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Note

Boat conformations☆ Synthesis, NMR spectroscopy, and molecular dynamics of methyl 4,6-*O*-benzylidene-3-deoxy-3-phthalimido-α-D-altropyranoside derivatives

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Abstract

Addition of the elements of phthalimide to methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) under fusion conditions has yielded methyl 4,6-*O*-benzylidene-3-deoxy-3-phthalimido-α-D-altropyranoside (**2**). The conformation of the pyranose ring of **2** has been shown to be non-chair by ^{1}H NMR spectroscopy, in contrast to the conformations of related derivatives having smaller substituents at C-3. Molecular dynamics simulations of **2** in explicit chloroform-*d* solvent have indicated four principal conformational possibilities. Of these, the $^7C_5/^1S_5$ chair/skew boat form **2d** has the lowest potential energy, and is largely consistent with the observed vicinal ^{1}H–^{1}H NMR coupling constants.

Keywords: Altropyranoside; Boat conformations; ^{1}H NMR spectroscopy; Molecular dynamics; Phthalimido derivative; Simulated annealing; Skew boat conformations; Vicinal coupling constants

1. Introduction

In three previous papers in this series, we have discussed some examples of pyranoid rings that are constrained to skew boat forms by the presence of bridging anhydro or cyclic acetal rings.[1–3] These molecules are of particular interest for studies of the angular dependence of homonuclear and heteronuclear NMR coupling constants, because of elimination of contributions to the observed coupling constants from alternative conformations. Boat conformations are also of interest as potential transition-state intermediates. The data from such studies could be of particular value in the structural and conformational analysis of oligosaccharide components of vaccines and aminoglycoside antibiotics. Also

☆ Part IV of a series, Boat conformations: for Parts I–III, see Refs. 1–3.

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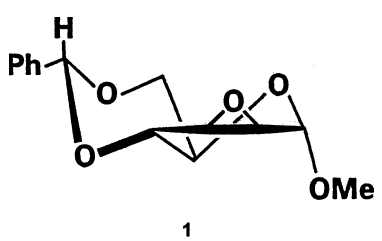
of interest, is a determination of which types of substituents have sufficiently large steric repulsions to cause the pyranose ring to deviate from the chair form. The 4,6-*O*-benzylidene acetals of glycopyranosides having the gluco, manno, altro, and allo configurations (*trans* fused benzylidene ring) are usually thought of as being conformationally homogeneous, and based on measurements of $^1H-^1H$ NMR coupling constants, there is little doubt that the vast majority of these derivatives exists in a conformation in which the pyranose ring is in the $^4C_1$ form.[4] Two interesting exceptions to this generalization are the observations that the pyranose rings of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-pentachlorophenyl-α-D-altropyranoside[5] and methyl 4,6-*O*-benzylidene-3-deoxy-3-diallylamino-α-D-altropyranoside[6] adopt non-chair forms, and some other examples of non-chair conformations are known that are due to the presence of large substituent atoms or groups, and/or the restrictive effects of acetal,[7–9] and lactone or lactam[10] rings.

During our studies of the synthesis of ^{15}N-labeled amino sugar derivatives in which the vicinal ^{15}N and ^1H nuclei have a defined stereochemical orientation, we have discovered another example of non-chair conformations in the methyl 4,6-*O*-benzylidene-3-deoxy-3-phthalimido-α-D-altropyranoside series. The conformations of a number of related methyl 4,6-*O*-benzylidene-α-D-altropyranoside derivatives (**2**–**7**, see Scheme 1) have been studied by ^1H NMR spectroscopy, and that of compound **2** also by molecular dynamics with simulated annealing,[11] with explicit treatment of the chloroform-*d* solvent.



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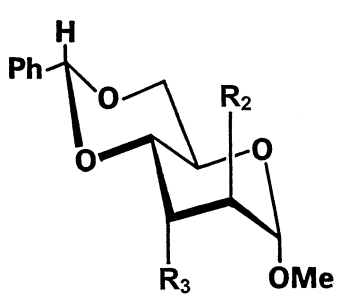


2 R_2 = OH, R_3 = phthalimido
3 R_2 = OH, R_3 = NH_2
4 R_2 = OAc, R_3 = phthalimido
5 R_2 = OBz, R_3 = phthalimido
6 R_2 = phthalimido, R_3 = OH
7 R_2 = OH, R_3 = OH
8 R_2 = pentachlorophenyl, R_3 = OH

Scheme 1.

