Tetrahedron Letters 51 (2010) 2400–2402

Contents lists available at ScienceDirect

Tetrahedron Letters

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

5-Trihydroxypropyl-dihydrouracil derivatives as precursors of 1-azasugars: application to the stereoselective synthesis of D-*galacto*-isofagomine

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ARTICLE INFO

Article history:
Received 7 October 2009
Revised 15 February 2010
Accepted 16 February 2010
Available online 23 February 2010

Keywords:
1-Azasugars
galacto-Isofagomine

ABSTRACT

A new route for the synthesis of isofagomine analogues has been carried out by using as precursors enantiopure 5-trihydroxypropyl-dihydrouracil derivatives obtained from aldol-type addition of 1,3-dibenzyl-dihydrouracil to isopropylidene-protected glyceraldehyde. The synthesis of D-*galacto*-isofagomine is reported.

Azasugars, a class of sugar-shaped molecules, have found a growing interest in the last years because of their ability to inhibit glycoprocessing enzymes.[1] These polyhydroxylated piperidine alkaloids are used as tools for studying the biological functions of oligosaccharides[2] and since many glycoprocessing enzymes have been identified as important therapeutic targets, azasugars are emerging as key molecules to find new drug candidates for antiviral,[3] anticancer[4] and metabolic disorder therapies.[4d,5] Two azasugar-based drugs such as miglustat[1a] (*N*-butyl-deoxynojirimicin) for the treatment of type-1 Gaucher's disease and recently for type-C Niemann–Pick disease[6] and miglitol[1a] (*N*-hydroxyethyl-deoxynojirimicin) for the treatment of type-2 diabetes mellitus have been already approved.

In the past few years, isofagomine-type monosaccharide mimics (1-azasugars) where the anomeric carbon is replaced by a nitrogen atom have shown an high and anomer-selective β-glycosidase inhibition activity (Fig. 1).[7] In their N-protonated form they mimic the carbenium ion in the enzymatic glycosyl cleavage and form a strong electrostatic interaction between the protonated endocyclic nitrogen and the catalytic nucleophile of the enzyme.

Recently, isofagomine derivatives have received a great attention because they are new therapeutic candidates for the treatment of Gaucher's disease in Phase II of clinical development,[8] and because they are potent inhibitors of liver glycogen phosphorylase with pharmaceutical application in the treatment of type-2 diabetes[9] and cardiovascular diseases.[10] As a consequence, the development of new stereoselective and versatile procedures for the synthesis of isofagomine-type azasugars constitutes an area of considerable interest.[11]

In the past we have performed a new diastereoselective and stereodivergent synthesis of 5-trihydroxypropyl-dihydrouracil derivatives based on the aldol-type addition of 1,3-dibenzyl-dihydrouracil (DBDHU) to isopropylidene-protected glyceraldehyde.[12] Here we wish to report a stereoselective and versatile new route to the synthesis of 1-azasugars by using these enantiopure polyfunctionalized compounds as precursors.

Our strategy for the synthesis of isofagomine-type azasugars is outlined in Figure 2, which shows that a disconnection of C2–N1 bond of the 1-azasugar molecule **A** would lead to amino polyol **B** obtainable from the ureido polyol **C** via reductive ring opening of the 5-trihydroxypropyl-dihydrouracil derivative **D**. This key intermediate is endowed with the appropriate three stereocentres met in the final 1-azasugars and can be stereoselectively synthesized from glyceraldehyde homologation using DBDHU.

The extremely potent and selective β-galactosidase inhibitor D-*galacto*-isofagomine **10** (IC_{50} = 12 nM; K_i = 4 nM) was first chosen to test our approach to 1-azasugars (Scheme 1).[13,14] The synthesis

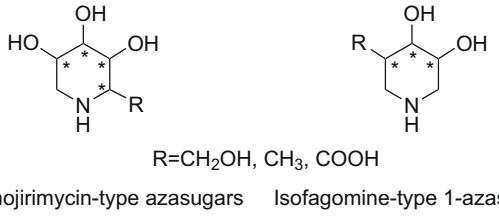

Figure 1. Structures of azasugars and 1-azasugars.

