Pergamon

Tetrahedron Letters, Vol. 35, No. 47, pp. 8791-8794, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01952-5

Chemo-Enzymatic Synthesis of Precursors of Fagomine and 1,4-Dideoxy-1,4-imino-D-Arabinitol

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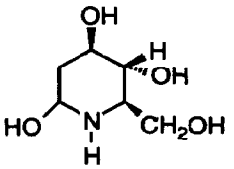
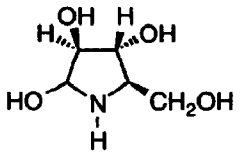
Abstract: The enantioselectivity of transketolase towards, α-hydroxy-aldehydes is used to prepare compounds bearing two asymmetric centres, precursors of natural products: 2,3-dideoxynojirimycine (fagomine), 1,4-dideoxy-1,4-imino-D-arabinitol, and its oxidised form.

Polyhydroxylated piperidines and pyrolidines have attracted attention in recent years[1], due to their antiviral[2] and antitumoral activities [3], ascribed to their ability to act as glycosidase inhibitors[4]. Fagomine, **1a** (2,3-dideoxynojirimycine) was isolated in seeds of Japanese buckweat[5] and, in a glyco-conjugated form, in seeds of the legume genus *Xanthocercis baill.*[6] This compound, in contrast with 2-deoxynojirimycine, is a poor glycosidase inhibitor.[6] No study has been reported on its hydroxylated form, 3-deoxy-nojirimycine**1b**. 1,4-dideoxy-1,4-imino-D-arabinitol, **2** is also a naturally-occurring product, isolated from *Angylocalyx boutiqueanus* and *Arachniodes standishii*[7], as is its oxidised form, **3**, a fungal metabolite isolated from *Nectria.*[8] Both are potent glycosidase inhibitors. [9]



1



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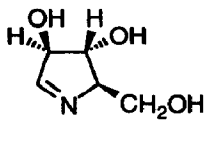
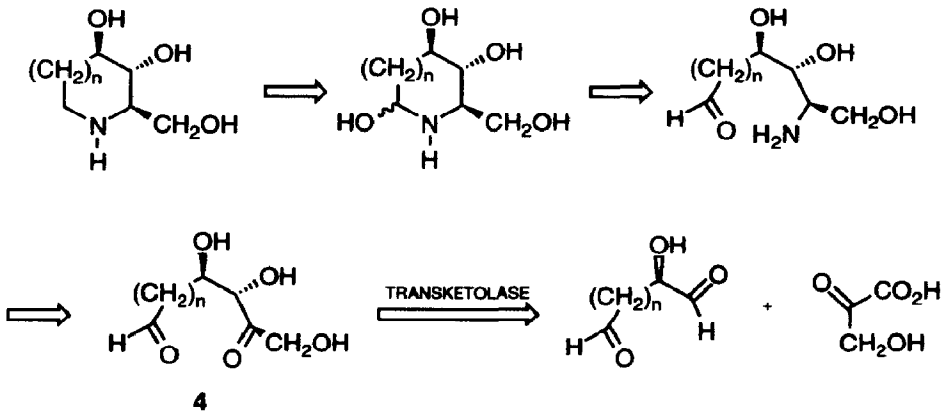


3

Various syntheses of **1**[10], **2**[11] and **3**[12] have been published, most starting from sugars as chiral precursors. Chemo-enzymatic syntheses using aldolase or transketolase to generate the chirality were also studied, the key step being an addition reaction on an aldehyde bearing an azido or protected amino group as the precursor of the nitrogen atom in the cycle.[13] We present here a novel approach based on the retrosynthetic route presented in scheme 1.

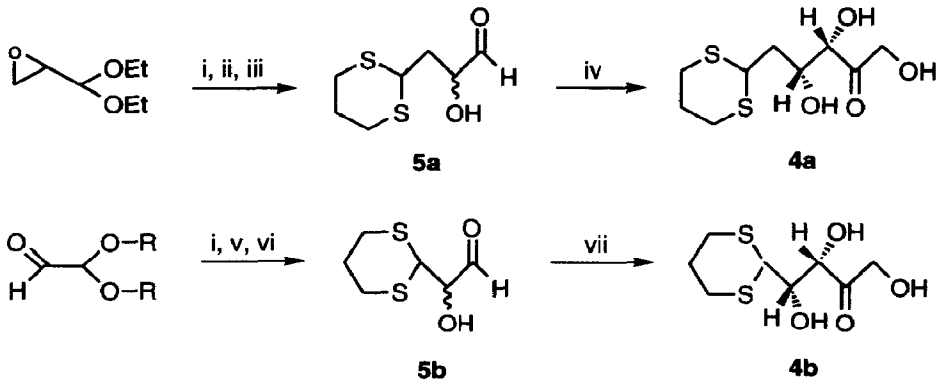


4

Scheme 1

Keto-aldehydes such as **4** are intermediates in various syntheses of azasugars.[14] They may also be involved in the biosynthetic pathway of **1** and **2** since 6-deoxy-6-oxo-D-fructose is an intermediate in the biosynthesis of mannojirimycine.[15]

