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Synthesis of an iminosugar based peptidomimetic analogue

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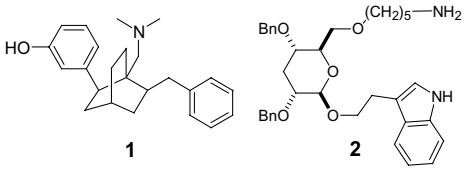
Abstract—The synthesis of 1-deoxymannojirimycin based analogue of a known HIV-protease inhibitor is described. The strategies employed for introduction of the pharmacophore groups onto the azasugar scaffold were based on regioselective reactions of the hydroxyl groups of the natural product and of D-fructopyranoside derivatives.

Peptidomimetic research has a goal of developing bioactive compounds with improved pharmacokinetic properties.[1] The general principle is that pharmacophoric groups are grafted onto a nonpeptide scaffold, which can orient them in the direction of their respective binding subsites. Farmer first proposed the use of cyclohexane as such a scaffold.[2] Later Belanger and Dufresne designed target **1** as an enkephalin mimic.[3] Subsequently researchers at the University of Pennsylvania introduced β-D-glucopyranose (e.g., **2**), its enantiomers and a diastereomer (β-D-mannopyranose) as scaffolds that provided bioactive compounds.[4] Concurrently Olson et al. reported a similar approach employing a cyclohexane scaffold.[5] Validation of the concept has led other groups to utilize sugar scaffolds in peptidomimetic and other research.[6,7]



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The design, synthesis, and evaluation of the first generation peptidomimetic inhibitors of HIV-1 protease that incorporate β-D-manno- and β-D-glucopyranoside scaffolds has been recently reported.[8] One of the compounds, which showed activity in this study was β-D-glucopyranose derivative **3**. We hypothesize that the activity of **3** is due to it binding competitively in the active site of the enzyme; the *t*-butyl groups and the phenyl group are oriented into enzyme subsites and the 2-OH group interacts with the catalytic aspartates in the active site (Fig. 1). Although **3** has the glucose configuration there were β-D-mannopyranosides that were also active.[8] On this basis we have designed the putative inhibitor **4**, which is based on the naturally occurring glycosidase inhibitor 1-deoxymannojirimycin (DMJ). Possible advantages of using DMJ or other azasugars as scaffolds in peptidomimetic design over the β-D-glucopyranose variants are that the azasugar could be charged at physiological pH and also be a hydrogen bond donor; this contrasts with **3** where the pyranose oxygen atom has hydrogen bond acceptor potential. Molecular modeling indicates that the protonated nitrogen of **4** could hydrogen bond with a carbonyl group of the HIV-protease amide backbone, assuming

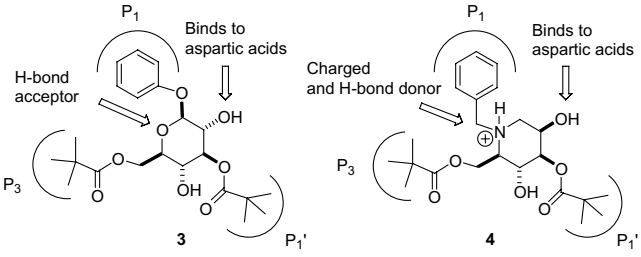

Figure 1. Design of putative azasugar peptidomimetic.

Keywords: Peptidomimetic; Scaffold; Deoxynojirimycin; Azasugar; 1-Deoxymannojirimycin; Protease inhibitor.
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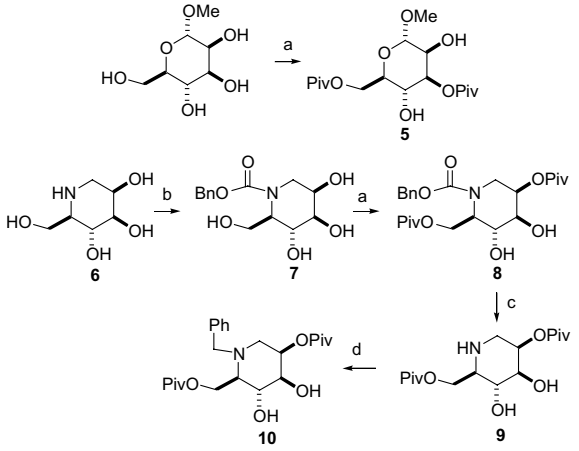
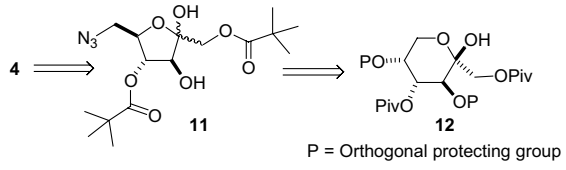


Scheme 1. Reagents and conditions: (a) PivCl (2 equiv), Py 2 h; (b) BnCOCl, $NaHCO_3$, dioxane, H_2O, 74%; (c) 10% Pd–C, H_2, MeOH, 61%; (d) K_2CO_3, BnBr, DMF, 71%.

