Tetrahedron Letters 51 (2010) 5574–5576

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A new and short synthesis of naturally occurring 1-deoxy-L-gulonojirimycin from tri-*O*-benzyl-D-glucal

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ARTICLE INFO

Article history:
Received 21 July 2010
Revised 13 August 2010
Accepted 17 August 2010
Available online 20 August 2010

Keywords:
L-Azasugars
1-Deoxy-L-gulonojirimycin
Regioselective cyclization
Glycosidase inhibitors

ABSTRACT

A new and short synthesis of naturally occurring 1-deoxy-L-gulonojirimycin from tri-*O*-benzyl-D-glucal, via a regioselective intramolecular cyclization of an amino triol intermediate, is described. Its absolute configuration was deduced from the single crystal X-ray analysis of compound **11**.

Since the isolation of nojirimycin **1** (NJ) (Fig. 1) as the first naturally occurring polyhydroxylated alkaloid,[1] syntheses of natural polyhydroxylated piperidines (azasugars or iminosugars) and their unnatural analogues continue to receive a great deal of attention due to their ability to selectively inhibit different types of enzymes of medicinal interest such as glycosyltransferases and glycosidases.[2] Though NJ was found to be a potent inhibitor of α- and β-glucosidases, 1-deoxynojirimycin **2** (DNJ), the stable analogue of NJ was found to be a more potent inhibitor than NJ itself.[3] As inhibitors of glycosidases, azasugars are thus expected to have therapeutic applications in the treatment of a variety of carbohydrate-mediated disorders such as diabetes, viral infections, HIV, hepatitis, cancer metastasis, and Gaucher's disease.[4] Over the years, extensive research work has been carried out on the synthesis and inhibition studies of D-iminosugars, as most of the naturally occurring DNJ analogues belong to D-family.[1,2,4,5] Successful development of synthetic six-membered-azasugar based clinical drugs such as Glyset® **3** and Zavesca® **4** (Fig. 1) represent significant research breakthrough in this area.[5] Recent studies reveal that L-DNJ and its analogues, though do not mimic the conformation of D-sugars, also display significant inhibition activities against D-glycosidases through a non-competitive mode of action against these enzymes.[6] In view of this, there has been an upsurge in research related to the synthesis of L-DNJ and its congeners. In this context, 1-deoxy-L-gulonojirimycin **6** (L-*gulo*-DNJ) (Fig. 1) represents a rare example of naturally occurring DNJ analogue belonging to the L-family. It was first collected as an amorphous hydroacetate in 1982 during degradative sugar analysis

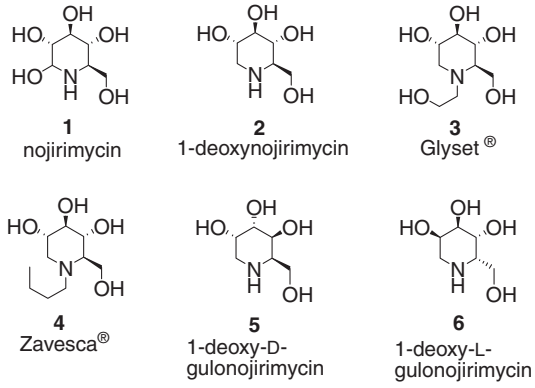

Figure 1. Representative examples of azasugars.

of the capsular polysaccharide isolated from *Streptococcus pneumoniae* type 12F.[7] L-*gulo*-DNJ **6**, is also a constituent entity of a novel disaccharide, 7-*O*-β-D-glucopyranosyl-α-homonojirimycin, a potent inhibitor of α-glucosidase and trehalase.[8] L-*gulo*-DNJ **6** was first isolated as a free base in 2001 from the extract of the bark *Angylocalyx pynaertii* along with a plethora of other DNJ analogues.[9] However, it was initially identified as D-*gulo*-DNJ **5** and not L-*gulo*-DNJ **6**. In 2005, the correct stereochemistry was established through asymmetric synthesis. Comparison of the specific rotation of the naturally occurring compound with that of the synthetic one revealed that the naturally occurring compound was indeed L-*gulo*-DNJ.[6b,10,11] It was found to be a highly specific inhibitor of α-L-fucosidase with a K_i value of 14 μm.[6b] Several syntheses of L-*gulo*-DNJ[6b,7,11,12] and

