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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 609–612

Synthesis of analogues of naturally occurring 3-*O*-(β-D-glucopyranosyl)-fagomine

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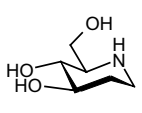
Received 24 October 2006; revised 6 November 2006; accepted 17 November 2006
Available online 12 December 2006

Abstract—Stereoselective synthesis of 3-α-*C*-glucosides of D- and L-fagomine from the corresponding *C*-disaccharides is reported. The ethyl glycoside of perbenzylated *C*-disaccharide **8** was converted via the corresponding thioglycoside **10** and reducing *C*-disaccharide **11**, into substituted alditol **12** which, upon oxidation and double reductive amination stereoselectively afforded pure perbenzylated D-fagomine *C*-glucoside **14**. In the same manner, the ethyl glycoside of perbenzylated *C*-disaccharide **9** was stereoselectively converted into perbenzylated L-fagomine *C*-glucoside **15**.

Many polyhydroxylated piperidines mimic the structure and spatial arrangement of pyranoses very well, differing only in the presence of a nitrogen atom instead of the ring oxygen atom. Therefore these compounds, together with other hydroxylated nitrogen heterocycles, are part of a greater family of compounds denoted as iminosugars. Some iminosugars occur naturally and have significant biological effects.[1] Replacement of the pyranose oxygen by nitrogen means that iminosugars are capable of strong interactions with the active site of glycosidases, acting as their inhibitors. Glycosidases participate in many biologically important processes such as intestinal digestion, post-translational processing of glycoproteins or lysosomal catabolism of glycoconjugates. As compounds influencing these processes by direct or indirect inhibition of glycosidases, iminosugars represent considerable therapeutic potential: they may exhibit antiviral, cancerostatic or antidiabetic effects. Methods of preparation of iminosugars, their natural occurrence and possibilities for therapeutic utilization are the subject of a recent special issue of Current Topics in Medicinal Chemistry.[2] Iminosugars have been comprehensively reviewed several times and pertinent data on hydroxylated piperidines can be found in the recent review and references cited therein.[3]



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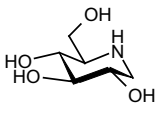

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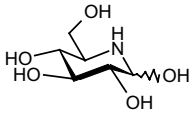

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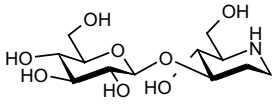

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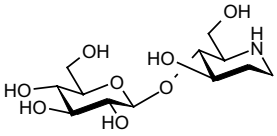

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Keywords: Iminosugars; *C*-Glycosides; Stereoselective synthesis; Reductive amination.
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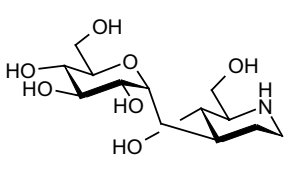
doi:10.1016/j.tetlet.2006.11.116

Fagomine **1**, which can be regarded as either a deoxy derivative of 1-deoxynojirimycin **2** or a dideoxy derivative of nojirimycin **3**, was isolated from the seeds of the Japanese buckwheat *Fagopyrum esculentum* Moench[4] and also from the seeds of *Castanospermum australe* (Leguminosae).[5] Together with 6-deoxyfagomine and the group of tropane alkaloids, it was derived from the Chinese crude drug 'Ti-koppi', the root of *Lycium chinenese* (Solanaceae).[6] It has been found[7] that the leaves and roots of the legume *Xanthocersis zambesiaca* contain not only fagomine **1** and its stereoisomers 3-*epi*-fagomine and 3,4-di-*epi*-fagomine but also glucosides of fagomine, that is, 3-*O*-(β-D-glucopyranosyl)-fagomine **4**, together with a small amount of 4-*O*-(β-D-glucopyranosyl)-fagomine **5**.

Several syntheses of D-fagomine have been described. The first time, it was prepared starting from D-glucose[8] and later from D-glucal.[9] Another synthesis made use of enzymatically catalyzed aldolization,[10] and recently, a synthesis of all the four possible D-fagomine stereoisomers (fagomine, 3-*epi*-fagomine, 4-*epi*-fagomine, and 3,4-di-*epi*-fagomine), starting from the Garner aldehyde and using ring-closing metathesis,[11] has been described.

