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Stereoselective Synthesis of a New cis Monocyclic β-lactam Bearing a Sugar Moiety at Its N1 Position and Its Physical Characterization

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Abstract: Synthesis of a new monocyclic β-lactam containing a sugar moiety at its N1 position *via* [2+2] cycloaddition reaction of ketene and imine is described. Reaction of achiral phenoxy ketene with chiral aldimine derived from chiral 2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosylamine and 2-hydroxy-3-methoxy benzaldehyde resulted in the formation of 2 as a single diastereomer. Then its physical characterization has been determined at the AM1 level of theory.

Introduction

O-Acyl-protected glycosylamines and their imine derivatives, particularly the 2,3,4,6-tetra-O-pivaloyl-D-galactopyranosylamine and its acetyl derivative are effective chiral auxiliaries in Strecker and Ugi syntheses of α-amino acids [1-3]. Glycosylamines are valuable intermediates in the preparation of nucleosides and drugs [4-7]. Carbohydrate-derived auxiliaries utilize an efficient stereoselective potential in a number of nucleophilic addition reactions on prochiral imines, α-Amino acids, β-amino acids and their derivatives can be synthesized in few synthetic steps, with high enantiomeric purity. The asymmetric Staudinger reaction utilizing 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosylimine or 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylimine as the chiral auxiliary in the synthesis of 2-azetidinones has been reported by us [8] and others [9]. In this paper a new sugar based monocyclic 2-azetidinone has been synthesized as a single diastereomer based on asymmetric synthesis and then its physical characterization has been determined at the AM1 level of theory.

Results and Discussion

D-(+)-Galactose was chosen as the starting material for the synthesis of β-D-galactosylamine. 2, 3, 4, 6-Tetra-O-acetyl-β-D-galactopyranosyl bromide was readily displaced by an azido group. Under this condition the replacement involves inversion of configuration at the anomeric site and thus the α-glycopyranosyl halide yields a β-glycopyranosyl azide through an oxonium ion. Heterogeneous reduction of the azide group with Raney Nickel in ethyl acetate gave 2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosylamine. The molecular structure of 1 is shown in Fig. 1. The N1—C7 bond length [1.273 (3) A °] conforms to the expected value for a normal C N bond. The methoxy group at C2 is rotated slightly around the C2—O2 bond; the torsion angle C8—O2—C2—C3 is 16.3 (4). The C7—C6 [1.448 (3)] and N1—C9 [1.435 (3) A °] bond lengths are consistent with those in a related structure we reported recently [10].The pyranosyl ring adopts a chair conformation. In the crystal structure, the bond lengths and angles are in normal ranges [11].

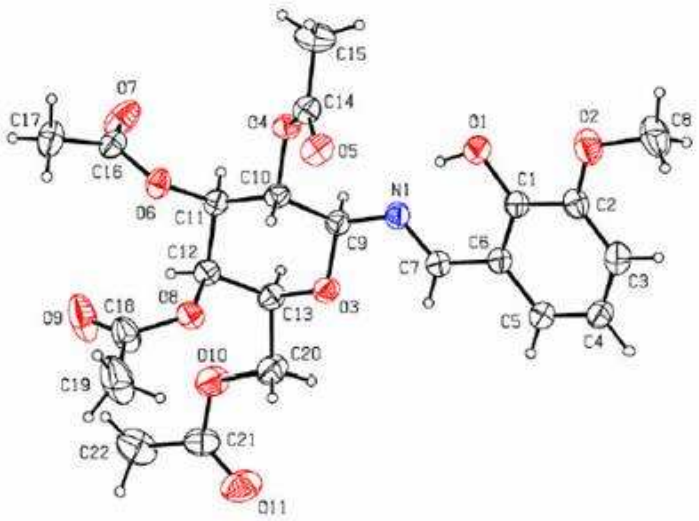
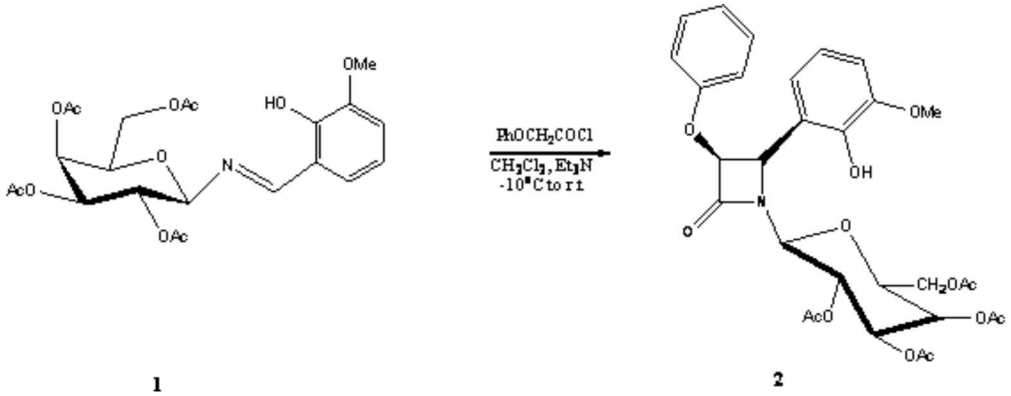


Figure 1. An *ORTEP-3* view of (I), with the atom-numbering scheme and 20% probability displacement ellipsoids.