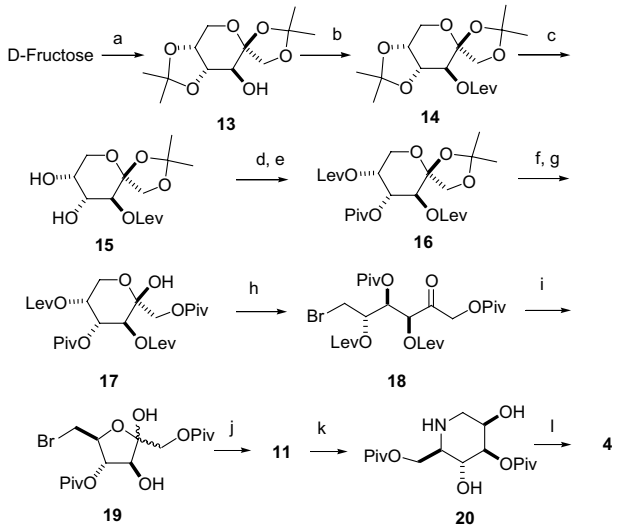


Scheme 2. Retrosynthetic analysis.

the compound would bind as predicted (Fig. 1). We thus developed a synthetic route to **4**.

There have been a number of syntheses of DMJ **6** including a route developed by our group.[9] Attempts to use DMJ as a starting compound for preparation of **4** were not successful. In general we found that reactions of DMJ were low yielding and the products obtained were prone to decomposition. Also the chemical behavior of DMJ and that of its derivatives cannot be compared directly to D-mannopyranosides. For example, whereas the di-*O*-pivaloylation of methyl α-D-mannopyranoside gave **5**[10] the corresponding reaction of **7** was found to proceed to give **8** as a result of pivaloylation at the 2- and 6-OH groups (Scheme 1). The reason for this is that introduction of the Cbz group to give **7** results in a conformational switch of the DMJ ring from $^4C_1$ to $^1C_4$; the 2-OH group is thus equatorial and more nucleophilic than the 3- or 4-OH groups. Attempts to alter the regioselectivity of the pivaloylation by using $(Bu_3Sn)_2O$/PivCl led only to intractable product mixtures or the recovery of **7**. However, it was possible to convert **8** into 2,6-di-*O*-pivaloylated DMJ derivative **9** and *N*-benzylated DMJ derivative **10**[11] as shown in Scheme 1.

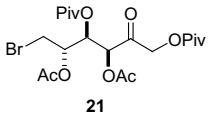
One of the shortest syntheses of DMJ has been achieved by Stütz and co-workers from D-fructose.[12] We thus investigated alternative routes to **4** via intermediates derived from this ketohexose. It was proposed (Scheme 2) that the 1,4-di-*O*-pivaloylated-6-azido-fructofuranoside **11** would be a viable intermediate and that it could be prepared from **12**.



Scheme 3. Reagents and conditions: (a) acetone, H_2SO_4, 54%; (b) levulinic acid, DCC (2 equiv), DMAP (cat.), THF, 91%; (c) 80% AcOH, 45 °C, 4 h; (d) PivCl (1.1 equiv), Py −78 °C to rt overnight, 98%; (e) levulinic acid (1.8 equiv), DCC (2 equiv), DMAP (cat.), THF, 77%; (f) TFA/H_2O (4:1), 2 h, 85%; (g) PivCl (1.2 equiv), Py 15 h, 90%; (h) PPh_3Br_2, Py CH_2Cl_2, 3 h, heat at reflux, 93%; (i) $NH_2NH_2{\cdot}H_2O$, AcOH, H_2O, 0 °C, 66%; (j) NaN_3, DMF, rt, 48 h, 53%; (k) 10% Pd–C, H_2, MeOH, 22%; (l) K_2CO_3 (0.6 equiv), BnBr (1.15 equiv), DMF, 60%.