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doi:10.1016/j.tetlet.2010.02.093

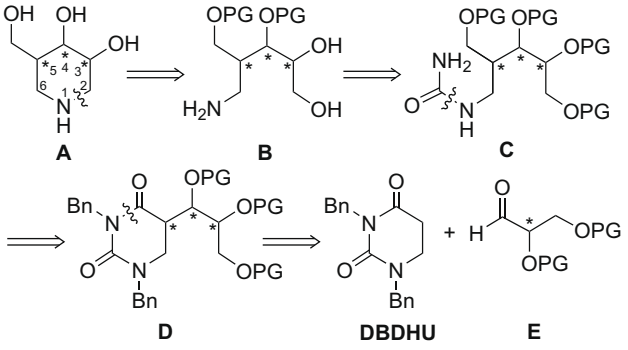


Figure 2. Retrosynthetic analysis.

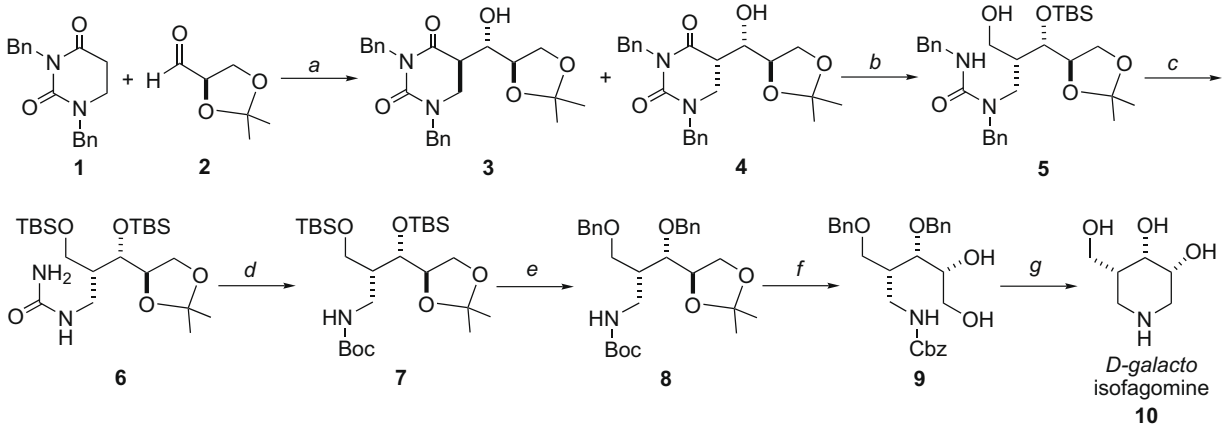
starts from the required (5*S*,1′*S*,2′*R*)-5-trihydroxypropyl-dihydrouracil **4** synthesized via aldol-type addition of lithium enolate of DBDHU **1** to 2,3-*O*-isopropylidene-D-glyceraldehyde **2** (**4**/**3** isomer ratio = 81/16) as previously reported.[12,15] After the protection of the C-1′ hydroxyl group of **4** as TBS-ether, the addition of a large excess of $NaBH_4$ in 3/1 EtOH/H_2O solution effected the reductive cleavage of DHU ring. The C-1 hydroxyl group of the ureido polyol **5** was protected as TBS-ether and then both benzyl groups of the urea functionality were removed by using lithium in liquid ammonia in good yield.[16] The next step of our synthetic plan was the transformation of the ureido group of **6** into amino *N*-Boc-protected functionality of compound **7**. It was obtained in good yield and in a single step by using copper(II) chloride/lithium *t*-butoxide.[17,18] Now, in aminopolyol **7** we have the complete skeleton with appropriate chirality of the three stereocentres needed to obtain the 1-azasugar target **10**. The silyl-protecting groups of compound **7** were easily substituted with Bn groups to give derivative **8** and then HCl was added to remove the ketal and the Boc groups.[19] The protection of the nitrogen as *N*-Cbz gave compound **9** in good yield.[20] To complete the synthesis, the free primary hydroxyl group of aminopolyol **9** was selectively oxidized to aldehyde[21], then catalytic reduction of the crude mixture gave in one pot the deprotection of Bn and Cbz groups and reductive amination furnished, after chromatographic purification, D-*galacto*-isofagomine **10** in 88% yield, 10% overall yield in 12 steps.[22]

Starting from the (5*R*,1′*S*,2′*R*)-5-trihydroxypropyl-dihydrouracil **3**,[23] the stereoselective synthesis of the β-galactosidase inhibitor L-*allo*-isofagomine could be performed using the same reaction protocol described for D-*galacto*-isofagomine derivatives **10**. In principle, the syntheses of L-*galacto*- and D-*allo*-isofagomine enantiomers are also possible simply by using readily available 2,3-*O*-isopropilidene-L-glyceraldehyde.

