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A general approach to the synthesis of dideoxy and trideoxyiminoalditols from β-D-glycosides

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Abstract

Imino sugars (also called azasugars), a class of compounds of which the 1,5-dideoxy and 1,5,6-trideoxyiminoalditols are members, are important glycosidase inhibitors with very high potential as drugs. Their potential therapeutic applications range from the treatment of diabetes to cancer and AIDS. We present here a general method for the preparation of such compounds with the D-gluco and D-galacto configurations starting from β-D-glycosides. The procedure is especially appealing because of its high stereoselectivity and straightforwardness. The key steps are the selective oxidation of the glycosides to hexulosonic acids and reduction of the oxime derivatives to lactams, which are further reduced to the target compounds. The C-6 position can be deoxygenated during the reduction if it bears an acetoxy group. Trideoxy imino sugars are then produced. Deacetylation prior to oxime reduction gives dideoxy compounds.

Keywords: Nitrogen heterocycles; Azasugars; Nojirimycin; 1,5-Imino-1,5-dideoxy alditols; 1,5-Imino-1,5,6-trideoxy alditols; Glycosidase inhibitors

1. Introduction

Over the last three decades there has been a continued interest in natural and synthetic imino sugars because of their high potency as glycosidase inhibitors [1]. They proved to be excellent drug candidates for diabetes [2], cancer [3] and HIV therapy [4]. This is why chemists are still trying to develop simple and general ways for their synthesis.

Our research has focused so far on the synthesis of imino-dideoxy and -trideoxy alditols.

We have been able to identify three chemical syntheses for 1,6-dideoxynojirimycin in the literature. The first one involves enzymatic aldol condensation of 3-azido-2-hydroxypropanal and dihydroxyacetone phosphate [5]. The second method is based on an asymmetric Diels–Alder reaction of sorbaldehyde *O*-methyloxime with a chiral chloronitroso derivative of mannose [6]. The last approach uses protected 6-deoxy-D-*xylo*-5-hexulose as substrate for a double reductive amination [7]. Although these are important contributions, they generally are not stereospecific for a given sugar derivative, and the yields are below 20%.

The literature contains many syntheses for deoxynojirimycin and its analogues. These often utilize carbohydrates [8], lactones [9] or other chiral pool sources [10] containing one or more chiral centers as starting materials. Enzymes [11] and bacteria [12] are also utilized. One method worthy of special mention

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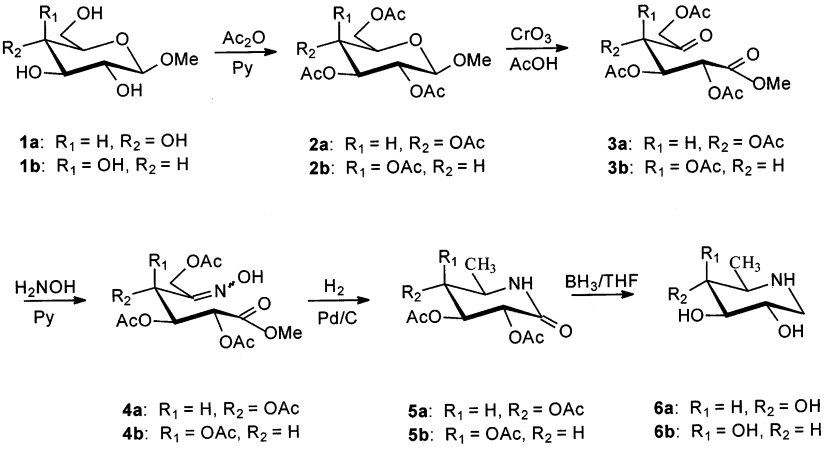
is Behling's short and enantiospecific synthesis of deoxynojirimycin starting from L-sorbose [13]. Its only drawback is that it cannot be extended to other sugars. Wong's aldolase-promoted Diels–Alder reactions [14] between dihydroxy acetone phosphate and a chiral N-containing aldehyde can afford a variety of deoxynojirimycin analogues, but the yields are low, and it is not clear whether the enzyme is available in sufficient quantity to allow large-scale synthesis. The chemo-microbiological method patented by Grabner and coworkers [15] provides an elegant method for transforming a sugar into its imino derivative by reductive amination of an aldo-5-ulose obtained by bacterial oxidation of glucose. Again the extension of this method to deoxy sugars and various substituted sugars is limited by the specificity of the organisms.

