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The intramolecular conjugate addition of benzylamine to a D-glucose derived α,β-unsaturated ester: an efficient synthesis of trihydroxylated pyrrolidine alkaloids as potential glycosidase inhibitors

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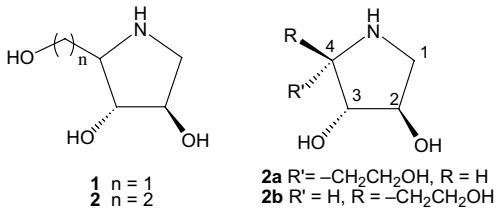
Abstract—A short and efficient synthesis of 1,4,5-trideoxy-1,4-imino-L-*xylo*-hexitol **2a** and 1,4,5-trideoxy-1,4-imino-D-*arabino*-hexitol **2b** is reported using the intramolecular conjugate addition of in situ generated benzylamine to the α,β-unsaturated ester **4**, derived from D-glucose, as the key step.

The stereoselective inter- or intramolecular conjugate addition of an ammonia equivalent to α,β-unsaturated esters is one of the most attractive strategies for the synthesis of β-aminoesters and has found wide utility in the synthesis of heterocyclic compounds.[1,2] In general, this route makes use of chiral amines and achiral α,β-unsaturated esters, however, a limited study is available using chiral conjugated acceptors. Among these, sugar derived α,β-unsaturated esters represent versatile substrates as they provide polyhydroxylated carbon frameworks as well as the opportunity for the stereoselective conjugate addition of the amine functionality.[3] In this context, we recently exploited the D-glucose derived α,β-unsaturated ester **3** in a highly diastereoselective intra- as well as intermolecular conjugate addition pathway for the synthesis of 1-deoxy-L-*ido*-homonojirimycin[4c] and 1-deoxy-castanospermine analogues,[4d] respectively.

This class of compounds, in particular, polyhydroxylated piperidine and pyrrolidine alkaloids, are known to be glycosidase inhibitors, which modify glycoconjugates by hydrolyzing glycosidic linkages, a process which is essential for normal cell growth, regulation, and development. In addition, glycosidase inhibitors are known to possess a variety of beneficial therapeutic effects toward tumor metastasis,[5] metabolic disorders,[6] viral infections,[7] antibacterial, antitumoral, or antidiabetic agents.[8] Among azasugars, the naturally occurring hydroxylated pyrrolidine alkaloids and their synthetic analogues are known to act as specific and potent inhibitors of glycosidases and display interesting bioactivities. In the search for structure–activity relationships, all the stereoisomers of 1,4-dideoxy-1,4-imino-pentitols **1** (Fig. 1) have been synthesized and evaluated.

However, among the related imino-hexitol derivatives **2** only four stereoisomers with the D,L-*lyxo*, D-*xylo*, and D-*ribo* configuration have been reported so far.[9] As a part of our interest in the synthesis of azasugars,[4] we now report the synthesis of the hitherto unknown 1,4,5-trideoxy-1,4-imino-L-*xylo*-hexitol **2a** and 1,4,5-trideoxy-1,4-imino-D-*arabino*-hexitol **2b**. It was thought



1 n = 1
2 n = 2

2a R'= –CH_2CH_2OH, R = H
2b R' = H, R = –CH_2CH_2OH

Figure 1.

Keywords: Alkaloids; Pyrrolidines; Enzyme inhibitors; Carbohydrate mimetics.
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that removal of C-1 from **3**, readily obtained from D-glucose, would provide the α,β-unsaturated ester **4** with the requisite aldehyde functionality. The in situ generation of the amine and intramolecular conjugate addition would lead to the formation of a five-membered nitrogen heterocycle that could be elaborated to the hydroxylated pyrrolidine analogues **2a**,**b**. Our results are reported herein.

