Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 111–113

TETRAHEDRON: *ASYMMETRY*

Synthesis of 6-deoxy-homoDMDP and its C(5)-epimer: absolute stereochemistry of natural products from *Hyacinthus orientalis*

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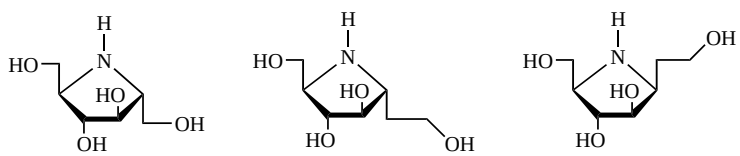
Received 21 December 2001; accepted 15 February 2002

Abstract—A concise enantioselective synthesis of 2,5-imino-2,5,6-trideoxy-D-*manno*-heptitol (6-deoxy-homoDMDP) and 2,5-imino-2,5,6-trideoxy-L-*gulo*-heptitol has been achieved. These compounds were used as stereochemical references to establish the absolute configuration of the corresponding naturally occurring stereoisomers, recently isolated from *Hyacinthus orientalis*.

1. Introduction

Iminosugars have gained increasing importance in the emerging field of glycosidase and glycosyltransferase inhibition. The ability of these alkaloids to interfere with the degradation or the formation of oligosaccharides is generally attributed to their potency in mimicking the putative cation-like transition state involved in both enzymatic reactions.[1] A number of natural and synthetic compounds in the pyrrolidine subgroup display interesting bioactivity.[2] Among these DMDP **1** originally isolated from *Derris elliptica*[3] was shown to be a potent inhibitor of a large range of α- and β-glucosidases[4] whilst DMDP exhibits interesting antiviral, anti-feedant and nematicidal activity.[5] The defined absolute configuration of natural DMDP (2*R*,3*R*,4*R*,5*R*)-2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine has been assigned a few years after the isolation of this metabolite from different sources (plants and micro-organisms) by enantiospecific synthesis and was found to be the opposite to the previously proposed one.[6] Recently, two new structurally related natural products, (+)-2,5-imino-2,5,6-trideoxy-*manno*-heptitol (6-deoxy-homoDMDP **2** or its enantiomer) and (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol **3** (or its enantiomer) have been isolated from *Hyacinthus orientalis* and were found to display interesting specific glycosidase inhibitory properties.[7] The relative configurations of these compounds were established by NMR studies but to date, no syntheses of these iminosugars have been performed to confirm their absolute configurations (Fig. 1).

In our aim dealing with research of new chitin synthetase inhibitors (*N*-acetylglucosaminyl transferase, EC 2.4.1.16), we planned to use 6-deoxy-homoDMDP **2** and its C(5)-epimer **3** as building blocks in molecular structures of new models of transition-state and bisub-



DMDP, **1** 6-deoxyhomoDMDP, **2** **3**

Figure 1. Structure of compounds **1**–**3**.

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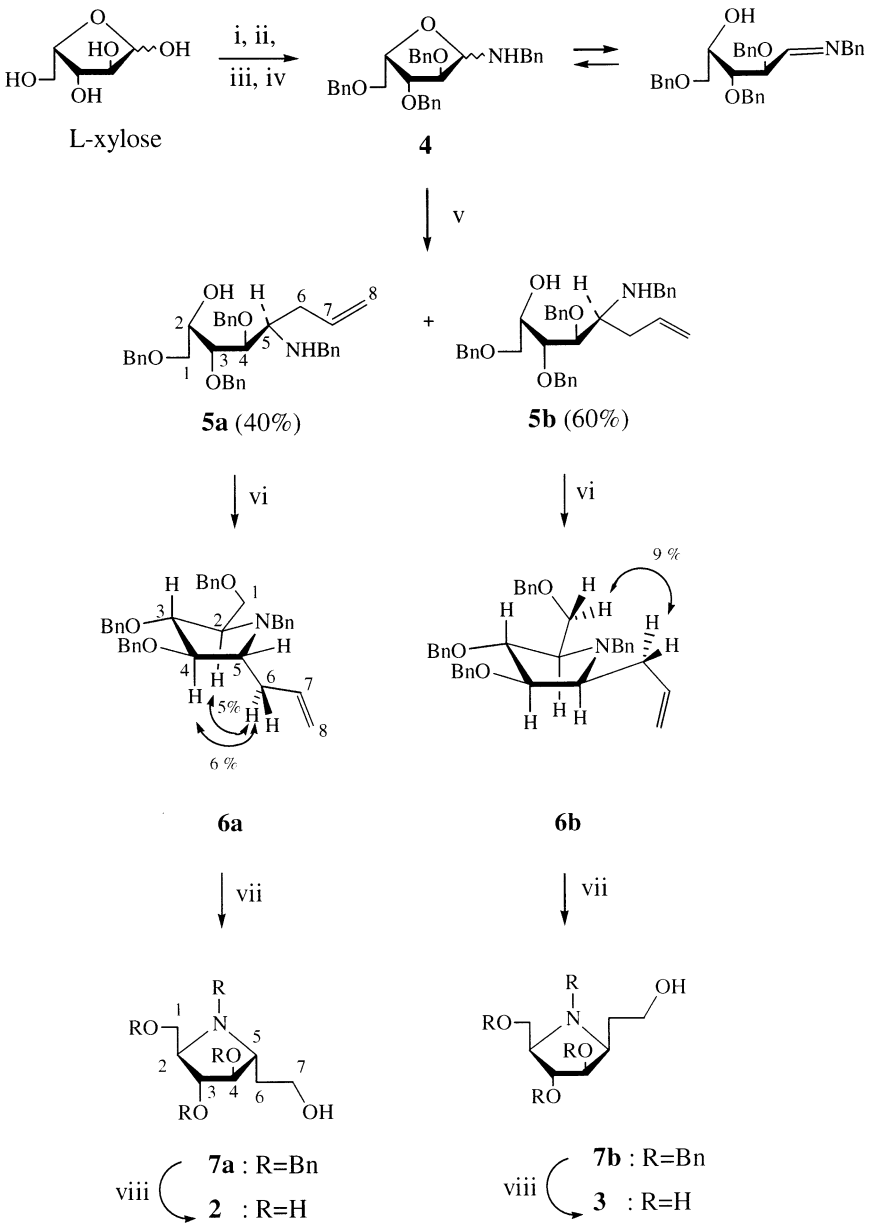
0957-4166/02/$ - see front matter
PII: S0957-4166(02)00081-2

