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Synthesis and evaluation of 3-deoxy and 3-deoxy-3-fluoro derivatives of gluco- and manno-configured tetrahydropyridoimidazole glycosidase inhibitors

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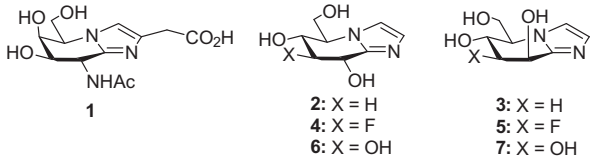
ABSTRACT

Three tetrahydropyridoimidazole-type glycosidase inhibitors have been synthesized with the 3-deoxy ribo- and arabino-, and 3-deoxy-3-fluoro gluco-configurations and two of them screened for activity against α- and β-gluco- and mannosidase enzymes. Only one substance, the 3-deoxy-3-fluoro-derivative of the gluco-configured tetrahydropyridoimidazole was found to have any activity against a single enzyme, sweet almond β-glucosidase, and even then at a level 100-fold lower than that of the corresponding simple gluco-configured tetrahydropyridoimidazole thereby underlining the importance of the 3-hydroxy group in the key substrate–enzyme interactions.

1. Introduction

The glycoimidazoles, inspired by the natural *N*-acetyl-β-D-glucosaminidase inhibitor nagstatin 1,[1] are some of the most potent inhibitors of glycosidase enzymes[2,3] and are considered to be good mimics of the transition state for glycosidic bond hydrolysis by these enzymes[4–7] for which they provide strong support for Vasella's lateral protonation model.[8,9] Work from the Davies group indicated the developing importance of the 3-OH–enzyme interaction in the course of the hydrolysis (i) of retaining β-mannopyranosides by the mannanase 26A from *Pseudomonas cellulosa* as the substrate proceeds along its $^{1}S_{5}\rightarrow B_{2,5}\rightarrow {}^{O}S_{2}$ pseudorotational conformational itinerary,[10] and (ii) of retaining β-glucopyranosides by endoglucanase enzymes in the course of the $^{4}C_{1}\rightarrow {}^{4}H_{3}\rightarrow {}^{1}S_{3}$ substrate pseudorotational itinerary for hydrolysis.[11–13] The importance of this interaction inspired the synthesis and evaluation of the 3-deoxy- and 3-deoxy-3-fluoro analogs **2**–**5** of the gluco- and manno-configured tetrahydropyridoimidazoles **6** and **7** originally prepared by Tatsuta et al.[14] Our interest in the synthesis of **2**–**5** was further heightened by the importance of the C3–O3 bond in the control of stereochemistry in the course of 4,6-*O*-benzylidene directed α-gluco- and β-mannopyranosylations noted in our laboratory,[15,16] and by the distortions of the pyranose ring conformations observed crystallographically for 3-deoxy and 3-deoxy-3-fluoroglucopyranoses.[17,18]



2. Results and discussion

Adapting Vasella's synthesis of **6** to our purposes,[19–21] allyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-naphthylmethyl)-α,β-D-glucopyranoside **8**[22] was converted to the pyranose **9** by treatment with potassium *tert*-butoxide followed by iodine and water (Scheme 1).[22] Swern oxidation[23] afforded the lactone **10**, which on exposure to methanolic ammonia gave the hydroxyl amide **11** (Scheme 1). Oxidation with the Dess–Martin periodinane[24] afforded an approximately 1:1 mixture of the two cyclic hemiamidals **12**, whose reduction with triethylsilane in the presence of boron trifluoride etherate provided the lactam **13**. Heating of **13** with Lawesson's reagent[25,26] gave the corresponding thionolactam **14** which on treatment with glycinal dimethylacetal followed by exposure to *p*-toluenesulfonic acid

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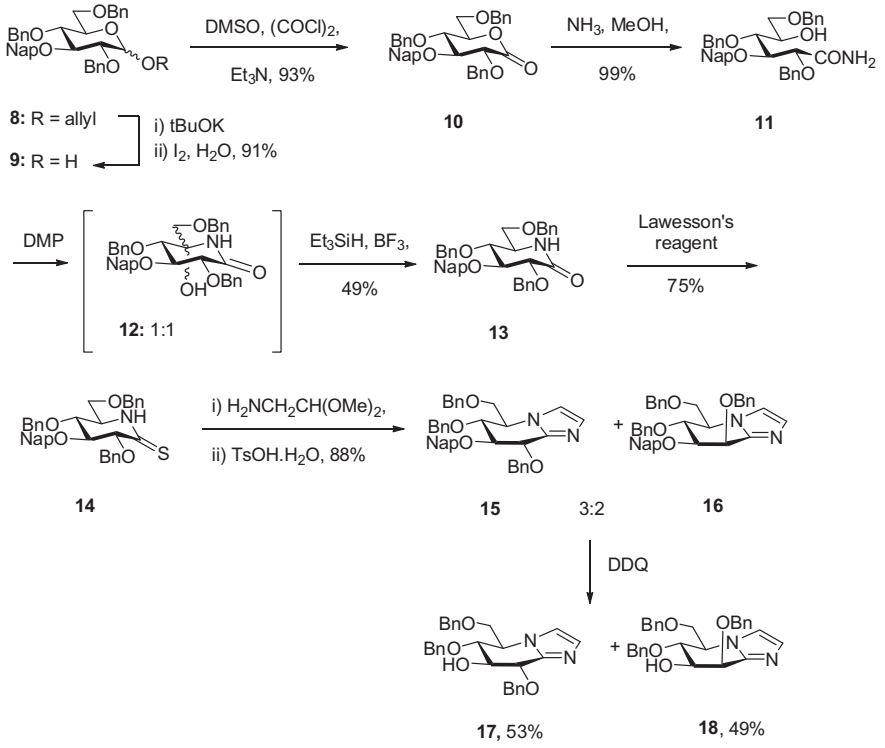


