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Chemoenzymatic Synthesis of Homoazasugars

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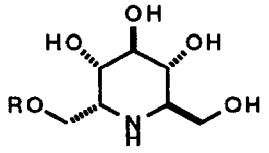
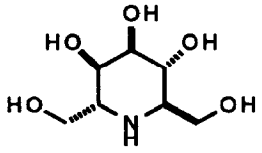
Abstract: A chemoenzymatic approach for the synthesis of homoazasugars is described, utilizing an aldolase to catalyze the key asymmetric aldol addition reaction. This approach is illustrated by the synthesis of β-D-homomannonojirimycin **(11)** using D-fructose diphosphate (FDP) aldolase.

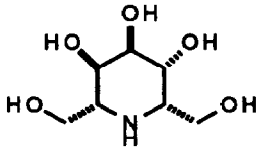
Currently there is significant interest in the synthesis and study of azasugars and their analogues. These compounds act as competitive inhibitors of glycosidases and glycosyltransferases by mimicking the putative oxonium ion intermediate formed during the processing of carbohydrates by these enzymes. As such, they have potential in a number of therepeutic areas, including cancer, diabetes and AIDS.[1,2] One class of azasugar that has yet to be investigated extensively is the homoazasugar or iminoheptitol. Homoazasugars are structurally very similar to other azasugars, but contain an extra hydroxymethylene at C-1. It has been proposed that this additional anomeric substituent, either alone or as a tether attaching another moiety, may enhance potency and/or specificity of inhibition.[1] The small number of these compounds which have been isolated or synthesized exhibit interesting biological activity; the naturally occurring α-homonojirimycin is a potent α-glucosidase inhibitor,[3] α-homomannonojirimycin (HMJ) is a relatively selective inhibitor of α-mannosidases,[4] and 6-*epi*-HMJ and β-L-homofuconojirimycin are good inhibitors of α-fucosidase.[4,5] The β-glucopyranosyl derivative of α-homonojirimycin (HDL) has been a drug candidate for antidiabetic therapy.[6] A chemoenzymatic strategy for the synthesis of β-D-homomannonojirimycin **(11)** is decribed here, based upon a D-fructose diphosphate (FDP) aldolase-catalyzed aldol addition reaction.



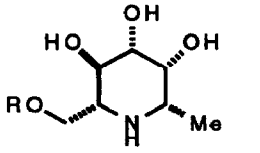
R = H, α-D-homonojirimycin
R = β-glucopyranosyl, MDL



HMJ



6-*epi*-HMJ

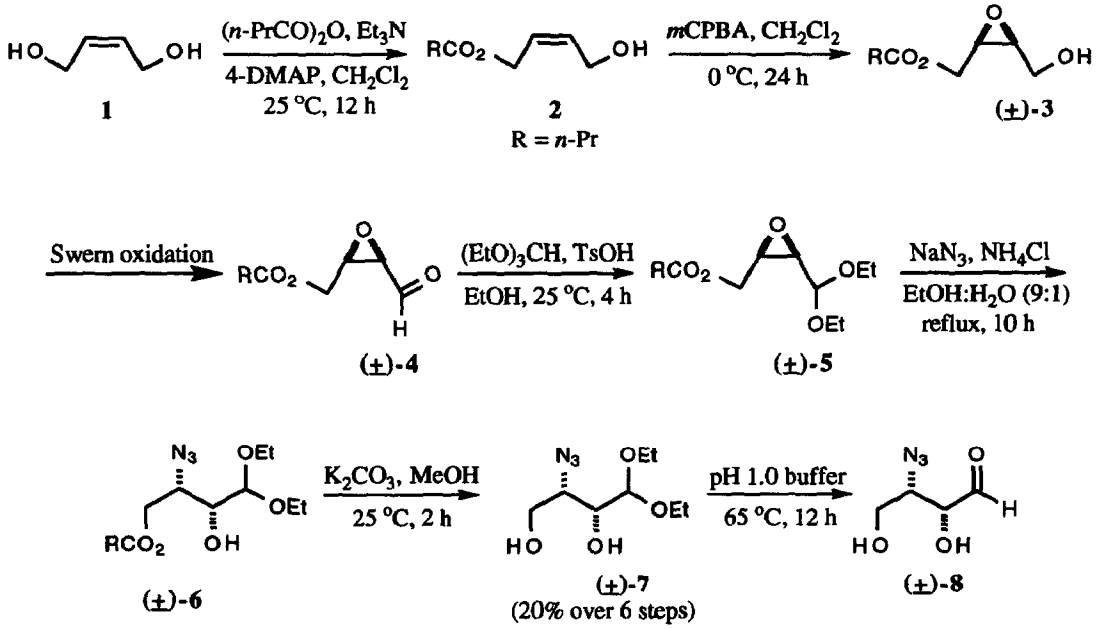


β-L-homofuconojirimycin

Racemic azidoaldehyde **8** required for the asymmetric aldol reaction was easily synthesized from cheap and readily avilable (*Z*)-2-butene-1,4-diol **(1)** (Scheme 1). Monoacylation of **1** using butyric anhydride to **2**, then epoxidation with *m*CPBA furnished epoxide alcohol **3**. Swern oxidation of **3** gave aldehyde **4**, which was immediately protected as diethyl acetal **5**. Regioselective opening of the epoxide in