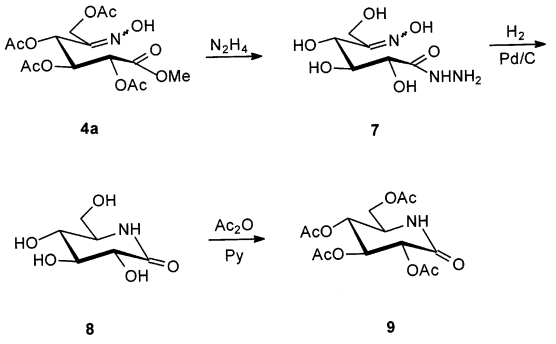
Here we present a general and simple new synthesis for imino sugars. The routes start from readily available β-glycosides and require just few steps with straightforward reaction conditions. They allow access to 1,5-dideoxy- and 1,5,6-trideoxy-1,5-iminoalditols. The enantiochemistry does not have to be induced but is derived from the starting sugar and is, therefore, always close to 100%. Hence the galacto isomers can be obtained simply by using a galactoside. The method also allows access to the 5-amino-5-deoxy-aldonic acid δ-lactams. They are excellent glycosidase inhibitors at concentrations 100 times lower than most of the other inhibitors tested [5]. The gluco isomer has been made previously by the oxidation of nojirimycin [5]. The approach we use here is based on the chromium trioxide oxidation of glycosides to yield ketoaldonic acid esters that are then converted to cyclic imino sugars by reductive ring closure with a nitrogen species. This paper focuses only on compounds with the D-gluco and D-galacto configurations.

2. Results and discussion

The oxidation of the anomeric carbon of glycosides is well documented in patents and papers. Examples are the microbiological oxidation with *Gluconobacter oxidans* [15] or the use of oxidants such as $(Bu_3Sn)_2O$ [16] and RuO_4 with or without partial protection of the hydroxyl groups. The chromium trioxide oxidation we use here typically employs a large excess of CrO_3 [17], but we obtained excellent results using only two equivalents. The peracetate of methyl β-D-glucopyranoside **2a** on oxidation with chromium trioxide gave the keto-ester **3a** in quantitative yield (Scheme 1). Our first attempts at reductive amination using $NaCNBH_3$ and different amino-group sources such as NH_4OH, NH_4Cl, NH_4OAc were unsuccessful. The use of the more nucleophilic agent, hydroxylamine, yielded the oxime **4a**, which crystallized as a mixture of syn and anti isomers in 95% yield. Reduction of this oxime with hydrogen in the presence of palladium-on-charcoal led to formation of the 5-amino-5-deoxy derivative, which spontaneously cyclized to form the δ-lactam. The hydrogenation conditions also led to reductive



Scheme 1. Preparation of 1,5,6-trideoxy-1,5-imino-D-glucitol (**6a**) and trideoxy galacitol, 1,5,6-trideoxy-1,5-imino-D-galacitol (**6b**).



Scheme 2. Preparation of 2,3,4,6-tetra-*O*-acetyl-5-amino-5-deoxy-D-glucono-1,5-lactam (**9**).

cleavage of the acetoxy group to form a 6-deoxy function. This preceded the reduction of the oxime and allowed access to the 1,5,6-trideoxyderivatives. Despite the presence of both the syn and anti oximes, no L-derivatives were formed. The desired isomer was formed exclusively. Lactam **5a** was formed quantitatively and was then reduced and deacetylated with borane·THF, to give the 6-dideoxynojirimycin **6a** in 84.8% total yield.

The same reaction sequence was applied to methyl β-D-galactopyranoside (**1b**), and while the first three reactions occurred with the same high yields, the catalytic reduction was accompanied by partial deacetylation, making chromatographic separation necessary and therefore decreasing the yield. Even so, this method affords a convenient and high-yield route for preparing 1,6-dideoxy-D-galactonojirimycin **6b**.