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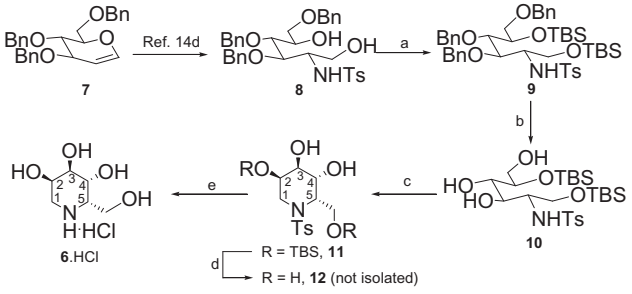
doi:10.1016/j.tetlet.2010.08.049

D-*gulo*-DNJ[6b,10,13] even prior to its isolation, have been reported. Most of the syntheses reported so far for L-*gulo*-DNJ utilize D-sugar-derived starting materials.[7,12] A couple of asymmetric syntheses are also available.[6b,11] Among the carbohydrate-based routes, except for a lone low-yielding indirect example,[7] glycals have hardly been used as starting materials for the synthesis of L-*gulo*-DNJ despite their ready availability. In continuation of our research work on the transformation of glycals into novel azasugars and other biologically important compounds,[14] we had recently accomplished a new and short synthesis of naturally occurring L-*gulo*-DNJ from readily available tri-*O*-benzyl-D-glucal **7** which we report herein.

Our synthesis relied on the use of amino diol **8**,[14d] prepared in three-steps from tri-*O*-benzyl-D-glucal **7**, as a convenient starting material (Scheme 1). Protection of the hydroxyl functional groups of **8** as their TBS ethers afforded compound **9** in high yield.[15] Deprotection of the benzyl groups of compound **9** was carefully carried out with hydrogen in the presence of 10% Pd on charcoal to give the triol **10** in 85% yield.[16] It should be noted that exposure of compound **9** toward hydrogenation reaction for a longer time led to the deprotection of the TBS ethers also.[17] Next, we attempted a regioselective intramolecular cyclization of the amino triol intermediate **10** to obtain the protected 1-deoxy-L-gulonojirimycin **11**. It was expected that, upon intramolecular cyclization, compound **10** would preferentially form the six-membered ring to afford compound **11**. Thus, amino triol **10** when subjected to an intramolecular cyclization under Mitsunobu condition underwent a smooth cyclization reaction to afford a single product in just 20 min. Upon careful analysis of ^{1}H and ^{13}C NMR spectral data, its structure was identified to be the expected product **11**.[18] The formation of the six-membered ring as well as the absolute configuration of **11** as 2*R*,3*R*,4*R*,5*S* (numbering as per parent 1-deoxynojirimycin **2**) could be inferred from the single crystal X-ray analysis of compound **11** (Fig. 2).[19] This is the first report on the single crystal X-ray structure of L-*gulo*-DNJ derivative. Subsequently, deprotection of the TBS and tosyl groups was carried out in a two-step one-pot fashion. Exposure of compound **11** to 0.1 M solution of TBAF led to a facile deprotection of the TBS groups to afford compound **12**, which without any work-up and/or purification was subjected to detosylation reaction under Birch condition to get L-*gulo*-DNJ **6** as a viscous liquid. For characterization purpose, L-*gulo*-DNJ **6** was converted into its hydrochloride salt by acidification with hydrochloric acid in methanol.[20] The specific rotation {$[\alpha]_D^{31}$ − 2.3 (*c* 0.6, MeOH)} and spectral data of L-*gulo*-DNJ.HCl (**6**·HCl) were found to be identical with the literature values reported by D'Alonzo and co-workers {$[\alpha]_D$ − 2.5 (*c* 0.5, MeOH)}.[11] Our synthesis along with the single crystal X-ray structure of compound **11** thus unambiguously proves that the naturally occurring *gulo*-DNJ indeed belongs to the L-family and has an absolute configuration of 2*R*,3*R*,4*R*,5*S* (numbering as per parent 1-deoxynojirimycin **2**).