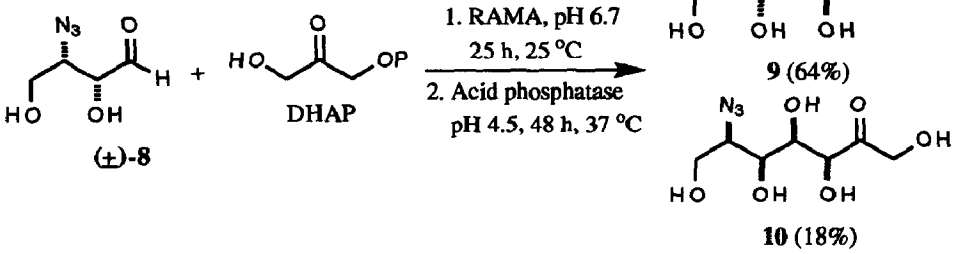
5 at C-3 using sodium azide gave **6**,[7] then subsequent ester removal produced **7**.[8] Acid-catalyzed acetal hydrolysis of **7** to produce racemic *syn* aldehyde **8** was performed immediately prior to the aldol reaction.

Scheme 1

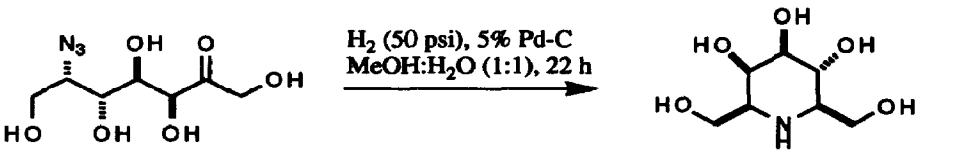


FDP aldolase-catalyzed aldol addition reaction of racemic **8** with dihydroxyacetone phosphate (DHAP) gave the two diastereomeric azidosugars **9** and **10** in a 3.5:1 ratio (Scheme 2).[9] Thus, both enantiomers of **8** are substrates for the enzyme, even though there is a partial resolution. After separation of the diastereomers by flash chromatography (10-25% MeOH in $CHCl_3$), the major isomer **9** was subjected to one pot reduction of the azide group and intramolecular reductive amination to give β-D-homomannonojirimycin (**11**).[10] As expected, the reductive amination was very stereoselective, and only one diastereomer was produced. (Scheme 3)

Scheme 2



Scheme 3



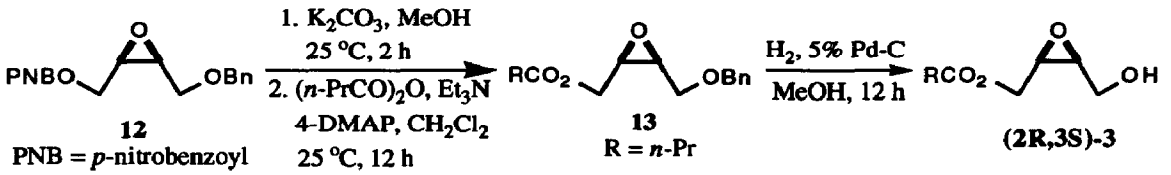
9

β-D-homomannonojirimycin (11)
(94%)

The route to **11** implies that aldol additions of racemic **8** with DHAP, catalyzed by other aldolases could be used to produce alternative stereoisomers of this homoazasugar.[11] However, since analysis and chromatographic separation of the probable diasteromeric aldol products may be difficult, a synthesis starting with enantiomerically pure **8** is thus necessary.

The synthesis of **(2R-3S)-8** was achieved using the commercially available epoxide **(2*R*,3*S*)-12** (Scheme 4). Hydrolysis of the *p*-nitrobenzoyl ester in **12**, followed by re-esterification with butyric anhydride furnished **13**, and final removal of the benzyl group gave **(2R,3S)-3**. Using the same procedure described for racemic **8**, **(2R,3S)-3** was then transformed into **(2R,3S)-8** and **9**. Similarly, compound **10** can be prepared from the commercially available **(2S,3R)-12**.

