or benzoyl chloride. As shown in Scheme 2, the novel procedure proceeds as follows: acetylation of amidoxime **8** takes place first at the hydroxyl group to form 1,2:4,5-di-*O*-isopropylidene-3-(*C*-carbamoacetylhydromoyl)-3-*O*-benzoyl-β-D-psicopyranose **A**.[23] The lone electron pair




**Scheme 2.** The possible mechanism for the intramolecular replacement reaction to form **14**.

on $NH_2$ with high density attacks the carbon of C=O group in 3-*O*-benzoyl group to produce the intramolecular replacement reaction through neighboring group participation and transfer. The resulting intermediate **B** undergoes ring closure reactions with the action of anhydrides or benzoyl chloride under reflux to remove the hydrogen from $NH_2$ and give rise to the compound **14**.

The 3-benzoyl group undergoing intramolecular replacement through neighboring participation has been found[24] previously on treatment of 3-*C*-(3,5-di-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranos-3-yl)-5-methyl or ethyl, phenyl-1,2,4-oxadiazoles with sodium meth- oxide in methanol at pH 7–8. Apparently, these intramolecular replacements took place under different reaction conditions and in diverse mechanisms.

With the aim of preparing 1,2,4-oxadiazole derivatives **13**, **15**–**17**, many efforts through the cyclization of **9** with acetic anhydride, chloroacetyl chloride, propanic anhydride, and benzoyl chloride under refluxing temperature, however, gave complex inseparable mixtures.

Deprotection with 80% AcOH, 1% HCl/MeOH, or $CF_3CO_2H/CH_2Cl_2$, only $CF_3CO_2H/CH_2Cl_2$ under reflux temperature for 1 day did successfully cleave up 4,5-*O*-isopropylidene group of **14** to afford the 1,2-*O*-isopropylidene derivative **18**.

In vitro antitumor activities of **14** and **18** against tumor cells HL-60, Bel-7402, KB and Hela were evaluated by MTT and SRB assays.[25,26] Assays were performed using 96-well plates (Falcon, Becton Dickinson, Mountain View, CA, USA) seeded with $10^3$ cells per well in 200 μL RPMI 1640 without phenol red and supplemented with 10% FCS. After 24 h incubation, the medium was replaced with fresh RPMI 1640 medium containing the tested chemicals **14** and **18**. Cells were incubated for 48 h with molecules **14**, **18** (0.1–10 μM), followed by MTT or SRB Cell Inhibition Assay (Promega, Madison, WI, USA) (Table 9). The absorbance of each well was measured using a microculture plate reader at 570 nm (MTT) and 540 nm (SRB).

**Table 9.** Inhibition ratio (%) of **14**, **18** on tumor cells

| | Compound **14** | | | Compound **18** | | |
|---|---|---|---|---|---|---|
| | 0.1 (μM) | 1 (μM) | 10 (μM) | 0.1 (μM) | 1 (μM) | 10 (μM) |
| **A** | 22.78 | 31.59 | 29.94 | 17.68 | 27.96 | 23.79 |
| **B** | 1.64 | −1.46 | 9.92 | −17.29 | −8.64 | −2.91 |
| **C** | −16.69 | −15.36 | −7.28 | −19.51 | −17.01 | −12.40 |
| **D** | −10.85 | −7.54 | −0.97 | −13.04 | −16.19 | −6.85 |

**A**: **HL-60**[a], **B**: **Bel-7402**[b], **C**: **KB**[b], **D**: **Hela**[b].
[a] Detected by the standard MTT method.
[b] Detected by the standard SRB method.

