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SYNTHESIS OF SOME NEW SUGAR BASED 3, 3-DISUBSTITUTED MONOCYCLIC B-LACTAMS BY ASYMMETRIC [2+2] CYCLOADDITION REACTIONS*

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Abstract – Synthesis of some new monocyclic β-lactams containing a quaternary carbon center *via* a [2+2] cycloaddition reaction is described. The reaction of achiral diphenyl ketene with chiral aldimines derived from chiral 2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosylamine, 2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosylamine and different benzaldehydes resulted in the formation of β-lactams as single diastereomers.

Keywords-2-azetidinone, asymmetric synthesis, chiral Schiff bases, sugar, [2+2] cycloaddition

1. INTRODUCTION

Carbohydrates constitute a class of inexpensive natural products of high chiral content [1], and play a central role in the posttranslational biological selectivity [2]. O-Acyl-protected glycosylamines, particularly the 2, 3, 4, 6-tetra-O-pivaloyl-D-galactopyranosylamine and its acetyl derivative are effective chiral auxiliaries in the Strecker and Ugi syntheses of α-amino acids [3-5]. Glycosylamines are valuable intermediates in the preparation of nucleosides and drugs [6-8]. Carbohydrate-derived auxiliaries utilize an efficient stereoselective potential in a number of nucleophilic addition reactions on prochiral imines, α-Amino acids, and β-amino acids, and their derivatives can be synthesized in few synthetic steps with high enantiomeric purity. A variety of chiral heterocyclic can readily be obtained from glycosyl imines by stereoselective transformations [9]. The asymmetric Staudinger reaction utilizing 2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosylamine or 2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosylamine as the chiral auxiliary in the synthesis of 2-azetidinones has been reported by the authors [10] and others [11]. 2-Azetidinone nucleus has been recognized as the central motif of the so-called β-lactam antibiotics, the most widely employed family of antimicrobial agents to date [12]. The importance of β-lactams as synthetic intermediates has been widely recognized in organic synthesis. β-lactam molecules with a quaternary carbon center have been used as building blocks for biologically active compounds [13].

2. RESULTS AND DISCUSSION

a) Synthesis of 2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosylamine and 2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosylamine 4

D-(+)-Galactose and D-(+)-Glucose **1** were chosen as the starting material for the synthesis of glycosylamines. For this purpose, 2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosyl bromide and 2, 3, 4, 6-

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tetra-O-acetyl-β-D-glucopyranosyl bromide2 were prepared by a reported method [14]. The thermodynamically more stable α-anomers were formed. The halogen in the acylglycosy l halide is reactive and may be readily displaced by an azido group. In the case of D-(+)-galactose and D-(+)-glucose derivatives, 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 (Fig. 1).

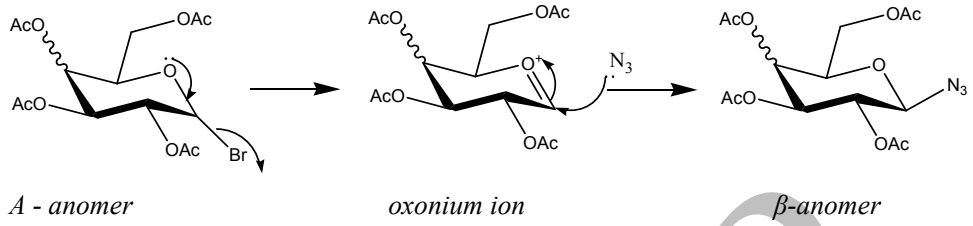
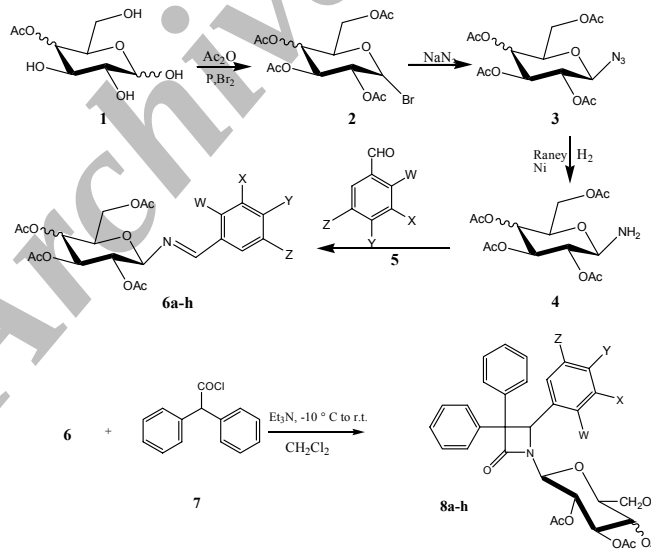