Schiff base 1 was transformed to β-lactam 2 by treatment with phenoxyacetyl chloride and triethylamine in dry methylene chloride with cooling in ice-salt bath. The reaction progress was monitored by TLC and the presence of a new compound was confirmed. The IR spectrum showed the characteristic absorption of β-lactam carbonyl at 1774.4 and ester carbonyls at 1743.5 cm^{-1}. The ^{1}H-NMR spectrum showed the methoxy protons at 3.77, and four methyl protons at 2.19-1.88.The β-lactam ring protons H_3, H_4 and sugar protons resonanced at 5.45-4.06 and aromatic protons at 7.61-6.72. The ^{13}C-NMR spectrum exhibited the following signals: $4CO\underline{C}H_3$ at 19.77-19.29, OCH_3 at 54.99, sugar carbons at 89.47-54.99, <u>C</u>HN at 59.44, PhO<u>C</u>HCO at 80.47, aromatic carbons at 128.69-114.38, $4\underline{C}OCH_3$, β-lactam C=O at 169.12-167.43.

The mass spectrum showed the base peak at 43($COCH_3$), 482 ($C_{22}H_{25}NO_{11}$) and a peak at 69 which is due to $C_3H_3NO_1$•.



1 **2**

We next performed theoretical calculations to present a viable structure for the product. All calculations in this work were carried out with the AM1 level of theory using the GAUSSIAN03 [12] suite of programs. More information about these methods is available elsewhere [13]. Figure 2 presents the optimized structure of the molecule with bond lengths and bond angles shown.

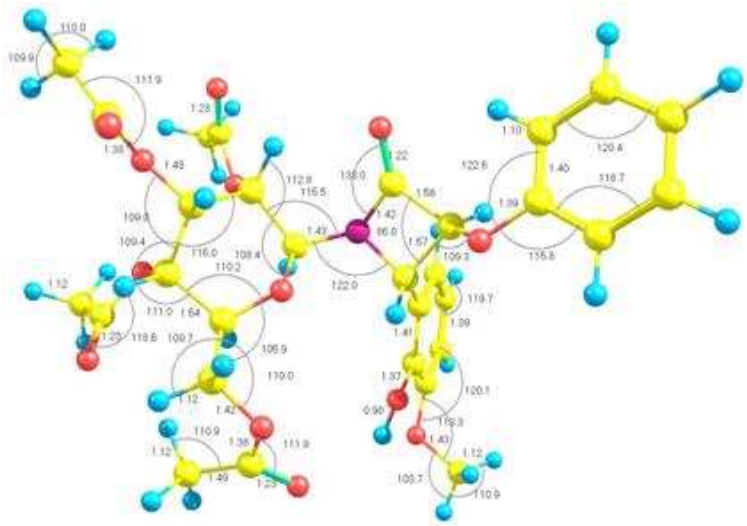


Figure 2. AM1 optimized geometry and with all bond lengths shown in angstroms (Å), and bond angles in degrees (°). In the figure, yellow spheres are carbon, blue spheres are hydrogen atoms, purple spheres are nitrogen, and red spheres are oxygen atoms.

Table 1 shows the thermodynamic properties for the structure in Figure 1 where T (temperature in K), S (entropy in J mol^{-1} K^{-1}), C_p (heat capacity at constant pressure in kJ mol^{-1} K^{-1}), and $\Delta H = H° - H°_{298.15}$ (enthalpy content, in kJ mol^{-1}), T_1=100 K, T_2=298.15 K, and T_3=1000 K calculated AM1 frequencies. The fits were performed according to the equations implemented by the National Institute of Standards and Technology (NIST) [14].

T (K)	C_p (J/mol.K)	S (J/mol.K)	H (kJ/mol)
100.00	319.39	684.05	20.67
200.00	486.26	957.20	61.03
298.15	654.17	1182.29	116.91
300.00	657.42	1186.35	118.12
400.00	829.87	1399.33	192.57
500.00	984.08	1601.52	283.47
600.00	1113.54	1792.76	388.55
700.00	1220.54	1972.71	505.42
800.00	1309.30	2141.66	632.05
900.00	1383.52	2300.29	766.80
1000.00	1446.07	2449.39	908.37

Table 1. Thermodynamic properties of the molecule in Figure 1, calculated at the AM1 level of theory, where C_p is the heat capacity in J mol^{-1} K^{-1}, S is the entropy in J mol^{-1} K^{-1}, and DH is the standard enthalpy kJ mol^{-1}.