## 3. Experimental

*General procedures*: Melting points were determined using an $X_4$ micromelting-piont apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241MC polarimeter. IR spectra were recorded with a Biorad FT-40 spectrophotometer (KBr pellets). All NMR spectra were recorded on a Varian MERCURY 400 spectrometer (400 MHz for $^1H$, 100 MHz for $^{13}C$) with $CDCl_3$ as solvent, $Me_4Si$ as an internal standard. Mass spectra were obtained on either ZAB-HS or HP 1100-MSD mass spectrometers. Column chromatography was performed on silica gel (200–300 mesh) and silica gel $GF_{254}$ for TLC was purchased from the Qingdao Chemical Company (China). Detection was effected by spraying the plates with 5% ethanolic $H_2SO_4$ (followed by heating at 110 °C for 10 min) or by direct UV irradiation of the plate. All the crystallographic measurements were carried out on a KUMA KM-4 diffractometer with graphite-monochromated Mo $K_\alpha$ radiation in a $\theta/2\theta$ scan mode. The unit cell parameters were determined from least-squares refinement based on the setting angles of 25 reflections. The stability of conditions was controlled by three control measurements every 100 reflections. The structures were solved by direct methods using the SHELXS (1990) program from the SHELX-97 package. Anisotropic displacement coefficients were applied to all nonhydrogen atoms. Refinement of all hydrogen atoms was done with idealized positions using isotropic temperature factors set to 1.2 times of the equivalent isotropic temperature factor of the neighboring C or O atoms. The structure refinements were performed using the SHELXL program.

### 3.1. 1,2:4,5-Di-*O*-isopropylidene-3-*C*-cyano-β-D-psicopyranose (2)

A solution of 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2-hexulopyranose-3-ulose (**1**) (1.29 g, 5 mmol) and tetrabutyl-ammonium bromide (0.48 g, 1.5 mmol) in $CH_2Cl_2$ (15 mL) was vigorously stirred at room temperature with the solution of NaCN (0.98 g, 20 mmol) in $H_2O$ (15 mL)

until TLC (95:5 benzene–MeOH) showed reaction complete. The organic layer was separated, washed, dried ($Na_2SO_4$), evaporated under reduced pressure to give a syrup, which was recrystallized from EtOH to yield white crystalline **2** (95–97%), mp 119–120 °C, $R_f$ 0.31 (9:1:1 benzene–MeOH–ether), $[\alpha]_D^{22}$ −162.5 (*c* 1.01, $CH_2Cl_2$), $\nu_{max}$: 3389.5 (m, OH) $cm^{-1}$. Like many other cyanosugars, the IR spectrum of **2** showed the absence of a CN band.[11,12] $\delta_H$: 4.33 (1H, d, $J_{1,1'}$ = 9.8 Hz, H-1), 4.04 (1H, d, H-1′), 4.78 (1H, d, $J_{4,5}$ = 2.9 Hz, H-4), 4.43 (1H, d, $J_{5,6}$ = 14.2 Hz, H-5), 4.15 (2H, s, H-6,6′), 3.33 (1H, s, OH-3), 1.62, 1.53, 1.49, 1.43 (12H, 4s, 4 × $CH_3$) ppm; $\delta_C$: 118.67 (C≡N), 114.24, 103.62 (2 × $CMe_2$), 73.15 (C-1), 110.25 (C-2), 74.04 (C-3), 70.13 (C-4), 69.74 (C-5), 59.91 (C-6), 26.44, 25.93, 25.62, 24.81 (4 × $CH_3$) ppm.

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.74, H, 6.67, N, 4.91. Found: C, 55.09, H, 6.81, N, 4.61.

