Tetrahedron Letters 57 (2016) 1351–1353

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Concise and highly stereoselective syntheses of D-fagomine and 2-*epi*-fagomine

Srinivasa Reddy Kallam [a,b], Rajender Datrika [a], Sandip R. Khobare [a], Vikas S. Gajare [a], Nagaraju Rajana [a], H. Rama Mohan [a], J. Moses Babu [a], V. Siddaiah [b], T. V. Pratap [a,*]

[a] Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Hyderabad 500049, India
[b] Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530 003, India

ARTICLE INFO

Article history:
Received 18 December 2015
Revised 10 February 2016
Accepted 12 February 2016
Available online 13 February 2016

Keywords:
Polyhydroxylated piperidine
D-Fagomine
2-*epi*-Fagomine
Inversion
Double inversion

ABSTRACT

Highly stereoselective total syntheses of polyhydroxylated piperidines D-fagomine and 2-*epi*-fagomine have been developed starting from 3,4,6-tri-*O*-benzyl-D-glucal which is a derivative of D-Glucose. Key steps in the synthesis of these azasugars involved *N*-Boc-protected amine preparation from oxime followed by stereo specific iodination of alcohol and cascade cyclization triggered by *N*-Boc deprotection.

© 2016 Published by Elsevier Ltd.

Polyhydroxylated piperidines are known for their biological activity as glycosidase inhibitors.[1] These compounds are found to possess effective therapeutic activity against a wide range of diseases including diabetes,[2] viral infection, and tumor metastasis.[3] Glycosidases are the enzymes involved in carrying out several fundamental biological processes, azasugars that are either agonistic or antagonistic to these enzymes have thus acquired great significance from synthesis perspective.

D-Fagomine (**1**), is a naturally occurring azasugar that was first isolated from Japanese buckwheat seeds of *Fagopyrum esculentum* austral Moench in 1974,[4] and *Castanospermum austral* (a member of *Leguminosae* family).[5] The stereo isomers of this compound were isolated from the leaves and roots of *Xanthocercis zambesiaca*.[6] This azasugar has an inhibitory activity against mammalian intestinal α-glucosidase and β-galactosidase (Fig. 1).[7]

Also, it has potent antihyperglycemic effect on diabetic mice via potentiation of glucose induced insulin secretion.[8] The hyperglycemic condition in mice was caused by inducing Streptozocin in them. These important biological properties of D-fagomine clubbed with its structural similarity with sugars have attracted chemists as an important synthetic target. Because of its limited natural occurrence increasing the availability of its analogs with different substitution patterns and stereochemistry would benefit

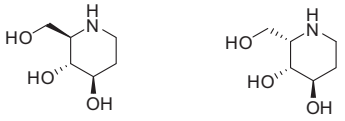
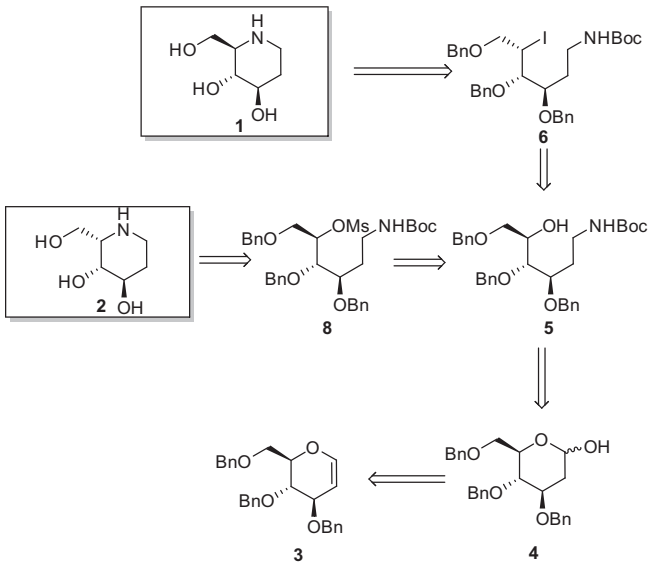