	Fitted Thermodynamic Equation (T/1000=t)
C_p	$6.75142*t +2502.912*t^2 -1184.28159*t^3 +117.34776*t^{-2}$
S	$-255.24191*\ln(t) +3247.10622*t -1361.86454*t^2/2 -334.36163 *t^3/3 -4.23578/(2*t^2) -10.40244$
ΔH	$274.78754*t +1460.20852*t^2/2+97.78182*t^3/3 -368.91094*t^4/4 +2.49268/t -38.3513$

Table 2. These were the fitted results to the Shomate equations [14] which are implemented by the JANAF tables of the NIST databases from the data in table 1. These equations converged to an R^2 value of 0.999 on average. These equations have been very good at predicting physical properties of various molecules, as we have tested in the past [15-17].

Experimental

All required chemicals were purchased from Merck and Fluka chemical companies. Dichloromethane and triethylamine were dried by distillation over CaH2 and then stored over 4Å molecular sieves. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ (compound 2) using a Bruker Avance DPX instrument (operating at 250 MHz for 1H and 62.9 MHz for 13C). Chemical shifts were reported in ppm (δ) downfield from TMS. All of the coupling constants (J) are in Hertz. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Melting points were determined in open capillaries with a Buchi 510 melting point apparatus and are not corrected. Thin-layer chromatography (t.l.c.) was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kieselgel (230-270 mesh).

N-(2-Hydroxy-3-methoxybenzylidene)-2,3,4,6-tetra-O-acetyl-β-D-galactopyranosylamine
o-Vanillin (0.87 g, 5.71 mmol) was added to a solution of 2,3,4,6-tetra-O-acetyl-_-d-galactosylamine (2.00 g, 5.76 mmol) in ethanol (35 ml).The mixture was refluxed for 5 h. The resulting yellow crystals of N-(2-hydroxy-3-methoxybenzylidene)-2,3,4,6-tetra-O-acetyl-β-d-galactopyranosylamine were collected in 90% yield by filtration. The Schiff base was recrystalized from ethanol to give prismatic
pale-yellow crystals.

Melting point: 180-182 °C.

IR (KBr):3150-3250 (OH), 1751.2 (C=O), 1635.5 (C=N) cm^{-1}.

^{1}H–NMR ($CDCl_3$, 250 MHz, ppm): 12.44 (OH, br, 1H), 8.53 (NCH, s, 1H), 7.22-6.77 (Ar-H, m, 4H), 5.43-4.07 (sugar protons, m, 7H), 3.86 (OCH_3, s, 3H), 2.10 -1.91 (4 $COCH_3$, s, 12H).

^{13}C-NMR ($CDCl_3$, 62.9 MHz, ppm):170.43-168.30 (4C=O), 164.63 (C=N), 150.79-114.83 (aromatic carbons), 89.31 (sugar carbon, C_3), 72.83 (sugar carbon, C_4), 71.40 (sugar carbon, C_2), 69.77 (sugar carbon, C_6), 68.31 (sugar carbon, C_1), 61.44 (sugar carbon, C_5), 56.07 (OCH_3), 20.69-20.56 (4CO$\underline{C}H_3$).

MS (m/z): 481,331,169,109, 43.

1-(2, 3, 4, 6-tetra-O-acetyl -β-D-galactopyranosyl)-3-phenoxy-4-(2-hydroxy-3-methoxyphenyl)-2-azetidinone
A solution of phenoxyacetyl chloride (3.00 mmol, 0.42 mL) in dry CH_2Cl_2 (15 mL) was slowly added to a solution of Schiff base 1 (1.0 mmol, 0.48 g) and triethylamine (9 mmol) in CH_2Cl_2 (15 mL) at -15 ^{oC}. The reaction mixture was then allowed to warm to room temperature and stirred for 15 h. It was then washed with water (2×20 mL), saturated $NaHCO_3$ (15 mL), brine (15 mL) and dried over Na_2SO_4.The organic solvent was evaporated to give the crude β-lactam which was then purified by column chromatography over silica gel (eluent: n-Hexane/EtOAc 1:1).

IR (KBr): 1743.5 ($\underline{CO}CH_3$), 1774.5 (CO, β-lactam) cm^{-1}.

^{1}H NMR ($CDCl_3$) (250 MHz) δ (ppm): 7.61-6.72 (ArH, m, 9H), 5.45-4.06 (sugar protons, m, 7H, plus C_3H, C_4H), 3.77 (OCH_3, s, 3H), 2.19-1.88 (4$COCH_3$, s, 12H)

^{13}C NMR ($CDCl_3$) (62.9 MHz) δ (ppm): 169.12-167.43 (4$\underline{C}OCH_3$, β-lactam C=O), 128.69-114.38 (aromatic carbons), 80.47 (PhO$\underline{C}$HCO), 59.44 ($\underline{C}$HN), 89.47-54.99 (sugar carbons), 54.99 (OCH_3), 19.77-19.29 (4CO$\underline{C}H_3$).

MS (m/z):558, 481, 431, 376, 331, 268, 161, 134, 69, 43.

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