Pergamon

Tetrahedron Letters 40 (1999) 3461–3464

TETRAHEDRON LETTERS

Synthesis of an 1-azaglucose analogue with ring-oxygen retained.

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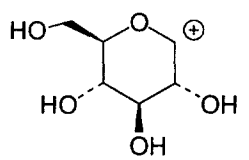
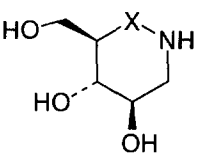
Received 5 January 1999; accepted 23 February 1999

Abstract: Synthesis of the glucose analogue 4,5-dihydroxy-6-hydroxymethyl-tetrahydrooxazine (**4**) is reported for the first time.

Selective inhibitors of glycoside cleaving enzymes are of considerable interest as potential antidiabetic, antiviral (HIV or influenza) or antimetastatic agents. There has consequently, in the last decade, been a focus on design and synthesis of transition state analogues of glycoside bond cleavage.[1-10] It has recently been found that mimics of cation **1**, namely the protonated forms of amines **2** and **3**, are strong inhibitors of a number of glycosidases and related enzymes.[11,12] Isofagomine (**2**) is, to our knowledge, the strongest inhibitor known of almond β-glucosidase and glycogen phosphorylase; 1-azafagomine (**3**) is slightly less potent (Fig 1).



1

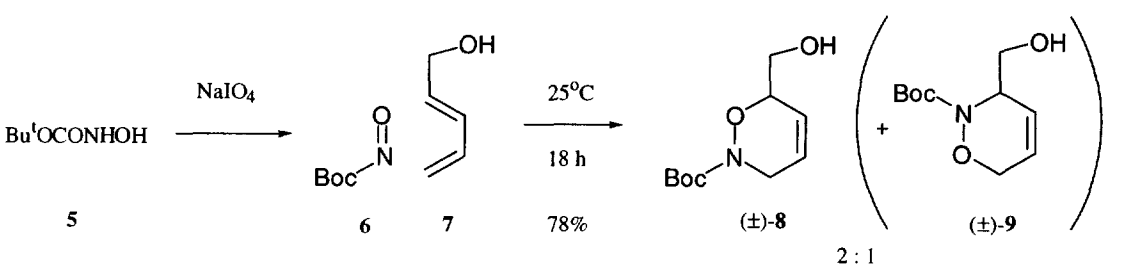


2 (X = CH_2)
3 (X = NH)
4 (X = O)

Fig 1. Glycosidase transition state and 1-azasugars

It can be argued that **2** and **3** are imperfect analogues of **1**, because they lack the ring oxygen. It can reasonably be supposed that retaining the ring oxygen by creating a oxazin derivative such as **4** would at least create a glycosidase inhibitor of equal strength to that of **2** and **3**. This compound was already proposed by Best *et al.* in 1994, and several efforts to synthesize this compound have been made,[13,14] including synthesis of a compound that was proposed to be the L-enantiomer of **4**.[13] With the desire to investigate the efficacy of **4** as a transition state analogue we have carried out and now report the synthesis of (±)-**4**.

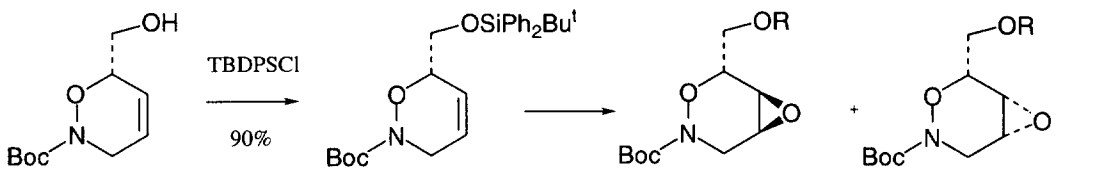
Our synthesis is based on a hetero Diels-Alder strategy. The *N*-Boc protected hydroxylamine **5**[15] was oxidized to the nitroso compound **6** using $NaIO_4$ as oxidant.[16] The dienophile **6** was then reacted *in situ* with the pentadienol **7**[17] to give the Diels-Alder adducts **8** and **9** in a ratio of 2:1 in a combined yield of 78 % (Scheme 1). These two regioisomers were separated to obtain (±)-**8** in a yield of 48 %.[18]



Scheme 1. Hetero Diels-Alder reaction

PII: S0040-4039(99)00423-2

Trans dihydroxylation of the alkenol **8** proved considerably more difficult than anticipated. It was expected that epoxidation of the double-bond could be achieved from the less hindered face, opposite to the hydroxymethyl group, and that the *trans*-epoxide would be hydrolysed by preferential attack γ to the hydroxymethyl group due to steric hindrance from the latter. This strategy was succesful in our recent synthesis of **3**.[19] To maximize the steric hindrance on the hydroxymethyl face the hydroxy group of compound **8** was protected using TBDPSCl and imidazol in DMF ([**8**] = 0.34 M, [TBDPSCl] = 0.37 M, [imidazol] = 0.85 M, 18h, 25 °C) to give the silyl ether (±)-**10** (90 %).