D-Glucose was converted to α,β-unsaturated ester **3** as reported earlier.[4h] Deprotection of the 1,2-acetonide group in **3** followed by oxidative cleavage using sodium metaperiodate afforded the requisite ethyl D-*threo*-hex-4-enoate **4**.[10] Compound **4** was found to be relatively unstable and was therefore directly reacted with benzylamine (1.0 equiv) in the presence of a catalytic amount of acetic acid in dry methanol followed by treatment with $NaCNBH_3$ at −20 °C to afford the γ-lactone **5a** and hydroxy ester **5b** in the ratio 58:42 (Scheme 1).[11,12] This overall one-pot, three-step transformation presumably involves the amine, the primary reaction product, undergoing intramolecular conjugate addition to yield the hydroxy ester **5b** as one of the products whilst, the other hydroxy ester undergoes lactonization to yield the γ-lactone **5a**. Our attempts to improve the diastereoselectivity of the intramolecular conjugate addition were unsuccessful. The reaction was found to be sluggish at −78 °C (40% yield) with poor diastereoselectivity (**5a**/**b** = 3:2). The formation of **5a** and **5b** can be explained by considering the transition states (TS) **A** and **B** (Fig. 2). In general, the stereochemical outcome of intramolecular conjugate addition reactions is controlled by stereoelectronic and steric factors.[13] However we believe that, under the reaction conditions of reductive amination and in situ conjugate addition, complexation of the boron by the nitrogen and the C-3 hydroxyl group determines the amine addition stereoselectively.[2] Thus, the complexation of boron with the C-3 hydroxyl and amino groups holds the nitrogen atom in such a way that the preferred *Si* face attack (TS **A**, Fig. 2) gives lactone **5a** as the major product while, the comparatively more crowded *Re* face attack (TS **B**) affords hydroxy ester **5b**. It is interesting to note that in our previous report[4c] the same reaction with the hemiacetal, derived from **3** by acetonide opening, at −78 °C to room temperature afforded the lactone **7**, an immediate precursor to 1-deoxy-L-*ido*-nojirimycin, as the only product with *Si* facial stereoselectivity in a six-membered transition state (TS **C**).

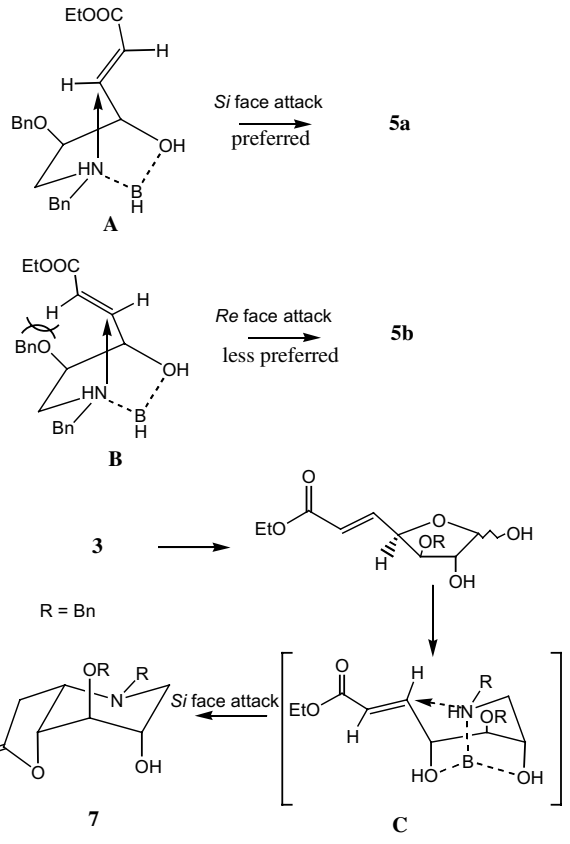
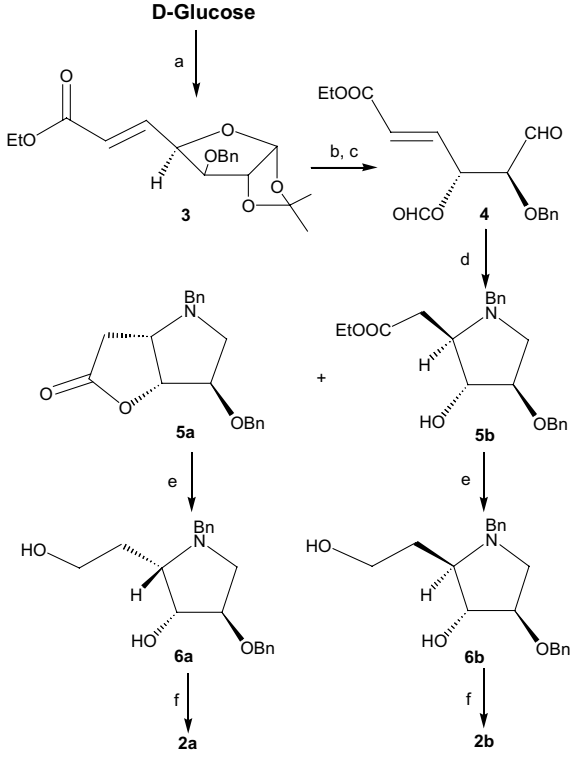


Figure 2.



Scheme 1. Reagents and conditions: (a) Ref. 4; (b) TFA–H_2O (3:2), 0–25 °C, 3 h; (c) $NaIO_4$ (1.2 equiv), acetone–water (8:1), 0–25 °C, 40 min, 83%; (d) $BnNH_2$ (1.0 equiv), cat. CH_3COOH, $NaCNBH_3$ (1.5 equiv) dry MeOH, −20 °C, 3 h then 25 °C, 8 h, for **5a** 47% and for **5b** 34%; (e) $LiAlH_4$, THF, 0–25 °C, 75 min, for **6a** 82% and for **6b** 88%; (f) H_2, Pd/C, 80 psi, MeOH, 18 h, for **2a** 89% and for **2b** 92%.

