Tetrahedron 66 (2010) 2830–2834

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of eight-membered iminocyclitols from D-glucose

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ARTICLE INFO

Article history:
Received 15 January 2010
Received in revised form 5 February 2010
Accepted 9 February 2010
Available online 13 February 2010

Keywords:
Baylis–Hillman reaction
Conjugate addition
Iminosugars
Diastereoselectivity

ABSTRACT

The Baylis–Hillman reaction of 3-*O*-benzyl-α-D-*xylo*-pentodialdo-1,4-furanose **2** afforded a diastereomeric mixture of L-*ido*- and D-*gluco*-configurated α-methylene-β-hydroxy esters **3a** and **3b**, respectively, in 1:1 ratio. Conjugate addition of benzyl amine on **3a** gave adduct **4a** as a major product while, addition of benzyl amine to **3b** gave only one diastereomer **4b**. Reduction of ester functionality in **4a**/**4b**, opening of 1,2-acetonide functionality followed by reductive amino-cyclization under hydrogenation condition afforded azocanes **1c**/**1d** in good yield.

1. Introduction

Iminocyclitol is a class of modified sugars in which ring oxygen atom is replaced with the nitrogen. These compounds, also known as iminosugars, are promising glycosidase inhibitors and have therefore become therapeutically useful in the treatment of diseases such as cancer,[1] diabetes[2] and viral infections including AIDS.[3] Amongst, monocyclic iminosugars the five-, six- and seven-membered iminosugars have witnessed spectacular development in the past three decades. However, no report is available on the natural occurrence of eight-membered iminosugars—commonly known as polyhydroxylated azocanes, and till date only two reports are available on their synthesis. In 2004, Martin and co-workers first reported the synthesis and biological evaluation of **1a** (Fig. 1)[4] and later on Chang and co-workers (in 2007) described the synthesis of another analogue of an eight-membered iminosugar **1b**.[5] While working in the area of mono- and bi-cyclic iminosugars,[6] we exploited the Baylis–Hillman reaction with D-glucose derived 3-*O*-benzyl-α-D-*xylo*-pentodialdose, followed by the conjugate addition of benzyl amine and reductive amino-cyclization, in the synthesis of new analogues of eight-membered iminocyclitols **1c**/**1d**. Our results in this direction are presented herein.

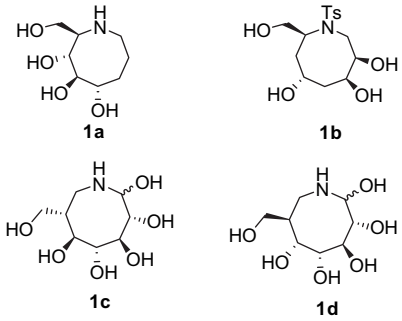

Figure 1. Eight-membered iminosugars/azocanes.

2. Result and discussion

As shown in Scheme 1, required 3-*O*-benzyl-α-D-*xylo*-pentodialdo-1,4-furanose **2** was prepared from D-glucose in 60% overall yield as reported earlier.[7] The Baylis–Hillman reaction of **2** with ethyl acrylate using DABCO as a base, in 1,4-dioxane/H_2O (1:1), afforded a diastereomeric mixture of α-methylene-β-hydroxy esters **3a** and **3b** in the ratio 1:1 as evident from the ^{1}H NMR spectrum of the crude product, in 85% yield. An appreciable difference in the R_f value allowed us to separate a diastereomeric mixture **3** by column chromatography. Assignment of absolute configuration at the newly generated C-5 stereocentre in **3a** and **3b** was made on the basis of coupling constant information between the H-4 and H-5 protons and comparing the ^{1}H NMR data with analogous products

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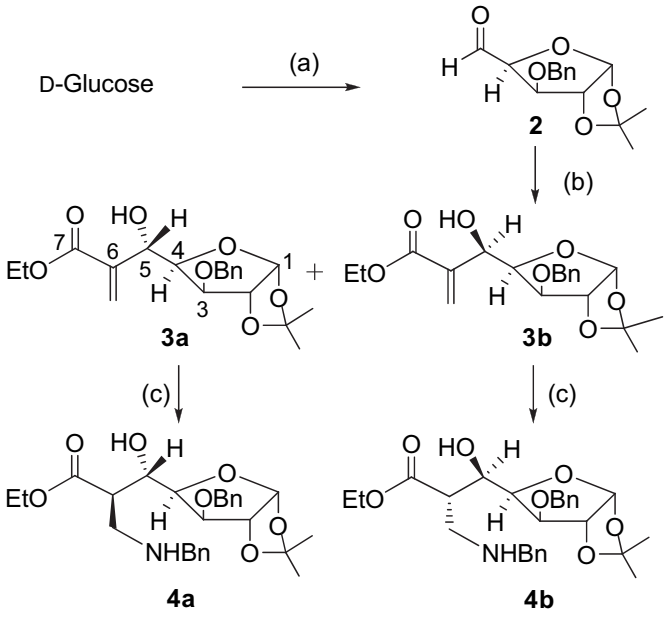
doi:10.1016/j.tet.2010.02.044