Scheme 1. Synthesis of the selectively protected gluco- and manno-configured tetrahydropyridoimidazoles **17** and **18**.

furnished the gluco and mannoimidazoles **15** and **16** in an approximately 3:2 ratio. Oxidative cleavage of the naphthylmethyl ether in **15** and **16** with DDQ[27] then gave the corresponding 3-hydroxy gluco- and manno-configured tetrahydropyridoimidazoles **17** and **18** (Scheme 1).

Compounds **17** and **18** were then processed to the corresponding 3-deoxy derivatives **21** and **22** in the standard manner by xanthate ester formation and subsequent treatment with tributyltin hydride and AIBN (Scheme 2).[28]

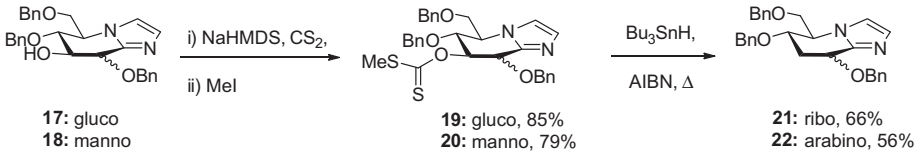
Individual treatment of **17** and **18** with sodium hexamethyldisilazide followed by *N,N*-ditriflyl-2-amino-5-chloropyridine (Comin's reagent)[29] gave the corresponding triflate esters **23** and **24**, which on stirring with *p*-nitrobenzoic acid and cesium carbonate followed by methanolysis gave the corresponding allo- and altroimidazoles **25** and **26**, respectively, albeit in low yields because of competing elimination of the triflate esters. Finally, treatment of the allo-isomer **25** with DAST[30] gave the 3-deoxy-3-fluoro derivative **27** of gluco-configured tetrahydropyridoimidazole (Scheme 3). Unfortunately, all attempts to obtain the corresponding 3-deoxy-3-fluoro derivative **28** of manno-configured tetrahydropyridoimidazole by the same method resulted in failure.

Finally, hydrogenolysis of compounds **21**, **22**, and **27** over palladium hydroxide on charcoal afforded the target glycoimidazoles **2**–**4**, which were isolated in the form of their acetate salts (Scheme 4).

The 3-deoxy derivative **3** of the manno-configured tetrahydropyridoimidazole and the 3-deoxy-3-fluoro derivative **4** of the gluco-configured tetrahydropyridoimidazole were assayed for inhibitory activity of *Saccharomyces cerevisiae* α-glucosidase, almond β-glucosidase, Jack bean α-mannosidase, and *Helix pomatia* β-mannosidase. The 3-deoxy derivative of manno-configured tetrahydropyridoimidazole **3** was inactive against all four enzymes, whereas the 3-deoxy-3-fluoro derivative of gluco-configured tetrahydropyridoimidazole showed modest activity for the inhibition of almond β-glucosidase but not for that of the other three glycosidases (Table 1). The IC_{50} value for the inhibition of almond β-glucosidase by **4** was determined to be 13.5 ± 1.5 μM, while that for potent β-glucosidase inhibitor isofagomine[2,3,31,32] **29** measured in parallel was 0.22 **±** 0.05 μM.

3. Conclusion

Three 3-deoxy or 3-deoxy-3-fluoro derivatives of tetrahydropyridoimidazole glycosidase inhibitors have been synthesized and two of them screened for activity against α- and β-gluco- and mannosidase enzymes. Only the 3-deoxy-3-fluoro derivative **4** of gluco-configured tetrahydropyridoimidazole showed any measureable activity and that only against sweet almond β-glucosidase. The IC_{50} for the inhibition of sweet almond β-glucosidase was approximately 100-fold less than that exhibited by the gluco-configured tetrahydropyridoimidazole **6** that retains the 3-hydroxy group, thereby underlining the importance of hydrogen bonding between the 3-hydroxy group and the enzyme noted by



Scheme 2. Deoxygenation of gluco and manno-configured tetrahydropyridoimidazoles **17** and **18**.