In the subsequent step (Scheme 1), reduction of the γ-lactone **5a** with LAH in dry THF afforded the primary alcohol **6a** which, on removal of the *O*- and *N*-benzyl groups by hydrogenolysis (10% Pd/C in MeOH) afforded 1,4,5-trideoxy-1,4-imino-L-*xylo*-hexitol **2a**. The same reaction sequence was repeated for the hydroxy ester **5b** wherein the LAH reduction gave the corresponding C4-epimeric alcohol **6b**, which on hydrogenolysis afforded 1,4,5-trideoxy-1,4-imino-D-*arabino*-hexitol **2b**. The ^1H and ^{13}C NMR spectra and analytical data of

the products were in agreement with the proposed structures **2a**,**b**.[12] Studies on their glycosidase inhibitory activity are in progress and will be reported elsewhere.

In summary, we have developed a simple and concise synthesis of the trihydroxylated pyrrolidine alkaloids **2a** and **2b** in an overall yield of 13.7% and 11.5%, respectively, starting from D-glucose.

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10. The ^{1}H NMR spectrum of the crude compound **4** showed the presence of a mixture of *E* and *Z* isomers and the hydrated form of the aldehyde.
11. *Procedure for* **5a** *and* **5b**: To a solution of benzylamine (0.178 mL, 1.63 mmol) and acetic acid (0.074 mL, 1.30 mmol) in dry methanol (6 mL) at −20 °C was added **4** (0.5 g, 1.63 mmol) in methanol (4 mL) over a period of 30 min under a nitrogen atmosphere. The solution was stirred at the same temperature for 1 h and $NaCNBH_3$ (0.153 g, 2.45 mmol) was added in three portions (10 min). The mixture was stirred at −20 °C for 2 h and allowed to warm to room temperature. After stirring at room temperature for 8 h, the solution was concentrated under reduced pressure. Saturated Na_2CO_3 solution was added to the residue, the solution was extracted with chloroform (15 mL × 3) and the combined extract was dried over anhydrous sodium sulfate. Removal of chloroform afforded a thick oil, which was purified by chromatography (pet. ether/ethyl acetate = 9.5/0.5) to gave **5a** in 47% yield and **5b** in 34% yield.
12. All new compounds were obtained in analytically pure form. Data for **5a**: $[\alpha]_D^{25}$ 4.45 (*c* 0.44, $CHCl_3$). IR (neat): 1780.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (dd, J = 8.2, 9.7 Hz, 1H, H-1a), 2.42 (dd, J = 0.8, 18.0 Hz, 1H, H-5a), 2.56 (dd, J = 6.7, 18.0 Hz, 1H, H-5b), 3.29 (dd, J = 6.7, 9.7 Hz, 1H, H-1b), 3.40 (dt, J = 0.8, 6.7 Hz, 1H, H-4), 3.42 (d, J = 12.9 Hz, 1H, NCH_2Ph), 3.79 (d, J = 12.9 Hz, 1H, NCH_2Ph), 4.14 (ddd, J = 2.3, 6.7, 8.2 Hz, 1H, H-2), 4.54 (ABq, J = 11.7 Hz, 2H, OCH_2Ph), 4.78 (dd, J = 2.3, 6.7 Hz, 1H, H-3), 7.22–7.36 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.68 (C-5), 57.62, 57.81 (C-1/C-4), 62.34 (NCH_2Ph), 72.05 (OCH_2Ph), 81.58 (C-2), 87.90 (C-3), 127.50, 127.80, 127.92, 128.43, 128.45, 128.81, 137.00, 137.11 (Ar-C), 175.92 (C-6). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55. Found C, 74.30; H, 6.52. Data for **5b**: $[\alpha]_D^{25}$ −11.42 (*c* 0.175, $CHCl_3$). IR (neat): 2733, 1724 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J = 7.3 Hz, 3H, CH_3), 2.55–2.75 (m, 3H, H-1a, H-5a, H-5b), 2.89–3.00 (m, 2H, H-1b, H-4), 3.31 (d, J = 13.1 Hz, 1H, NCH_2Ph), 3.61 (s, exchangeable with D_2O, 1H, OH), 3.86 (dd, J = 0.8, 5.8 Hz, 1H, H-3), 3.97 (d,