In summary we have shown a new stereoselective and versatile route for the synthesis of isofagomine analogues starting from 5-trihydroxypropyl-dihydrouracil derivatives obtained from the simple diastereoselective homologation of isopropylidene-protected glyceraldehyde with DBDHU. The stereoselective synthesis of D-*galacto*-isofagomine derivatives **10** was reported and the extension of this procedure for the synthesis of L-*allo*-isofagomine starting from compound **3** as well as the synthesis of D-*allo* and L-*galacto* enantiomers by using isopropylidene-protected L-glyceraldehyde is under investigation.

References and notes

1. (a) Compain, P.; Martin, O. R. *Iminosugars: from Synthesis to Therapeutic Applications*; Wiley: Chichester, 2007; (b) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimicin and Beyond*; Wiley-VCH: Weinheim, 1999.
2. Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720.
3. (a) Robina, I.; Moreno-Vargas, A. J.; Carmona, A. T.; Vogel, P. *Curr. Drug Metab.* **2004**, *4*, 329–361; (b) Greimel, P.; Spreitz, J.; Stütz, A. E.; Wrodnigg, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513–523; (c) Ratner, L.; Heyden, N. V.; Dedera, D. *Virology* **1991**, 180–192. and references therein; (d) Fenouillet, E.; Papandreou, M. J.; Jones, I. M. *Virology* **1997**, *231*, 89–95.
4. (a) Wrodnogg, T. M.; Steiner, A. J.; Ueberbacher, B. J. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 77–85; (b) Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *Mini-Rev. Med. Chem.* **2006**, *6*, 1043–1052; (c) Nishimura, Y. *Curr. Top. Med. Chem.* **2003**, *3*, 575–591; (d) Balfour, J. A.; McTavish, D. *Drugs* **1993**, *46*, 1025–1054.
5. (a) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683–4696; (b) Fan, J.-Q. *Trends Pharmacol. Sci.* **2003**, *24*, 355–360.
6. Patterson, M. C.; Vecchio, D.; Prady, H.; Abel, L.; Wraith, J. E. *Lancet Neurol.* **2007**, *6*, 765–772.
7. Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–554. and references therein.
8. (a) Dulsat, C.; Mealy, N. *Drugs Future* **2009**, *34*, 23–25; (b) Tropak, M. B.; Kornhaber, G. J.; Rigat, B. A.; Maegawa, G. H.; Buttner, J. D.; Blanchard, J. E.; Murphy, C.; Tuske, S. J.; Coales, S. J.; Hamuro, Y.; Brown, E. D.; Mahuran, D. J. *ChemBioChem* **2008**, *9*, 2650–2662; (c) Lockhart, D. PCT Int. Appl., WO 2008128106, 2008.; (d) Zhu, X.; Sheth, K. A.; Li, S.; Chang, H. H.; Fan, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7450–7453.
9. (a) Oikonomakos, N. G.; Tiraidis, C.; Leonidas, D. D.; Zographos, S. E.; Kristiansen, M.; Jessen, C. U.; Norskov-Lauritsen, L.; Agius, L. *J. Med. Chem.* **2006**, *49*, 5687–5701; (b) Somsak, L.; Nagy, V.; Hadady, Z.; Docsa, T.; Gergely, P. *Curr. Pharm. Des.* **2003**, *9*, 1177–1189; (c) Jakobsen, P.; Lundbeck, J. M.; Kristiansen, M.; Breiholt, J.; Demuth, H.; Pawlas, J.; Torres Candela, M. P.; Andersen, B.; Westergaard, N.; Lundgren, K.; Asano, N. *Bioorg. Med. Chem.* **2001**, *9*, 733–744.
10. Rytved, K. A.; Dragsted, N.; Nyborg, N. Chresten B.; Iversen, L.; Kristiansen, M. U.S. Patent Appl. Publ., US 2004082641, 2004.
11. For recent syntheses of isofagomine derivatives, see: (a) Imahori, T.; Ojima, H.; Yoshimura, Y.; Takahata, H. *Chem. Eur. J.* **2008**, *14*, 10762–10771; (b) Mugrace, B.; Tretyakov, A.; Fuerst, D.; Sheth, K. A.; Rybczynski, P. J.; Zhu, X. PCT Int. Appl.,WO 2008144773, 2008.; (c) da Cruz, F. P.; Horne, G.; Fleet, G. W. J.