strate analogue inhibitors of this enzyme.[8] We wish to report herein the synthesis of both iminosugars **2** and **3**, which could permit a definitive assignment of the absolute configurations of the natural occurring 6-deoxy-homoDMDP **2** and its diastereoisomer **3** recently isolated by Asano et al.[7]

2. Synthesis

Many synthetic approaches have been described for the preparation of iminosugars, including chemical and enzymatic methods.[9] Among these, the procedure initially described by Nicotra involving amination of the anomeric carbon followed by treatment with a Grignard reagent and subsequent cyclisation is an easy process which has widely been used for the preparation of functionalised pyrrolidines.[10] Compounds **2** and **3** were prepared by this process starting from L-xylose, as depicted in Scheme 1.

Anomerisation of L-xylose with methanol/HCl gave a mixture of both methyl glycosides which were benzylated using classical procedures.[11] After deprotection of the acetal (1 M HCl in dioxane), the resulting protected L-xylofuranose was treated with an excess of benzylamine to give the corresponding glycosylamine **4** in quantitative yield. Addition of allylmagnesium chloride



Scheme 1. *Reagents and conditions*: (i) MeOH/HCl, 100%; (ii) BnBr, $Ba(OH)_2$, DMF, 40%; (iii) aq. HCl, reflux. Dioxane, 50%; (iv) $BnNH_2$, CH_2Cl_2, 4 Å MS, 98%; (v) allylmagnesium choride, THF, 0°C; 91%; (vi) MsCl, Py (**6a**, 79%; **6b**, 97%); (vii) H_2SO_4, O_3; then $NaBH_4$, MeOH, 74%; (viii) 10% Pd–C, $HCOONH_4$, MeOH, 60°C, 40%.

to imine **4** at 0°C afforded a mixture (40:60) of the two possible diastereoisomers **5a** and **5b** in good yield (91%).

Isomers **5a** and **5b** can be easily separated at this stage by chromatography on silica gel eluting with diethyl ether/petroleum ether (v/v, 1/1). The configuration of the newly created C(5) stereogenic centre in **5a** $[\alpha]_D^{20} = +9.9$ ($c = 1.56$, $CHCl_3$) and **5b** $[\alpha]_D^{20} = -3.7$ ($c = 0.86$, $CHCl_3$) was unambiguously assigned after their conversion to the respective pyrrolidines **6a** and **6b** (Scheme 1). This was easily achieved in one step by treating amino alcohols **5a** and **5b** with methanesulfonyl chloride. The corresponding mesylates formed, which were not isolated, underwent intramolecular cyclisation with the secondary amine with concomitant inversion at C(2) to give pyrrolidines **6a** and **6b**. Oxidation of the double bond by ozonolysis was performed on the sulphate salts of **6a** and **6b** to avoid oxidation of the amine function, and led to the corresponding aldehydes, which were somewhat unstable and could not be further purified. Subsequently, reduction with sodium borohydride gave alcohols **7a** and **7b** in 74% yield from **6a** and **6b**, respectively. Final deprotection was best achieved by transfer-catalysed hydrogenation (ammonium formate, 10% Pd–C in refluxing MeOH), to give after purification by preparative HPLC, compound **2** $[\alpha]_D^{20} = +46.0$ (*c* 1.15; H_2O), and its C(5)-epimer **3** $[\alpha]_D^{20} = +37.9$ (*c* 1.8; H_2O).[†] The compounds thus obtained were analytically pure as checked by LCMS (ESI).

