Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 749–752

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis of an α-Fucosidase Inhibitor, 5a-Carba-β-L-fucopyranosylamine, and Fucose-Type α- and β-DL-Valienamine Unsaturated Derivatives

Seiichiro Ogawa,* Maiko Watanabe, Ayako Maruyama and Seiichi Hisamatsu

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522 Japan

Received 9 October 2001; accepted 14 December 2001

Abstract—Discovery of a very potent α-fucosidase inhibitor 5a-carba-α-L-fucopyranosylamine (**1**) led to preparation of its β-anomer **4** and the respective unsaturated derivatives, fucose-type α- and β-valienamines (**5** and **6**), in order to elucidate the structure–activity relationship of carba-aminosugar inhibitors of this kind. Compound **4** was demonstrated to be a potent inhibitor ($K_i = 2.0 \times 10^{-7}$ M, bovine kidney), possessing ca. one-tenth of the activity of the parent **1**. Interestingly, **5** and **6** were found to be rather weak inhibitors, contrary to the expectations based on the activity relationships between the α-glucosidase inhibitors, α-glucose-type validamine and valienamine.

Previously we reported[1,2] the α-fucose-type analogue **1** of the α-glucosidase inhibitor validamine[3] to possess very strong inhibitory activity ($K_i = 1.2 \times 10^{-8}$ M) against α-L-fucosidase (bovine kidney). Furthermore, 5a-carba-α- and β-L-fucopyranose derivatives[2] (**2** and **3**) with branched-aminomethyl groups in the C-1 anomeric position, were also found to be strong α-fucosidase inhibitors ($K_i = 0.3$ and 2.8×10^{-6} M). The above rather surprising findings prompted us to prepare the β-anomer **4** of **1** and evaluate its α-fucosidase inhibitory activity, in order to elucidate structure–activity relationships of the lead compounds. Two unsaturated derivatives **5** and **6** were additionally designed, in the expectation of a possible increase of activity based on the analogy with the relationship of validamine[3] **7**, mimic of the ground state of α-D-glucopyranoside, to valienamine[4] **8**, with the transition state oxocarbenium ion **A** featured in α-D-glucopyranoside hydrolysis. Thus, the half-chair conformations of **5** and **6** resemble the transition state **B** during α-L-fucopyranoside hydrolysis.

Synthesis of 5a-carba-β-L-fucopyranosylamine (**4**) was envisaged starting from the key intermediate anhydro compound **14**, as well as **15**, expected to be a potential donor intermediate for incorporation of 5a-carba-fucopyranose residues into oligosaccharide chains (Fig. 1).