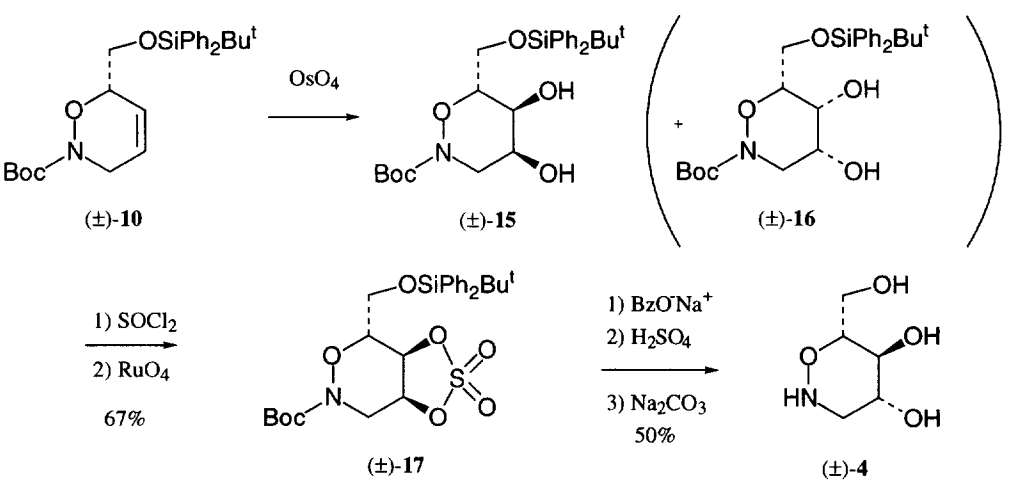


Scheme 2. Epoxidation of **10**

Epoxidation of **8** or **10** with m-chloroperbenzoic acid (MCPBA) in $ClCH_2CH_2Cl$ ([S] = 0.37 M, [MCPBA] = 0.67 M, 80 °C, 4h) or trifluoromethyl(methyl)dioxirane[19] ([S] = 0.09 M, [CF_3COMe] = 1.1 M, [$NaHCO_3$] = 0.7 M, [oxone] = 0.9 M, 1:2 H_2O-MeCN, 0-25 °C, 18h) gave mixtures of *trans* and *cis* epoxides (Scheme 2). When epoxidising **8** with MCBPA the Henbest effect was observed giving preferential *cis* epoxidation (table 1). Best *trans* selectivity, 4:1, was obtained by MCPBA epoxidation of **10**. However neither the epoxide pair **11/12** nor **13/14** could be separated satisfactorily by chromatography and therefore this modest selectivity was inadequate. Furthermore, hydrolysis of a mixture of each of the pairs of epoxides gave a mixture of diastereomeric *trans* diols.

Substrate	Reagent	Yield	Ratio **11/12** or **13/14**
8	MCBPA	77%	1:2
8	CF_3MeCO_2	86%	1:1
10	MCPBA	72%	4:1
10	CF_3MeCO_2	91%	2:1

Table 1 Epoxidation experiments



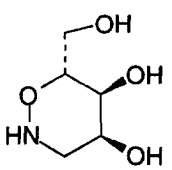
Scheme 3. Introduction of the *cis*-diol

On the other hand it was found that when compound **10** was subjected to OsO_4 catalysed dihydroxylation (0.25% OsO_4, [**10**] = 0.56 M, [NMO] = 0.9 M, Me_2CO/H_2O/tBuOH 4:4:3, 25 °C, 6 d) a good diastereoselectivity for formation of the *trans-cis* diol (±)-**15** was obtained. This compound was isolated in 45 % yield from **8**, while minute amounts of the *cis-cis* diol (±)-**16** (2 %) and recovered starting material **10** (18%) were removed by chromatography.

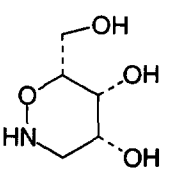
The diol (±)-**15** was now converted to the cyclic sulphate (±)-**17** in 67% yield through reaction with thionyl chloride[20] in CH_2Cl_2 ([**15**] = 0.3 M, [$SOCl_2$] = 0.9 M, [Et_3N] = 1.2 M, 0 °C, 20 min.) and subsequent oxidation[20] with RuO_4 in $CHCl_3$/MeCN/H_2O (4:4:5, [S] = 0.1 M, [RuO_4] = 0.01 M, [$NaIO_4$] = 0.2 M, 0 °C, 7 h). The sulphate (±)-**17** was reacted with sodium benzoate in DMF ([**17**] = 0.1 M, [NaOBz] = 0.2 M, 100 °C, 18 h), and then hydrolysed with acid and base (1. [S] = 0.2 M, 0.25% H_2SO_4 & 0.13% H_2O in dioxane, 25 °C, 18 h. 2. MeOH, [S] = 0.08 M, [Na_2CO_3] = 0.28 M, 25 °C, 18 h.). This gave the crude oxazin (±)-**4** in 50% yield for the two steps.[20]

The ^1H and ^{13}C NMR spectra of **4** were not identical to those reported for a compound proposed to be the L-enantiomer,[13] and it was clear that the two compounds were not identical. Both our spectra[21] and those of ref. 13 were plausible for the proposed structure, but only in our spectra did we observed large couplings between H-3, H-4 and H-5 fitting the anticipated $^4C_1$ conformation of a 6-ring with glucose stereochemistry. Another remarkable difference was that the ^{13}C NMR spectrum of our compound showed a signal at 81.3 ppm. This could be the C-5 being deshielded by the hydroxylamine substituent.