Figure 1. D-Fagomine **1** and 2-*epi*-fagomine **2**.

the scientific community to establish the structure activity relationship. Several syntheses of D-fagomine (**1**) and 2-*epi*-fagomine (**2**), both from carbohydrate[9] and from non-carbohydrate[10] precursors have been reported in the literature. Yaswanth et al. reported the total synthesis of D-fagomine and 2-*epi*-fagomine by intramolecular reductive amination from 2-deoxy-1-azido sugars.[9d] Yokoyama and co-workers reported the synthesis of D-fagomine by Sharpless asymmetric dihydroxylation and Pd(II)-catalyzed cyclization starting from 3-(*t*-butoxylcarbonylamino) propanol.[10e] Chemo-enzymatic synthesis of D-fagomine was reported by Jesús Joglar and Pere Clapés with FSA-catalyzed aldol addition of dihydroxyacetone (DHA) to *N*-Cbz-3-aminopropanal and reductive amination.[10g] Kim et al. reported the synthesis of D-fagomine by stereoselective intramolecular oxazine formation catalyzed by palladium(0) and piperidine formation by catalytic hydrogenation of oxazine.[10i] The diastereoselective synthesis of D-fagomine was reported by Min et al. from D-lyxose.[10j] Bates

* Corresponding author. Fax: +91 (40) 44658699.
E-mail address: tvpratap@drreddys.com (T.V. Pratap).

http://dx.doi.org/10.1016/j.tetlet.2016.02.046
0040-4039/© 2016 Published by Elsevier Ltd.



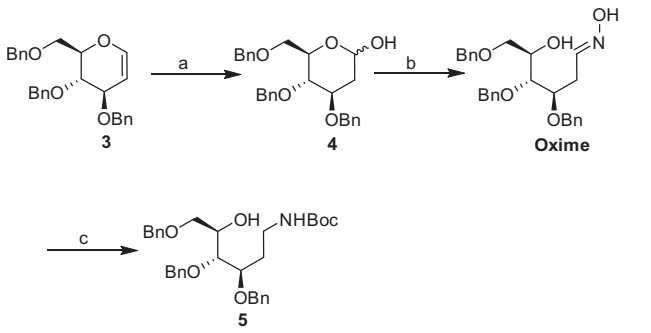
Scheme 1. Retrosynthetic analysis.

and Shuyi Ng reported the synthesis of 2-*epi*-fagomine by gold(I)-catalyzed allene cyclization.[10k] These syntheses though resulted in desired product in high yields, the use of complex reagents, reaction conditions, and multistep synthetic sequences involved in these syntheses invite even simple and scalable approaches for the synthesis of these natural products.

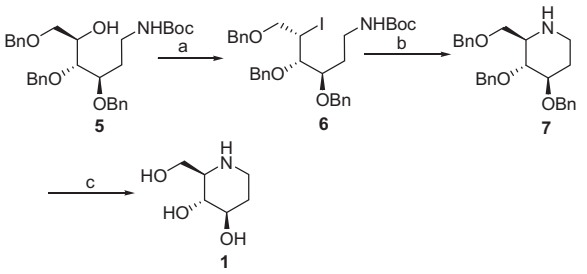
Herein we describe our successful effort toward the highly stereoselective total synthesis of D-fagomine (**1**) and its epimer 2-*epi*-fagomine (**2**) from a common intermediate **5**, which was derived from 3,4,6-tri-*O*-benzyl-D-glucal. The retrosynthetic approach for synthesis **1** and **2** is described in Scheme 1. The D-fagomine (**1**) could be obtained from *tert*-butyl((3*R*,4*S*,5*S*)-3,4,6-*tris*(benzyloxy)-5-iodohexyl)carbamate (**6**) by intramolecular N-alkylation triggered by *N*-Boc deprotection. The compound **6** could be obtained from a common intermediate *tert*-butyl ((3*R*,4*R*,5*R*)-3,4,6-*tris*(benzyloxy)-5-hydroxyhexyl)carbamate (**5**) by iodination with inversion of configuration at C5 position. The compound **5** in turn could be obtained from (4*R*,5*S*,6*R*)-4,5-*bis*(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-ol (**4**) by oxime formation followed by one pot reduction of oxime and *N*-Boc protection. The compound **4** is traced from 3,4,6-tri-*O*-benzyl-D-glucal (**3**) which on catalytic hydration affords compound **4**. On the other hand, the 2-*epi*-fagomine (**2**) could be obtained from (2*R*,3*S*,4*R*)-1,3,4-*tris*(benzyloxy)-6-((*tert*-butoxycarbonyl)amino) hexan-2-yl methanesulfonate (**8**) by Boc deprotection followed by N-alkylation. The compound **8** could be obtained from *tert*-butyl ((3*R*,4*R*,5*R*)-3,4,6-tris(benzyloxy)-5-hydroxyhexyl)carbamate (**5**) by mesylation with retention of configuration at C5 position.

