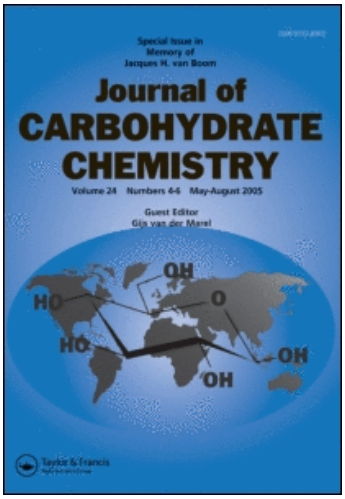

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SYNTHESIS, X-RAY DIFFRACTION, AND NMR ANALYSIS OF (2*S*, 3a'*R*, 6'*S*, 7a'*R*)-3-ACETYL-2', 2', 2'', 2''-TETRAMETHYL-5-PHENYL-2, 3-DIHYDRO-1, 3, 4-OXADIAZOLE-2-SPIRO-7'-{1', 3'-DIOXOLANO [4, 5-*c*] PYRANO}-6'-SPIRO-4''-(1'', 3''-DIOXOLANE)

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COMMUNICATION

SYNTHESIS, X-RAY DIFFRACTION, AND NMR ANALYSIS OF (2*S*, 3a′*R*, 6′*S*, 7a′*R*)-3-ACETYL-2′, 2′, 2″, 2″-TETRAMETHYL-5-PHENYL-2, 3-DIHYDRO-1, 3, 4-OXADIAZOLE-2-SPIRO-7′-{1′, 3′-DIOXOLANO [4, 5-*c*] PYRANO}-6′-SPIRO-4″-(1″, 3″-DIOXOLANE)

Jianxin Yu,[1,2,*] Suna Zhang,[2] Zhongjun Li,[1] Wenjie Lu,[3] Lijing Zhang,[2] Rong Zhou,[2] Yuting Liu,[2] and Mengshen Cai[1]

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Spiroheterocyclic derivatives have considerable importance as drugs and a wide scope of application.[1] Recently, a number of oxadiazolines have been reported to possess anti-HIV activity.[2] In addition, the incorporation of heterocyclic moieties in the carbohydrate framework has gained much importance.[3–5] In this paper we present the synthesis, NMR spectra and crystal structure of a novel spiroheterocyclic oxadiazoline, with a spiral junction at C-3 of fructopyranose.

Reaction of 1,2**:**4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose(**1**)[6] with benzoylhydrazine in methanol in the presence of acetic acid as catalyst afforded 3- benzoylhydrazono-1,2**:**4,5-di-*O*-isopropylidene-β-D-*erythro*-2-hexulopyranose (**2**). Treatment of **2** with boiling acetic anhydride gave rise to a crystalline product **3** after chromatography, the elemental analysis of which indicated the introduction of one acetyl group. The product had an IR peak at 1751.8 cm^{-1} for NAc, but none for NH. The shift of the NAc band to a lower frequency compared to that of **2** rules out an *N*-acetylated hydrazone structure. According to

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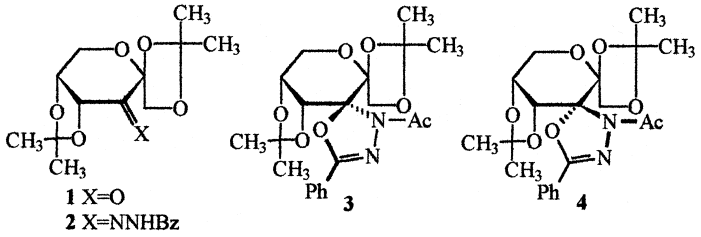
the results of Kubota et al.,s7 the generation of a new chiral centre during the formation of the oxadiazole ring in **3** could also result in formation of the other diastereoisomer **4**. However, from the ^{13}CNMR spectrum of the products, only one diastereoisomer (**3** or **4**) was found, indicating that the new asymmetric centre was formed with total stereoselectivity.

