Pergamon

Tetrahedron Letters 39 (1998) 5841–5844

TETRAHEDRON LETTERS

Synthesis and Evaluation of a 5-Membered Isoiminosugar as Glycosidase Inhibitor

Michael Godskesen, Inge Lundt*

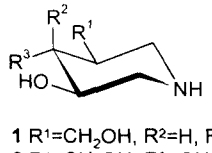
Department of Organic Chemistry, Technical University of Denmark, Building 201, DK-2800 Lyngby, Denmark

Received 29 April 1998; accepted 1 June 1998

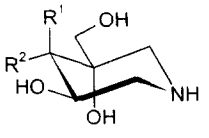
Abstract: (3*R*, 4*R*)-4-hydroxy-3-hydroxymethylpyrrolidine (**6**) was prepared from D-xylose and found to be a weak inhibitor of α-D-, β-D-glucosidase and α-L-fucosidase.

Since the first synthesis of Isofagomin (**1**),[1] a potent β-glucosidase inhibitor (K_i 0.11 μM), several other isoiminosugars[2] with the anomeric carbon replaced by a nitrogen and the ring oxygen by a methylene group have been synthesised and shown to be potent inhibitors of their corresponding β-glycosidases. Thus, the isoiminosugar **2**, having D-*lyxo*-configuration, inhibited β-galactosidase (K_i 0.41μM)[3] while **3**, having D-*arabino*-configuration and being a 6-carboxylate, inhibited β-D-glucuronidase (K_i 7.9 μM).[4] The isoiminosugars **4** and **5** are analogues of **1** and **2**, respectively, both with an OH-group on the quaternary carbon of the heterocyclic ring. This change in substitution pattern makes both compounds somewhat weaker inhibitors, however, compared to **1** and **2**: compound **4** and **5** inhibit β-glucosidase (K_i 4.3 μM)[5] and β-galactosidase (K_i 5.7 μM),[6] respectively.

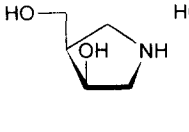
The iminosugars, in which the ring oxygen is replaced by a nitrogen, are well documented as glycosidase inhibitors[7] and this holds for both 6-membered (hydroxylated piperidines) and 5-membered (hydroxylated pyrrolidines) iminosugars. It would thus be of interest to investigate the inhibitory properties of 5-membered isoiminosugars. So far, compound **7**, which has an OH-group on the quaternary carbon of the ring, is the only 5-membered isoiminosugar to have been synthesised,[8] but did not have any significant glycosidase inhibitory properties.[8] We here report on the first synthesis of the 5-membered isoiminosugar **6** and evaluation of its inhibitory properties against several glycosidases.



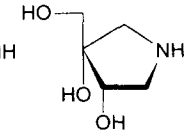
1 R^1=CH_2OH, R^2=H, R^3=OH
2 R^1=CH_2OH, R^2=OH, R^3=H
3 R^1=COOH, R^2=H, R^3=OH