Results and discussion

Synthesis of D-fagomine (**1**) and 2-*epi*-fagomine (**2**) commenced with 3,4,6-tri-*O*-benzyl-D-glucal **3** a derivative of D-Glucose.[11] The synthesis of key intermediate **5** is described below (Scheme 2). Thus 3,4,6-tri-*O*-benzyl-D-glucal **3** was converted to lactal **4** by catalytic hydration[12] with PPh_3–HBr in THF–water mixture at ambient temperature. Lactal **4** was converted to oxime with hydroxylamine hydrochloride and sodium acetate in methanol at ambient temperature.[13] The oxime was further reduced with $NaBH_4$ and $NiCl_2$ in methanol[14] and amine thus obtained reacts with di-*tert*-butyl dicarbonate in the same pot to afford the intermediate **5**.



Scheme 2. Reagents and conditions: (a) PPh_3·HBr, THF, water, rt, 4 h, 85%; (b) NH_2OH·HCl, sodium acetate, methanol, water, rt, 3 h, 91%; (c) $NaBH_4$, $NiCl_2$·$6H_2O$, Boc_2O, methanol, 0 °C–rt, 74%.

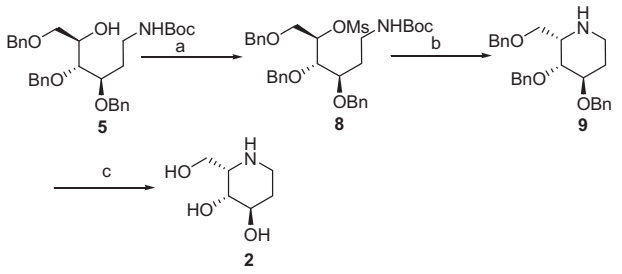


Scheme 3. Reagents and conditions: (a) I_2, PPh_3, imidazole, toluene, reflux, 2 h, 79%; (b) (i) 10% EtOH–HCl, rt, 2 h; (ii) K_2CO_3, acetonitrile, reflux, 4 h, 95%; (c) 10% Pd/C, conc. HCl, H_2, methanol, rt, 18 h, 82%.

The secondary alcohol of intermediate **5** was converted into iodide **6** using iodine, triphenylphosphine, and imidazole[15] in toluene at reflux temperature for 2 h. This reaction proceeds by activation of triphenylphosphine with iodine, followed by attack of the alcohol oxygen at phosphorus to generate an oxyphosphonium intermediate. The oxygen is then transformed into a leaving group undergo S_N2 displacement by iodide with inversion of configuration at C5 position. Iodide **6** on treatment with ethanolic HCl leads to deprotection of the tertiary butoxy carbamate and the amine got converted into corresponding amine hydrochloride salt. After distillation of ethanol this intermediate was treated with K_2CO_3 in acetonitrile at reflux temperature for 2 h which triggers the amine to participate in S_N2 reaction at C5 with inversion of configuration to afford tri-*O*-benzyl-D-fagomine with desired stereochemistry. Later it was subjected to debenzylation using catalytic hydrogenation in the presence of Pd/C to furnish the target molecule D-fagomine **1** (Scheme 3). The spectral data of obtained D-fagomine **1** were found to be in accordance with the reported data.