Scheme 1. Synthesis of 1-deoxy-L-gulonojirimycin from tri-*O*-benzyl-D-glucal. Reagents and conditions: (a) TBSCl, Imd, DMF, rt, 1 h, 82%; (b) 10% Pd/C, MeOH, 42 °C, 40 min, 85%; (c) Ph_3P, DEAD, THF, 0 °C to rt, 20 min, 90%; (d) 1.0 M, TBAF in THF, rt, 10 min; (e) (i) Na–liq. NH_3, THF, −78 °C, 3 h; (ii) HCl, MeOH, rt, 10 min, 75% (from **11**).

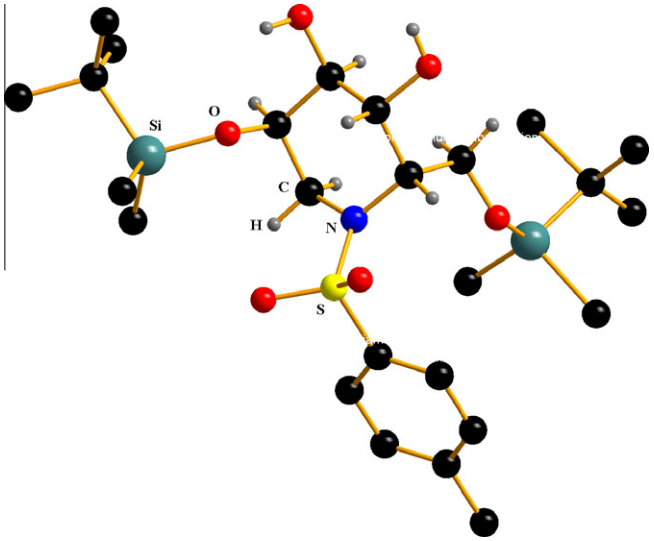


Figure 2. Single crystal X-ray structure of compound **11**. Hydrogens (except those in the piperidine ring) are omitted for clarity.

In conclusion, we have reported a new and a short synthesis of naturally occurring 1-deoxy-L-gulonojirimycin from readily available tri-*O*-benzyl-D-glucal under very mild reaction conditions in a high overall yield. The methodology is simple to carry out and amenable for large-scale preparations. We have also deduced the absolute configuration of naturally occurring 1-deoxy-L-gulonojirimycin from the single crystal X-ray analysis of compound **11**.

Acknowledgments

The authors thank the Department of Science and Technology, New Delhi, India for the financial support and Mr. Nem Singh for his help with the single crystal X-ray analysis. The authors thank the DST-FIST and IITD for funding of the single crystal X-ray diffraction facility at IITD.

Supplementary data

Supplementary data (experimental procedure, spectral data and copies of ^{1}H and ^{13}C NMR spectra of all new compounds and crystallographic data of compound **11**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.049.