4 R^1=H, R^2=OH
5 R^1=OH, R^2=H



6



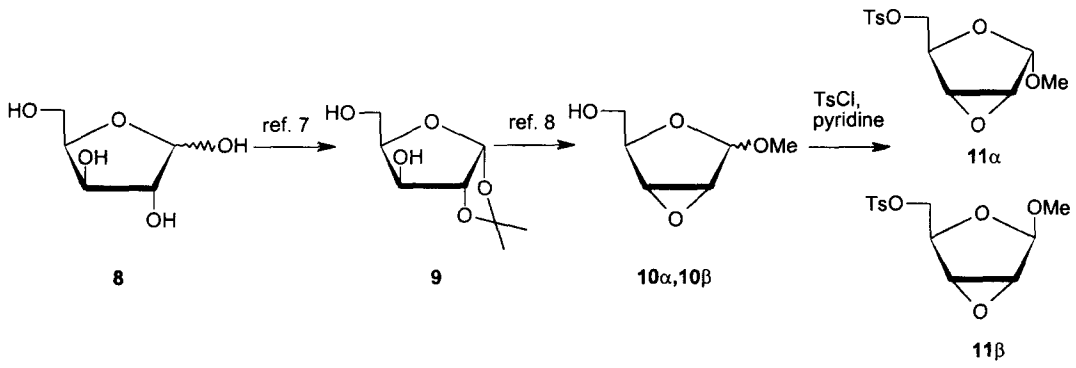
7

Synthesis of isoiminosugars required in all cases formation of a C-C bond since none of the molecules from the chiral pool has the desired carbon skeleton. The syntheses of both

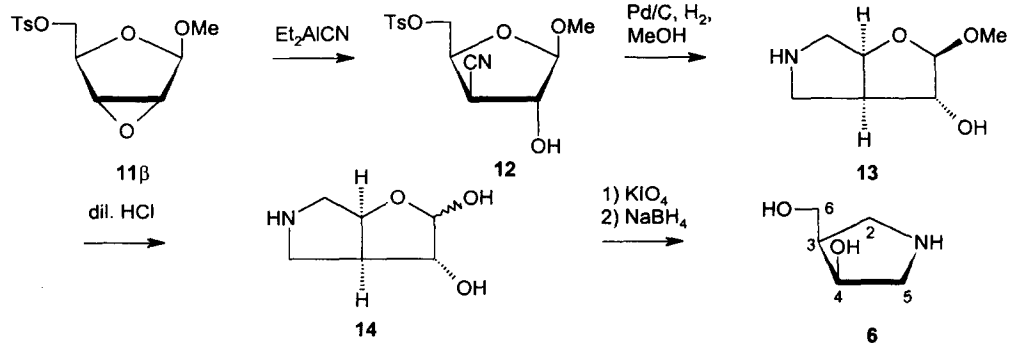
0040-4039/98/$19.00
PII: S0040-4039(98)01157-5

the 6-membered isoiminosugars **1-5** as well as the 5-membered analogue **7** have been accomplished by multistep syntheses using sugars as the chiral synthons where the branching carbon was introduced by use of carbon nucleophiles. The formation of the heterocyclic ring was performed via a reductive amination. Our retrosynthetic analysis suggested introduction of a CN-group to the sugar, with this group ultimately becoming part of the heterocyclic ring. Our target for the preparation of the 5-membered isoiminosugar **6** was thus compound **12** (Scheme 2). Previously, it has been shown[9] that methyl β-D-ribofuranoside could be opened stereoselectively at C-3 by reaction with diethylaluminium cyanide. Since the reagent is a Lewis acid it might be used in the presence of a tosyloxy group without any risk of a substitution reaction.

Treatment of D-xylose (**8**) with acetone under acidic conditions afforded the diacetonide which could be partially hydrolysed to give **9** in a one-pot reaction.[10] Following the procedure of Anderson et al., **9** was transformed into an anomeric mixture of the two methyl glycosides **10α** and **10β**,[11] which upon tosylation afforded the corresponding 5-*O*-tosylated epoxides **11α** and **11β** (Scheme 1). The anomers could be separated either by crystallisation or by flash chromatography also on a large scale. Both **11α** and **11β** have formerly been synthesised from pure **10α** and **10β**, respectively, which were separated by distillation at very low pressure.[12]



Scheme 1



Scheme 2

Reaction of **11β** with diethylaluminium cyanide in toluene at 60 °C afforded the pure cyano compound **12** after chromatography.[13] Hydrogenation (100 bar) of **12** in the presence of Pd on carbon gave the desired pyrrolidine derivative **13**. The methyl glycoside was then hydrolysed to give **14**. Cleavage of the bond between the two adjacent carbon atoms bearing oxygen was done with potassium (meta) periodate and subsequent reduction of the formed aldehyde with sodium borohydride furnished **6**. The isoiminosugar **6** could be crystallised as the p-nitrobenzoate.[14]

Evaluation of the 5-membered isoiminosugar **6** as glycosidase inhibitor revealed that the inhibitory properties of **6** were modest compared to the 6-membered isoiminosugars (Table 1).