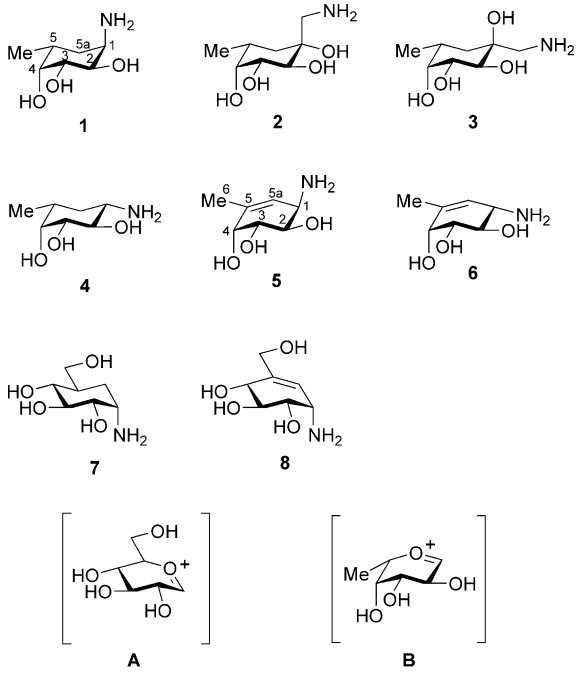


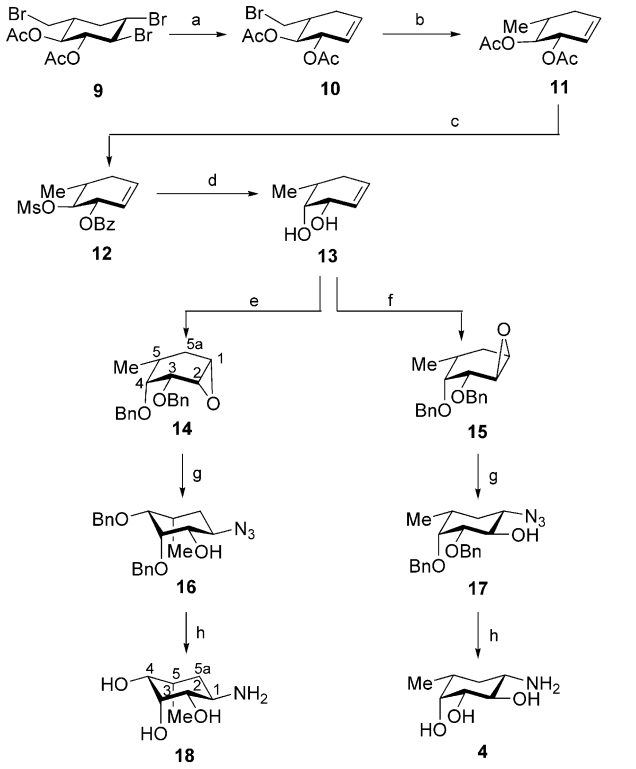
Figure 1.

*Corresponding author. Tel.: +81-45-566-1559; fax: +81-45-566-1551; e-mail: ogawa@applc.keio.ac.jp

0960-894X/02/$ - see front matter
PII: S0960-894X(02)00004-5

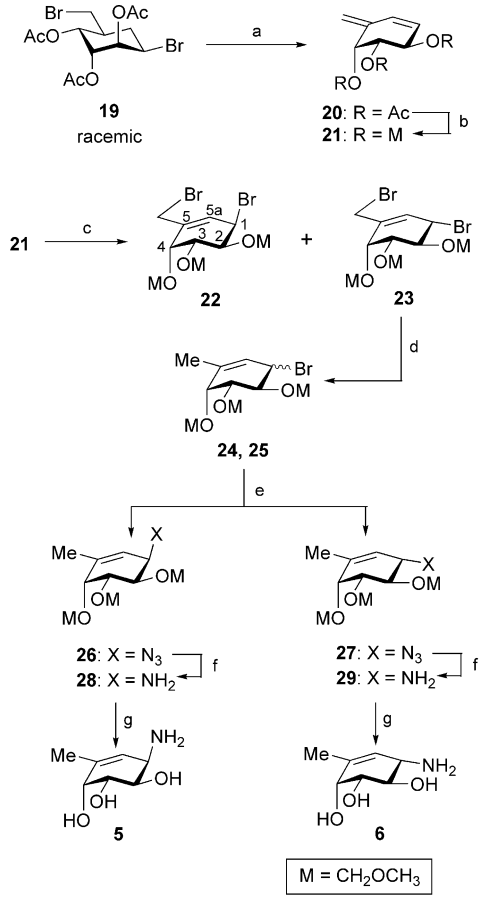
Treatment of 3,4-di-*O*-acetyl-2,6-dibromo-2,6-dideoxy-5a-carba-β-L-glucopyranosyl bromide[5] (**9**) with zinc powder in AcOH at 80 °C gave (1*SR*,2*SR*,3*SR*)-1,2-diacetoxy-3-(bromomethyl)-5-cyclohexene (**10**, 59%), along with the debrominated compound **11** (32%). The bromide **10** was also readily debrominated with tributyltin hydride in toluene to give **11** (86%) (Scheme 1).

Zemplén deacylation of **11** gave the diol, the allylic hydroxyl group of which was selectively benzoylated, followed by mesylation, giving the 2-mesylate **12** in overall yield of 64%. Treatment of **12** with sodium benzoate in aqueous DMF at 110 °C underwent a direct S_N2 reaction to give, after deacylation, the 2-epimeric diol **13** in 93% yield. Compound **13** was then oxidized with *m*CPBA in CH_2Cl_2, the resulting β-epoxide being isolated as a dibenzyl ether[5] **14** in 85% yield. The allylic hydroxyl group is likely to participate through hydrogen bonding in β-side attack of the peracid. On the other hand, the diol **13** was first benzylated and then subjected to a similar epoxidation, giving a mixture of **14** (53%) and the α-epoxide derivative **15** (36%). Preference for β-selectivity was not markedly suppressed by incorporation of the benzyl ether group.[6] Treatment of the β-epoxide **14** with an excess of sodium azide in aqueous 2-methoxyethanol resulted in a diaxial cleavage of the epoxide, producing a single azide[7] **16** in 91% yield. Hydrogenolysis of **16** in ethanol containing 1 M HCl in the presence of 10% Pd/C gave, after purification on a column of Dowex 50W × 2 (H^+) resin with aqueous ammonia, free aminocyclitol **18**, the 2-epimer of **1**, in 80% yield. The α-epoxide **15** was found to be comparatively unreactive. Its azidolysis proceeded very slowly but regioselectively in DMF for 5 days at 110 °C, affording a sole azide[8] **17** in 81% yield, which was similarly hydrogenolyzed and purified to give the β-anomer[9] **4** of **1** in 89% yield (Scheme 2).

