Pergamon

Tetrahedron Letters 42 (2001) 6447–6449

TETRAHEDRON LETTERS

Polyhydroxylated aziridinylcyclopentanes as glycomimetics: a new competitive inhibitor of α-mannosidase

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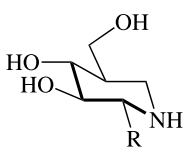
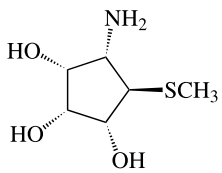
Received 2 July 2001; revised 20 July 2001; accepted 23 July 2001

Abstract—The synthesis of **6**, a new competitive inhibitor of jackbean α-mannosidase, was achieved in three steps from pyridine, illustrating the promising potential of substituted 6-azabicyclo[3.1.0]hexanes as glycomimetics.

Sugar-specific inhibitors of glycoside hydrolysis, whether naturally-occurring[1] or synthetic,[2] may be useful in treating carbohydrate-mediated metabolic disorders.[3] Potent glycosidase inhibitors based on both 6- and 5-membered cyclic structures have been described, including the 1-azasugars isofagomine **1**[2] and noeuromycin **2**,[4] and the aminocyclopentitols mannostatin **3**[5] and trehazolin **4**.[6]



1 R= H
2 R= OH



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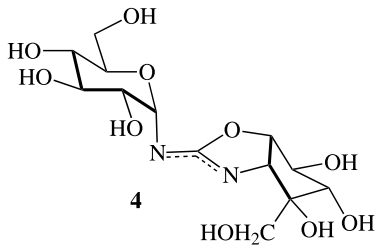

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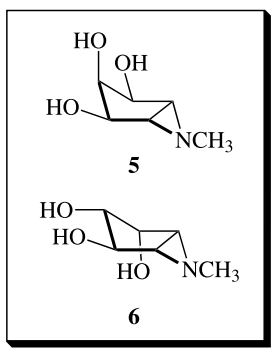

5

6

Our own interest in glycomimetic design led us to investigate the 6-azabicyclo[3.1.0]hexane ring system, as represented in **5** and **6**. These structures incorporate a polyhydroxylated aminocyclopentane within a conformationally constrained 1-azasugar framework,[7] thus displaying structural and stereochemical elements found in both families of glycosidase inhibitors. Given that **1** binds to β-glucosidase in its *N*-protonated form,[8] it was of interest to learn whether protonated **5** and **6** might serve as irreversible enzyme inactivators, as was noted for an aziridinyl glycomimetic several years ago.[9] Here we report the synthesis and biological activity of **5** and **6**. Compound **6** is a potent competitive inhibitor of jackbean α-mannosidase, suggesting that aziridinylcyclopentitols of defined stereochemistry represent useful new scaffolds for the design of glycomimetics.

Two considerations led us to select triols **5** and **6** as synthetic targets for this pilot study. First, both triols should be accessible by osmylation of aziridinyl alcohol **8** (Scheme 1), first prepared in 1973 by Kaplan et al. in unspecified yield by photo-induced hydrolysis of pyridinium salt **7**.[10] Secondly, molecular models indicated that triols **5** and **6** represented reasonable mimics of D-galactose and D-mannose, respectively, as depicted below. Superimposing **5** on galactose positioned the aziridine nitrogen on the anomeric carbon, whereas superimposing **6** (depicted after a 180° rotation) on mannose more closely aligned the nitrogen with the saccharide's pyranose oxygen.

Despite their ready availability from pyridinium salts, the synthetic utility of bicyclic aziridines like **8** has not been extensively studied. Mariano et al. investigated the

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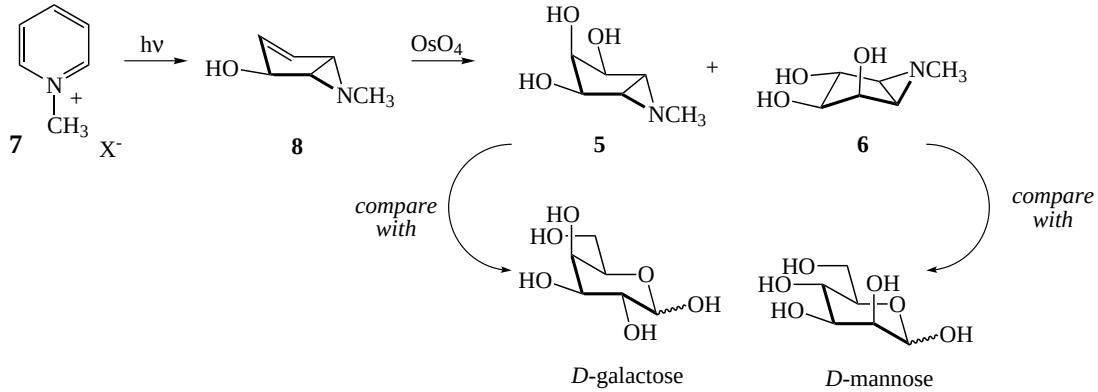
PII: S0040-4039(01)01343-0