The biological activity of fagomine **1** is not as broad as that of deoxynojirimycin **2** and nojirimycin **3**, however, it has been proven that fagomine **1** and 3-*epi*-fagomine show inhibitory activity against mammalian gut α-glucosidase and β-galactosidase.[7] Furthermore, fagomine exhibits a potent antihyperglycemic effect in streptozocin-induced diabetic mice and potentiates glucose-induced insulin secretion.[12] Also, inhibition of lysosomal α-galactosidase A activity in Fabry lymphoblasts by 4-*epi*-fagomine has been reported.[13]

So far, the role of the glycosides of iminosaccharides in Nature is not quite clear. Thus, for example, it has been found[7] that the inhibitory activity of fagomine against glycosidases is lost in the case of 3-*O*-(β-D-glucopyranosyl)-fagomine **4** and 4-*O*-(β-D-glucopyranosyl)-fagomine **5**. On the other hand, inhibition studies on various glucosylated 1-deoxynojirimycins have shown that, for example, the inhibitory activity of 3-*O*-(α-D-glucopyranosyl)-1-deoxynojirimycin toward rat intestinal sucrase is the same as the activity of 1-deoxynojirimycin, whereas its inhibitory activity toward rice α-glucosidase is even slightly higher than the activity of 1-deoxynojirimycin itself.[14] In order to gain more information on the role of glycosylated iminosaccharides in these processes, we set out to synthesize some of their *C*-glycosides. In these compounds the glycosidic bond is replaced by the C–C bond which mimics the glycosidic bond well but cannot undergo enzymatic hydrolysis and thus cannot liberate the iminosugar under in vivo conditions.



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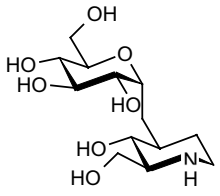

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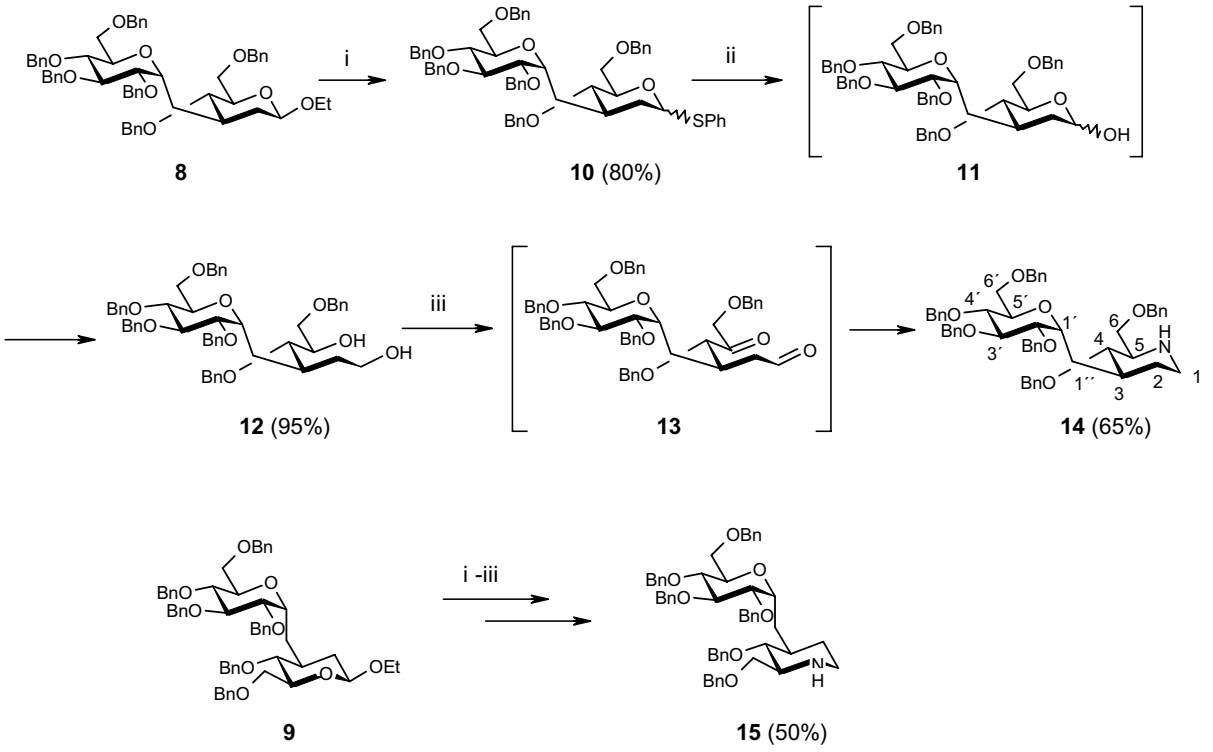
In the present letter we describe our approach to the synthesis of 3-*deoxy*-3-(α-D-glucopyranosylmethyl)-D-fagomine **6** and its stereoisomer 3-*deoxy*-3-(α-D-glucopyranosylmethyl)-L-fagomine **7**. Our interest in L-iminosaccharides has been aroused by recent publications drawing attention to the fact that both D-enantiomers and L-enantiomers of iminosaccharides show inhibitory activity toward glycosidases; D-iminosaccharides are competitive inhibitors whereas their L-enantiomers are noncompetitive ones.[15]