Fig. 1. Inversion of configuration at anomeric center

The IR spectrum of compound 3 showed the azide group at 2129 cm^{-1}, and the ester carbonyl functions at 1747-1753 cm^{-1}. Heterogeneous reduction of the azide group of 3 with Raney Nickel in ethyl acetate gave 2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosylamine and 2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosylamine 4. The IR spectrum of compound 4 (galactosyl amine) showed the amino group at 3446.6- 3284.5 cm^{-1}, ester carbonyl functions at 1741.6-1750 cm^{-1}. The amino group of glucosyl amine appeared at 3467-3261 cm^{-1} and the ester carbonyl functions at 1753 cm^{-1}. The mass spectrum of 4 showed the molecular ion at 348 and the base peak at m/e 43, which is due to the acetyl group. The ^{1}H-NMR spectrum of 4 exhibited the methyl protons at 2.24-1.69 ppm, sugar H_3 as a triplet at 5.30, sugar H_4, H_2 as triplets at 4.99-4.86, sugar H_6, H_7 and H_1 doublet of doublet at 4.08-3.94, and sugar H_5 as a multiplet at 3.88-3.78. The ^{13}C-NMR spectrum of 4 showed the following signals: 170.44-170.06 (C=O), 85.27-61.75 (sugar carbons), 20.88-20.56(OCH_3) (Fig. 2)



8a: W = -OH, X = -H, Y = -H, Z = -H, OAc4 axial
8b: W = -OH, X = -OH, Y = -H, Z = -H, OAc4 ax
8c: W = -OH, X = -H, Y = -H, Z = -NO2, OAc4 ax
8d: W = -OH, X = -H, Y = -H, Z = -Br, OAc4 ax
8e: W = -OH, X = -H, Y = -H, Z = -H, OAc4 equatorial
8f: W = -OH, X = -OH, Y = -H, Z = -H, OAc4 eq
8g: W = -OH, X = -H, Y = -H, Z = -NO2, OAc4 eq
8h: W = -OH, X = -H, Y = -H, Z = -Br, OAc4 eq

Fig. 2. Synthesis of monocyclic β-lactams 8a-h

3. SYNTHESIS OF SCHIFF BASES 6A-H

Schiff bases 6a-h were obtained by condensation of 2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosyl amine and 2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosyl amine with different aromatic aldehydes 5 in refluxing ethanol. The IR spectrum of these Schiff bases showed an absorption band at 1627-1635 cm^{-1} for the imine group. The ^{1}H-NMR spectrum showed a singlet for azomethin (CHN) of Schiff-bases at 8.50 ppm.

a) Synthesis of 3, 3-disubstituted monocyclic β-lactams 8a-h

Monocyclic β-lactams 8a-h were prepared by the reaction of chiral imines 6a-h with diphenylacetyl chloride 7 in dry CH_2Cl_2 in the presence of triethylamine. The reaction progress was monitored by TLC and the presence of a new compound was confirmed. The IR spectrum showed the β-lactam carbonyl absorption at 1774-1778 cm^{-1}. The mass spectra of these azetidinones showed the base peak at 43, and another peak at 221, due to $C_{15}H_{11}NO$ (Fig. 3) along with other fragments.

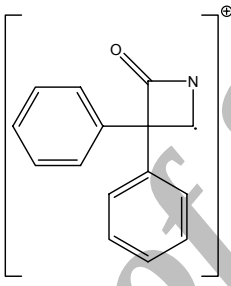


Fig. 3. The fragment found in all β-lactams

4. EXPERIMENTAL SECTION

b) General Experimental

Chemical materials and solvents were obtained from Merck, Fluka and Aldrich chemical companies. Melting points were determined in open capillary tubes in a Buchi 530 circulating oil apparatus and have not been corrected. FT-IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250(^{1}H-NMR 250 MHz, ^{13}C-NMR 62.9 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 solvents using TMS as an internal standard. Mass spectra were obtained on a Shimadzu GCMS-QP 1000 EX instrument at 70 ev. The determination of the prepared products and reaction monitoring were carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was carried out by silica gel 60 Merck (230-270).

b) General procedure for the preparation of imines 6a-h

Benzaldehyde (5.73 mmol) was added to a solution of 2, 3, 4, 6-tetra-O-acetyl-β-D-galactosylamine or 2, 3, 4, 6-tetra-O-acetyl-β-D-glucosylamine (5.76 mmol) in ethanol (35 mL). The mixture was refluxed for five h. The resulting product was collected by filtration.