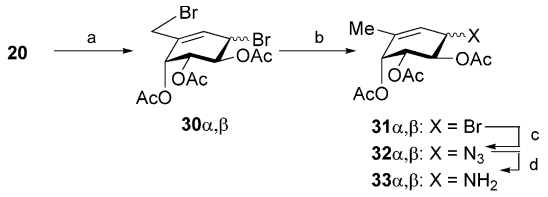


Scheme 1. Reagents and conditions: (a) Zn, AcOH, 80 °C; (b) Bu_3SnH, AIBN, toluene, reflux; (c) NaOMe, MeOH, rt; BzCl (1.4 mol equiv), pyridine, −15 °C, then MsCl, DMAP; (d) NaOBz (5 mol equiv), 90% aq DMF, 110 °C; NaOMe, MeOH, rt; (e) NaH, BnBr, DMF; *m*CPBA, CH_2Cl_2; (f) *m*CPBA, CH_2Cl_2; NaH, BnBr, DMF; (g) NaN_3 (15 mol equiv), 15-crown-5 ether, DMF, 110 °C, 5 days; (h) NaN_3 (3 mol equiv), 90% aq $MeOCH_2CH_2OH$, 80 °C; (i) H_2, 10% Pd/C, 1 M HCl aq EtOH.

Compounds **5** and **6** were first synthesized in a racemic modification in order to evaluate rough activity toward α-L-fucosidase. (1*RS*,2*SR*,3*RS*)-1,2,3-Tri-*O*-acetyl-6-methylene-4-cyclohexene-1,2,3-triol[10] (**20**) was prepared in 50–60% yield by treatment of 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-5a-carba-β-DL-altropyranosyl bromide[10] (**19**) with sodium acetate in HMPA at 120 °C. As a side product, DL-1,2,3-tri-*O*-acetyl-6-acetoxymethy-4-cyclohexene-1,2,3-triol was obtained in 30–40% yields. The protecting groups were initially replaced with methoxymethyl groups, in order to eliminate neighboring participation of the acyloxy groups during subsequent processing, thus converting **20** into the trimethoxymethyl ether **21** in quantitative yield. Treat-



Scheme 2. For convenience, the formulas depict only one enantiomer of the respective racemates. Reagents and conditions: (a) NaOAc (4 mol equiv), HMPA, 120 °C; (b) NaOMe, MeOH, rt; $MeOCH_2Cl$, $(iPr)_2NET$, CH_2Cl_2, 40 °C; (c) Br_2, CCl_4, rt; (d) $NaBH_4$, HMPA, rt, a 1:1 mixture of **24** and **25**; (e) NaN_3 (2 mol equiv), DMF, rt; (f) PPh_3, aq THF, 60 °C; (g) 4 M HCl, 60 °C.



Scheme 3. For convenience, the formulas depict only one enantiomer of the respective racemates. Reagents and conditions: (a) Br_2, CCl_4, rt; (b) $NaBH_4$ (2 mol equiv), 80% aq HMPA, rt; (c) NaN_3 (2 mol equiv), DMF, rt; (d) 90% aq pyridine, PPh_3, 60 °C, 2 days.