The levulinate ester **14** was first prepared by DCC–DMAP promoted coupling of levulinic acid[13] with **13**.[14] Selective deprotection of the 4,5-di-*O*-isopropylidene using 80% aqueous acetic acid at 45 °C gave **15**. Regioselective pivaloylation of the 4-OH of **15** was followed by introduction of a second levulinate group at O-5 and gave **16**. The 1,2-di-*O*-isopropylidene was next removed using aqueous TFA and subsequent pivaloylation gave **17**. Reaction of **17** with triphenylphosphine-bromine as described by Stütz gave the 6-deoxy-6-bromo-fructose derivative **18** (93%). The levulinate groups were then removed using hydrazine hydrate to give furanose **19** and its subsequent reaction with sodium azide in DMF gave **11**. The catalytic hydrogenation of **11** gave the 3,6-di-*O*-pivaloylated DMJ **20** (22%), which was then converted to the desired *N*-benzyl derivative **4**[15] using potassium carbonate and benzyl bromide in DMF (60%) (Scheme 3).

The use of the levulinate as opposed to other protecting groups was necessary in order to complete the synthesis of **4**. Other potential intermediates such as **21** were prepared but the selective removal of the acetates could not be achieved in our hands. Also the reaction of **21** with sodium azide led to decomposition and resulted in an intractable product mixture.



We have demonstrated a strategy for selective manipulation of hydroxyl groups of 1-deoxymannojirimycin so

that pharmacophoric groups could be grafted onto this scaffold. Herein we have focused on synthesis of a compound that might prove useful as a peptidomimetic based HIV protease inhibitor. The biological evaluation of **4** and related compounds are underway. To the best of our knowledge azasugar derived peptidomimetics have not been synthesized previously. They may have potential applications more widely as scaffolds for presentation of pharmacophore groups and have application in other areas of bioorganic and medicinal chemistry.

Acknowledgements

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11. Analytical data for **10**: $[\alpha]_D = -93$ (*c* 0.33, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$, 1.30 (2s, 9H each, Piv), 2.26 (dd, 1H, $J_{1b-2} = 2.8$, $J_{1a-1b} = -13.2$, H-1b), 2.44 (dd, 1H, $J_{4-5} = 8.4$, H-5), 2.99 (dd, 1H, $J_{1a-2} = 3.6$, $J_{1a-1b} = -13.2$, H-1a), 3.09 (d, 1H, $J = -17.4$, CH_2), 3.67–3.79 (m, 2H, H-3, H-4), 4.30 (d, 1H, $J = -17.4$, CH_2), 4.56 (d, 1H, $J_{5-6b} < 0.5$, $J_{6a-6b} = -12.6$, H-6b), 4.73 (dd, 1H, $J_{5-6a} < 0.5$, $J_{6a-6b} = -12.6$, H-6a), 5.12 (br s, 1H, H-2), 7.27–7.38 (m, 5H, Bn); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 27.2$, 27.3 (CH_3, Piv), 39.0 (C, Piv), 52.9, 56.6, 60.5 (CH_2, C-1, C-6), 65.8, 69.2, 69.4, 74.0 (C-2, C-3, C-4, C-5), 127.2, 127.4, 128.3, 128.4 (CH-arom), 138.7 (C-arom), 178.5, 179.5 (CO, Piv); MS: $[M+H]^+ = 422.3$, $[M+Na]^+ = 444.3$.
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14. This was prepared by thermodynamically controlled acetonation of fructose in acetone with sulfuric acid. See Brady, R. F., Jr. *Carbohydr. Res.* **1970**, *15*, 35.
15. Analytical data for **4**: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (s, 18H, Piv), 2.33 (br d, 1H, $J_{1b-2} < 0.5$, $J_{1a-1b} = -12.0$, H-1b), 2.55 (dt, 1H, H-5), 2.87 (dd, 1H, $J_{1a-2} = 4.5$, $J_{1a-1b} = -12.0$, H-1a), 3.35 (d, 1H, $J = -13.2$, CH_2), 3.86–3.91 (m, 2H, H-2, H-4), 4.15 (d, 1H, $J = -13.2$, CH_2), 4.54 (dd, 1H, $J_{5-6b} = 2.7$, $J_{6a-6b} = -12.6$, H-6b), 4.61 (dd, 1H, $J_{5-6a} = 3.3$, $J_{6a-6b} = -12.6$, H-6a), 4.68 (dd, 1H, $J_{2-3} = 3.0$, $J_{3-4} = 9.0$, H-3), 7.26–7.38 (m, 5H, Bn); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 26.1$, 26.2 (CH_3, Piv), 37.9, 38.1 (C, Piv), 52.9, 55.8, 59.3 (CH_2, C-1, C-6), 65.8, 65.9, 67.4, 77.2 (C-2, C-3, C-4, C-5), 126.5, 127.6, 127.7, 127.9 (CH-arom), 136.8 (C-arom), 177.8, 178.0 (CO Piv); ESMS: $[M+H]^+ = 422.3$, $[M+H_2O]^+ = 439.5$, $[M+Na]^+ = 444.3$.