Subsequently attention was paid on the synthesis of 2-*epi*-fagomine **2**. The hydroxyl group of intermediate **5** was converted to a leaving group here in this case a mesylate **8** by reacting with mesyl chloride, triethylamine and DMAP in dichloromethane.[16] Deprotection of the tertiarybutyl carbamate followed by reaction with K_2CO_3 in acetonitrile led to intramolecular cyclization[17] with net inversion of configuration at C5 position to afford tri-*O*-benzyl-2-*epi*-fagomine. Later it was subjected to debenzylation using catalytic hydrogenation in the presence of Pd/C[18] to afford 2-*epi*-fagomine **2** (Scheme 4).

In summary, a highly stereoselective synthesis of D-fagomine (**1**) and 2-*epi*-fagomine (**2**) has been developed with good yields. The double inversion of stereochemistry at C5 position via iodide gave the D-fagomine **1** while single inversion via mesylate gave the 2-*epi*-fagomine **2**. The route of synthesis developed for these



Scheme 4. Reagents and conditions: (a) MsCl, DMAP, TEA, DCM, 0 °C–rt, 2 h, 90%; (b) (i) 10% EtOH–HCl, rt, 2 h; (ii) K_2CO_3, acetonitrile, reflux, 4 h, 92%; (c) 10% Pd/C, conc. HCl, H_2, methanol, rt, 18 h, 76%.

iminosugars utilizes fairly inexpensive reagents and operationally friendly processes. This strategy can be utilized for the stereoselective synthesis of other polyhydroxylated piperidines. The application of this methodology for the synthesis of other biologically active complex polyhydroxylated piperidines is currently underway.

Acknowledgments

The authors would like to thank Dr. Vilas Dahanukar and Dr. Rashid Abdul Rahman Khan of Dr. Reddy's Laboratories for continued support. We also thank the Analytical Department, Dr. Reddy's Laboratories, for providing the analytical support.

DRL-IPD Communication No.: IPDO IPM-00471.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.046.