Scheme 1.

scope of the Kaplan reaction,[11] and applied it to the enantioselective synthesis of mannostatin **3**.[12] Penkett and Simpson showed that the aziridine group in related photoalcoholysis products underwent ring-opening addition of organocuprates[13] as well as oxidative Meisenheimer rearrangements to furnish nitrones.[14]

While conditions for synthesizing **8** were not reported by Kaplan,[6] we observed that irradiation of **7** (X= ClO_4) in KOH–H_2O at 254 nm under argon afforded essentially pure **8** in 98% yield on 0.5–1 g scale. Catalytic dihydroxylation of **8** (OsO_4, *N*-methylmorpholine oxide) afforded the *meso* diastereomer **5** (83%)[15] and (±)-**6** (9%),[16] which were easily separated by flash chromatography.

Both **5** and **6** were assayed against yeast α-glucosidase, almond β-glucosidase, green coffee bean α-galactosidase, bovine liver β-galactosidase, and jackbean α-mannosidase. Despite its resemblance to galactose, racemic **5** had no effect on any of the enzymes tested at concentrations of 1 mM. However, (±)-**6** only inhibited α-mannosidase. Preincubation studies with **6** and the enzyme showed no time-dependent effects, thus ruling out covalent inactivation by the aziridinyl group of **6**. From analysis of a Lineweaver–Burk plot (Fig. 1), mannosidase inhibition by (±)-**6** was found to be competitive, with $K_I = 8.0 \pm 4$ μM.

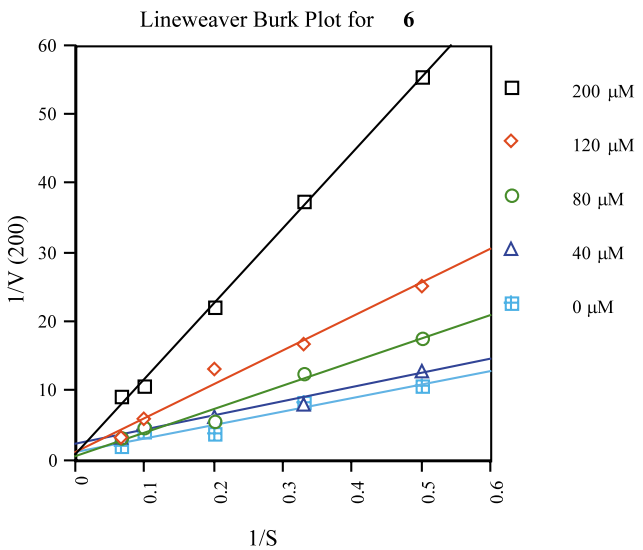


Figure 1.

In summary, the photohydration of *N*-alkylpyridinium salts provides ready synthetic access to structures displaying promising, saccharide-like properties. By choosing the appropriate *N*-alkyl group in **7** and performing suitable *O*-alkylations of **8**, it should be possible to prepare *N*- and *O*-linked congeners of oligosaccharides.

Acknowledgements

Financial support for this work was provided by the US National Institutes of Health (GM 35712). In addition, a Sokol Summer Fellowship to R.C.S. is gratefully acknowledged. Support of the Cornell NMR Facility has been provided by the National Science Foundation (CHE 7904825, PGM 8018643) and NIH (RR02002).

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15. For **5**: R_f 0.16 (CH_2Cl_2:MeOH:conc NH_4OH 50:40:1); ^1H NMR (CD_3OD): δ 3.93 (d, 2H, $J=4.8$ Hz), 3.70 (t, 1H, $J=4.8$ Hz), 2.30–2.15 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (CD_3OD): δ 74.4, 71.2, 49.9, 45.1; IR (film) 3310, 2920, 2900, 1630, 1450, 1410, 1320, 1220, 1110, 1080, 940, 850, 800 cm^{-1}; ESIMS m/z 146 (M+1, 100%) 128 (M−OH, 12%).
16. For **6**: R_f 0.46 (CH_2Cl_2:MeOH:conc NH_4OH 50:40:1); ^1H NMR (CD_3OD): δ 4.29 (dd, 1H, $J=5.4$, 6 Hz), 4.12 (s, 1H), 3.89 (b, 3H), 3.54 (d, 1H, $J=5.4$ Hz), 2.29 (s, 3H), 2.26 (m, 1H), 2.18 (m, 1H); ^{13}C NMR (CD_3OD): δ 75.4, 74.6, 71.7, 47.2, 46.1, 44.1; IR (film) 3310, 2910, 2880, 1600, 1460, 1420, 1260, 1210, 1110, 1050, 1030, 950, 910, 860, 830 cm^{-1}; ESIMS m/z 146 (M+1, 100%) 128 (M−OH, 8%).