obtained by us[8] in the Baylis–Hillman reaction of 3-*O*-allyl-α-D-*xylo*-pentodialdo-1,4-furanose.[9] In case of **3a,** the observed small coupling constant value (3.3 Hz) between the H-4 and H-5 indicated the L-*ido*-configuration with 5*S* absolute configuration and in case of **3b**, the observed large coupling constant (7.5 Hz) is in agreement with the D-*gluco*-configuration with 5*R* absolute configuration. This assignment was confirmed by the X-ray crystallographic data of the compound obtained in the next step.



Scheme 1. Reagents and conditions: (a) Ref. 7; (b) DABCO, ethyl acrylate, 1,4-dioxane/H_2O (1:1), rt, 48 h; (c) $BnNH_2$. rt, 6 h.

In subsequent step, conjugate addition of benzyl amine to L-*ido*-configurated α-methylene-β-hydroxy ester **3a** gave an inseparable mixture of C-6 epimeric products in the ratio 4:1 (Scheme 1) as evident from the ^{1}H NMR of crude product. Our attempts to separate a mixture by flash/column chromatography were unsuccessful, however keeping the hexane solution of C6-epimeric mixture at 0 °C for 24 h afforded major isomer **4a** as a colourless crystalline solid in 70% yield.[10] Single crystal X-ray analysis[11] of **4a** (Fig. 2) firmly established the absolute configurations as 5*S* and 6*R* and confirmed our earlier assignment in the Baylis–Hillman products **3a** and **3b** with L-*ido*- and D-*gluco*-configuration, respectively.

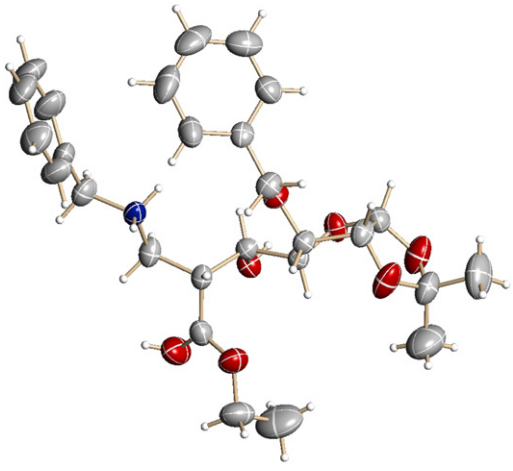
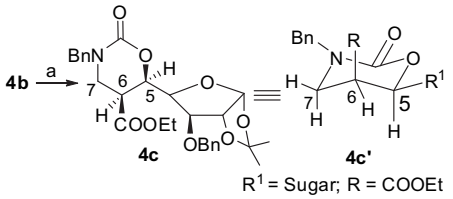


Figure 2. ORTEP diagram of **4a**.

Analogously, conjugate addition of benzyl amine to D-*gluco*-configurated α-methylene-β-hydroxy ester **3b** afforded a single diastereomer **4b** as thick oil in 88% yield. The stereo chemical assignment at the newly generated C-6 stereocentre in **4b** was made by correlation study. Thus, reaction of **4b** with phosgene in toluene at 0 °C afforded a six-membered cyclic carbamate **4c** (Scheme 2) wherein, the coupling constant information between the H-5 and H-6 protons is diagnostic in assigning the stereochemistry at C-6. We assume that **4c** attains chair conformation **4c′** in which the bulky sugar group (R^1) preferably adopts an equatorial position with axial orientation of the H-5. As evident from the ^{1}H NMR and decoupling experiments of **4c**, the H-5 appeared as a doublet of doublet ($J_{4,5}$=8.7 Hz and $J_{5,6}$=4.2 Hz) and the H-6 appeared as an apparent quartet with $J_{5,6}$=$J_{6,7}$=4.2 Hz. The lower coupling constant between the H-5 and H-6 indicated their relative axial–equatorial relationship (axial orientation of the –COOEt group), with 6*S* absolute configuration. As carbamate **4c** is obtained from **4b**, the same 6*S* absolute configuration was assigned in compound **4b**.