References and notes

1. (a) Asano, N. *Glycobiology* **2003**, *13*, 93R–104R; (b) Butters, T. D.; Dwek, R. A.; Platt, M. F. *Chem. Rev.* **2000**, *100*, 4683–4696; (c) Heightman, T. D.; Vasella, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 750–770.
2. (a) Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007–3018; (b) Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605–611.
3. Zitzmann, N.; Mehta, A. S.; Carrouee, S.; Butters, T. D.; Platt, F. M.; McCauley, J.; Blumberg, B. S.; Dwek, R. A.; Block, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11878–11882.
4. Koyama, M.; Sakamura, S. *Agric. Biol. Chem.* **1974**, *38*, 1111.
5. Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198.
6. Kato, A.; Asano, N.; Kizu, H.; Matsui, K. *J. Nat. Prod.* **1997**, *60*, 312–314.
7. Kato, A.; Asano, N.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *J. Nat. Prod.* **1997**, *60*, 312–314.
8. (a) Nojima, H.; Kimura, I.; Chen, F. J.; Sugiura, Y.; Haruno, M.; Kato, A.; Asano, N. *J. Nat. Prod.* **1998**, *61*, 397–400; (b) Taniguchi, S.; Asano, N.; Tomino, F.; Miwa, I. *Horm. Metab. Res.* **1998**, *30*, 679–683.
9. (a) Fleet, G. W. J.; Fellows, L. E.; Smith, P. W. *Tetrahedron* **1987**, *43*, 979–990; (b) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119–136; (c) Désiré, J.; Dransfield, P. J.; Gore, P. M.; Shipman, M. *Synlett* **2001**, 1329–1331; (d) Kumari, N.; Gopal Reddy, B.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, *1*, 160–169; (e) Jiang, F. X.; Liu, Q. Z.; Zhao, D.; Luo, C. T.; Guo, C. P.; Ye, W. C.; Luo, C.; Chen, H. *Eur. J. Med. Chem.* **2014**, *77*, 211–222; (f) Corkran, H. M.; Munneke, S.; Dangerfield, E. M.; Stocker, B. L.; Timmer, M. S. M. *J. Org. Chem.* **2013**, *78*, 9791–9802.
10. (a) von der Osten, C. H.; Sinskey, A. J.; Barbas, C. F.; Pederson, R. L.; Wang, Y. F.; Wang, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 3924–3927; (b) Pederson, R. L.; Wang, C. H. *Heterocycles* **1989**, *28*, 477–480; (c) Effenberger, F.; Null, V. *Liebigs Ann. Chem.* **1992**, 1211–1212; (d) Takahata, H.; Banba, Y.; Cheimi, A.; Hideo, N.; Kato, A.; Adachi, I. *Tetrahedron: Asymmetry* **2001**, *12*, 817–819; (e) Hirai, Y.; Yokoyama, H.; Ejiri, H.; Miyazawa, M.; Yamaguchi, S. *Tetrahedron: Asymmetry* **2007**, *18*, 852–856; (f) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem.* **2003**, *68*, 3603–3607; (g) Castillo, J. A.; Calveras, J.; Casas, A.; Mitjans, M.; Vinardell, M. P.; Parella, T.; Inoue, T.; Sprenger, G. A.; Joglar, J.; Clapés, P. *Org. Lett.* **2006**, *8*, 6067–6070; (h) Kato, A.; Miyauchi, S.; Kato, N.; Nash, R. J.; Yoshimura, Y.; Nakagome, I.; Hirono, S.; Takahata, H.; Adachi, I. *Bioorg. Med. Chem.* **2011**, *19*, 3558–3568; (i) Kim, J. Y.; Mu, Y.; Jin, X.; Park, S. H.; Pham, V. T.; Song, D. K.; Lee, K. Y.; Ham, W. H. *Tetrahedron* **2011**, *67*, 9426–9432; (j) Min, I. S.; Kim, S. I.; Hong, S.; Kim, I. S.; Jung, Y. H. *Tetrahedron* **2013**, *69*, 3901–3906; (k) Bates, R. W.; Ng, P. S. *Tetrahedron Lett.* **2011**, *52*, 2969–2971; (l) Kundu, P. K.; Ghosh, S. K. *Tetrahedron: Asymmetry* **2011**, *22*, 1090–1096.
11. (a) Madhusudan, S. K.; Geetanjali, A.; Devendra, S. N.; Misra, A. K. *Carbohydr. Res.* **2005**, *340*, 1373–1377; (b) Buda, S.; Golebiowska, P.; Mlynarski, J. *Eur. J. Org. Chem.* **2013**, *19*, 3988–3991.
12. (a) Niu, Y.; Cao, X.; Ye, X. S. *Helv. Chim. Acta* **2008**, *91*, 746–752; (b) Bucher, C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 8724–8728.
13. Fukase, H. *J. Org. Chem.* **1992**, *57*, 3651–3658.
14. (a) Zhang, G. L.; Zhang, L. H.; Ye, X. S. *Org. Biomol. Chem.* **2010**, *8*, 5062–5068; (b) Neisius, N. M.; Plietker, B. *J. Org. Chem.* **2008**, *73*, 3218–3227.
15. (a) Chavan, S. P.; Praveen, C.; Ramakrishna, G.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 6027–6028; (b) Zhang, S.; Chen, X.; Zhang, J.; Wang, W.; Duan, W. *Synthesis* **2008**, 383–386; (c) Subhash, P. C.; Nilesh, B. D.; Kailash, P. P. *RSC Adv.* **2014**, *4*, 40852–42858.
16. Kumari, N.; Reddy, B. G.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, 160–169.
17. (a) Preeti, G.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, 1925–1933; (b) Kumari, N.; Vankar, Y. D. *Org. Biomol. Chem.* **2009**, *7*, 2104–2109.
18. (a) Desire, M.; Dransfield, P. J.; Gore, P. M.; Shipman, M. *Synlett* **2001**, 1329–1331; (b) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 5819–5833.