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Enantioselective Synthesis of a New Family of α-L-Fucosidase Inhibitors

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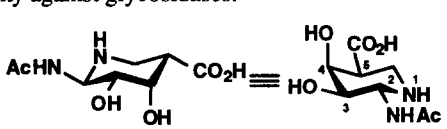
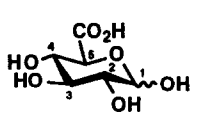
Abstract: *Gem*-diamine 1-*N*-iminosugars of L-fucose-type, a new type of glycosidase inhibitor, have been synthesized from D-ribono-γ-lactone, involving the formation of a *gem*-diamine 1-*N*-iminopyranose ring by the Mitsunobu reaction of an aminal as a key step. The analogue, (2*S*,3*S*,4*R*,5*R*)-2-trifluoroacetamido-5-methylpiperidine-3,4-diol was proved to be an extremely potent inhibitor against α-L-fucosidase (IC_{50} 3 ngmL^{-1}, Ki 5x10^{-9}M).

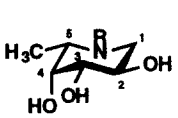
Glycosidase inhibitors are of particular interest in the development of potential pharmaceuticals such as antiviral, antimetastatic, antitumor proliferative, immunoregulatory agents, and so forth.[1] In the course of our study on developing a specific and potent glucuronidase inhibitor modeled on siastatin B (**1**) isolated from *Streptomyces* culture for treatment of tumor metastasis, we recognized its structure and shape are reminiscent of D-glucuronic acid (**2**) as a 1-*N*-iminosugar in which an anomeric carbon atom is replaced by a nitrogen atom.[2] We have demonstrated that *gem*-diamine 1-*N*-iminosugars are very potent and specific glycosidase inhibitors and that some of them show inhibition of the invasion of metastatic tumor cells through the reconstituted basement membrane and potent suppression of experimental and spontaneous pulmonary metastasis in mice.[2,3] In particular, 2-trifluoroacetamido-1-*N*-iminosugars have been proved very potent inhibitors against glycosidases. On the other hand, *N*-(5-carboxymethyl-1-pentyl)derivative (LFT, **3**) of 1,5-dideoxy-1,5-imino-L-fucitol (**4**), an α-L-fucosidase inhibitor has been demonstrated to inhibit the cytopathic effect of HIV and yield of infectious virus.[4] It was also suggested that fucosidase in invasive human overian carcinoma cell mediates degradation of the subendothelial extracellular matrix.[5] Furthermore, L-fucose residue in sialyl Lewis X (**5**) expressed on the surface of leukocyte and some kinds of tumor cells is essential for their adhesion to the endothelial basement membrane through cell-surface endothelial-leukocyte adhesion molecules (ELAMs).[6,7] Therefore, fucosidase inhibitors are currently of increasing interest for anti-HIV, antimetastatic and anti-inflammatory drugs. We now report the extension of our study on glycosidase inhibitors of *gem*-diamine 1-*N*-iminosugars to the enantioselective synthesis of L-fucose-type 1-*N*-iminosugars (**6**, **7**) and their inhibitory activity against glycosidases.



Siastatin B (1)



D-Glucuronic acid (2)