Scheme 4



12
PNB = *p*-nitrobenzoyl

13
R = *n*-Pr

(2R,3S)-3

In summary, the synthesis of β-D-homomannonojirimycin (**11**) has successfully demonstrated the viability of this chemoenzymatic approach for the formation of stereoisomers of the parent homoazasugar. By using both enantiomers of **8**, and the corresponding diastereomeric *anti* aldehydes,[12] as substrates for other DHAP-utilizing aldolases, it should be possible to access more of the remaining thirty-one stereoisomers.[13] Similarly, alternative four carbon azidoaldehydes could be used to synthesize homoazasugar analogs by the same route. These and related studies are currently in progress.

References and Notes

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7. Compound **6** was shown to be the desired regioisomer by derivatization to the monoacetate and subsequent ^{1}H NMR decoupling experiment.

8. 3-azido-2,4-dihydroxybutanal diethyl acetal (7): oil, R_f 0.5 (60% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 4.56 (d, J = 6.5 Hz, 1H), 3.90-3.96 (m, 2H), 3.77-3.83 (m, 2H), 3.69-3.73 (m, 1H), 3.59-3.65 (m, 3H), 2.45 (d, J = 3.5 Hz, 1H), 2.26 (dd, J = 5.1 & 7.1 Hz, 1H), 1.25 (t, J = 7.3 Hz, 3H), 1.23 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 102.8 (CH/ CH_3), 71.7 (CH/ CH_3), 64.4 (CH_2), 63.7 (CH_2), 62.8 (CH_2), 62.6 (CH/ CH_3), 15.3 (CH/ CH_3), 15.2 (CH/ CH_3); IR (neat) 3420 (br st), 2110 (st) cm^{-1}; MS (LSIMS+) *m/z* (rel. intensity) 242 (100, M+Na+); HRMS calcd for $C_8H_{17}N_3O_4$+Na 242.1117, found 242.1117.

9. The conditions for the aldol reaction and reductive amination are essentially the same as those described previously, Liu, K.C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.*; **1991**, *56*, 6280. **9** (major product) R_f 0.24 (7:3:0.5 $CHCl_3$:MeOH:H_2O); ^{13}C NMR (D_2O) δ 102.5 (C), 80.0 (CH/ CH_3), 76.0 (CH/ CH_3), 75.7 (CH/CH_3), 65.4 (CH/ CH_3), 63.2 (CH_2), 61.7 (CH_2); MS (LSIMS$^+$) *m/z* (rel. intensity) 258 (50, M+Na$^+$), 198 (100); HRMS calcd for $C_7H_{13}N_3O_6$+Na 258.0702, found 258.0724. **10** (minor product) R_f 0.30 (7:3:0.5 $CHCl_3$:MeOH:H_2O); ^{13}C NMR (D_2O) δ 102.8 (C), 77.4 (CH/ CH_3), 77.0 (CH/ CH_3), 75.9 (CH/ CH_3), 64.3 (CH_2), 63.4 (CH/ CH_3), 62.2 (CH_2); MS (LSIMS+) *m/z* (rel. intensity) 258 (50, M+Na$^+$), 198 (100); HRMS calcd for $C_7H_{13}N_3O_6$+Na 258.0702, found 258.0724.

10. Compound **11** (O-acetate) 1H NMR (CDCl3) δ 5.40 (dd, J = 1.5 Hz, 1 H, H-5), 5.13 (t, J=10 Hz, 1 H, H-3), 4.96 (dd, J = 3.5, 10.5 Hz, 1 H, H-4), 4.10 (dd, J = 11.5, 54 Hz, 1 H, H-1); 4.09 (dd, J=11.5, 52 Hz, 1 H, H-1'), 4.01 (d, J = 6 Hz, 2 H, H-7,H-7'), 3.20 (dt, J = 1, 6.5 Hz, 1 H, H-6), 2.96 (ddd, J=2.5, 5, 10 Hz, 1 H, H-4); ^{13}C NMR (D_2O) of **11** (free OH) δ 75.1 (CH/ CH_3), 69.4 (CH/ CH_3), 68.6 (CH/ CH_3), 61.7 (CH_2), 61.1 (CH_2), 60.6 (CH/ CH_3), 58.6 (CH/ CH_3); MS (LSIMS+) *m/z* (rel. intensity) 194 (100, M+H$^+$); HRMS calcd for $C_7H_{15}NO_5$+H 194.1028, found 194.1020.

11. Small hydroxylated aldehydes such as 8 are often good substrates for aldolases.

12. Optically pure ***anti*-8** is available via a Sharpless epoxidation on monoprotected (E)-2-butene-1,4-diol followed by a synthetic route similar to that described for ***syn*-8**.

13. This work was supported by the NIH (GM44154)

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