We describe here the transketolase-catalysed synthesis of **4a** (n=1) and **4b** (n=0) in a protected form (scheme 2). Transketolase, a transferase involved in sugar metabolism catalyses the irreversible transfer of a hydroxyacetyl group from a ketose to an aldose. When the hydroxyacetyl group comes from hydroxypyruvate, the reaction becomes irreversible and therefore very useful for synthetic purposes: various aldehydes, especially α-hydroxy-aldehydes, can serve as substrates, the enzyme being in this latter case enantioselective, leading to ketose analogs with 3S,4R configuration.[16]



Scheme 2: Chemo-enzymatic synthesis of ketose analogs.

Reagents and conditions: i, BuLi, THF, -78°C -> -25°C, 2 hours; ii, epoxyde, -50°C -> -35°C, 3 hours -> r.t.; iii, HCl-KCl buffer pH 1 / ethanol 70/30, 60°C, 12 hours; iv, hydroxypyruvate, transketolase, TRIS buffer, pH 7.5; v, aldehyde ($(BuO)_2CHCHO$), -70°C 2hours -> -50°C 1 hour -> r.t.; vi, HCl-KCl buffer, pH 1/ ethanol, 80/20, 70°C, 12 hours.

5a is easily obtained by reaction of the dithiane anion on glycidaldehyde diethylacetal followed by acid hydrolysis. No attempt was made to isolate **5a**; the solution was neutralised and directly used for the enzymatic step. This reaction was carried out in 50 mL of TRIS buffer (25 mM, pH 7) containing the aldehyde (40 mM), hydroxypyruvate (40 mM), $MgCl_2$ (14 mM), thiamine pyrophosphate (2 mM) and spinach transketolase (100 units).[17] The reaction was monitored by enzymatic titration of hydroxypyruvate[18]. When its concentration was stable, 150 mL of ethanol was added to precipitate proteins, the solution was concentrated under vacuum, and the residue purified by chromatography leading to **4a** with a 12% yield. The structure of **4a** was unequivocally assigned by ^1H and ^{13}C NMR.[19]

Aldehyde **5b** was synthesised by addition of dithiane anion on the monoacetal of glyoxal[20] followed by acid hydrolysis. Once again, the aldehyde was not isolated; the solution was used as above for the enzymatic reaction. **4b** was isolated with a 10% yield and characterised by ^1H and ^{13}C NMR spectroscopy[21].

4a and **4b** were obtained with modest yields, but the synthesis was not optimised and further work is in progress to improve these syntheses. Nevertheless, the method is attractive: precursors **5a** and **5b** are easily prepared from inexpensive racemic material in an optical pure form since transketolase is enantioselective towards α-hydroxy-aldehydes, and leads to compounds bearing two asymmetric centres. Deprotection of **4a** and **4b**, followed by reductive amination by published procedures[14] to give **1, 2** and **3** is under investigation. This approach will provide a new route to polyhydroxylated chiral pyrolidines and piperidines.

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19. Selected spectral data for **4a** : $[\alpha]_J^{25}$ +9 (c 0,017, $CHCl_3$), ^1H NMR (400 MHz, $CDCL_3$) δ 1.90 (1H, m, H5 or H8); 2.02 (2H, m, H5 or H8); 2.12 (1H, m, H5 or H8); 2.88 (4H, m, H7 or H9); 3.2-4.00 (3H, m, H1 and H3 and H4); 4.22 (1H, m, H4); 4.25 (1H, m, H3); 4,31 (1H,m,H7); 4.46 1H, H1, *J* 19.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8 (C8), 29.7 (C7 or C9), 29.9 (C7 or C9), 38.8 (C5), 66.6 (C1), 69.3 (C4), 77.7 (C3), 210.8 (C2).
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21. Selected spectral data for **4b** : $[\alpha]_J^{25}$ +22 (c 0,0058, $CHCl_3$), ^1H NMR (400 MHz, $CDCL_3$) δ 2.07 (2H, m, H7); 2.20 (2H, m, H7); 2.68 (2H, m, H6 or H8); 3.00 (2H, m, H6 or H8); 3.25-4.20 (3H, m, H1 and H3 and H4); 4.36 (3H, m, H3, H4 and H5); 4.5 (1H, d, H1, *J* 20 Hz); 4,66 (1H, d,H1, *J* 20 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6 (C7), 29.7 (C6 or C8), 30.9 (C6 or C8), 45.0(C5), 66.9 (C1), 70.6 (C4), 74.9 (C3), 207.0 (C2).

(*Received in France* 4 *August* 1994; *accepted* 28 *September* 1994)