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15. Data for **9**: $[\alpha]_D^{33} + 4.3$ (*c* 0.62, $CHCl_3$); υ_{max} (KBr)/cm^{-1}: 3283, 3062, 3032, 2857, 1952, 1744, 1598, 1334, 1251, 1158, 839, 777, 740, 700, 668, 606, 554, 460, and 403; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.40–7.22 (m, 17H), 4.96 (d, *J* = 9.3 Hz, exchangeable with D_2O, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.70 (d, *J* = 11.1 Hz, 1H), 4.63 (d, *J* = 11.1 Hz, 1H), 4.61–4.53 (m, 2H), 4.48 (d, *J* = 10.8 Hz, 1H), 4.24 (m, 1H), 4.09 (br d, *J* = 7.5 Hz, 1H), 3.77 (br d, *J* = 7.5 Hz, 1H), 3.68 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.56–3.50 (m, 2H), 3.38 (t, *J* = 9.3 Hz, 1H), 3.28 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.41 (s, 3H), 0.98 (s, 9H), 0.83 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H), −0.06 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.1, 139.1, 139.0, 138.6, 138.3, 129.6 (2×-C), 128.3 (4×-C), 128.1 (2×-C), 127.9 (2×-C), 127.7 (4×-C), 127.6, 127.5, 127.2, 126.9 (2×-C), 82.7, 75.9, 75.2, 74.8, 73.3, 72.6, 71.5, 61.9, 56.4, 25.9 (3×-C), 25.8 (3×-C), 21.4, 18.1 (2×-C), −4.5, −4.8, −5.6, −5.7; HRMS (ESI) calcd for $C_{46}H_{67}NO_7SSi_2Na$ $[M+Na]^+$ 856.4075, found: 856.4061.
16. Data for **10**: $[\alpha]_D^{33} - 2.2$ (*c* 0.76, $CHCl_3$); υ_{max} (KBr)/cm^{-1}: 3426, 2081, 1636, 1415, 1256, 1159, 1090, and 666; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 5.19 (d, *J* = 7.8 Hz, exchangeable with D_2O, 1H), 3.83 (br m, 1H), 3.66–3.54 (m, 3H), 3.49–3.46 (m, 2H), 3.39–3.30 (m, 1H), 3.25 (s, 1H), 3.05–2.99 (m, exchangeable with D_2O, 2H), 2.3 (s, CH_3 and an exchangeable proton, 4H), 0.78 (s, 9H), 0.73 (s, 9H), 0.002 (s, 6H), −0.12 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.8, 137.0, 129.8 (2×-C), 127.2 (2×-C), 72.1, 71.9, 68.3, 63.9, 62.2, 57.2, 25.8 (6×-C), 21.5, 18.2, 17.9, −4.7, −4.9, −5.7 (2×-C); HRMS (ESI) calcd for $C_{25}H_{49}NO_7SSi_2Na$ $[M+Na]^+$ 586.2666, found 586.2675.
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18. Data for **11**: $[\alpha]_D^{28} - 22.0$ (*c* 0.41, $CHCl_3$); υ_{max} (KBr)/cm^{-1}: 3518, 3444, 3277, 2930, 2856, 1757, 1698, 1595, 1575, 1470, 1399, 1310, 1253, 1192, 1157, 1098, 1037, 953, 837, 787, 715, 686, 634, 559, 467, and 429; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.2 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 2H), 4.06–3.84 (m, 7H), 3.55 (d, *J* = 13.5 Hz, 1H), 3.03 (s, exchangeable with D_2O, 1H), 2.43 (s, 3H), 2.17 (s, exchangeable with D_2O, 1H), 0.94 (s, 9H), 0.84 (s, 9H), 0.15 (s, 6H), 0.015 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.3, 137.9, 129.6 (2×-C), 127.3 (2×-C), 71.7, 69.5, 69.2, 61. 3, 56.0, 48.1, 25.9 (3×-C), 25.8 (3×-C), 21.5, 18.3, 18.0, −4.5, −4.9, −5.7, −5.9; HRMS (ESI) calcd for $C_{25}H_{48}NO_7SSi_2$ $[M+H]^+$ 546.2741, found 546.2730.
19. The crystallographic data for the structure **11** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-782793. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@cam.ac.uk.
20. Data for **6**.HCl: $[\alpha]_D^{31} - 2.3$ (*c* 0.6, MeOH) [lit.[11] $[\alpha]_D - 2.5$ (*c* 0.5, MeOH) and for its D-enantiomer[13d] $[\alpha]_D + 2.6$ (*c* 1.6, MeOH)]; υ_{max} (KBr)/cm^{-1}: 3134 (br), 2332, 2135, 1597, 1409, 1343, 1119, 974, 733, 619, and 470; ^1H NMR (300 MHz, D_2O) δ 4.17–4.12 (m, 1H), 4.03–4.01 (m, 1H), 3.96 (br m, 1H), 3.80 (dd, *J* = 12, 4.8 Hz, 1H), 3.72 (m, 1H), 3.45–3.40 (m, 1H), 3.21(dd, *J* = 12.0, 4.8 Hz, 1H), 3.02 (t, *J* = 11.7 Hz, 1H); ^{13}C NMR (300 MHz, D_2O) δ 68.4, 67.1, 62.5, 58.8, 55.3, 42.2 [lit.[11] ^{13}C NMR (125 MHz, D_2O) δ 68.5, 67.2, 62.6, 59.0, 55.5, 42.4]; HRMS (ESI) calcd for $C_6H_{14}NO_4$ $[M+H]^+$ 164.0923, found 164.0924.