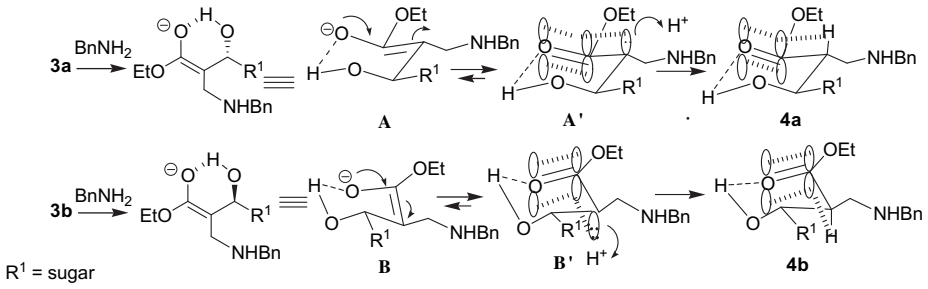
Scheme 2. Reagents and conditions: (a) $COCl_2$, Et_3N, toluene, 0 °C, 10 min, 86%.

2.1. Explanation for the observed stereoselectivity

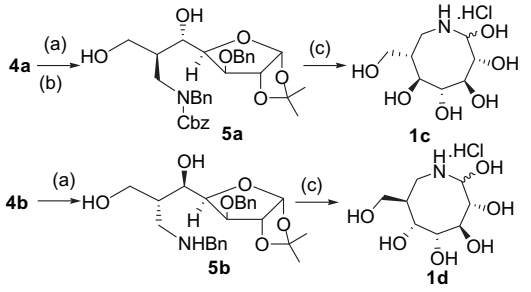
It is interesting to note that the conjugate addition of benzyl amine to α-methylene-β-hydroxy esters **3a** and **3b** was found to be highly stereoselective affording *anti*-isomers **4a** and **4b**, respectively, as a major product. This fact could be rationalized as follows (Scheme 3). We assume that addition of benzyl amine to **3a** and **3b** in a conjugate fashion will lead to the corresponding ester enolates that exist in chair conformations **A** and **B**, due to intramolecular hydrogen bonding, with preferred equatorial orientation of bulky sugar group (R^1). Reversion of ester enolates **A**/**B** will give transition states **A′**/**B′** wherein an empty lone pair of electrons will adopt axial orientation due to the favourable overlap of the lone pair of electrons with the carbonyl group.[12] Subsequently, the axially oriented electron lone pair in **A′**/**B′** will take up a proton (thus orienting the benzyl amine group equatorially) to give **4a**/**4b**. The sigma electrons of the axial hydrogen bond are favourably located for overlap with the π-electrons of the carbonyl functionality as shown in Scheme 3. The equatorial orientation of the bulky benzyl amine group further stabilizes the structure **4**.

Targeting the synthesis of azocanes, compound **4a** was reacted with LAH and the diol thus obtained was directly subjected to selective –*N*Cbz protection, using benzyl chloroformate, to give **5a** (Scheme 4). In the final steps, hydrolysis of 1,2-acetonide functionality in **5a** using TFA/water (3:2) gave a mixture of hemiacetal that on hydrogenation using 10% Pd/C in MeOH/HCl (9:1) afforded azocane **1c** as a hydrochloride salt. Similarly, reduction of ester functionality in compound **4b** with LAH gave **5b** in 67% yield that on 1,2-acetonide cleavage (TFA/water) and hydrogenation (10% Pd/C in MeOH/HCl) afforded azocane **1d** as a hydrochloride salt. All the compounds were characterized by spectral and analytical techniques and the data was found to be in agreement with the structures.

In the ^{1}H NMR spectrum of **1c**, the most deshielded doublet at δ 5.10 ($J_{1,2}$=4.2 Hz) and a broad singlet at δ 4.8 (W_H=1.5 Hz), integrating in the ratio 1:1.5 were assigned to the C-1 protons of two



Scheme 3. Plausible mechanism for observed stereoselectivity.



Scheme 4. Reaction conditions: (a) LAH, THF, 0 °C to rt, 2 h.; (b) CbzCl, $NaHCO_3$, $MeOH/H_2O$ (4:1), rt, 12 h.; (c) (i) TFA/H_2O, 0 °C to rt, 2 h.; (ii) H_2, Pd/C, MeOH, one drop concd HCl, 80 psi, 12 h.