2. Results and discussion

Fusion of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) with a mixture of phthalimide and potassium phthalimide at 240 °C yielded methyl 4,6-*O*-benzylidene-3-deoxy-3-phthalimido-α-D-altropyranoside (**2**) as a major product (see Scheme 1). The formation of a *trans* product by addition of the elements of phthalimide to the epoxide ring of **1** parallels other reactions of this type.[2,12] The configuration of **2** was proved by hydrazinolysis to the known methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (**3**). Phthalimido derivative **2** was also characterized as its 2-*O*-acetyl (**4**) and 2-*O*-benzoyl (**5**) derivatives.

NMR spectroscopy.—The ^1H NMR spectra of the α-D-altropyranoside derivatives **2**–**7** were mostly well dispersed at 400 MHz and were readily assigned. ^1H chemical shifts and coupling constants are reported in Tables 1 and 2, respectively. The small values of the vicinal coupling constants $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ (1.1–3.5 Hz) observed for the 3-amino-3-deoxy and 3-hydroxy derivatives **3** and **7**, respectively (see Table 2), are typical of the $^4C_1$ chair conformation.[4] By contrast, the $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ values for the 3-deoxy-3-phthalimido derivative **2** are much larger (6.8–9.2 Hz), and these extreme values are consistent with either **2b**, in which the pyranoid ring has the $B_{2,5}$ form, or **2d** with the pyranoid ring in a $^1S_5$ skew form (structures **2a**–**2d**).

The $J_{1,2}$ and $J_{2,3}$ values for the 2-*O*-acetyl **4** and 2-*O*-benzoyl **5** derivatives are intermediate in magnitude (4.4–4.6 and 5.7 Hz, respectively) and probably reflect the effects of a conformational equilibrium. However, in our hands, measurements of the ^1H NMR spectra

Table 1
^{1}H NMR chemical shifts [a] of methyl 4,6-*O*-benzylidene-α-D-altropyranoside derivatives

Derivative	R_2	R_3	H-1	H-2	H-3	H-4	H-5	H-6e	H-6a	OMe	OH	PhC*H*	Ph	Phthalimido
2	OH	$C_8H_4NO_2$ [b]	4.684	4.934	4.799	4.057	4.681	4.397	3.665	3.502	2.553	5.460	7.134–7.229	7.689, 7.828
3	OH	NH_2	4.650	3.955	3.296	4.020	4.052	4.325	3.865	3.404	2.044 [c]	5.651	7.351–7.492	
4	OAc	$C_8H_4NO_2$	4.736	5.635	4.825	4.114	5.036	4.430	3.664	3.409		5.535	7.192–7.315	7.694, 7.836
5	OBz	$C_8H_4NO_2$	4.911	5.991	5.044	4.239	5.125	4.460	3.781	3.427		5.593	7.190–7.551	7.774
6 [d]	$C_8H_4NO_2$	OH	4.94	4.65	4.34	4.57	4.30	4.36	3.87	3.34	4.20	5.76	7.36, 7.53	7.88
7 [e]	OH	OH	4.663	4.012	4.101	3.963	4.206	4.339	3.829	3.442	2.181, 2.883	5.630	7.337–7.514	

[a] In ppm from internal Me_4Si at 297 K. Estimated standard uncertainty 0.001 ppm.
[b] Phthalimido.
[c] Includes the NH_2 signal.
[d] Literature data for an acetone-d_6 (CD_3COCD_3) solution at 360 MHz.[12]
[e] Measured at 304 K.