Initially, we intended to determine the specific configuration of **3** through its NOESY spectrum by use of the correlation between H-5 or 11, 12, 13 and the methyl protons of the *N*-acetyl group. However, the molecular modelling studies of **3** and **4** showed that the distances between H-5 or H-11, H-12, H-13 and the methyl protons of the *N*-acetyl group are all above 2.5 Å, indicating that NOSEY experiments

Table 1. Crystal Data and Structure Refinement for 3



Empirical formula	$C_{21}H_{26}N_2O_7$
Formula weight	418.44
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.6810(10) Å, α= 90°
	b = 11.216(2) Å, β= 90°
	c = 20.163(3) Å, χ= 90°
Volume, Z	2189.3(6) Å^3, 4
$D_{calc.}$	1.269 mg/m^3
Absorption coefficient	0.096mm^{-1}
F(000)	888
Crystal size	0.54 × 0.54 × 0.50 mm
Θ range for data collection	2.02 to 25.99°
Limiting indices	$0 \le h \le 11$, $0 \le K \le 13$, $-1 \le l \le 24$
Reflections collected	2702
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	0.920
Final R indices [I > 2σ (I)]	R^1 = 0.0330, WR^2 = 0.0734
R indices	R^1 = 0.0490, WR^2 = 0.0780
Absolute structure parameter	−1.9(12)
Extinction coefficient	0.0176(10)
Largest diff. peak and hole	0.136 and −0.149 e Å^{-3}

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Table 2. Fractional Atomic Coordinates and Equivalent Thermal Parameters of 3

Atom	x	y	z	U (eq)
O-1	6105(2)	3732(1)	−507(1)	52(1)
O-2	4975(2)	5553(1)	−630(1)	54(1)
O-3	3265(2)	4266(2)	−912(1)	75(1)
O-4	5727(2)	3807(1)	827(1)	42(1)
O-5	4896(2)	7442(1)	450(1)	68(1)
O-6	7738(2)	5436(1)	1035(1)	53(1)
O-7	8729(2)	4062(1)	360(1)	55(1)
N-1	4619(2)	5568(2)	847(1)	44(1)
N-2	4030(2)	4821(2)	1330(1)	45(1)
C-1	3727(3)	3938(2)	−271(1)	54(1)
C-2	5128(3)	4532(2)	−236(1)	45(1)
C-3	5468(2)	4901(2)	452(1)	50(1)
C-4	7065(2)	5505(2)	413(1)	43(1)
C-5	8054(3)	4897(2)	−64(1)	52(1)
C-6	7402(3)	4284(2)	−648(1)	63(1)
C-7	3814(3)	5392(2)	−1070(1)	61(1)
C-8	4329(4)	5344(3)	−1776(1)	95(1)
C-9	2820(3)	6381(3)	−945(2)	91(1)
C-10	4699(2)	3844(2)	1288(1)	39(1)
C-11	4455(2)	2771(2)	1681(1)	42(1)
C-12	3350(3)	2472(2)	2122(1)	63(1)
C-13	3087(3)	1725(3)	2482(1)	75(1)
C-14	3899(4)	742(3)	2410(1)	75(1)
C-15	4991(3)	761(2)	1977(2)	73(1)
C-16	5269(3)	1777(2)	1610(1)	55(1)
C-17	4264(2)	6778(2)	847(1)	51(1)
C-18	3365(3)	7211(2)	1372(2)	77(1)
C-19	8918(3)	4639(2)	979(2)	58(1)
C-20	10222(3)	5388(3)	987(2)	87(1)
C-21	8869(3)	3722(3)	1519(1)	76(1)

could not construct the correlation of the methyl protons of the *N*-acetyl group with other protons. The difference between the two lowest energy forms of **3** and **4** is below 1 KJ mol^{-1}, it was clear that the energy difference could not be used to determine the configuration of **3** and **4**. Fortunately, we obtained crystals of the spiroheterocyclic product from 1:1 AcOEt-cyclohexane, which were suitable for X-ray crystallographic analysis. The X-ray diffraction studies clearly indicated that the structure of the isolated spiroheterocyclic compound was structure **3**, with the pyranoid ring adopting a $^4C_1$ chair conformation. Crystallographic data, data collection and structure refinements are summarized in Table 1. The atomic coordinates of the non-hydrogen atoms are listed in Table 2. The bond lengths and torsion angles are listed in Table 3 and 4, respectively. The ORTEP plot for compound **3** is shown in Fig. 1, and the puckering of the molecule is shown in Fig. 2.