anomers. The small coupling constant between the H-1 and H-2 in both the anomers indicated the equatorial orientation of the H-2, and based on this analogy two chair–boat conformations **I** and **II**, with most substituents adopting quasi-equatorial orientation, were assumed for **1c** (Fig. 3). In conformation **I** (α-anomer), the drieding model showed dihedral angle of ~90° between the axially oriented H-1 and the equatorial H-2 accounting for a broad singlet (very small coupling) while; in conformation **II** (β-anomer) the dihedral angle of ~30° between both the equatorially oriented H-1 and H-2 explains the coupling constant of 4.2 Hz. Thus, azocane **1c** exists in D_2O solution as a mixture of α- and β-anomers **I** and **II**, respectively, in the ratio 1:1.5. Similarly, the ^1H NMR spectra of **1d** showed two most deshielded doublets—one at δ 5.18 ($J_{1,2}$=3.9 Hz) and other at δ 4.58 ($J_{1,2}$=7.8 Hz), integrating in the ratio 1:2 for two different anomeric protons. We assumed two chair–boat conformations **III** and **IV** (with most quasi-equatorial substituents) for **1d**. A doublet at δ 5.18 (for H-1) with small coupling constant (3.9 Hz) between the H-1 and H-2 protons accounts for their equatorial and axial relationship in consistence with conformation **III** for α-anomer. While a doublet at δ 4.58 with the large coupling constant (7.8 Hz) indicated the axial–axial orientation for both the H-1 and H-2 accounting conformation **IV** for the β-anomer. Thus, **1d** exists in D_2O solution as a mixture of α- and β-anomers with conformations **III** and **IV**, respectively, in the ratio 1:2.

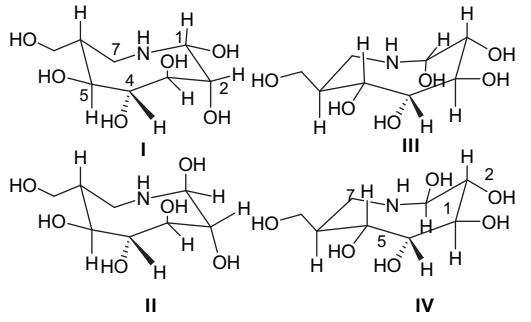


Figure 3. Conformations of **1c** and **1d**.

3. Conclusions

In summary, we have adroitly exploited the Baylis–Hillman reaction with 3-*O*-benzyl-α-D-*xylo*-pentodialdose **2** that afforded two α-methylene β-hydroxy esters **3a** and **3b**. The conjugate addition of benzyl amine to **3a** and **3b** was found to be highly stereoselective to give *anti*-adducts **4a** and **4b**, respectively, which were elaborated to the new eight-membered iminocyclitols **1c** and **1d** in overall yields of 19 and 20%, respectively, from easily available α-D-*xylo*-pentodialdose **2**.

4. Experimental

4.1. General methods

Melting points were recorded with Thomas Hoover Capillary melting point apparatus and are uncorrected. IR spectra were recorded with Shimadzu FTIR-8400 as a thin film or in Nujol mull or using KBr pellets and are expressed in cm^{-1}. ^1H (300 MHz) and ^{13}C (75/100 MHz) NMR spectra were recorded with Varian Mercury instrument using $CDCl_3$ or D_2O as the solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and *J* values are given in hertz. Elemental analyses were carried out with Thermo-Electron Corporation CHNS analyzer Flash-EA 1112 at Department of Chemistry, University of Pune, Pune. Optical rotations were measured using Bellingham Stanley-ADP 220 digital polarimeter with sodium light (589.3 nm) at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Visualization was made by absorption of UV light or by thermal development after spraying with 3.5% solution of 2,4-dinitrophenylhydrazine in ethanol/H_2SO_4 and with basic aqueous potassium permanganate solution. Column chromatography was carried out with silica gel (100–200 mesh). Reactions were carried out in oven-dried glassware under dry N_2 atmosphere. Distilled hexane and EtOAc were used for column chromatography. After quenching of the reaction mixture with water, reaction workup involved washing of the combined organic layer with water, brine, drying over anhydrous Na_2SO_4 and evaporation of solvent at reduced pressure.

4.2. Ethyl-3-*O*-benzyl-6-deoxy-6-methylene-1,2-*O*-isopropylidene-β-L-*ido*-1,4-hepto-furanoate (3a) and ethyl-3-*O*-benzyl-6-deoxy-6-methylene-1,2-*O*-isopropylidene-α-D-*gluco*-1,4-hepto-furanoate (3b)

To a solution of sugar aldehyde **2** (1.40 g, 5.03 mmol) in 1,4-dioxane/H_2O (1:1, 50 mL) were added DABCO (0.56 g, 5.03 mmol) and ethyl acrylate (1.51 mL, 15.10 mmol) at 30 °C. Reaction mixture was stirred for 48 h and quenched by adding saturated NH_4Cl solution. The solution was extracted with ethyl acetate (3×20 mL) and ethyl acetate was evaporated to give crude product. Purification by column chromatography and elution first with 10% EtOAc/*n*-hexane gave **3b** (0.80 g, 43%) as a thick liquid. Found: C, 63.60; H, 7.01.