J = 13.1 Hz, 1H, NCH_2Ph), 4.12 (m, 1H, H-2), 4.17 (q, J = 7.3 Hz, 2H, OCH_2CH_3), 4.54 (ABq, J = 12.0 Hz, 2H, OCH_2Ph), 7.23–7.37 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.09 (CH_3), 37.03 (C-5), 57.15, 57.87 (C-1/C-4), 61.06 (NCH_2Ph), 67.20(C-3), 71.00 (OCH_2Ph), 82.71, 82.83 (C-2/OCH_2CH_3), 127.18, 127.53, 127.76, 128.02, 128.30, 128.60, 128.80, 128.88, 128.92, 138.06 (Ar-C), 173.59 (C-6). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37. Found C, 71.48; H, 7.40. Data for **6a**: $[\alpha]_D^{25}$ 84.84 (c 0.33, $CHCl_3$). IR (neat): 3355.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.90–1.97 (m, 2H, H-5), 2.18 (dd, J = 6.4, 10.8 Hz, 1H, H-1a), 2.73–2.79 (m, 1H, H-4), 3.22 (d, J = 12.8 Hz, 1H, NCH_2Ph), 3.24 (dd,J = 6.3, 10.8 Hz, 1H, H-1b), 3.56 (br s, exchangeable with D_2O, 1H, OH), 3.67–3.75 (m, 1H, H-6a), 3.81–3.86 (m, 1H, H-6b), 3.89 (dt, J = 2.6, 6.4 Hz, 1H, H-2), 4.00 (d, J = 12.8 Hz, 1H, NCH_2Ph), 4.19 (dd, J = 2.6, 5.8 Hz, 1H, H-3), 4.52 (ABq, J = 11.7 Hz, 2H, OCH_2Ph), 7.22–7.36 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.98 (C-5), 57.15 (C-1), 58.33 (C-4), 59.82 (NCH_2Ph), 66.44 (C-6), 71.61 (OCH_2Ph), 76.66, 83.48 (C-2/C-3), 127.24, 127.65, 127.69, 128.34, 129.03, 137.65, 137.89 (Ar-C). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70. Found C, 73.41; H, 7.71. Data for **6b**: $[\alpha]_D^{25}$ − 30.88 (c 1.36, $CHCl_3$). IR (neat): 3357.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.99–2.03 (m, 2H, H-5), 2.51–2.57 (m, 2H, H-1a, H-4), 2.99 (dd, J = 2.0, 11.0 Hz, 1H, H-1b), 3.20 (d, J = 12.9 Hz, 1H, NCH_2Ph), 3.86–3.95 (m, 3H, H-2, H-6a, H-6b), 4.15 (d, J = 12.9 Hz, 1H, NCH_2Ph), 4.19 (dd, J = 3.2, 6.7 Hz, 1H, H-3), 4.55 (s, 2H, OCH_2Ph), 7.27–7.37 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.79 (C-5), 56.98 (C-1), 58.20 (C-4), 60.62 (NCH_2Ph), 70.38 (C-6), 71.23 (OCH_2Ph), 81.03, 82.75 (C-2/C-3), 127.18, 127.65, 127.75, 128.37, 128.85, 137.85, 138.01 (Ar-C). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70. Found C, 73.44; H, 7.75. Data for **2a**: $[\alpha]_D^{25}$ 12 (c 1.5, MeOH). ^1H NMR (300 MHz, D_2O): δ 1.58–1.73 (m, 2H, H-5), 2.56 (dd, J = 2.3, 12.9 Hz, 1H, H-1a), 3.08–3.17 (m, 1H, H-4), 3.21 (dd, J = 5.5, 12.9 Hz, 1H, H-1b), 1.62 (t, J = 6.7 Hz, 2H, H-6), 3.84 (dd, J = 0.8, 3.5 Hz, 1H, H-3), 4.03 (ddd, J = 0.8, 2.3, 5.5 Hz, 1H, H-2); ^{13}C NMR (75 MHz, D_2O): δ 30.27 (C-5), 51.00 (C-1), 57.36 (C-4), 59.52 (C-6), 76.88, 77.48 (C-2/C-3). Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90. Found C, 48.91; H, 8.94. Data for **2b**: $[\alpha]_D^{25}$ 10 (c 0.4, MeOH). ^1H NMR (300 MHz, D_2O): δ 1.85–1.93 (m, 2H, H-5), 3.12 (dd, J = 2.6, 12.6 Hz, 1H, H-1a), 3.29–3.42 (m, 1H, H-4), 3.32 (dd, J = 4.9, 12.6 Hz, 1H, H-1b), 3.50–3.57 (m, 2H, H-6), 3.87 (dd, J = 3.5, 4.0 Hz, 1H, H-3), 4.09 (ddd, J = 2.6, 3.5, 4.9 Hz, 1H, H-2); ^{13}C NMR (75 MHz, D_2O): δ 32.43 (C-5), 49.70 (C-1), 58.34 (C-4), 63.17 (C-6), 74.05, 78.57 (C-2/C-3). Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90. Found C, 48.88; H, 8.87.

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