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Table 3. The Bond Lengths (Å) for 3

O(1)—C(2)	1.414(3)	O(1)—C(6)	1.428(3)
O(2)—C(2)	1.401(2)	O(2)—C(7)	1.443(3)
O(3)—C(7)	1.410(3)	O(3)—C(1)	1.419(3)
O(4)—C(10)	1.362(2)	O(4)—C(3)	1.444(2)
O(5)—C(17)	1.209(3)	O(6)—C(19)	1.456(3)
O(6)—C(4)	1.415(3)	O(7)—C(5)	1.427(3)
O(7)—C(19)	1.417(3)	N(1)—C(17)	1.379(3)
N(1)—N(2)	1.405(2)	N(1)—C(3)	1.480(3)
N(2)—C(10)	1.274(3)	C(6)—C(5)	1.504(3)
C(5)—C(4)	1.518(3)	C(4)—C(3)	1.532(3)
C(3)—C(2)	1.532(3)	C(2)—C(1)	1.513(3)
C(7)—C(9)	1.490(4)	C(7)—C(8)	1.509(4)
C(19)—C(21)	1.497(4)	C(19)—C(20)	1.517(4)
C(10)—C(11)	1.461(3)	C(11)—C(16)	1.373(3)
C(11)—C(12)	1.391(3)	C(16)—C(15)	1.385(3)
C(15)—C(14)	1.372(4)	C(14)—C(13)	1.362(4)
C(13)—C(12)	1.376(3)	C(17)—C(18)	1.513(3)

Table 4. The Torsion Angles (°) for 3

C(2)—O(1)—C(6)	112.91(17)	C(2)—O(2)—C(7)	109.16(18)
C(7)—O(3)—C(1)	108.32(18)	C(10)—O(4)—C(3)	107.00(16)
C(4)—O(6)—C(19)	109.08(18)	C(19)—O(7)—C(5)	106.69(18)
C(17)—N(1)—N(2)	120.9(2)	C(17)—N(1)—C(3)	128.20(2)
N(2)—N(1)—C(3)	110.15(16)	C(10)—N(2)—N(1)	105.11(17)
O(1)—C(6)—C(5)	114.31(19)	O(7)—C(5)—C(6)	111.20(2)
O(7)—C(5)—C(4)	101.81(19)	O(6)—C(5)—C(4)	115.90(2)
O(6)—C(4)—C(5)	104.24(17)	O(6)—C(4)—C(3)	110.03(18)
C(5)—C(4)—C(3)	113.46(18)	O(4)—C(3)—N(1)	100.54(16)
O(4)—C(3)—C(2)	105.27(15)	N(1)—C(3)—C(2)	113.79(17)
O(4)—C(3)—C(4)	110.80(17)	N(1)—C(3)—C(4)	113.98(16)
C(2)—C(3)—C(4)	111.54(18)	O(2)—C(2)—O(1)	111.77(18)
O(2)—C(2)—C(1)	103.84(18)	O(1)—C(2)—C(1)	107.60(17)
O(2)—C(2)—C(3)	109.08(16)	O(1)—C(2)—C(3)	107.56(18)
C(1)—C(2)—C(3)	117.03(19)	O(3)—C(1)—C(2)	102.47(19)
O(3)—C(7)—O(2)	105.80(19)	O(3)—C(7)—C(9)	112.40(2)
O(2)—C(7)—C(9)	107.90(2)	O(3)—C(7)—C(8)	107.90(2)
O(2)—C(7)—C(8)	109.10(2)	C(9)—C(7)—C(8)	113.50(3)
O(7)—C(19)—O(6)	104.30(2)	O(7)—C(19)—C(21)	108.80(2)
O(6)—C(19)—C(21)	109.90(2)	O(7)—C(19)—C(20)	111.70(2)
O(6)—C(19)—C(20)	108.17(19)	C(21)—C(19)—C(20)	113.60(3)
N(6)—C(10)—O(4)	116.30(2)	N(2)—C(10)—C(11)	126.1(2)
O(4)—C(10)—C(11)	117.58(19)	C(16)—C(11)—C(12)	119.3(2)
C(16)—C(11)—C(10)	121.30(2)	C(12)—C(11)—C(10)	119.40(2)
C(11)—C(16)—C(15)	120.10(2)	C(14)—C(15)—C(16)	120.20(3)
C(13)—C(14)—C(15)	120.00(3)	C(14)—C(13)—C(12)	120.60(3)
C(13)—C(12)—C(11)	119.90(3)	N(1)—C(17)—C(18)	115.50(2)
O(5)—C(17)—C(18)	122.60(2)	O(5)—C(17)—N(1)	121.90(2)