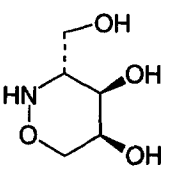
To confirm this we prepared the isomers **18-20** (Fig 2). Compound **18** and **19** were obtained in almost quantitative yield by acidic hydrolysis (4 M HCl, 100 °C, 2 h) of **15** and **16**, respectively. Compound **20** was obtained by dihydroxylation (OsO_4/NMO/t-BuOH, 25 °C, 5 d) of **9** followed by quantitative deprotection with TFA in CH_2Cl_2. Compounds **18** and **19** had the characteristic ^{13}C NMR peak of C-5 at 82.6 and 81.1, respectively, while the lowest field peak in **20** was at 71.7 ppm.[22] We thus have strong evidence[23] that compound **4** is the cyclic glucooxazin, and accordingly suggest that the assignation of that structure to Best *et al.*'s compound is incorrect.



(±)-**18**



(±)-**19**



(±)-**20**

Fig 2. Isomers of **4**.

The oxazin (±)-**4** inhibited almond β-glucosidase with a Ki of 60 μM, while very low inhibition of yeast α-glucosidase and galactosidases was observed. Compound (±)-**4** is thus a 500 fold weaker inhibitor of β-glucosidase than **2** and a 100 fold weaker inhibitor than (±)-**3**.[11] The explanation for this remarkable difference may be the low basicity of the nitrogen: the pKa of **4** is 3.6, compared to the pKa of 8.6 of **2**.

In this communication we reported the first synthesis of an 1-azaglucose analogue in which ring-oxygen has been retained. The compound is a relatively weak glucosidase inhibitor perhaps because it is a weak base. Further studies will try to elucidate this.

ACKNOWLEDGEMENTS

We acknowledge financial support from the Danish National Research Council through the THOR program.

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15. Prepared in 86% yield by reacting 1.2 M NH_2OH, HCl with 0.3 M $(Me_3COCO)_2O$ in the presence of 1.44 M NaOH in 50% aqueous THF analogues to the synthesis of 2,2,2-trichloroethyl N-hydroxycarbamate in ref. 16.
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18. Typical procedure: To 2,4-pentadienol (0.832 g, 10 mmol) in EtOAc (10 ml) was added a solution of $NaIO_4$ (1.71 g, 12 mmol) in citric acid buffer (0.5 M, pH 6, 20 ml). At 0 °C a solution of $Me_3COCONHOH$ (2.0 g, 15 mmol) in EtOAc (10 ml) was added over 10 min. The mixture was allowed to reach room temperature and was stirred over night. The mixture was then washed consecutively with solutions of $Na_2S_2O_3$ (10%, 20 ml), NaOH (10%, 20 ml) and NaCl (10%, 20 ml). The organic phase was dried ($MgSO_4$) and concentrated to a 2:1 mixture of **8** and **9** (1.7 g, 78%). By flash chromatography (EtOAc-pentane 1:2) **8** was isolated in 48% yield.
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21. ^{1}H-NMR (D_2O): δ 3.79 (dd, 1H, J_{6a6b} 12.5 Hz, J_{56a} 2.0 Hz, H-6a), 3.34-3.66 (m, 3H, H-3, H-5, H-6b), 3.30 (t, 1H, J_{34} , J_{45} 9.1 Hz, H-4), 3.17 (dd, 1H, J_{2ax2eq} 13.3 Hz, J_{2eq3} 5.4 Hz, H-2eq), 2.81 (dd, 1H, J_{2ax3} 10.7 Hz, H-2ax). ^{13}C-NMR (D_2O): δ 81.3 (C-5), 68.1 (C-3), 68.0 (C-4), 57.6 (C-6), 50.3 (C-2).
22. ^{13}C-NMR (D_2O): δ 82.6 (C-5), 66.4 (C-3), 65.3 (C-4), 61.7 (C-6), 53.9 (C-2). **19**: ^{13}C-NMR (D_2O): δ 81.1 (C-5), 63.0 (C-3), 61.1 (C-4), 58.1 (C-6), 42.3 (C-2). **20**: ^{13}C-NMR (D_2O): δ 71.7 (C-2), 64.7 (C-3), 64.5 (C-4), 57.2 (C-6), 57.1 (C-5).
23. For comparison the CH_2 ^{13}C chemical shifts in $HOCH_2CH{=}CH_2$ and $NH_2OCH_2CH{=}CH_2$ are 63.7 and 74.4 ppm, respectively (Aldrich NMR spectral collection).