### 3.2. 1,2:4,5-Di-*O*-isopropylidene-3-*C*-cyano-3-*O*-acetyl-β-D-psicopyranose (4)

A solution of 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-β-D-psicopyranose (**2**) (0.29 g, 1 mmol) in $Ac_2O$–pyridine (1:2, 5 mL) was stirred at room temperature until TLC (9:1:1 benzene–MeOH–ether) showed that the reaction completed, then poured onto ice water, extracted with $CH_2Cl_2$ (3 × 20 mL), the organic extracts were washed with water, dried ($Na_2SO_4$), and evaporated under reduced pressure to give the syrup, which was chromatographed on a short silica gel column to afford white crystalline **4** (0.31 g, 96%) [1:1 AcOEt–cyclohexane], mp 149–150 °C, $R_f$ 0.47 (9:1:1 benzene–MeOH–ether), $[\alpha]_D^{22}$ −195.8 (*c* 1.01, $CH_2Cl_2$), $\nu_{max}$: 1735.6 (vs, CO) $cm^{-1}$; $\delta_H$: 4.53 (1H, d, $J_{1,1'}$ = 9.9 Hz, H-1), 3.96 (1H, d, H-1′), 4.78 (1H, d, $J_{4,5}$ = 5.7 Hz, H-4), 4.33 (1H, dd, $J_{5,6}$ = 3.9 Hz, $J_{5,6'}$ = 6.0 Hz, H-5), 4.24 (1H, dd, $J_{6,6'}$ = 13.5 Hz, H-6), 4.13 (1H, d, H-6′), 2.04 (3H, s, $CH_3CO$), 1.58, 1.50, 1.49, 1.39 (12H, 4s, 4 × $CH_3$) ppm; $\delta_C$: 168.71 (CO), 116.12 (C≡N), 113.41, 104.32 (2 × $CMe_2$), 72.90 (C-1), 109.55 (C-2), 54.61 (C-3), 75.03 (C-4), 70.55 (C-5), 60.12 (C-6), 26.71, 26.07, 25.13, 24.65, 23.69 (5 × $CH_3$) ppm; ESI-MS (%): *m/z* 328 $[M+1]^+$ (100).

Anal. Calcd for $C_{15}H_{21}NO_7$: C, 55.02, H, 6.47, N, 4.28. Found: C, 55.04, H, 6.50, N, 4.30.

### 3.3. 1,2:4,5-Di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-psicopyranose (6) and 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-fructopyranose (7)

Cyanohydrins **2** (1.0 g, 3.51 mmol) was dissolved in a solution of $CH_2Cl_2$ (5 mL) and pyridine (4 mL), BzCl (1.6 mL, 14 mmol) was then added dropwise to the well-stirred reaction mixture at 0 °C and the stirring continued for an overnight from 0 °C to room temperature until TLC showed the compound **2** disappear, the mixture was poured onto ice water, extracted with $CH_2Cl_2$ (3 × 30 mL), washed, dried ($Na_2SO_4$), concentrated, and purified by column chromatography on silica gel (3:1 cyclohexane–EtOAc) to give 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-psicopyranose **6** and 1,2:4,5-di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-fructopyranose **7**.

1,2:4,5-Di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-psicopyranose **6** (0.82 g, 60%) as white needle crystals, mp 124–125 °C, $R_f$ 0.62 (3:2 cyclohexane–EtOAc), $[\alpha]_D^{22}$ −148.5 (*c* 1.0, $CH_2Cl_2$). $\nu_{max}$: 1741.0 (vs, PhCO) $cm^{-1}$; $\delta_H$: 8.10–7.46 (5H, m, Ph–H), 4.58 (1H, d, $J_{1,1'}$ = 12.8 Hz, H-1), 4.03 (1H, d, H-1′), 5.09 (1H, d, $J_{4,5}$ = 9.2 Hz, H-4), 4.43 (1H, m, H-5), 4.34 (1H, dd, $J_{5,6}$ = 4.0 Hz, $J_{6,6'}$ = 13.0 Hz, H-6), 4.04 (1H, d, H-6′), 2.17, 1.55, 1.53, 1.35 (12H, 4s, 4 × $CH_3$) ppm; $\delta_C$: 163.96 (CO), 134.04, 130.24, 128.68 (Ph–C), 115.29 (C≡N), 113.00, 103.92 (2 × $CMe_2$), 73.04 (C-1), 110.55 (C-2), 71.98 (C-3), 74.09 (C-4), 70.83 (C-5), 61.75 (C-6), 26.06, 25.86, 25.69, 24.89 (4 × $CH_3$) ppm; ESI-MS (%): *m/z* 390 $[M+1]^+$ (100), 374 $[M-CH_3]^+$ (90), 332 (85), 185, 105, 77, 59, 43.

Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.69, H, 5.91, N, 3.59. Found: C, 61.63, H, 6.04, N, 3.62.