LFT (3): R=$(CH_2)_5CO_2CH_3$
4: R=H

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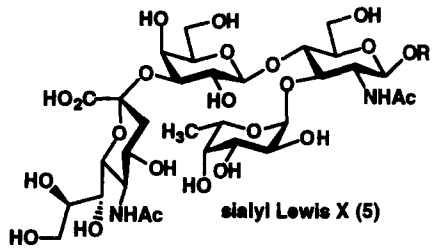
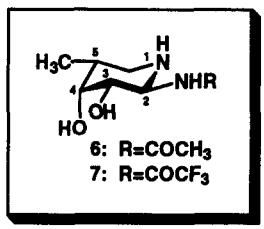
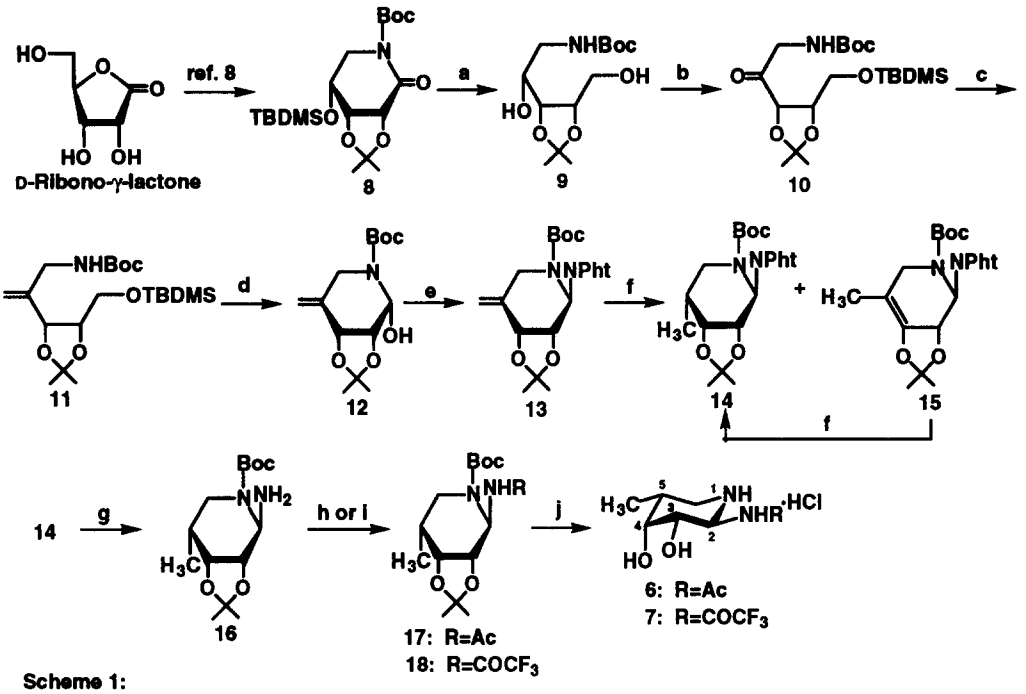
PII: S0040-4039(99)00184-7





Our key intermediate for the synthesis of **6** and **7** was the aminal **12**. The synthesis of **12** began with the known lactam **8**[8] which was transformed in good yield into the diol **9**[9] by $NaBH_4$ reduction and removal of the protecting group. Selective protection of the hydroxymethyl group in **9** followed by the Dess-Martin oxidation[10] afforded the ketone **10**[9] in 95% yield. One-carbon extension of **10** was carried out by the Wittig reaction to give the *exo*-methylene **11**[9] in 81% yield. Stereoselective introduction of the hydroxyl group at C(2) was best achieved by removal of a *tert*-butyldimethylsilyl group and the Swern oxidation[11] to afford the key intermediate **12**[9] in excellent yield. The same stereochemical outcome controlled by an anomeric effect[12] as those of the previous 1-*N*-iminosugar syntheses[2] was observed. Displacement of the axial hydroxyl group to the equatorial amino group was nicely achieved by the Mitsunobu reaction[13] (PPh_3, diethyl azodicarboxylate, phthalimide) in DMF to give the iminophthalimide **13**[9] in good yield. Catalytic hydrogenation of **13** afforded the desired **14**[9] and the rearrangement derivative **15**[9] in 75 and 18% yield, respectively. Compound **15** was also effectively hydrogenated to **14** in 75% yield. The absolute stereochemistry of **14** was confirmed by the X-ray crystallographic analysis. The prolonged reaction period in reduction of **13** was rather inefficient. Hydrazinolysis of **14** gave the amine **16**[9] in 99% yield. Conventional acetylation and trifluoroacetylation of **16** furnished the acetamide **17**[9] and the trifluoroacetamide **18**[9] in good yields, respectively. Simultaneous removal of both the isopropylidene and *t*-Boc groups in **17** with 4M hydrogen chloride in dioxane afforded the desired L-fucose-type 2-acetamido-1-*N*-iminosugar **6**[9] in 99% yield. The other fucose-type 2-trifluoroacetamido-1-*N*-iminosugar **7**[9] was similarly obtained in good yield. The large coupling constants (10.3~12.5 Hz) between H-2 and H-3 and between H-5 and H-6ax in ^1H NMR spectra of **6** and **7** are clearly indicative of $^1C_4$ conformers in water solution.

The inhibitory effect of **6** and **7** on various glycosidases was examined (Table 1).[14] As expected, the trifluoroacetamide **7** showed very strong, specific inhibition against α-L-fucosidase from bovine kidney (IC_{50} 0.003 μgmL^{-1}), and the acetamide **6** also affected the enzyme with an IC_{50} of 0.11 μgmL^{-1}. On the other hand, the analogues **6** and **7** showed no significant inhibition against all other glycosidases. These results indicate that the analogues having the $^1C_4$ conformation are significantly distinct from the known analogues[2,3b,c] of 1-*N*-iminosugars having the $^4C_1$ conformation on the inhibition of D-sugar hydrolases, and suggest that the $^1C_4$ conformation of 1-*N*-iminosugars is important for specificity and potency of 1-*N*-iminosugar inhibitors against L-sugar hydrolase.[3d] Further evaluation of the biological activities of these analogues using metastatic tumor cells, human leukocyte cells, HIV, and so forth is in progress.