Access to the 6-hydroxy derivatives (deoxy-D-galacto and D-gluconojirimycins) was readily achieved by deacetylating the oxime with hydrazine prior to reduction. The deacylation yielded the acyl hydrazide **7** in quantitative yield (Scheme 2). Catalytic hydrogenation of the latter with Pd–C provided the δ-lactam **8**. To facilitate isolation, **8** was reacetylated to **9**, which was recovered in 35% total yield by chromatography. This can be reduced with BH_3·THF, using the previously indicated procedure to yield deoxynojirimycin.

In summary, we have developed a facile and effective synthesis of 1,6-dideoxynojirimycin, 1,6-dideoxygalactonojirimycin and deoxynojirimycin as well as the corresponding 5-amino-5-deoxy-aldonic acid δ-lactams using β-glycosides as starting materials. This approach should be general to any β-glycoside, especially deoxy sugars and those with substituents such as ether groups, to give general access to substituted or functionalized iminosugars. The use of alkylamines instead of hydroxylamine should give access to N-alkylated iminosugars. Further research in this area is in progress and will be reported on later.

3. Experimental

General methods.—Melting points were measured on a Fisher–Johns melting point apparatus. Optical rotations were measured ($\lambda = 589$ nm) at room temperature (rt) using a Perkin–Elmer 341 polarimeter in a 1 mL cell. The ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz on a Varian VXR spectrometer. The HRMS FAB mass spectra were obtained using a Jeol HX-110 double-focusing mass spectrometer operating in positive ion mode.

*Preparation of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside* (**2a**).—The tetraacetate has been prepared from methyl β-D-glucopyranoside (**1a**), pyridine and Ac_2O according to standard procedures [18].

*Preparation of methyl 2,3,4,6-tetra-*O*-acetyl-D-xylo-hex-5-ulosonate* (**3a**).—To a soln of **2a** (7 g, 19.34 mmol) in AcOH (125 mL) and Ac_2O (10 mL), CrO_3 (3.8 g, 38 mmol) was added, and the suspension was stirred at 50 °C for 2 h. The mixture was then poured slowly, with stirring, into cold water (500 mL). The water was extracted three times with $CHCl_3$. The combined $CHCl_3$ layers were decolorized with activated charcoal, filtered, and washed with satd $NaHCO_3$ soln and then with water. After drying with Na_2SO_4 and rotary evaporation of the solvent, the ketone **3a** (7.25 g, 100%) was obtained as a colorless syrup: $[\alpha]_D^{23}$ −2.4° (*c* 1.67, CH_3Cl), lit. −5.8° (*c* 1.65, CH_3Cl) [17]; ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.13 (s, 3 H, OAc), 3.70 (s, 3 H, OCH_3), 4.73 (d, 1 H, $J_{6a,6b}$ 17.3 Hz, H-6a), 4.84 (d, 1 H, H-6b), 5.26 (d, 1 H, $J_{2,3}$ 4.4 Hz, H-2), 5.43 (d, 1 H, $J_{3,4}$ 4.4 Hz, H-4), 5.65 (t, 1 H, H-3); ^{13}C NMR ($CDCl_3$) δ 20.1, 20.2, 20.3, 52.8, 66.4, 69.3, 69.6, 73.6, 167.0, 169.1, 169.3, 169.7, 197.0.

Preparation of methyl 2,3,4,6-tetra-O-*acetyl*-D-xylo-*hex*-5-*ulosonate oxime* (**4a**).—The ketone **3a** (7 g, 18.61 mmol) was dissolved in pyridine (16 mL), and the soln was cooled to 0 °C. Hydroxylamine hydrochloride (2 g, 28.77 mmol) was then added, and the soln was stirred at 0 °C for 15 min, and then for another 2 h at rt. The mixture was poured onto ice and water and then extracted three times with $CHCl_3$. The combined $CHCl_3$ layers were subsequently washed with water, dried with Na_2SO_4 and then evaporated. Crystallization from hot EtOH gave white crystals of the oxime **4a** (6.9 g, 95%) as a 3:2 mixture of syn–anti isomers:

Isomer 1: ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3 H, OAc), 1.94 (s, 3 H, OAc), 2.00 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 3.56 (s, 3 H, OCH_3), 4.36 (d, 1 H, $J_{6a,6b}$ 12.4 Hz, H6-a), 4.72 (d, 1 H, H6-b), 4.99 (d, 1 H, $J_{3,4}$ 2.6 Hz, H-4), 5.72 (dd, 1 H, $J_{3,2}$ 7.8 Hz, H-3), 6.28 (d, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 20.5, 20.4, 52.8, 61.3, 66.1, 69.5, 69.8, 149.9, 167.3, 169.4, 169.5, 170.1; HRFABMS ($M + H^+$) calcd. 392.1193, found 392.1198.

Isomer 2: mp 121–122 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3 H, OAc), 1.89 (s, 3 H, OAc), 1.98 (s, 3 H, OAc), 2.00 (s, 3 H, OAc), 3.56 (s, 3 H, OCH_3), 4.82 (s, 2 H, H-6), 5.16 (d, 1 H, $J_{3,4}$ 2.6 Hz, H-4), 5.62 (d, 1 H, $J_{3,2}$ 8.5, H-2), 5.78 (dd, 1 H, H-3); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.4, 20.5, 52.8, 56.4, 69.8, 70.1, 70.4, 150.8, 167.2, 169.4, 169.6, 170.2, 170.3.

Preparation of 2,3,4-tri-O-*acetyl-5-amino-5,6-dideoxy*-D-*glucono-1,5-lactam* (**5a**).—A soln of **4a** (6.9 g, 17.64 mmol) in glacial AcOH (275 mL), containing 10% Pd–C (2.76 g), was hydrogenated in a Parr reactor under a H_2 pressure of 300–400 psi for 40 h at 55 °C. The reaction mixture was filtered through Celite and washed with EtOH. The solvent was rotary evaporated and the lactam **5a** (5 g, 100%) was obtained as a light yellow syrup: $[\alpha]_D^{23}$ + 70.0° (*c* 1.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.11 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6), 1.94 (s, 3 H, OAc), 1.98 (s, 3 H, OAc), 2.00 (s, 3 H, OAc), 3.51 (m, 1 H, $J_{4,5}$ 9.7, Hz, H-5), 4.94 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.7 Hz, H-3), 4.96 (d, 1 H, H-2), 5.40 (t, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 18.0, 20.3, 20.4, 48.7, 70.6, 70.9, 71.4, 166.7, 169.4, 169.6, 169.8; HRFABMS ($M + H^+$) calcd. 288.1083, found 288.1089.

Preparation of 1,5,6-trideoxy-1,5-imino-D-*glucitol* (**6a**).—1 M BH_3·THF (50 mL, 50 mmol) was added under N_2 to a soln of **5a** (5 g, 17.41 mmol) in THF (33 mL). The mixture was stirred at rt for 1.5 h and then refluxed for another 1.5 h. After cooling to rt, 9% methanolic HCl (40 mL) was carefully added, and the resulting soln was refluxed for 30 min. The THF was removed by rotary evaporation, and the reaction mixture was dissolved repeatedly in MeOH, followed by evaporation to remove borates. Water was added to the dry crude product and the soln was passed through an anion-exchange resin (Amberlite IR-45 OH-form) and then dried on the rotary evaporator. To remove the last traces of borates, a soln of 1 M NaOH (15 mL) and EtOH (6 mL) were added to the crude product, and the mixture was stirred overnight at rt. The EtOH was evaporated, and the aq soln was lyophylized. A methanolic HCl soln was added, which precipitated NaCl while the methanolic soln was dried, to give product **6a** (2.43 g, 95%): $[\alpha]_D^{23}$ + 15.5° (*c* 1.88, H_2O), lit. + 13° (*c* 1.0, H_2O) [7]; ^{1}H NMR (D_2O) δ 1.25 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6), 2.77 (dd, 1 H, $J_{1a,1e}$ 12.4 Hz, $J_{1a,2}$ 11.7 Hz, H-1a), 3.02 (m, 1 H, H-5), 3.23 (dd, 1 H, $J_{3,4}$ 9.0 Hz, H-4), 3.33 (dd, 1 H, $J_{1e,2}$ 5.1 Hz, H-1e), 3.31 (dd, 1 H, $J_{2,3}$ 9.2 Hz, H-3), 3.63 (ddd, 1 H, H-2); ^{13}C NMR (D_2O) δ 17.5, 49.5, 55.2, 71.4, 76.7, 79.0.