1,2:4,5-Di-*O*-isopropylidene-3-*C*-cyano-3-*O*-benzoyl-β-D-fructopyranose **7** (0.41 g, 30%) as white prism crystals, mp 118–119 °C, $R_f$ 0.55 (3:2 cyclohexane–EtOAc), $[\alpha]_D^{22}$ 65.5 (*c* 1.0, $CH_2Cl_2$). $\nu_{max}$: 1734.0 (vs, PhCO) $cm^{-1}$; $\delta_H$: 8.09–7.44 (5H, m, Ph–H), 4.62 (1H, d, $J_{1,1'}$ = 12.8 Hz, H-1), 4.28 (1H, d, H-1′), 4.64 (1H, d, $J_{4,5}$ = 7.6Hz, H-4), 4.44 (1H, m, H-5), 4.30 (1H, dd, $J_{5,6}$ = 4.0 Hz, $J_{6,6'}$ = 13.2 Hz, H-6), 4.25 (1H, d, H-6′), 1.82, 1.54, 1.49, 1.43 (12H, 4s, 4 × $CH_3$) ppm; $\delta_C$: 163.40 (C=O), 133.92, 130.03, 128.62 (Ph–C), 115.23 (C≡N), 113.92, 104.05 (2 × $CMe_2$), 74.61 (C-1), 110.61 (C-2), 73.02 (C-3), 77.48 (C-4), 72.23 (C-5), 61.32 (C-6), 26.21, 26.08, 25.57, 24.99 (4 × $CH_3$) ppm; ESI-MS (%): *m/z* 390 $[M+1]^+$ (100), 374 $[M-CH_3]^+$ (94), 332 (88), 185, 105, 77, 59, 43.

Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.69, H, 5.91, N, 3.59. Found: C, 61.58, H, 6.05, N, 3.54.

### 3.4. 1,2:4,5-Di-*O*-isopropylidene-3-*C*-amidoximino-3-*O*-benzoyl-β-D-psicopyranose (8)

A solution of **6** (1.20 g, 3.08 mmol) and hydroxylamine (6.5 mmol) in anhydrous MeOH (15 mL) (pH = 7–8) was refluxed with stirring for 8 h, After the reaction was complete (TLC 1:2 cyclohexane–EtOAc), the solvent was removed by distillation, the residue was purified by silica gel column chromatography with 2:3 cyclohexane–EtOAc affording **8** (0.75 g, 58%) as white crystals, mp 109–112 °C, $R_f$ 0.62 (1:2 cyclohexane–EtOAc), $[\alpha]_D^{22}$ −102.3 (*c* 1.0, $CH_2Cl_2$). $\nu_{max}$: 3394.0 (vs, OH, $NH_2$), 1687.0 (m, CO) $cm^{-1}$; $\delta_H$: 9.85 (1H, br s, OH, exchangeable with $D_2O$), 8.11–7.45 (5H, m, Ph–H), 5.23 (2H, s, $NH_2$, exchangeable with $D_2O$) 4.81 (1H, d, $J_{1,1'}$ = 7.5 Hz, H-1), 3.82 (1H, d, H-1′), 5.61 (1H, d, $J_{4,5}$ = 7.8 Hz, H-4), 4.43 (1H, ddd, $J_{5,6}$ = 2.7 Hz, $J_{5,6'}$ = 6.0 Hz, H-5), 4.18 (1H, dd, $J_{6,6'}$ = 10.8 Hz, H-6), 3.86 (1H, d, H-6′), 1.55, 1.53, 1.50, 1.41 (12H, 4s, 4 × $CH_3$) ppm; $\delta_C$: 170.71 (C=O), 151.86 (C=N), 133.59, 130.19, 128.42 (Ph–C), 111.86,

103.30 (2 × *C*Me$_2$), 73.92 (C-1), 110.97 (C-2), 73.45 (C-3), 75.73 (C-4), 65.04 (C-5), 63.04 (C-6), 26.63, 26.19, 25.96, 25.01 (4 × *C*H$_3$) ppm; ESI-MS (%): *m*/*z* 445 $[M+Na]^+$ (100).

Anal. Calcd for $C_{20}H_{26}N_2O_8$: C, 56.80, H, 6.16, N, 6.64. Found: C, 56.76, H, 6.18, N, 6.70.