In our previous papers,[16] we described a simple and expedient stereoselective synthesis of α-*C*-(1 → 3)-linked disaccharides in which D-glucose is linked by a methylene bridge with 2,3-dideoxy-*arabino*-hexopyranose of the D- or L-configuration. Compounds **8** and **9**, easily accessible by this synthesis[16] (Scheme 1), may serve as starting material for the synthesis of other compounds; among other things, their dideoxy-*arabino*-hexopyranose ring can be easily transformed into a piperidine for formation of D- and L-fagomine 3-α-*C*-glucosides **6** and **7.** We decided to perform such a transformation using a method based on double reductive amination of the corresponding dicarbonyl sugar intermediate. This reaction has been reported to give very good results in the preparation of *all-equatorial* substituted piperidines and it was used in the highly stereoselective preparation of 1-deoxynojirimycin[17] and β-homonojirimycin[18] from D-glucose derivatives. Although this method had not previously been employed for the synthesis of fagomine, we supposed that derivatives of 2-deoxyhexopyranose might afford stereoselectively fagomine derivatives in an analogues fashion.

Since classical hydrolysis of the starting ethyl glycoside **8** to *C*-disaccharide **11** gave unsatisfactory results, this conversion was performed in two steps. Ethyl glycoside **8** on reaction with thiophenol afforded an anomeric mixture of thioglycosides **10** in 80% yield. By treating the thioglycosides **10** with *N*-bromosuccinimide in aqueous acetone, the thiophenyl group was replaced by a free OH group, thus affording an anomeric mixture of benzylated *C*-disaccharides **11**. This mixture was reduced in situ with $NaBH_4$ to give the corresponding alditol **12**, with the overall yield from **10** to **12** being 95%. Swern oxidation of **12** smoothly afforded keto aldehyde **13** which, without isolation, was subjected to reductive amination, resulting in a 65% yield (after two steps) of pure protected D-fagomine *C*-glucopyranoside **14** as a crystalline substance, mp 125–127 °C. Another stereoisomer was not detected in the crude reaction mixture. Application of the same procedure to ethyl glycoside **9** afforded pure protected L-fagomine *C*-glucopyranoside **15** in the same overall yield. In addition to NOE experiments, the structure of the fagomine moiety (*all-equatorial* substitution) in compounds **14** and **15** was unequivocally confirmed by the values of coupling constants in ^{1}H NMR spectra[19] (for **14**: J H-3/H-4 = J H-4/H-5 = 9.7 Hz, and for **15**: J H-3/H-4 = J H-4/H-5 = 9.8 Hz).



Scheme 1. Reagents and conditions: (i) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 3 h, −78 °C, then → rt; (ii) (a) NBS, moist acetone (1% H_2O), −15 °C, 1 h, exclusion of light; (b) $NaBH_4$, MeOH; (iii) (a) DMSO, $COCl_2$, Et_3N, CH_2Cl_2, −78 °C; (b) $NH_4{}^+HCOO^-$, $NaBH_3CN$, MeOH.

In conclusion, we have shown that the 2-deoxyhexopyranose moiety in the easily accessible perbenzylated α-*C*-(1 → 3)-linked disaccharides **8** and **9** can be converted in high yields to the corresponding dicarbonyl intermediates, which undergo stereoselective double reductive amination to the perbenzylated *C*-glucosides of D-fagomine and L-fagomine (**14** and **15**, respectively).

Acknowledgments

This study was supported by the Ministry of Education, Youth and Sport of the Czech Republic (Grant No. VZ 6046137305) and by the Grant Agency of the Czech Republic (Grant No. 203/03/0497).