Table 1

	α-D-Glucosidase Bakers yeast	β-D-Glucosidase almonds	α-D-Galactosidase green coffee beans	β-D-Galactosidase *Aspergillus niger*	α-D-Mannosidase jack bean	β-D-Mannosidase snail acetone powder	β-D-Xylosidase *Aspergillus niger*	α-L-Fucosidase bovine kidney
6	0.8 mM	1.0 mM	NI	NI	NI	NI	NI	0.9 mM

NI: no inhibition, pH 6.8

Acknowledgements: Financial support to this project by the Danish Technical Research Council is greatefully acknowledged.

References and notes:

1. Jespersen, T. M., Dong, W., Sierks, M.R., Skrydstrup, T., Lundt, I., Bols, M. *Angew. Chem.* **1994**, *106*, 1858 (Int. Ed. Engl. **1994**, *33*, 1778); Jespersen, T.M., Bols, M., Sierks, M.R., Skrydstrup, T. *Tetrahedron* **1994**, *50*, 13449.
2. Instead of Isoiminosugar the terms 1-N-Iminosugar (Ichikawa, M., Igarashi, Y., Ichikawa, Y. *Tetrahedron Letters* **1995**, *36*, 1767) or 1-Aza-sugar (Bols, M. *Accounts Chem. Res.* **1998**, *31*, 1) have been used.
3. Ichikawa, Y.; Igarashi, Y. *Tetrahedron Lett.* **1995**, *36*, 4585.
4. Igarashi, Y.; Ichikawa, M.; Ichikawa, Y. *Tetrahedron Lett.* **1996**, *37*, 2707.
5. Ichikawa, M.; Igarashi, Y.; Ichikawa, Y. *Tetrahedron Lett.* **1995**, *36*, 1767.
6. Ichikawa, M.; Ichikawa, Y. *Bioorg. Med. Chem.* **1995**, *3*, 161.
7. Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319