Table 2
^1H–^1H NMR coupling constants [a] (Hz) of methyl 4,6-*O*-benzylidene-α-D-altropyranoside derivatives

Derivative	R_2	R_3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6e}$	$J_{5,6a}$	$J_{6e,6a}$
2 [b]	OH	$C_8H_4NO_2$ [c]	6.8		8.7	9.2	10.0	5.1	9.9	10.4
3	OH	NH_2	1.1	0.9	2.4	3.5	9.9	4.4	10.0	10.2
4	OAc	$C_8H_4NO_2$	4.4		5.7	8.3	10.1	5.0	10.0	10.4
5	OBz	$C_8H_4NO_2$	4.6		5.7	8.5	10.0	5.1	10.2	10.4
6 [d]	$C_8H_4NO_2$	OH	2.0		2.2	3.9	9.5	5.2	9.8	9.8
7	OH	OH	1.2	<1.1	2.4	3.0	9.8	5.1	10.0	10.2

[a] Measured for solutions in $CDCl_3$ at 400 MHz, with an estimated standard uncertainty of 0.2 Hz.
[b] $J_{2,OH}$ 3.7 Hz
[c] Phthalimido.
[d] Literature data for an CD_3COCD_3 solution at 360 MHz; $J_{3,OH}$ 3.4 Hz.[12]

of **4** at temperatures down to −100 °C failed to detect the signals of multiple conformers. We have found previously[12] that methyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-α-D-altropyranoside (**6**) shows small values of $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ (see Table 2), and, therefore, exists predominantly with its pyranoid ring in the $^4C_1$ chair form. The difference with the 3-deoxy-3-phthalimido derivative **2** may be attributed to the presence in the latter chair form of a 1,3 syn–diaxial interaction between the large phthalimido group and the methoxyl group, an interaction that is absent in **6**. In marked contrast to the 2-phthalimido derivative **6**, the ^1H–^1H coupling constants of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-pentachlorophenyl-α-D-altropyranoside **8** indicate that it exists in a boat conformation.[5] Moreover, our simulations show that the molecular volumes of the 2-*C*-pentachlorophenyl and 3-phthalimido derivatives are 341 and 297 Å^3, respectively, a difference that must be due mainly to the larger size of the 2-*C*-pentachlorophenyl group.

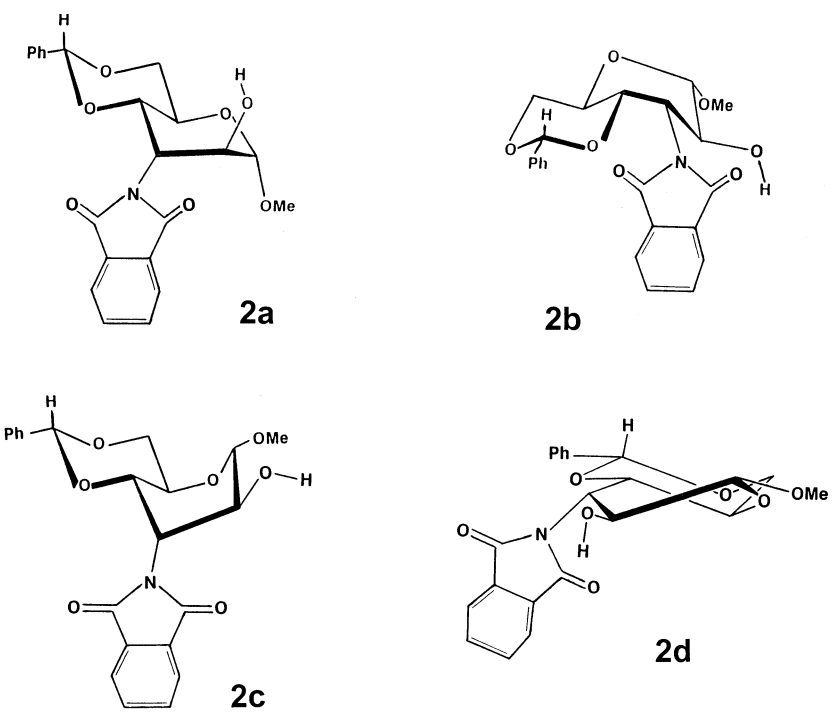
Molecular modeling.—The 3-phthalimido derivative **2** was simulated by molecular dynamics with explicit chloroform-*d* solvent and the use of the CVFF forcefield.[13] The applicability of this and other forcefields to carbohydrates has recently been reviewed.[14] During simulated annealing from 800 down to 300 K, molecule **2** made excursions to four principal conformations, including the $^7C_5/^4C_1$ chair/chair (**2a**), $^7C_5/B_{2,5}$ chair/boat (**2b**), $^7C_5/^{1,4}B$ chair/boat (**2c**), and $^7C_5/^1S_5$ chair/skew boat (**2d**, see Scheme 2)[2]. In each of these conformations, the 4,6-*O*-benzylidene ring exists in the $^7C_5$ chair form with the phenyl group equatorial. According to this simulation for a chloroform-*d* solution, the chair/skew boat form **2d** has the lowest potential energy, and the $^7C_5/^4C_1$ (**2a**), $^7C_5/B_{2,5}$ (**2b**), and $^7C_5/^{1,4}B$ (**2c**) conformations have higher relative energies of 58.2 (13.9), 28.9 (6.9), and 35.6 kJ mol^{-1} (8.5 kcal mol^{-1}), respectively. By means of the relationship $\Delta G = -RT \ln K$, equilibrium constants were calculated from the potential energy differences for the equilibria **2a** ⇌ **2b**, **2b** ⇌ **2c**, and **2c** ⇌ **2d**, giving K values of 1.26×10^5, 6.81×10^{-2}, and 1.58×10^6, respectively. From the K values, the BIOEQCALC program was then used to calculate the concentrations of the conformational species, from which the mole fractions of **2a**, **2b**, **2c**, and **2d** were calculated to be 7.38×10^{-11}, 9.29×10^{-6}, 6.33×10^{-7}, and 0.9999901, respectively. It is apparent that the energetics of the simulation of **2** in explicit chloroform-*d* favors greatly the skew boat form **2d**.