Preparation of methyl 2,3,4,6-tetra-O-*acetyl-β*-D-*galactopyranoside* (**2b**).—This compound was prepared from methyl β-D-galactopyranoside hydrate (**1b**, 5 g, 24.63 mmol) using the same procedure described for the gluco compound.

Preparation of methyl 2,3,4,6-tetra-O-*acetyl*-L-arabino-*hex*-5-*ulosonate* (**3b**).—This compound was prepared from **2b** using the same procedure as described for **3a**, except that the reaction time was 3 h. Yield was 100%: $[\alpha]_D^{23}$ − 24.3° (*c* 1.4, $CHCl_3$), lit. 12.0° (*c* 2.8, $CHCl_3$) [18]; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.16 (s, 3 H, OAc), 3.71 (s, 3 H, OCH_3), 4.80 (d, 1 H, $J_{6a,6b}$ 17.5 Hz, H-6a), 4.92 (d, 1 H, H-6b), 5.20 (d, 1 H, $J_{2,3}$ 8.7 Hz, H-2), 5.27 (d, 1 H, $J_{3,4}$ 2.4 Hz, H-4), 5.66 (dd, 1 H, H-3); ^{13}C NMR ($CDCl_3$) δ 20.1, 20.2, 20.3, 20.4, 52.8, 67.1, 69.3, 69.5, 71.0, 167.0, 168.9, 169.4, 169.8, 198.1.

Preparation of methyl 2,3,4,6-tetra-O-*acetyl*-L-arabino-*hex*-5-*ulosonate oxime* (**4b**).—This compound was prepared from the ketone **3b** as described for the corresponding D-xylo compound. White crystals of **4b** (85%) were obtained as a mixture of syn–anti isomers: ^{1}H NMR ($CDCl_3$) δ: Isomer 1: 1.98 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 3.70 (s, 3 H, OCH_3), 4.82 (d, 1 H, $J_{6a,6b}$ 14.6 Hz, H6-a), 5.11 (d, 1 H, H6-b), 5.35 (d, 1 H, $J_{3,4}$ 1.9 Hz, H-4), 5.68 (d, 1 H, $J_{3,2}$ 9.0, Hz, H-2), 5.84 (dd, 1 H, H-3); ^{13}C NMR ($CDCl_3$) δ 20.2, 20.3, 20.4, 20.5, 52.6, 56.4, 68.7, 69.2, 69.6, 149.9, 167.5, 168.9, 169.3, 170.0, 170.3.

Preparation of 1,5,6-trideoxy-1,5-imino-D-*galactitol* (**6b**).—This compound was prepared from **4b** (7.4 g, 18.92 mmol) as described for the corresponding gluco compound **5a**. A total of 7.4 g of the crude product was obtained, which was subjected to borane reduction. The product was isolated as described for the gluco isomer. Flash column chromatography using a 6:1 $CHCl_3$–EtOH mixture gave product **6b** (1.5 g, 30%): $[\alpha]_D^{23}$ +27.0° (*c* 1.3, $CHCl_3$), lit +49.0° (*c* 1, $CHCl_3$) [6b]; ^{1}H NMR (D_2O) δ 1.21 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 2.73 (t, 1 H, $J_{1a,1e} = J_{1a,2}$ 11.9 Hz, H-1a), 3.30 (dd, 1 H, $J_{1e,2}$ 5.4 Hz, H-1e), 3.37 (m, 1 H, H-5), 3.50 (dd, 1 H, $J_{2,3}$ 9.6 Hz, $J_{3,4}$ 3.1 Hz, H-3), 3.90 (d, 1 H, $J_{4,5}$ 3.1 Hz, H-4), 3.91 (ddd, 1 H, H-2); ^{13}C NMR (D_2O) δ 14.2, 46.1, 55.0, 64.4, 69.9, 73.1.