$C_{20}H_{26}O_7$ requires C, 63.48; H, 6.93; R_f (30% EtOAc/*n*-hexane) 0.6; $[\alpha]_D^{25}$ −10.5 (*c* 0.023, $CHCl_3$); IR (neat) 3200–3600 (br), 1713, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, s, CH_3), 1.31 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.47 (3H, s, CH_3), 2.90–3.60 (1H, br s, exchangeable with D_2O), 4.10 (1H, d, *J*=3.3 Hz, *H*-3), 4.23 (2H, q, *J*=7.2 Hz, $-OCH_2CH_3$), 4.39 (1H, dd, *J*=7.5 and 3.3 Hz, *H*-4), 4.57 (1H, d, *J*=11.4 Hz, $-OCH_2Ph$), 4.58 (1H, d, *J*=3.6 Hz, *H*-2), 4.69 (1H, d, *J*=11.4 Hz, $-OCH_2Ph$), 4.77 (1H, d, *J*=7.5 Hz, *H*-5), 5.87 (1H, br s, C=C), 5.93 (1H, d, *J*=3.6 Hz, *H*-1), 6.33 (1H, br s, C=C), 7.20–7.40 (5H, m, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 26.4, 26.8, 60.9, 69.7, 72.5, 80.1, 82.0, 82.4, 105.0, 111.7, 127.5, 127.7, 128.0, 128.4 (s), 137.0, 137.5, 139.1, 166.2. Further elution with 15% EtOAc/*n*-hexane afforded **3a** (0.79 g, 42%) as a thick liquid. Found: C, 63.55; H, 7.10. $C_{20}H_{26}O_7$ requires C, 63.48; H, 6.93; R_f (30% EtOAc/*n*-hexane) 0.59; $[\alpha]_D^{25}$ −39.1 (*c* 0.006, $CHCl_3$); IR (neat) 3200–3600 (br), 1713, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.32 (3H, s, CH_3), 1.46 (3H, s, CH_3), 3.40–3.90 (1H, br s, exchangeable with D_2O), 4.09 (1H, d, *J*=3.3 Hz, *H*-3), 4.18 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 4.47 (1H, t, *J*=3.3 Hz, *H*-4), 4.51 (1H, d, *J*=11.7 Hz, $-OCH_2Ph$), 4.64 (1H, d, *J*=3.9 Hz, *H*-2), 4.73 (1H, d, *J*=11.7 Hz, $-OCH_2Ph$), 4.88 (1H, d, *J*=3.0 Hz, *H*-5), 6.00 (1H, d, *J*=3.9 Hz, *H*-1), 6.05 (1H, br s, C=C), 6.38 (1H, br s, C=C), 7.25–7.44 (5H, m, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 26.8, 27.2, 61.1, 68.9, 72.5, 80.2, 82.5, 84.3, 105.2, 112.2, 127.8, 128.0 (s), 128.5, 128.9(s), 136.7, 138.7, 166.1.

4.3. Ethyl-3-*O*-benzyl-6-deoxy-6(*R*)-(*N*-benzylaminomethyl)-1,2-*O*-isopropylidene-α-L-*ido*-1,4-hepto-furanoate (4a)

To compound **3a** (0.7 g, 1.85 mmol) was added benzyl amine (0.3 mL, 2.77 mmol) and stirred for 6 h at rt. After completion of the reaction, the reaction mixture was directly adsorbed on silica and purified by column chromatography (20% EtOAc/*n*-hexane) to give **4a** and **4a**′ as a mixture of solid and liquid (0.77 g, 86.5%). After keeping the mixture of **4a** and **4a**′ in hexane at 0 °C for 24 h, solid **4a** crystallized out. Found: C, 66.83; H, 7.00. $C_{27}H_{35}NO_7$ requires C, 66.79; H, 7.27; R_f (40% EtOAc/*n*-hexane) 0.5; $[\alpha]_D^{25}$ −22.5 (*c* 0.6, $CHCl_3$); IR (neat) 3200–3600 (br), 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.37 (3H, s, CH_3), 1.50 (3H, s, CH_3), 2.61 (1H, m, *H*-6), 2.83 (1H, dd, *J*=12.0, 6.0 Hz, *H*-7a), 3.07 (1H, dd, *J*=12.0, 4.2 Hz, *H*-7b), 3.77 (2H, ABq, *J*=13.5 Hz, $-NCH_2Ph$), 3.90–4.27 (3H, m, OCH_2COOEt, *H*-3), 4.29 (1H, dd, *J*=6.6, 3.3 Hz, *H*-4), 4.36 (1H, dd, *J*=6.6, 3.3 Hz, *H*-5), 4.48 (1H, d, *J*=11.7 Hz, $-OCH_2Ph$), 4.68 (1H, d, *J*=3.9 Hz, *H*-2), 4.74 (1H, d, *J*=11.7 Hz, $-OCH_2Ph$), 6.03 (1H, d, *J*=3.9 Hz, *H*-1), 7.20–7.40 (10H, m, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 26.5, 26.9, 46.7, 49.3, 54.1, 60.7, 71.6, 71.7, 81.1, 82.1, 82.8, 105.1, 111.8, 127.1, 127.8, 128.1, 128.4, 128.6, 136.9, 139.7, 172.9.