The dihedral angles that were measured on the energy-minimized, principal conformational possibilities are shown in Table 3. The $^7C_5/^4C_1$ chair/chair conformation **2a** has the pyranose ring in a flattened chair form in which $\phi_{2,3}$ is distorted from ~60 to 90°, a dihedral angle that is totally inconsistent with the observed value $J_{2,3}$ 8.7 Hz. At least in the molecular model **2a**, the splaying out of the syn–axial phthalimido and methoxyl groups, and consequent flattening of the pyranose ring may be attributed to steric repulsion between these groups. In the $^7C_5/B_{2,5}$ chair/boat conformation **2b**, all substituents on the pyranose

[2] C-7 is the benzylic carbon atom.

ring are equatorial, although the C-1–O-5 and C-3–C-4 bonds are not quite parallel, with C-3 tilted up slightly above the C-1–C-4–O-5 plane. Similarly, in the $^{7}C_{5}/^{1,4}B$ chair/boat conformation **2c**, the C-2–C-3 and C-5–O-5 bonds are not quite parallel and C-2 is tilted up slightly above the C-3–C-5–O-5 plane. In **2c**, the phthalimido group occupies a less favorable axial orientation, but changes to a more favorable quasi-equatorial orientation in the chair/skew boat **2d**.

In principle, the chair/boat conformations **2b** and **2c** and chair/skew boat conformation **2d** could be stabilized by hydrogen bonding between the 2-hydroxyl hydrogen atom and one of the phthalimido carbonyl oxygen atoms, a supposition that might be made on the basis that the 2-*O*-acyl derivatives **4** and **5** (in which this type of bonding is not possible) appear to exist as a mixture of conformations. However, the molecular modeling of **2a**, **2b**, **2c**, and **2d** did not reveal any evidence of such hydrogen bonding in terms of the close approach or overlap of the hydroxyl hydrogen and carbonyl oxygen atomic spheres. Measurements of the energy-minimized molecular models indicated hydroxyl hydrogen atom–carbonyl oxygen atom distances of 5.2 and 5.0, 4.0 and 3.3, 4.7 and 5.5, and 4.7 and 4.5 Å, respectively for **2a**, **2b**, **2c**, and **2d**. All of these distances appear to be rather long for strong hydrogen bonding, but it may be sig-



Scheme 2.