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19. Selected data of compound **14**: ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.11–7.42 (m, 30H, H arom.), 4.42–4.99 (m, 12H, CH_2Ph), 4.22 (ddd, 1H, H-1′, $J(1',1''A) = 12.7$ Hz, $J(1',2') = 5.8$ Hz, $J(1',1''B) = 2.6$ Hz), 3.56–3.80 (m, 8H, H2′, H3′, H4′, H5′, CH_2-6′, CH_2-6), 3.03 (dd, 1H, H-4, $J(4,3) = J(4,5) = 9.7$ Hz), 2.95 (ddd, 1H, H-1eq, $J(1eq,1ax) = 12.2$ Hz, $J(1eq,2ax) = 4.0$ Hz, $J(1eq,2eq) \approx 1$ Hz), 2.78 (m, 1H, H-5), 2.57 (ddd, 1H, H-1ax, $J(1ax,1eq) = 12.2$ Hz, $J(1ax,2ax) = 10.3$ Hz, $J(1ax,2eq) = 2.1$ Hz), 2.33 (ddd, 1H, H-1″B, $J(1''B,1''A) = 14.6$ Hz, $J(1''B,1') = 2.6$ Hz, $J(1''B,3) = 3.4$ Hz), 2.14 (dddd, 1H, H-2eq, $J(2eq,2ax) = 10.8$ Hz, $J(2eq,1ax) = 2.1$, $J(2eq,3) = J(2eq,1eq) \approx 1$ Hz), 1.74 (m, 1H, H-3), 1.48 (ddd, 1H, H-1″A, $J(1''A,1''B) = 14.6$ Hz, $J(1''A,1') = 12.7$ Hz, $J(1''A,3) = 8.3$ Hz), 1.24 (dddd, 1H, H-2ax, $J(2ax,2eq) = 10.8$ Hz, $J(2ax,1ax) = J(2ax,3) = 12.5$ Hz, $J(2ax,1eq) = 4.0$ Hz). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 138.71, 138.19, 138.11, 138.01 (C arom.), 128.42, 128.36, 128.29, 127.91, 127.85, 127.79, 127.73, 127.69, 127.62, 127.60, 127.54 (CH arom.), 75.31, 75.01, 73.86, 73.47, 73.43, 72.80, 71.35, 69.11 (CH_2), 82.19, 80.02, 78.17, 71.35 (CH-2′, CH-3′, CH-4′, CH-5′), 81.55 (CH-4), 75.38 (CH-1′), 61.39 (CH-5), 45.54 (CH_2-1), 42.55 (CH-3), 32.68 (CH_2-2), 26.54 (CH_2-1″). ES MS: 848.3 (M+1).
Selected data of compound **15**: ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.12–7.44 (m, 30H, H arom.), 4.32–4.99 (m, 12H, CH_2Ph), 4.10 (ddd, 1H, H-1′, $J(1',2') = J(1',1''A) = 2.6$ Hz, $J(1',1''B) = 12.4$ Hz), 3.53–3.86 (m, 8H, H2′, H3′, H4′, H5′, CH_2-6′, CH_2-6), 3.04–3.16 (m,2H, overlap H-1, H-4), 2.74 (m, 1H, H-5), 2.60 (ddd, 1H, H-1ax, $J(1ax,1eq) = J(1ax,2ax) = 12.3$ Hz, $J(1ax,2eq) = 1.8$ Hz), 2.31 (ddd, 1H, H-1″B, $J(1''B,1''A) = 13.5$ Hz, $J(1''B,1') = 12.4$ Hz, $J(1''B,3) \approx 0$ Hz), 1.90 (dddd, 1H, H-2eq, $J(2eq,2ax) = 12.2$ Hz, $J(2eq,1ax) = 1.8$ Hz, $J(2eq,3) = J(2eq,1eq) \approx 1$ Hz), 1.69 (m, 1H, H-3), 1.30 (ddd, 1H, H-1″A, $J(1''A,1''B) = 13.5$ Hz, $J(1''A,3) = 12.0$ Hz, $J(1''A,1') = 2.6$ Hz), 1.20 (dddd, 1H, H-2ax, $J(2ax,2eq) = 12.2$ Hz, $J(2ax,1ax) = J(2ax,3) = 12.5$ Hz, $J(2ax,1eq) = 3.2$ Hz). ^{1}H NMR of H-4 and H-1eq (500.13 MHz, CD_2Cl_2) δ 3.13 (dd, 1H, H-4, $J(4,3) = J(4,5) = 9.8$ Hz), 3.09 (m, 1H, H-1eq). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 138.80, 138.68, 138.29, 138.28, 138.01, 137.91, 137.88 (C arom.), 128.57, 128.44, 128.34, 128.22, 128.17, 128.07, 127.99, 127.95, 127.89, 127.80, 127.78, 127.58, 127.55, 127.40 (CH arom.), 75.44, 74.97, 74.63, 73.51, 73.23, 73.18, 68.90 (CH_2), 82.54, 80.14, 78.13, 70.50 (CH-2′, CH-3′, CH-4′, CH-5′), 80.14 (CH-4), 70.13 (CH-1′), 61.60 (CH-5), 45.23 (CH_2-1), 37.78 (CH-3), 30.34 (CH_2-2), 26.46 (CH_2-1″). ES MS: 848.3 (M+1).