4.4. 3-*O*-Benzyl-6-deoxy-6(*S*)-(*N*-benzylaminomethyl)-1,2-*O*-isopropylidene-α-D-*gluco*-1,4-hepto-furanoate (4b)

Reaction of **3b** (0.7 g, 1.85 mmol) with benzyl amine (0.3 mL, 2.77 mmol) as described for **4a** gave after column purification (20% EtOAc/*n*-hexane) **4b** (0.79 g, 88.7%) as a thick liquid. Found: C, 66.90; H, 7.01. $C_{27}H_{35}NO_7$ requires C, 66.79; H, 7.27; R_f (40% EtOAc/*n*-hexane) 0.5; $[\alpha]_D^{25}$ −61.39 (*c* 0.25,$CHCl_3$); IR (neat) 3200–3600 (br), 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.30 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.80–2.86 (1H, m, *H*-6), 2.92 (1H, dd, *J*=12.6, 3.3 Hz, *H*-7a), 3.32 (1H, br d, *J*=12.6, 1.8 Hz, *H*-7b), 3.76 (2H, ABq, *J*=13.2 Hz, $-NCH_2Ph$), 4.02 (1H, dd, *J*=10.0, 2.7 Hz, *H*-4), 4.15–4.35 (3H, m, *H*-3, OCH_2CH_3), 4.56 (1H, d, *J*=3.6 Hz, *H*-2), 4.60 (1H, dd, *J*=10.0, 2.7 Hz, *H*-5), 4.72 (2H, ABq, *J*=12.0 Hz, $-OCH_2Ph$), 5.86 (1H, d, *J*=3.6 Hz, *H*-1), 7.17–7.42 (10H, m, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 26.3, 27.1, 45.1, 46.3, 54.2, 60.9, 70.1, 72.9, 81.1, 81.5, 82.9, 105.0, 111.6, 127.2, 127.6 (s), 128.0 (s), 128.2 (s), 128.4 (s), 137.7, 138.8, 173.8.

4.5. 3-*O*-Benzyl-6,7-dideoxy-7-*N*-benzylamino-6(*S*)-carboethoxy-[7-*N*,5-*O*-carbonyl]-α-D-*gluco*-hepto-1,4-furanose (4c)

To a solution of compound **4b** (0.2 g, 0.4 mmol) in dry toluene were added Et_3N (0.07 g, 0.8 mmol) and phosgene (0.27 mL, 0.6 mmol) at 0 °C and allowed to stir for 10 min. The reaction mixture was then quenched by adding saturated NH_4Cl (5 mL). Toluene was then evaporated and the reaction mixture was extracted with ethyl acetate (1×10 mL) and ethyl acetate was evaporated to give the crude product, which was purified by column chromatography (10% EtOAc/*n*-hexane) to give **4c** (0.18 g, 86%) as a thick liquid. Found: C, 65.70; H, 6.60. $C_{28}H_{33}NO_8$ requires C, 65.74; H, 6.50; R_f(20% EtOAc/*n*-hexane) 0.5; $[\alpha]_D^{25}$ −29.7 (*c* 1.10, $CHCl_3$); IR (neat) 1749, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.30 (3H, s, CH_3), 1.39 (3H, s, CH_3), 3.11 (1H, q, *J*=4.2 Hz, *H*-6), 3.40 (1H, dd, *J*=12.3, 5.4 Hz, *H*-7a), 3.60 (1H, dd, *J*=12.3, 3.3 Hz, *H*-7b), 4.00–4.25 (4H, m, *H*-3, *H*-4, OCH_2CH_3), 4.41 (1H, d, *J*=14.4, OCH_2Ph), 4.59 (1H, d, *J*=3.6 Hz, *H*-2), 4.65–4.83 (3H, m, OCH_2Ph, NCH_2Ph), 5.11 (1H, dd, *J*=8.7, 4.2 Hz, *H*-5), 5.85 (1H, d, *J*=3.6 Hz, *H*-1), 7.25–7.42 (10H, m, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 26.2, 27.0, 39.9, 43.8, 52.9, 61.7, 73.0, 73.5, 79.2, 81.1, 82.5, 105.2, 112.2, 127.8, 128.0, 128.2, 128.5, 128.7, 136.0, 137.3, 152.2, 169.8.