Scheme 1:

(a) $NaBH_4$, EtOH, 0°C to rt; *n*-Bu_4NF, THF, rt, 94% (b) *t*-$BuMe_2SiCl$, imidazole, DMF, rt, 99%; Dess-Martin periodinane, CH_2Cl_2, 96% (c) Ph_3PCH_3Br, $(Me_3Si)_2NLi$, THF, 0°C to rt, 81% (d) *n*-Bu_4NF, THF, rt 99%; $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C to rt, 82% (e) phthalimide, Ph_3P, DEAD, DMF, rt, 95% (f) H_2/Pd-C, MeOH, rt (13 → 14: 75%, 13 → 15: 18%, 15 → 14: 75%) (g) $H_2NNH_2{\cdot}xH_2O$, MeOH, rt, 99% (h) Ac_2O, DMAP, Py, rt, 99% (i) $(CF_3CO)_2O$, Py, CH_2Cl_2, rt, 99% (j) 4M HCl/dioxane, 0°C to rt (6: 99%, 7: 97%)

Table 1. Inhibitory activity of **6** and **7** against glycosidases.

Enzyme	IC_{50} (μgmL^{-1}) **6**	**7**
α-L-Fucosidase[a]	0.11	0.003
α-D-Glucosidase[b]	40	5
β-D-Glucosidase[c]	2.3	55
α-D-Mannosidase[d]	>50	>50
β-D-Mannosidase[e]	>50	>50
α-D-Galactosidase[f]	>50	>50
β-D-Galactosidase[f]	>50	>50
β-D-Glucuronidase[g]	>50	>50
α-D-*N*-Acetylgalactosaminidase[h]	>50	>50
β-D-*N*-Acetylglucosaminidase[i]	>50	>50

a) Bovine kidney b) Baker's yeast c) Almonds d) Jack beans e) Snail f) *Escherichia coli* g) Bovine liver h) Chicken liver i) Bovine epididymis

In summary, a new family of α-L-fucosidase inhibitors, 2-trifluoroacetamido- and 2-acetamido-1-*N*-iminosugars, have been synthesized from D-ribono-γ-lactone. That these 1-*N*-iminosugars are potent inhibitors of α-L-fucosidase further supports the hypothesis of our design of the new-type inhibitor.

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9. **9**: $[\alpha]_D^{23}$ +38° ($CHCl_3$). **10**: $[\alpha]_D^{23}$ -36° (MeOH). **11**: $[\alpha]_D^{23}$ -44° ($CHCl_3$). **12**: $[\alpha]_D^{23}$ -10° ($CHCl_3$). **13**: $[\alpha]_D^{23}$ +58° ($CHCl_3$). **14**: $[\alpha]_D^{23}$ -33° ($CHCl_3$). **15**: $[\alpha]_D^{23}$ +56° ($CHCl_3$). **16**: $[\alpha]_D^{23}$ +14° ($CHCl_3$). **17**: $[\alpha]_D^{23}$ -34° ($CHCl_3$). **18**: $[\alpha]_D^{23}$ -37° ($CHCl_3$). **6**: $[\alpha]_D^{23}$ -32° (MeOH); a part of ^{1}H NMR (CD_3OD, 400 MHz) δ 2.92 (dd, *J*=3.9, 12.5 Hz, H-6eq), 3.05 (br t, *J*=12.5 Hz, H-6ax), 3.72 (dd, *J*=2.4, 10.3 Hz, H-3), 4.91 (d, *J*=10.3 Hz, H-2). **7**: $[\alpha]_D^{23}$ -42° (MeOH); a part of ^{1}H NMR (CD_3OD, 400 MHz) δ 2.97 (dd, *J*=4.4, 12.5 Hz, H-6eq), 3.09 (br t, *J*=12.5 Hz, H-6ax), 3.84 (dd, *J*=2.4, 10.3 Hz, H-3), 4.99 (d, *J*=10.3 Hz, H-2).
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13. For a review, see: Mitsunobu, O. *Synthesis* **1981**, 1-28.
14. All enzymes were purchased from Sigma Chemical Co., St. Louis. Enzyme assays were similarly evaluated as described previously.[3c]