3. Structural analysis

In both of the synthesised pyrrolidines **2** and **3**, the absolute configuration at C(2), C(3) and C(4) derived from the utilisation of L-xylose as a chiral precursor of the target molecules. Configurations at C(3) or C(4) were unchanged during the synthetic process, whereas the stereochemistry at C(2), which resulted from a stereocontrolled cyclisation process, is the opposite to that in the starting material. Examination of nuclear Overhauser effects carried out on **6a** and **6b** allowed the assignment of the configuration at the newly formed asymmetric carbon C(5). Thus for **6a**, the enhancement observed on H(2) and H(4) signals after irradiation of the allylic protons proved that the orientation of these atoms is directed to the same side of the pyrrolidine ring plane. Irradiation of allylic protons in pyrrolidine **6b** gave a substantial NOE on C(1) protons, showing the *cis* relationship between both substituents (Scheme 1).

The enantiopure 2,5-imino-2,5,6-trideoxy-D-*manno*-heptitol (6-deoxy-homoDMDP) **2** and 2,5-imino-2,5,6-trideoxy-L-*gulo*-heptitol **3** synthesised in this study share identical spectral data (^1H and ^{13}C NMR) with the corresponding natural occurring compounds. Their dextrorotatory optical properties unambiguously establish the absolute configuration of (+)-**2**[7] $[\alpha]_D = +98.5$ (*c* 1.13; H_2O) and (+)-**3**[7] $[\alpha]_D = +41.4$ (*c* 0.56; H_2O).

In summary, a concise enantioselective synthesis of optically pure polyhydroxypyrrolidines **2** and **3** has been achieved starting from L-xylose as chiral precursor, thereby establishing for the first time the absolute configuration of two new iminosugars isolated from *Hyacinthus orientalis*.[7] A significant difference in the specific rotation value between the synthetic and naturally occurring 6-deoxy-homoDMDP **2** has to be noted.

Acknowledgements

The authors would like to thank Dr. Geoff Bird and Dr. Jean-Claude Arnould for their contribution to some aspects of this project.

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[†] **Compound 2**: $[\alpha]_D = +46.0$ ($c = 1.15$; H_2O). ^1H NMR (D_2O–TSP, 500 MHz): δ 3.85 (t, 1H, $J = 7.2$, 3-H), 3.76 (dd, 1H, $J = 7.2$, 7.6, 4-H), 3.72 (dd, 1H, $J = 4.2$, 12.0, 1a-H), 3.66 (dd, 1H, $J = 6.1$, 12.0, 1b-H), 3.68–3.62 (m, 2H, H-7a,b), 3.17 (ddd, 1H, $J = 4.2$, 6.1, 7.2, 2-H), 3.13 (ddd, 1H, $J = 5.6$, 7.6, 8.3, 5-H), 1.93 (dddd, 1H, $J = 5.6$, 6.7, 8.3, 13.7, 6_a-H), 1.75 (ddt, 1H, $J = 2\times6.2$, 8.3, 13.7, 6_b-H). ^{13}C NMR (D_2O–TSP, 125 MHz): δ 84.0 (4-C); 80.2 (3-C); 64.7 (1-C); 64.1 (2-C); 61.8 (7-C); 60.0 (5-C); 38.0 (6-C). MS (ESI) m/z 178 $(MH)^+$ (100). Compound **3**: $[\alpha]_D = +37.9$ ($c = 1.8$; H_2O). ^1H NMR (D_2O–TSP, 500 MHz): δ 4.05 (dd, 1H, $J = 1.8$, 3.2, 4-H), 3.92 (dd, 1H, $J = 1.8$, 2.8, 3-H), 3.78 (dd, 1H, $J = 5.1$, 11.9, 1a-H), 3.72 (dd, 1H, $J = 7.6$, 11.9, 1b-H), 3.71 (t, 2H, $J = 6.3$, 7a,b-H), 3.50 (dt, 1H, $J = 3.2$, 2×7.2, 5-H), 3.25 (ddd, 1H, $J = 2.8$, 5.1, 7.6, 2-H), 1.90 (ddt, 1H, $J = 2\times6.3$, 7.2, 14.9, 6a-H), 1.72 (ddt, 1H, $J = 2\times6.3$, 7.2, 14.9, 6b-H). ^{13}C NMR (D_2O–TSP, 125 MHz): δ 81.6 (3-C); 80.4 (4-C); 68.7 (2-C); 64.2 (1-C); 61.8 (5-C); 60.7 (7-C); 32.6 (6-C).