Preparation of 2,3,4,6-tetra-O-*acetyl-5-amino-5-deoxy*-D-*glucono-1,5-lactam* (**9**).—The acetylated oxime **4a** (1.5 g, 3.84 mmol) was deacetylated with concomitant conversion to the acyl hydrazide by treatment with anhyd hydrazine (0.75 mL, 23.89 mmol) in EtOH (15 mL) at rt for 2 h. Evaporation of the solvent gave crude **7**: ^{1}H NMR (D_2O) δ 4.18 (dd, 1 H, $J_{2,3}$ 4.6 Hz, $J_{3,4}$ 7.0 Hz, H-3), 4.43 (d, 1 H, $J_{6a,6b}$ 14.9 Hz, H-6a), 4.51 (d, 1 H, H-4), 4.53 (d, 1 H, H-6b), 5.18 (d, 1 H, H-2); ^{13}C NMR (D_2O) δ 61.1, 69.1, 73.4, 73.5, 160.7, 173.4.

Compound **7** was hydrogenated in glacial AcOH with 10%, Pd–C (0.4 g) at 50 °C and 300 psi pressure of H_2 for 2 days. After filtration through Celite, the soln was dried on the rotary evaporator, and the crude product was acetylated with Ac_2O (15 mL) and pyridine (15 mL) for 5 h at rt. The mixture was poured into cold water and extracted with $CHCl_3$. The $CHCl_3$ layer was dried with Na_2SO_4. Evaporation of the solvent gave crude product (1.47 g), which was subjected to flash chromatography on silica (eluent: 2:1 hexane–acetone) to give the peracetylated lactam **9** (0.5 g, 34% total yield from **4a**) and its C-5 epimer, 2,3,4,6-tetra-*O*-acetyl-5-amino-5-deoxy-L-idono-1,5-lactam in a 3:2 ratio.

Data for **9**: mp 177–178 °C; $[\alpha]_D^{23}$ +88.6° (*c* 1.11, $CHCl_3$), lit +104° (*c* 1.73, $CHCl_3$) [5]; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3 H, OAc), 2.06 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 3.75 (ddd, 1 H, $J_{4,5}$ 9.7 Hz, $J_{5,6a}$ 2.9 Hz, $J_{5,6b}$ 6.5 Hz, H-5), 3.96 (dd, 1 H, $J_{6a,6b}$ 11.7 Hz, H6-b), 4.22 (dd, 1 H, H-6a), 5.06 (d, 1 H, $J_{3,2}$ 9.5 Hz, H-2), 5.20 (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 5.53 (dd, 1 H, H-4), 6.48 (s, 1 H, NH);^{13}C NMR ($CDCl_3$) δ 20.5, 20.5, 20.5, 20.6, 52.4, 62.7, 67.2, 70.4, 70.5, 166.2, 169.4, 169.6, 170.0, 170.4. HRFABMS ($M + H^+$) calcd. 346.1060, found 346.1143.

Data for C-5 epimer of **9**: $[\alpha]_D^{23}$ +3.1° (*c* 1.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3 H, OAc), 1.99 (s, 3 H, OAc), 2.00 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 3.88 (m, 1 H, H-5), 4.04 (dd, 1 H, $J_{6a,6b}$ 11.4 Hz, $J_{5,6b}$ 6.3 Hz, H6-b), 4.18 (dd, 1 H, $J_{5,6a}$ 3.9 Hz, H-6a), 5.15 (dd, 1 H, $J_{4,5}$ 9.5 Hz, $J_{3,4}$ 7.5 Hz, H-4), 5.15 (d, 1 H, $J_{2,3}$ 7.5 Hz, H-2), 5.39 (t, 1 H, H-3), 7.27 (s, broad, 1 H, NH);^{13}C NMR ($CDCl_3$) δ 20.2, 20.3, 20.4, 50.0, 62.0, 68.0, 69.8, 70.0, 166.7, 169.3, 169.7, 170.3, 170.6.

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