8. Bols, M., Persson, M.P., Butt, W.M., Jørgensen, M., Christensen, P., Hansen, L.T. *Tetrahedron Lett.* **1996**, *37*, 2097.
9. Wantanabe, S.; Kavai, I.; Bobek, M. *J. Carbohydr. Chem.* **1995**, *14*, 685.
10. Moravcová, J.; Čapková, J.; Stanek, J. *Carbohydr. Res.* **1994**, *263*, 61.
11. Anderson, C. D.; Goodman, L.; Baker, B. R. *J. Am. Chem. Soc.* **1958**, *80*, 5247.
12. Goodman, L. *J. Am. Chem. Soc.* **1964**, *86*, 4167.
13. *Methyl 3-C-cyano-5-O-p-toluenesulfonyl-β-D-xylofuranoside* (**12**): Methyl 2,3-anhydro-5-*O*-p-toluenesulfonyl-β-D-ribofuranoside (**11**β) (8.00 g) was added a solution of diethylaluminium cyanide in toluene (1 M, 40 ml), under nitrogen, kept at 60 °C for 6.5 h and then left overnight at room temperature. [CAUTION: Et_2AlCN is very toxic.] Ethylacetate (100 ml) was added and the mixture was poured on ice/water (150 g). After stirring for 20 min the phases were separated and the water phase was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated. Purification was done by chromatography EtOAc/hexane to give **12**, 6.01 g (69%); mp. 108-109.5 °C, $[\alpha]_D^{20}$ -33.3° (*c* 1.0, $CHCl_3$). Anal. C, H, N
^{13}C NMR ($CDCl_3$): δ 145.3, 132.4, 129.9, 128.0 (aromatic carbon), 115.4 (CN), 109.3 (C-1), 78.7 (C-4) 75.7 (C-2), 69.8 (C-5), 55.0 (OMe), 38.2 (C-3) and 21.5 (Ph-$\underline{C}H_3$).
^1H NMR ($CDCl_3$): δ 7.82 (d, 2H, Ph, J = 8 Hz), 7.37 (d, 2H, Ph), 4.88 (s, H-1), 4.69 (dt, H-4, $J_{3,4}$ = 7.4 Hz, $J_{4,5}$ = 7.0 Hz, $J_{4,5'}$ = 5.9 Hz), 4.53 (s, H-2), 4.29 (dd, H-5, $J_{5,5'}$ = 10.4 Hz), 4.19 (dd, H-5'), 3.29 (s, OMe), 3.25 (d, H-3), 2.71 (bs, O$\underline{H}$) and 2.46 (s, Ph-$\underline{C}H_3$).
14. *(3R, 4R)-4-hydroxy-3-hydroxymethylpyrrolidine* (**6**): Methyl 3-*C*-cyano-5-*O*-p-toluene-sulfonyl-β-D-xylofuranoside (**12**) (1.00 g) was dissolved in methanol (20 ml), mixed with Pd/C (5 %, 300 mg) and kept at 100 bar H_2, rt. for 18h. [CAUTION: methanol might spontaneous burn when mixed with Pd/C. This can be circumvented by using a N_2 atmosphere.] Filtration and treatment with ion exchange resin (IRA-420, OH-, 13 ml) purified the methylglycoside **13**. ^{13}C NMR (H_2O): δ 110.9, 87.6, 80.9, 55.6, 54.4, 51.4, 50.4. Crude **13** was dissolved in HCl (2M, 10 ml) and heated to 75 °C for 10 h. Concentration left an anomeric mixture of **14** (1:7). ^{13}C NMR (H_2O): δ 97.2, 79.1, 76.2, 51.4, 49.5, 48.6 and 101.5, 81.9, 79.7, 52.7, 48.8, 47.8. Cleavage of the bond between the two hydroxy substituted carbon atoms was accomplished by addition of potassium (meta) periodate (0.84 g) at 0 °C to a solution of **14** in water (10 ml) and stirring was continued for 2h at rt. Sodium borohydride (0.46 g) was subsequent added and the mixture was stirred over night. Water was removed and methanol (acidic) was evaporated from the mixture twice. The pyrrolidine **6** was treated with ion exchange resin (IR-120, H^+, 8 ml), eluated with conc. aqueous ammonia and concentrated. A crystalline product was obtained by addition of p-nitrobenzoic acid (271 mg, 1 eq.) to give the p-nitrobenzoate of **6** as colourless crystals (347 mg, 40%); mp. 147-148 °C, $[\alpha]_D^{20}$ -10.2° (*c* 0.6, MeOH). Anal. C, H, N.
^{13}C NMR ($CDCl_3$): δ 149.5, 143.4, 130.2, 124.1 (aromatic carbon), 70.1 (C-4), 59.0 (C-6), 54.1 (C-5), 46.2 (C-2) and 45.6 (C-3).
^1H NMR ($CDCl_3$): δ 8.18 (d, 2H, Ph, J = 8.8 Hz), 7.91 (d, 2H, Ph, J = 8.8 Hz), 4.53 (t, H-4, $J_{3,4} = J_{4,5}$ = 3.6 Hz, $J_{4,5'}$ = 0 Hz), 3.77 (dd, H-6, $J_{3,6}$ = 7.3 Hz, $J_{6,6'}$ = 11.2 Hz), 3.68 (dd, H-6', $J_{3,6'}$ = 6.6 Hz), 3.50 (dd, H-2, $J_{2,3}$ = 8.6 Hz, $J_{2,2'}$ = 11.6 Hz), 3.41(dd, H-5, $J_{5,5'}$ = 12.8 Hz), 3.34 (d, H-5'), 3.12 (t, H-2', $J_{2',3}$ = 11.5 Hz) and 2.49 (m, H-3).