c) General procedure for the synthesis of β-lactams 8a-h

A solution of diphenylacetyl chloride (1.30 mmol) in dry CH_2Cl_2 (15 mL) was slowly added to a solution of Schiff base (1.0 mmol) and triethylamine (2.60 mmol) in CH_2Cl_2 (15 mL) at -15 ^{o}C. 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 either by column

chromatography or a thick layer over silica gel using n-hexane-EtOAc 9:1 as eluent.

d) 1-(2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosyl)-3, 3-diphenyl 4-(2-hydroxyphenyl)-2-azetidinone (8a)

IR (KBr, ν_{max}): 3200-3300 (OH), 1774 (CO, β-lactam) cm^{-1}, 1747 (ester carbonyls). ^1H NMR ($CDCl_3$) (250 MHz) δ (ppm): 7.71-6.85 (ArH, m, 9H), 5.30-4.18 (sugar protons, m, 7H, plus C_3H), 2.08-1.92 ($4COCH_3$, s, 12H). ^{13}C NMR ($CDCl_3$) (62.9 MHz) δ (ppm): 169.67-164.09 ($4\underline{C}OCH_3$, β-lactam C=O), 139.44-116.25 (aromatic carbons), 94.34 ($Ph_2\underline{C}CO$), 56.77 (<u>C</u>HN), 88.79-60.87 (sugar carbons), 19.75-19.52 ($4CO\underline{C}H_3$). MS (m/z): 645, 560, 451, 331, 169, 109, 43.

e) 1-(2, 3, 4, 6-tetra-O-acetyl -β-D-galactopyranosyl)-3, 3-diphenyl 4-(2, 3-dihydroxyphenyl)-2-azetidinone (8b)

IR (KBr, ν_{max}):3200 (OH), 1774 (β-lactam C=O), 1747 ($\underline{CO}CH_3$) cm^{-1}. ^1H NMR ($CDCl_3$) (250 MHz) δ (ppm): 7.78-6.78 (ArH, m, 13H), 5.43-4.02 (sugar protons, m, 7H, plus C_3H), 2.09-1.80 ($4COCH_3$, s, 12H). ^{13}C NMR ($CDCl_3$) (62.9 MHz) δ (ppm): 170.32-164.24 ($4\underline{C}OCH_3$, β-lactam C=O), 138.88-118.36 (aromatic carbons), 56.78 (<u>C</u>HN), 89.47-61.46 (sugar carbons), 20.72-20.63 ($4CO\underline{C}H_3$). MS (m/z):467, 331, 330, 194, 167,169, 141, 145, 109, 43.

f) 1-(2, 3, 4, 6-tetra-O-acetyl -β-D-galactopyranosyl) -3, 3-diphenyl 4-(2-hydroxy-5-nitrophenyl)-2-azetidinone (8c)

IR (KBr, ν_{max}): 3423-3165 (OH), 1774 (β-lactam C=O), 1747 ($\underline{CO}CH_3$,) cm^{-1}.^1H NMR ($CDCl_3$) (250 MHz) δ (ppm): 8.25-7.18 (ArH, m, 13H), 5.41-4.07 (sugar protons, m, 7H, plus C_3H), 2.11-1.91 ($4COCH_3$, s, 12H). ^{13}C NMR ($CDCl_3$) (62.9 MHz) δ (ppm): 170.00-163.07 ($4\underline{C}OCH_3$, β-lactam C=O), 149.12-118.76 (Ar), 93.73 ($ph_2\underline{C}CO$), 56.22 (<u>C</u>HN), 88.68-61.49 (sugar carbons), 20.21-19.93 ($CO\underline{C}H_3$). MS (m/z): 496, 331, 194, 139,167, 109, 43.

g) 1-(2, 3, 4, 6-tetra-O-acetyl -β-D-galactopyranosyl) -3, 3-diphenyl 4-(5-bromo-2-hydroxyphenyl)-2-azetidinone (8d)

IR (KBr, ν_{max}): 3435 (OH), 1776 (β-lactam C=O), 1747 ($\underline{CO}CH_3$) cm^{-1}. ^1H NMR ($CDCl_3$) (250 MHz) δ (ppm): 8.10-6.93 (ArH, m, 13H), 5.29-4.07 (sugar protons, m, 7H, plus C_4H), 2.10-1.84 ($4COCH_3$, s, 12H). ^{13}C NMR ($CDCl_3$) (62.9 MHz) δ (ppm): 169.40-168.11 ($4\underline{C}OCH_3$, β-lactam C=O), 148.63-123.20 (Ar), 94.03 ($Ph_2\underline{C}CO$), 55.97 (<u>C</u>HN), 91.28-60.41 (sugar carbons), 19.70-19.58 ($4CO\underline{C}H_3$). MS (m/z):727, 331, 167, 109, 43.