Scheme 1. Reagents and conditions: (a) LDA, THF, 4 h, −78 °C, 88%; (b) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2; (ii) $NaBH_4$, EtOH/H_2O 3/1 rt, 61% two steps; (c) (i) TBSCl, imidazole, DMF; (ii) Li/NH_3 liq., 52% two steps; (d) $CuCl_2$–LiO^tBu, THF, 81%; (e) Bu_4NF, THF then BnBr, NaOH in CH_2Cl_2, 76%; (f) HCl, THF then CbzCl, $NaHCO_3$, $CHCl_3$/H_2O, 85% two steps; (g) TCC, TEMPO, CH_2Cl_2 then H_2, Pd/C, 88% two steps.

Tetrahedron Lett. **2008**, *49*, 6812–6815; (d) Chen, C.; You, B. *Tetrahedron Lett.* **2008**, *49*, 672–674; (e) Mihara, Y.; Ojima, H.; Imahori, T.; Yoshimura, Y.; Ouchi, H.; Takahata, H. *Heterocycles* **2007**, *72*, 633–645; (f) Goddard-Borger, E. D.; Stick, R. V. *Aust. J. Chem.* **2007**, *60*, 211–213; (g) Ouchi, H.; Mihara, Y.; Takahata, H. *J. Org. Chem.* **2005**, *70*, 5207–5214. and references therein; (h) Ouchi, H.; Mihara, Y.; Watanabe, H.; Takahata, H. *Tetrahedron Lett.* **2004**, *45*, 7053–7056; (i) Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 357–360; (j) Pandey, G.; Kapur, M. *Org. Lett.* **2002**, *4*, 3883–3886; (k) Pandey, G.; Kapur, M. *Synthesis* **2001**, 1263–1267; (l) Andersch, J.; Bols, M. *Chem. Eur. J.* **2001**, *7*, 3744–3747; (m) Kim, Y. J.; Ichikawa, M.; Ichikawa, Y. *J. Org. Chem.* **2000**, *65*, 2599–2602; (n) Pandey, G.; Kapur, M. *Tetrahedron Lett.* **2000**, *41*, 8821–8824; (o) Mehta, G.; Mohal, N. *Tetrahedron Lett.* **2000**, *41*, 5747–5751; (p) Hansen, S. U.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 911–915; (q) Schneider, C.; Kazmaier, U. *Eur. J. Org. Chem.* **1998**, 1155–1159; (r) Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett.* **2001**, *3*, 3257–3260; (s) Liang, X.; Lohse, A.; Bols, M. *J. Org. Chem.* **2000**, *65*, 7432–7437; (t) Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007–3018.