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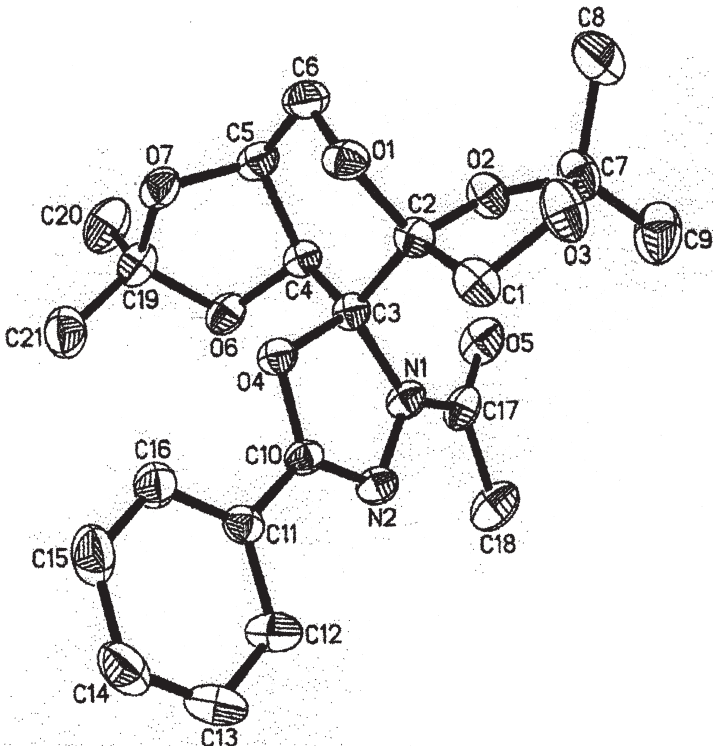

Figure 1. The ORTEP plot for compound 3.

EXPERIMENTAL

General Procedures. Melting points were determined using an X_4 micromelting-point 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 (400MHz for ^1H, 100MHz for ^{13}C) with $CDCl_3$ as solvent, and Me_4Si as an internal standard. Column chromatography was performed on silica gel(200~300mesh) and silica gel GF_{254} (purchased from the Qingdao Marine Chemical Company, China) was used for TLC. Detection on TLC 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 MoKα radiation, and θ/2θ 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 hundred 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 non-hydrogen atoms. Refinement of all hydrogen atoms was done with idealized positions using isotropic

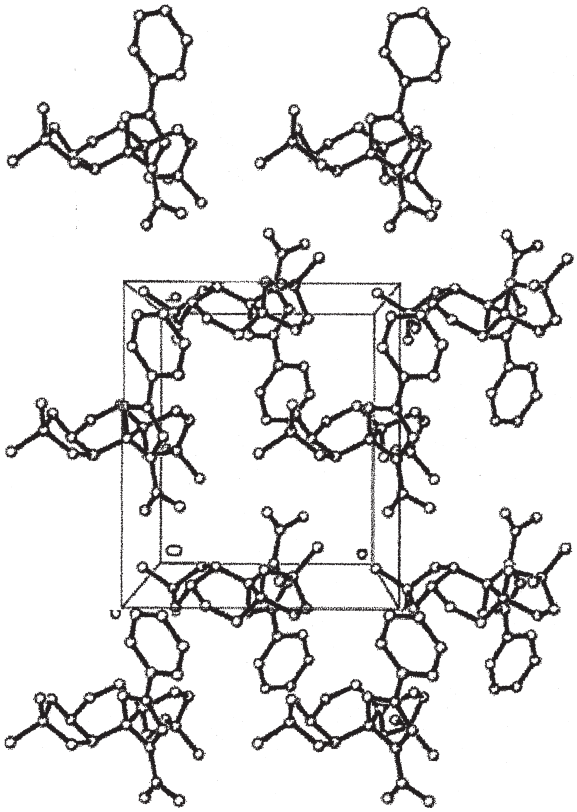

Figure 2. The arrangement of the molecules in the unit cell.

temperature factors set to 1.2 times of the equivalent isotropic temperature factor of the neighbouring C or O atoms. The structure refinements were performed using the SHELXL program.