Table 3
Dihedral angles [a] (°) of methyl 4,6-*O*-benzylidene-3-deoxy-3-phthalimido-α-D-altropyranoside (**2**) conformers obtained from molecular dynamics models [b]

Atom pair	H-1, H-2	H-2, H3	H-3, H-4	H-4, H-5	H-5, H-6e	H-5, H-6a
Conformer						
$^{7}C_{5}/^{4}C_{1}$ (**2a**)	−74.9	90.0	37.4	−177.9	−56.1	−172.8
$^{7}C_{5}/B_{2,5}$ (**2b**)	−161.8	178.7	−11.0	−174.0	−57.8	−175.0
$^{7}C_{5}/^{1,4}B$ (**2c**)	−159.1	121.0	46.0	−174.0	−60.8	−177.9
$^{7}C_{5}/^{1}S_{5}$ (**2d**)	−171.0	158.7	21.9	176.1	−52.2	−168.6

[a] Estimated standard uncertainty 0.1°.
[b] Energy minimization with the CVFF forcefield.[13]

nificant that the distance of closest approach of the hydroxyl hydrogen and carbonyl oxygen atoms is 3.3 Å, in the chair/boat **2b**. Taken together, the results of ^{1}H NMR spectroscopy and molecular modeling favor **2d** as the most stable conformer, with minute proportions of **2a**, **2b**, and **2c**.

Clearly, it is the juxtaposition of an axial, large substituent at C-3 with the syn–axial methoxyl and H-5 that causes steric instability in the chair/chair conformations of the *N*,*N*-disubstituted methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside derivatives, thus leading to the adoption of a non-chair conformation. In this sense, 'large substituent' implies that the nitrogen atom bonded to C-3 has two bulky non-hydrogen, substituents such as two allyl groups[6] or the carbonyl groups of the phthalimido moiety. Noteworthy is the fact, that if these large groups attached to nitrogen are absent (as in the 3-amino derivative **3**), then the chair/chair conformation is favored. In compound **8**, the larger size of the pentachlorophenyl group causes the adoption of a non-chair form by the pyranose ring,[5] even when this group is syn–diaxial with only one hydrogen atom (H-4) in the chair/chair conformation. At this juncture, no value is available for the energy barrier between the skew boat cycle and the chair form.

3. Experimental

General.—Reactions were monitored by thin layer chromatography (TLC) on Silica Gel G plates (E. Merck) that were eluted with 97:3 (v/v) CH_2Cl_2–MeOH. Compounds were detected by charring with 5% aq H_2SO_4 and the amino derivative was deleted by reaction with ninhydrin. Melting points are uncorrected.

NMR spectroscopy.—^{1}H NMR spectra were recorded at 400 MHz and 297 K by using a Bruker Instruments WM 400 spectrometer. A 32,768 point data set was used, together with a spectral width of 3.26 kHz, a 90° pulse (30 μs), and a pulse recycle time of 8.52 s, giving a digital resolution of 0.2 Hz/point in the Fourier transform. The solutions contained 10–11 mg of compound in chloroform-*d* (0.45 mL) containing Me_4Si as an internal reference. Spectral assignments were confirmed by matching of spin multiplet spacings and homonuclear spin decoupling experiments.