h) 1-(2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranosyl)-3, 3-diphenyl 4-(2-hydroxyphenyl)-2-azetidinone (8e)

IR (KBr, ν_{max}): 3300-3400 (OH), 1774 (β-lactam C=O), 1747 (CO,) cm^{-1}. ^1H NMR ($CDCl_3$) (250 MHz) δ (ppm): 7.71-6.85 (ArH, m, 9H), 5.30-4.18 (sugar protons, m, 7H, plus C_3H), 2.08-1.92 ($4COCH_3$, s, 12H). ^{13}C NMR ($CDCl_3$) (62.9 MHz) δ (ppm): 169.67-164.09 ($4\underline{C}OCH_3$, β-lactam C=O), 139.44-116.25 (aromatic carbons), 94.34 ($Ph_2\underline{C}CO$), 56.77 (<u>C</u>HN), 88.79-60.87 (sugar carbons), 19.75-19.52 ($4CO\underline{C}H_3$). MS (m/z):645, 560, 451, 331, 169, 109, 43.

i) 1-(2, 3, 4, 6-tetra-O-acetyl -β-D-glucopyranosyl) -3, 3-diphenyl 4-(2, 3-dihydroxyphenyl)-2-azetidinone (8f)

IR (KBr, ν_{max}): 1774 (β-lactam C=O), 1753 ($\underline{CO}CH_3$) cm^{-1}. ^1H NMR ($CDCl_3$) (250 MHz) δ (ppm):

7.75-6.78 (ArH, m, 9H), 5.29-4.18 (sugar protons, m, 7H, plus C_3H), 2.04-1.95 ($4COCH_3$, s, 12H). ^{13}C NMR ($CDCl_3$) (62.9 MHz) δ (ppm): 169.39-164.41 ($4\underline{C}OCH_3$, β-lactam C=O), 129.99-118.40 (aromatic carbons), 56.77 (<u>C</u>HN), 89.24-61.83 (sugar carbons), 20.78-20.51 ($4CO\underline{C}H_3$). MS (m/z): 661, 662, 663, 467, 331, 222, 167, 145, 109, 43.

j) 1-(2, 3, 4, 6-tetra-O-acetyl -β-D-glucopyranosyl) -3, 3-diphenyl 4-(2-hydroxy-5-nitrophenyl)-2-azetidinone (8g)

IR (KBr, ν_{max}): 3200-3300 (OH), 1778 (β-lactam C=O), 1752 ($\underline{C}OCH_3$) cm^{-1}. ^1H NMR ($CDCl_3$) (250 MHz) δ (ppm): 8.27-7.19 (ArH, m, 9H), 4.97-4.20 (sugar protons, m, 7H, plus C_3H), 2.06-1.91 ($4COCH_3$, s, 12H). ^{13}C NMR ($CDCl_3$) (62.9 MHz) δ (ppm): 168.43-162.27 ($4\underline{C}OCH_3$, β-lactam C=O), 128.03-117.25 (aromatic carbons), 55.79 (<u>C</u>HN), 87.66-60.70 (sugar carbons), 19.61-19.55 ($4CO\underline{C}H_3$). MS (m/z):690, 660, 632, 615, 496, 331, 194, 169, 127, 109, 81, 43.

k) 1-(2, 3, 4, 6-tetra-O-acetyl -β-D-glucopyranosyl) -3, 3-diphenyl 4-(5-bromo-2-hydroxyphenyl)-2-azetidinone (8h)

IR (KBr, ν_{max}): 3445 (OH), 1776 (β-lactam C=O), (1752 ($\underline{C}OCH_3$) cm^{-1}. ^1H NMR ($CDCl_3$) (250 MHz) δ (ppm): 7.33-6.78 (ArH, m, 13H), 5.25-4.07 (sugar protons, m, 7H, plus C_4H), 2.02-1.82 ($4COCH_3$, s, 12H). ^{13}C NMR ($CDCl_3$) (62.9 MHz) δ (ppm): 169.21-162.12 ($4\underline{C}OCH_3$, β-lactam C=O), 144.90-117.15 (aromatic carbons), 92.07 ($Ph_2\underline{C}CO$), 55.81 (<u>C</u>HN), 87.50-60.20 (sugar carbons), 19.61-19.55 ($4CO\underline{C}H_3$). MS (m/z): 727, 531, 331, 194, 169, 167, 109, 43.

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