3-Benzoylhydrazono-1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-2-hexulopyranose (2). A solution of 1,2**:**4,5-di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose (**1**, 0.52 g, 2.04 mmol) and benzoylhydrazine (0.30 g, 2.16 mmol) in MeOH (10 mL) containing acetic acid (0.2 mL) was stirred at 60∼65°C in a water bath for 6 h until TLC (solvent**:** benzene-MeOH 95**:**5) showed that the reaction was complete. The mixture was concentrated under reduced pressure to give the syrupy product which was recrystallized from EtOH—H_2O to yield white crystalline **2** (0.62 g, 82%), mp 123∼125°C, $[\alpha]_D^{22}$ −308.1° (*c* 1.03, CH_2Cl_2), υ_{max}: 3329.9 (m, NH), 1697.9 (s, C═O)cm^{-1}; δ_H: 11.49 (br, 1H, NH), 7.89∼7.40 (m, 5H, Ph), 5.09 (d, 1H, $J_{1,1'}$ = 9.6Hz, H-1), 4.97 (d, 1H, $J_{1,1'}$ = 9.6Hz, H-1′), 4.51 (d, 1H, $J_{4,5}$ = 2.7Hz, H-4), 4.23 (d, 1H, $J_{5,6}$ = 13.5Hz, H-5), 4.01 (s, 2H, H-6,6′), 1.57, 1.53, 1.46, 1.41 (4s, 12H, 4×CH_3)ppm; δ_C: 195.03 (**C**O), 133.07∼128.03 (Ph), 113.07, 110.77 (**C**Me_2), 71.73 (C-1), 112.32 (C-2), 104.11 (C-3), 71.54 (C-4), 65.17 (C-5), 59.07 (C-6), 27.27, 26.73, 26.17, 25.73 (4× **C**H_3)ppm.

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Anal. Calcd for $C_{19}H_{24}N_2O_6$(%): C, 60.63, H, 6.43, N, 7.44; Found: C, 60.48, H, 6.40, N, 7.38.

(2*S*,3a′*R*,6′*S*,7a′*R*)-3-Acetyl-2′,2′,2″,2″-tetramethyl-5-phenyl-2,3-dihydro-1,3,4-oxadiazole-2-spiro-7′-{1′,3′-dioxolano[4,5-*c*]pyrano}-6′-spiro-4″-(1″,3″-dioxolane)(3). A solution of (**2**, 0.5 g, 1.3 mmol) in acetic anhydride (3 mL) was boiled under reflux with stirring in an oil bath until TLC (95**:**5 benzene-MeOH) showed that the reaction was complete. The reaction mixture was then cooled, poured onto crushed ice and neutralised with a cold 10% aqueous KOH solution. The syrup was extracted with CH_2Cl_2, the organic extracts were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to give a syrup which was purified by chromatography on a short silica gel column to afford white crystalline **3** (52%)[1:1 AcOEt-cyclohexane], mp 117∼118°C, $[\alpha]_D^{22}$ 332.6° (*c* 0.1, CH_2Cl_2), υ_{max}: 1751.8 (s, NAc), 1698.5 (m, C═N)cm^{-1}; δ_H: 7.95∼7.40 (m, 5H, Ph), 6.01 (d, 1H, $J_{1,1'}$ = 6.0Hz, H-1), 4.40 (d, 1H, $J_{1,1'}$ = 6.0Hz, H-1′), 4.33 (d, 1H, $J_{4,5}$ = 2.8Hz, H-4), 4.22 (d, 1H, $J_{5,6}$ = 14.1Hz, H-5), 3.97 (s, 2H, H-6,6′), 2.40 (s, 3H, NAc), 1.52, 1.42, 1.38, 1.35 (4s, 12H, 4×CH_3)ppm; δ_C: Sugar unit: 114.07, 105.41 (**C**Me_2), 73.63 (C-1), 109.91 (C-2), 97.69 (C-3), 71.28 (C-4), 69.64 (C-5), 59.93 (C-6), 26.18, 25.62, 25.54, 25.32 (4× **C**H_3), Oxadiazole ring: 168.53 (**C**O), 153.85 (C-5′), 97.69 (C-2′), 131.61∼121.00 (Ph), 23.93 (NAc)ppm.

Anal. Calcd for $C_{21}H_{26}N_2O_7$(%): C, 60.27, H, 6.26, N, 6.69; Found: C, 60.26, H, 6.25, N, 6.66.

SUPPLEMENTARY MATERIAL

Full crystallographic details, excluding structure features, have been deposited with the Cambridge Crystallographic Data Centre (Accession No. CCDC 164729). These data may be obtained, on request, from the Director of CCDC, 12 Union Road, Cambridge, CB2, 1EZ, UK(Tel: +44 1223 336408, Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk).

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