4.6. 3-*O*-Benzyl-6-deoxy-6(*S*)-(*N*-benzyl-*N*-benzyloxy-carbonylamino-methyl)-1,2-*O*-isopropylidene-α-L-*ido*-1,4-hepto-furanose (5a)

To a solution of lithium aluminium hydride (0.082 g, 2.16 mmol) in THF (10 mL) at 0 °C was added compound **4a** (0.7 g, 1.44 mmol) and the resulting reaction mixture was stirred at 0 °C to room temperature for 2 h. The reaction mixture was quenched by adding saturated NH_4Cl (5 mL). The reaction mixture was filtered through Celite and washed with ethyl acetate. Now to this aminodiol in methanol/water (9 mL, 8:1), benzyl chloroformate (0.37 mL, 2.16 mmol) was added along with sodium bicarbonate (0.36 g, 4.32 mmol) at 0 °C and stirred for 12 h. Methanol was evaporated under reduced pressure and the residue was extracted with ethyl acetate (1×20 mL). Usual workup and purification by column chromatography (25% EtOAc/*n*-hexane) gave **5a** (0.57 g, 77%) as a thick liquid. Found: C, 68.40; H, 6.66. $C_{33}H_{39}NO_8$ requires C, 68.61; H, 6.80; R_f (50% EtOAc/*n*-hexane) 0.5; $[\alpha]_D^{25}$ −29.2 (*c* 1.6, $CHCl_3$); IR (neat) 3442, 3350, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.20–4.20 (8H, m), 4.30–4.80 (5H, m), 5.14 (2H, br s, $NCOOCH_2$), 6.01 (1H, d, *J*=3.6 Hz, *H*-1), 7.20–7.40 (15H, m, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 28.2, 41.5, 50.8, 60.3, 67.6, 70.2, 71.9, 80.5, 81.9, 83.7, 104.9, 111.9, 127.3, 127.4, 127.5, 127.7, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 136.3, 136.7, 137.4, 157.3.

4.7. 3-*O*-Benzyl-6-deoxy-6(*R*)-*N*-benzyl-methylene-1,2-*O*-isopropylidene-α-D-*gluco*-hepto-1,4-furanose (5b)

To a solution of lithium aluminium hydride (0.082 g, 2.16 mmol) in THF (10 mL) at 0 °C was added compound **4b** (0.7 g, 1.44 mmol) and the resulting reaction mixture was stirred at 0 °C to room temperature for 2 h. The reaction mixture was quenched by adding saturated NH_4Cl (5 mL). The reaction mixture was filtered through Celite and washed with ethyl acetate, which was purified by column chromatography (80% EtOAc/*n*-hexane) to give **5b** (0.42 g, 67%) as a thick liquid. Found: C, 67.5; H, 7.30. $C_{25}H_{33}NO_6$ requires C, 67.70; H, 7.50; R_f (100% EtOAc) 0.2; $[\alpha]_D^{25}$ −51.84 (*c* 0.05,$CHCl_3$); IR (neat) 3400–3600 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, s, CH_3),1.38(3H, s, CH_3), 1.94 (2H, s), 2.03 (2H, br s, exchangeable with D_2O), 3.11 (2H, s), 3.80–3.95 (3H, m), 3.98 (1H, dd, *J*=8.7, 2.7 Hz, *H*-4), 4.06 (1H, d, *J*=2.7 Hz, *H*-3), 4.15 (1H, dd, *J*=8.7, 3.9 Hz, *H*-5), 4.52 (1H, d, *J*=3.6 Hz, *H*-2), 4.63 (2H, s, OCH_2Ph), 5.20–5.60 (1H, br s, exchangeable with D_2O), 5.82 (1H, d, *J*=3.6 Hz, *H*-1), 7.31 (10H, s, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.9, 40.4, 47.4,

52.5, 64.1, 69.9, 72.5, 80.6, 81.5, 82.1, 104.9, 111.6, 127.7, 127.8, 128.4 (s), 128.8 (s), 128.9 (s), 133.3, 137.3.