Molecular modeling.—Molecular modeling computations were performed by using one processor of a SGI Onyx 2 multiprocessor system equipped with eight R-10000 250 MHz CPUs and Molecular Simulations Inc (MSI)/BIOSYM INSIGHT II/DISCOVER software, version 980. Three-dimensional structures were built in the MSI/BIOSYM SKETCHER program, version 950 running on an SGI R4400 200 MHz workstation. Energy computations were performed by using the CVFF forcefield.[13] The calculations were done with explicit chloroform-*d* solvent at a density of 1.488 g/cc, under periodic boundary conditions, using a unit cell size of $35 \times 35 \times 35$ Å, a cutoff distance of 17 Å, and a dielectric constant of 1.0. Initially, a steepest descent energy minimization was conducted for 3000 steps, followed by a VA09A minimization for 1000 steps, until a maximum rms derivative of 4.2 kJ mol^{-1} Å^{-1} (1.0 kcal mol^{-1} Å^{-1}) was reached. Molecular dynamics with simulated annealing was then performed over the temperature range 800–300 K, with 50 K decrements. At each temperature, 1000 equilibration steps of 1 fs each were run, followed by 5000 dynamics steps of 1 fs each, and then a VA09A energy minimization, typically with < 400 iterations. The conformation and the potential energy value were inspected after each minimization. The energy of each major conformer was then exhaustively minimized by further VA09A computations, followed by conjugate gradient minimization (up to 3000 steps) to a maximum rms derivative of 0.0004 kJ mol^{-1} Å^{-1} (0.0001 kcal mol^{-1} Å^{-1}). Finally, ^{1}H–^{1}H dihedral angles were measured on the annealed, energy-minimized final structure of each major conformer by means of the INSIGHTII/DISCOVER software. The configuration of each chiral carbon atom was monitored for constancy during the computations using the INSIGHTII/DISCOVER software.

Calculations on equilibrium constants were performed by using the BIOEQCALC module running within the MATHEMATICA program on a personal computer.[15]

*Methyl 4,6-*O*-benzylidene-3-deoxy-3-phthalimido-α-*D*-altropyranoside* (**2**).—A mixture of phthalimide (1.34 g, 9.11 mmol) and potassium phthalimide (0.082 g, 0.44 mmol) was heated at 238 °C for 5 min, then treated with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**)[16] (1.00 g, 3.79 mmol). The mixture was heated at 240 °C for 30 min, and the resulting dark residue was extracted with CH_2Cl_2 (60 mL). The dark extract was cooled in the freezer, washed with ice-cold 5% aq NaOH (50 mL), followed by water (5 × 200 mL), dried (anhyd Na_2SO_4), and decolorized (Norit A charcoal). Filtration of the extract through a Norit A/Celite pad, followed by evaporation, yielded crude **2** as a pale-yellow syrup (0.71 g, 45%) that was crystallized from aq MeOH to give **2** as colorless plates (0.56 g): mp 168–169 °C. IR ν_{max} ($CHCl_3$) 3675w and 3590m (OH), 1785m and 1720s (fused lactam ring C=O), and 1619w cm^{-1} (Ar). Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.22; H, 5.15; N, 3.41. Found: C, 64.09; H, 5.24; N, 3.77. Seed crystals were obtained from a preliminary preparation in which chromatography on a silicic acid column was used to purify the product.

*Methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-*D*-altropyranoside* (**3**).—A solution of the phthalimido derivative **2** (0.21 g) in warm EtOH (10 mL) was treated with 85% aq hydrazine hydrate (0.07 mL), and the mixture was boiled under reflux for 2 h. Evaporation of the solution yielded a solid that was treated with 5% aq KOH. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined extracts were washed with water (2 × 20 mL), dried (Na_2SO_4), and evaporated to clear syrup. Crystallization from warm EtOH afforded two crops of plates (81 mg, 56%): mp 183–186 °C, which on recrystallization from EtOH yielded pure **3**, mp 188–190 °C. Lit.[17] mp 188–190 °C.

*Methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-phthalimido-α-*D*-altropyranoside* (**4**).—Ac_2O (1 mL) was added to a solution of **2** (116 mg) in dry Py (1 mL). The solution was kept at rt for 16 h, poured into ice–$NaHCO_3$, and then extracted with CH_2Cl_2 (3 × 20 mL). Drying (Na_2SO_4) and concentration of the combined extracts, followed by crystallization from EtOH, yielded the 2-*O*-acetyl derivative **4** as needles (106 mg, 83%): mp 186–187 °C, unchanged by further recrystallization. Anal. Calcd for $C_{24}H_{23}NO_8$: C, 63.57; H, 5.11; N, 3.09. Found: C, 63.36; H, 5.26; N, 3.07. The 2-*O*-benzoyl derivative **5** was prepared (as an oil) in a similar way by treatment of **2** with Py–BzCl.

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