### 3.5. 1,2:4,5-Di-*O*-isopropylidene-3-*C*-amidoximino-β-D-psicopyranose (9)

The procedure described for the preparation of **8** was followed starting from **2** (0.50 g, 1.75 mmol), hydroxylamine (3.7 mmol) in anhydrous MeOH (10 mL), TLC (1:3 cyclohexane–EtOAc) of the reaction showed complete conversion of the cyanohydrins **2** to the amidoxime **9**, the purification by silicon gel column chromatography with 1:3 cyclohexane–EtOAc afforded the compound **9** (0.26 g, 46%) as white crystals, mp 148–149 °C, $R_f$ 0.42 (1:3 cyclohexane–EtOAc), $[\alpha]_D^{22}$ −85.3 (*c* 1.1, $CH_2Cl_2$). $\nu_{max}$: 3470.4, 3440.0, 3387.0 (vs, OH, $NH_2$) cm$^{-1}$; $\delta_H$: 9.00 (2H, br s, $NH_2$), 8.78 (1H, br s, OH, exchangeable with $D_2O$), 4.73 (1H, d, $J_{1,1'}$ = 7.5 Hz, H-1), 4.02 (1H, d, H-1′), 5.48 (1H, d, $J_{4,5}$ = 7.5 Hz, H-4), 4.34 (1H, ddd, $J_{5,6}$ = 3.0 Hz, $J_{5,6'}$ = 8.7 Hz, H-5), 4.12 (1H, dd, $J_{6,6'}$ = 12.0 Hz, H-6), 3.86 (1H, d, H-6′), 2.11 (1H, s, OH-3), 1.48, 1.45, 1.39, 1.30 (12H, 4s, 4 × $CH_3$) ppm; ESI-MS (%): *m*/*z* 341 $[M+Na]^+$ (100), 319 $[M+1]^+$ (90).

Anal. Calcd for $C_{13}H_{22}N_2O_7$: C, 49.05, H, 6.97, N, 8.80. Found: C, 49.07, H, 6.80, N, 8.82.

An alternative synthesis from **8** (100 mg, 0.24 mmol) by treatment with methanolic NaOMe (1 M, 10 mL) at room temperature for 18 h gave **9** (72 mg, 96%), which is identical in all respects to the product obtained in the above procedure.

### 3.6. 1,2:4,5-Di-*O*-isopropylidene-3-*C*-(5-phenyl-1,2,4-oxadiazol-3-yl)-β-D-psicopyranose (14)

A solution of **8** (0.20 g, 0.47 mmol) in redistilled $Ac_2O$ (8 mL) was heated at 80 °C under nitrogen atomosphere for 18 h until the TLC (1:2 acetone–cyclohexane) showed the reaction complete. Anhydrous EtOH (10 mL) was added and stirred for 30 min. Then the solvent was distilled off and further co-evaporated with toluene, the resultant brown syrup was purified on a column of silica gel chromatography using acetone–cyclohexane (1:3) as eluent to give white crystals **14** (0.17 g, 88%), mp 116–117 °C, $R_f$ 0.26 (1:2 acetone–cyclohexane), $[\alpha]_D^{22}$ −148.5 (*c*, 1.0 $CH_2Cl_2$). $\nu_{max}$: 3397.0 (s, OH), 1603.0 (s, C=N), 1555.0 (s, C–N) cm$^{-1}$; $\delta_H$: 8.16 (2H, dd, $J_{2,3}$ = $J_{5,6}$ = 6.0 Hz, $J_{2,4}$ = $J_{4,6}$ = 1.8 Hz, ArH-2,6), 7.57 (1H, dd, $J_{3,4}$ = $J_{4,5}$ = 4.8 Hz, ArH-4), 4.60 (1H, d, $J_{1,1'}$ = 9.5 Hz, H-1), 4.03 (1H, d, H-1′), 5.23 (1H, d, $J_{4,5}$ = 5.5 Hz, H-4), 4.41 (1H, m, H-5), 4.37 (1H, dd, $J_{5,6}$ = 3.0 Hz, $J_{6,6'}$ = 12.5 Hz, H-6), 4.30 (1H, d, H-6′), 3.33 (1H, s, HO-3, exchangeable with $D_2O$), 1.63, 1.48, 1.43, 1.11 (12H, 4s, 4 × $CH_3$) ppm; $\delta_C$: 175.84 (C-3′), 170.89 (C-5′), 132.83, 129.05, 128.23, 124.01 (Ph–C), 112.97, 105.36 (2 × *C*Me$_2$), 72.18 (C-1), 109.58 (C-2), 71.89 (C-3), 73.83 (C-4), 71.01 (C-5), 60.03 (C-6), 25.04, 25.79, 25.64, 25.21 (4 × *C*H$_3$) ppm; FABMS (%): *m*/*z* 443 $[M+K]^+$ (90), 427 $[M+Na]^+$ (100); ESI-MS (%): *m*/*z* 405 $[M+1]^+$ (100).