4.8. Azocane-7-(hydroxymethyl)-(3*R*,4*S*,5*R*,6*S*,7*S*)-2,3,4,5,6-pentanol (1c)

A solution of **5a** (0.2 g, 0.35 mmol) in TFA/H_2O (3 mL, 2:1) was stirred at 25 °C for 2 h and trifluoroacetic acid was co-evaporated with benzene to furnish a thick liquid. To a solution of above product in methanolic hydrochloric acid (5 mL, 9:1) was added 10% Pd/C (0.1 g). The solution was hydrogenated at 80 psi for 12 h. The catalyst was filtered through Celite and washed with methanol. The filtrate was concentrated and purified by column chromatography (70% MeOH/$CHCl_3$) to give **1c** (0.08 g, 88%) as a semisolid. Found: C, 37.50; H, 7.30. $C_8H_{18}ClNO_6$ requires C, 37.00; H, 6.99; R_f (50% $CHCl_3$/MeOH) 0.25; $[\alpha]_D^{25}$ +46.8 (*c* 0.17, MeOH); IR (neat) 3200–3600 (br) cm^{-1}; ^1H NMR (300 MHz, D_2O) for major isomer δ 1.50–1.80 (1H, m), 3.20–3.37 (2H, m), 3.38–3.52 (2H, m), 3.61–3.88 (2H, m), 4.15–4.24 (1H, m), 4.26–4.43 (1H, m), 4.85 (1H, br s); ^{13}C NMR (100 MHz, D_2O) for major isomer δ 39.3, 40.8, 55.5, 69.2, 74.8, 76.4, 79.6, 101.7.

4.9. Azocane-7-(hydroxymethyl)-(3*R*,4*S*,5*R*,6*R*,7*R*)-2,3,4,5,6-pentanol (1d)

Reaction of **5b** (0.2 g, 0.45 mmol) with TFA/H_2O (3 mL, 2:1), 10% Pd/C (0.1 g) and column purification (70% MeOH/$CHCl_3$) gave **1d** (0.11 g, 84%) as a semisolid. Found: C, 37.25; H, 7.23. $C_8H_{18}ClNO_6$ requires C, 37.00; H, 6.99; R_f (MeOH/$CHCl_3$) 0.25; $[\alpha]_D^{25}$ +23.9 (*c* 0.021, MeOH); IR (neat) 3200–3600 (br) cm^{-1}; ^1H NMR (300 MHz, D_2O) for major isomer δ 2.30–2.42 (1H, m), 3.12–3.35 (2H, m), 3.39–3.42 (2H, m), 3.43–3.62 (1H, m), 3.65 (1H, br d, J=9.6 Hz), 3.77–3.88 (2H, m), 4.58 (1H, d, J=7.8 Hz); ^{13}C NMR (75 MHz, D_2O) for the major isomers δ 37.8, 38.1, 61.6, 70.5, 74.2, 74.5, 75.9, 96.4.

Acknowledgements

We are thankful to the UGC, New Delhi, for Senior Research Fellowship to V.H.J. and University of Pune, Pune for the financial support under BCUD Seed Money project (2009).

References and notes

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9. In case of the Baylis–Hillman adducts, obtained from 3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose, the compound with large coupling constant ($J_{4,5}$=8.9 Hz) was assigned the L-*ido*-configuration and the product having small coupling constant ($J_{4,5}$=5.9 Hz) was assigned the D-*gluco*-configuration see: (a) Radha Krishna, P.; Kannan, V.; Sharma, G. V. M.; Ramana Rao, M. H. V. *Synlett* **2003**, 888; (b) Radha Krishna, P.; Manjuvani, A.; Kannan, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2691 An opposite trend was noticed in case of **3a** and **3b**. However, we have unambiguously assigned the configurations at C5 and C6 by single crystal X-ray data of subsequent Michael addition product. In case of the Baylis–Hillman adduct **3a** with L-*ido* configuration, we observed small coupling constant $J_{4,5}$=3.0 Hz, while large coupling constant $J_{4,5}$=7.5 Hz was observed for the D-*gluco* configurated product.
10. The minor isomer was all the time contaminated with the major compound.
11. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition no. CCDC-761145 (**4a**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk].
12. We have extrapolated the ^1H NMR analogy of six-membered chair conformation system wherein; equatorial proton is deshielded as compared to the axial proton and the axial–axial proton coupling is larger than the axial–equatorial or equatorial–equatorial. Jackman, L. M.; Sternehell, S. *Application of nuclear magnetic resonance spectroscopy in organic chemistry*; International Series in Organic Chemistry, 2nd ed.; University of California: Pergamon, 1969; Vol. 10, pp 238–248 and 280–300.