12. Ulgheri, F.; Bacsa, J.; Nassimbeni, L.; Spanu, P. *Tetrahedron Lett.* **2003**, *44*, 671–675.
13. Ichikawa, Y.; Igarashi, Y. *Tetrahedron Lett.* **1995**, *36*, 4585–4586.
14. The stereoselective syntheses of *galacto*-isofagomine were reported by using a chemoenzymatic approach (10% overall yield, 10 steps),[11s] via Wittig rearrangement of a chiral 3-hydroxypiperidene obtained via enzymatic resolution,[11e] via chiral auxiliary approach in very low yield[11r] or starting from D-lyxose in 12 steps.[11t]
15. Three percent of a third diastereomer was detected by NMR analysis.
16. *Compound* ***6****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (br s, 1H), 4.71 (br s, 2H), 4.12–4.03 (m, 2H), 3.91 (dd, J = 6.8, 2.4, 1H), 3.76 (dd, J = 7.6, 6.0, 1H) 3.66 (d, J = 6.8, 2H), 3.42–3.33 (m, 1H), 3.18–3.10 (m, 1H), 2.06–1.96 (m, 1H), 1.39 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 109.3, 77.1, 72.7, 67.9, 62.4, 44.7, 39.5, 26.8, 26.1, 25.5, 18.4, −4.0, −4.3, −5.2. $[\alpha]_D^{22}$ +8.7 (*c* 1.6, $CHCl_3$). Anal. Calcd for $C_{22}H_{48}N_2O_5Si_2$: C, 55.42; H, 10.15; N, 5.88. Found: C, 55.38; H, 10.23; N, 5.79.
17. Yamaguchi, J.-i.; Shusa, Y.; Suyama, T. *Tetrahedron Lett.* **1999**, *40*, 8251–8254.
18. *Compound* ***7****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (br s, 1H), 4.11–4.02 (m, 2H), 3.92 (dd, J = 6.4, 1.8, 1H), 3.79–3.73 (m, 1H), 3.72–3.64 (m, 2H), 3.70 (ddd, J = 13.6, 6.8, 4.8, 1H), 3.17 (ddd, J = 13.6, 6.0, 3.6, 1H), 2.30–1.96 (m, 1H), 1.42 (s, 9H), 1.39 (s, 3H), 1.32 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 108.9, 78.5, 76.8, 72.9, 67.6, 62.5, 43.6, 39.4, 28.4, 26.5, 25.8, 25.7, 25.2, 18.1, 18.0, −4.3, −4.6, −5.5. $[\alpha]_D^{22}$ +5.2 (*c* 1.4, $CHCl_3$). Anal. Calcd for $C_{26}H_{55}NO_6Si_2$: C, 58.49; H, 10.38; N, 2.62. Found: C, 58.41; H, 10.43; N, 2.69.
19. *Compound* ***8****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.22 (m, 10H), 5.19 (br s, 1H), 4.72–4.40 (m, 4H), 4.16 (q, J = 6.4, 1H), 4.04 (dd, J = 8.4, 6.8, 1H), 3.83 (dd, J = 8.4, 6.8, 1H), 3.79 (dd, J = 5.6, 4.0, 1H), 3.58–3.51 (m, 2H), 3.41–3.33 (m, 1H), 3.31–3.23 (m, 1H), 2.20–2.12 (m, 1H), 1.42 (s, 9H), 1.41 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 138.1, 128,4, 127.8, 127.7, 126.9, 108.9, 79.1, 78.8, 74.3, 73.2, 69.8, 66.7, 40.7, 39.7, 28.4, 26.6, 25.2. $[\alpha]_D^{22}$ −3.0 (*c* 3.7, $CHCl_3$). Anal. Calcd for $C_{28}H_{39}NO_6$: C, 69.25; H, 8.09; N, 2.88. Found: C, 69.31; H, 8.08; N, 2.81.
20. *Compound* ***9****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.13 (m, 15H), 5.45–5.35 (br s, 1H), 5.0 (s, 1H), 4.55–4.41 (m, 4H), 3.83–3.72 (m, 2H), 3.68–3.50 (m, 5H), 3.16 (dd, J = 13.6, 6.0, 1H), 2.76 (br s, 2H), 2.30 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 137.9, 137.6, 136.5, 128.5, 128.0, 127.8, 78.4, 73.7, 73.3, 71.9, 69.8, 66.7, 63.9, 40.6, 40.1. $[\alpha]_D^{22}$ −8.8 (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94; N, 2.92. Found: C, 70.10; H, 7.12; N, 2.96.
21. De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041–3043.
22. Spectral data for compound **10** were found in good agreement with the reported values from the literature (Ref. 11t): ^{1}H NMR (400 MHz, D_2O + DCl) δ 3.94 (br s, 1H), 3.83 (ddd, J = 11.2, 4.4, 2.4, 1H), 3.55 (dd, J = 11.0, 6.8, 1H), 3.45 (dd, J = 11.6, 6.6, 1H), 3.22 (dd, J = 12.8, 4.4, 1H), 3.17 (dd, J = 12.6, 5.2, 1H), 2.92 (d, J = 11.6, 1H), 2.79 (t, J = 12.2, 1H), 1.95–2.02 (m, 1H). ^{13}C NMR (100 MHz, D_2O) δ 68.3, 67.8, 62.0, 44.1, 41.9, 41.2. $[\alpha]_D^{22}$ −2.7 (*c* 0.93, EtOH). Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 49.02; H, 8.96; N, 9.48.
23. Compound **3** can be preferentially synthesized by using the procedure reported in Ref. 12 (LDA, $SnCl_4$, Et_2O, −78 °C).