Anal. Calcd for $C_{20}H_{24}N_2O_7$: C, 59.40, H, 5.94, N, 6.93. Found: C, 59.38, H, 5.96, N, 6.91.

Treatment of **8** (0.20 g, 0.47 mmol) with chloroacetyl chloride, propanic anhydride and benzoyl chloride (10 mL), respectively, at 120–130 °C under nitrogen atmosphere for 22 h until the TLC (1:2 acetone–cyclohexane) showed the reaction complete, the mixture was poured onto ice water, extracted with $CH_2Cl_2$ (3 × 20 mL), washed, dried ($Na_2SO_4$), concentrated, and purified by column chromatography on silica gel to give compound **14** (81–83%) as white crystals, which is consistent with the product obtained in the above procedure in all physical and spectral data.

### 3.7. 1,2-*O*-Isopropylidene-3-*C*-(5-phenyl-1,2,4-oxadiazol-3-yl)-β-D-psicopyranose (18)

Compound **14** (0.40 g, 1 mmol) was dissolved in a solution of $CH_2Cl_2$ (10 mL), $CF_3CO_2H$ (0.5 mL, 90%) was added, the reaction mixture was stirred for 24 h at reflux temperature until TLC showed the compound **14** disappear, cooled to 0 °C, and neutralized with $NaHCO_3$, the mixture was evaporated, and the residue was purified by silica gel column chromatography (10:1 $CHCl_3$–MeOH) to give compound **18** (0.29 g, 80%) as white crystals, mp 149–151 °C, $R_f$ 0.53 (9:1 $CHCl_3$–MeOH), $[\alpha]_D^{22}$ −166.5 (*c*, 1.0 $CH_2Cl_2$). $\nu_{max}$: 3485.1, 3433.2, 3377.1 (vs, OH), 1612.5 (s, C=N), 1566.2 (s, C–N) cm$^{-1}$; $\delta_H$: 8.15–7.50 (5H, m, Ph–H), 4.57 (2H, br s, OH-4,5), 4.20 (1H, d, $J_{1,1'}$ = 12.0 Hz, H-1), 4.00 (1H, d, H-1′), 4.52 (1H, d, $J_{4,5}$ = 9.6 Hz, H-4), 4.02 (1H, m, H-5), 4.07 (1H, dd, $J_{5,6}$ = 4.8 Hz, $J_{6,6'}$ = 14.7 Hz, H-6), 3.98 (1H, d, H-6′), 3.40 (1H, br s, HO-3), 1.45, 1.07 (6H, 2s, 2 × $CH_3$) ppm; $\delta_C$: 175.84 (C-3′), 169.97 (C-5′), 133.02, 129.12, 128.26, 123.76 (Ph–C), 113.00 (*C*Me$_2$), 69.04 (C-1), 106.18 (C-2), 69.03 (C-3), 72.21 (C-4), 67.87 (C-5), 64.60 (C-6), 26.06, 25.68 (2 × *C*H$_3$) ppm; ESI-MS (%): *m*/*z* 403 $[M+K]^+$ (42), 387 $[M+Na]^+$ (98), 307 (100).

Anal. Calcd for $C_{17}H_{20}N_2O_7$: C, 56.04, H, 5.49, N, 7.69. Found: C, 55.94, H, 5.60, N, 7.59.

## 4. Supplementary data

CCDC 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 Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

## Acknowledgements

This work was supported by the financial support of the National Natural Science Foundation of China (No.

29862006) and in part by the National Laboratory of Natural and Biomimetic Drugs of Peking University. We are grateful to Professor Ralph P. Mason (UT Southwestern Medical Center at Dallas) for editorial correction of this manuscript and Professor Jacques Defaye (Université Joseph Fourier-Grenoble 1) for helpful discussions and suggestions.

## References and notes

1. Yoshimura, Y. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69–136.
2. Sheban, M. A. E. *Adv. Heterocycl. Chem.* **1998**, *70*, 163–337.
3. Gervay, J.; Flaherty, T. M.; Holmes, D. *Tetrahedron* **1997**, *53*, 16355–16364.
4. El-Ashry, E. H.; El-Kilany, Y. *Adv. Heterocycl. Chem.* **1998**, *69*, 129–215.
5. Altonare, C.; Monforte, A. M.; Gasparrini, F.; Villani, C.; Grills, M.; Mazza, F. *Chirality* **1996**, *8*, 556–566.
6. Yu, J. X.; Zhang, S. N.; Li, Z. J.; Lu, W. J.; Liu, Y. T.; Cai, M. S. *J. Carbohydr. Chem.* **2001**, *20*, 877–884.
7. De Las Heras, G. *Tetrahedron* **1985**, *41*, 3867–3873.
8. Zhdanov, Y. A.; Alekseev, Yu. E.; Zinchenko, G. V.; Doroshenko, S. S. *Duklady Akad. Nauk S. S. S. R.* **1976**, *231*, 868–869.
9. Tipson, R. S.; Brady, R. F., Jr.; West, B. F. *Carbohydr. Res.* **1971**, *16*, 383–393.
10. Prisbe, E. J.; Smejkal, J.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1976**, *41*, 1836–1846.
11. Bourgeois, J. M. *Helv. Chim. Acta* **1975**, *58*, 363–372.
12. Vas, G.; Sepulchre, A. M.; Gero, S. D. *Tetrahedron* **1977**, *33*, 321–324.
13. Yu, J. X.; Liu, Y. T. *J. Xinjiang Univ.* **1991**, *8*, 64–66.
14. Yu, J. X.; Liu, Y. T. *Chem. Res. Chin. Univ.* **1992**, *8*, 169–172.
15. (a) Thang, T. T.; Winternitz, F.; Lagrange, A.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.* **1980**, *21*, 4495–4498; (b) Thang, T. T.; Winternitz, F.; Olesker, A.; Lagrange, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1979**, 153–154.
16. Rocherolle, V.; Lukacs, G. *J. Carbohydr. Chem.* **1989**, *8*, 645–662.
17. (a) Yoshimura, J.; Matsuzawa, M.; Sato, K.; Funabashi, M. *Chem. Lett.* **1977**, 1403; (b) Yoshimura, J.; Matsuzawa, M.; Sato, K.; Nagasawa, Y. *Carbohydr. Res.* **1979**, *76*, 67–78.
18. Perez-Perez, M. J.; Camarasa, M. J.; Diaz-Ortiz, A.; Felix, A. S.; De Las Heras, F. G. *Carbohydr. Res.* **1991**, *216*, 399–411.
19. Myers, R. W.; Lee, Y. C. *Carbohydr. Res.* **1984**, *132*, 61–82.
20. Repke, D. B.; Albrecht, H. P.; Moffatt, J. G. *J. Org. Chem.* **1975**, *40*, 2481–2487.
21. Dong, L. J.; Li, L.; Ma, L. T.; Zhang, L. H. *Chin. Chem. Lett.* **1992**, *3*, 597–600.
22. Dong, L. J.; Li, L.; Ma, L. T.; Zhang, L. H. *Gaodeng Xuexiao Huaxue Xuebao* **1992**, *13*, 617–622.
23. Tronchet, J. M. J.; Zosimo-Landolfo, G.; Bernardinelli, G.; Arrizabalaga, P.; Geoffroy, M. *J. Carbohydr. Chem.* **1986**, *5*, 631–645.
24. Zhang, M. L.; Zhang, H. Y.; Yang, Z. J.; Ma, L. T.; Min, J. M.; Zhang, L. H. *Carbohydr. Res.* **1999**, *318*, 157–161.
25. Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107–1112.
26. Carmichael, J.; DeGraff, W. G.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B. *Cancer Res.* **1987**, *47*, 936–942.