ment of **21** with bromine in CCl_4 at room temperature gave, after silica gel chromatography, 6-bromo-6-deoxy-2,3,4-tri-*O*-methoxymethyl-5a-carba-*altro*-hex-5(5a)-enopyranosyl bromides (**22** and **23**) in 21 and 48% yields, respectively. The ^{1}H NMR spectra of **22** and **23** featured 1-H signals at $\delta = 4.85$ (dd, $J_{1,2} = 4.3$, $J_{1,5a} = 4.6$ Hz) and 4.56 (dd, $J_{1,2} = 6.6$, $J_{1,5a} = 3.4$ Hz), respectively. Selective debromination of the major **23** was conducted by treatment with sodium borohydride in HMPA at room temperature to give a 1:2 anomeric mixture of 6-deoxy-5a-carba-*altro*-hex-5(5a)-enopyranosyl bromides (**24** and **25**) in 57% yield, together with a mixture of **22** and **23** (~45% recovered). Direct nucleophilic substitution with a bromide ion generated in situ is likely to occur at allylic C-1, resulting in epimerization to form an equilibrium mixture of the anomers. Therefore, the mixture of **24** and **25** should be furnished directly from a crude mixture of the dibromides. The mixture was treated with an azide ion (2 mol equiv) in DMF at 0 °C to give a 1:2 mixture of the azides[10] **26** and **27** in 88% yields. Reduction of the azides with triphenylphosphine in aqueous THF gave a mixture of the amines **28** and **29**, which was separated by a silica gel column to give yields of 17 and 33%, respectively. Their ^{1}H NMR spectra showed 1-H signals at $\delta = 3.66$ (dd, $J_{1,2} = 4.3$, $J_{1,5a} = 1.8$ Hz) and 3.22 (dd, $J_{1,2} = 6.7$, $J_{1,5a} = 2.7$ Hz), respectively, supporting the assigned structures. Deprotection of **28** and **29** was effected by heating with 4 M hydrochloric acid to afford, after similar purification by a resin column, the respective free bases **5** and **6** in quantitative yields, the ^{1}H NMR spectra[11] of which confirmed the assigned structures (Scheme 3).

An alternative route was later shown to improve the preparative processing and overall yields of **5** and **6**. Thus, the acetate **20** could similarly be converted into a mixture (90%) of **30α,β** dibromides, which were directly debrominated to give a mixture (90%) of the **31α,β** monobromides. Conventional azidolysis afforded a mixture (86%) of the azides **32α,β**, quantitatively, then hydrogenolyzed to provide, after separation on a silica gel column, the amines[12] **33α** (21%) and **33β** (71%).

Biological assay

Preliminary biological assays[13] of the inhibitory activities of compounds **4**, **5**, and **6** towards α-L-fucosidase (bovine kidney) were performed. 5a-Carba-β-L-fucopyranosylamine **4** was earlier demonstrated to be a strong inhibitor ($K_i = 2.0 \times 10^{-7}$ M), with decrease to only one seventeeth of the value of the α-anomer[2] ($K_i = 1.2 \times 10^{-8}$ M). Furthermore, contrary to the expectations, the transition state mimics racemic **5** and **6** were found to be rather weak α-L-fucosidase inhibitors, possessing $K_i = 45$ and 1.2×10^{-5} M, respectively.

The ground state mimics **1** and **4** have, thus, actually been shown to possess very higher potency, being promising lead compounds for design of new L-fucosidase inhibitors of this type. The present results might indirectly suggest that the hydrolytic reaction of the α-L-fucosidase (bovine kidney) feature an S_N2-type mechanism with nucleophilic displacement rather than an S_N1-type one through an oxocarbenium ion intermediate. On the other hand, the L-enantiomer of **6** would be expected to act as a moderate L-fucosidase inhibitor on chemical modification of the amino function.

References and Notes

1. Ogawa, S.; Sekura, R.; Maruyama, A.; Yuasa, H.; Hashimoto, H. *Eur. J. Org. Chem.* **2000**, 2089.
2. Ogawa, S.; Maruyama, A.; Odagiri, T.; Yuasa, H.; Hashimoto, H. *Eur. J. Org. Chem.* **2001**, 967.
3. Kameda, Y.; Takai, N.; Asanao, N.; Matsui, K. *Chem. Pharm. Bull.* **1990**, *38*, 1970.
4. Takeuchi, M.; Kamata, K.; Yoshida, M.; Kameda, Y.; Matsui, K. *J. Biochem.* **1990**, *108*, 42.
5. Ogawa, S.; Uematsu, Y.; Yoshida, S.; Sasaki, N.; Suami, T. *J. Carbohydr. Chem.* **1987**, *6*, 471.
6. α-Selectivity in oxidation of **13** is highly enhanced by protecting the hydroxyls with cyclohexylidene group, which produce, under similar epoxidation conditions, the corresponding α-epoxide in 62% yield.
7. The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the 2-*O*-acetyl derivative of **16** indicated a 2-H signal at $\delta = 4.79$ (dd, $J_{1,2} = 10.0$, $J_{2,3} = 2.9$ Hz), supporting the assigned structure, the conformer of which adopts the C1 form, having the methyl group in an axial position.
8. The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the 2-*O*-acetyl derivative of **17** obtained in the usual manner revealed 1-H, 2-H, and 3-H signals at $\delta = 3.35$ [ddd, $J_{1,2} = J_{1,5a(ax)} = 10.0$, $J_{1,5a(eq)} = 4.1$ Hz], $\delta = 5.45$ (dd, $J_{2,3} = 10.0$ Hz), and $\delta = 3.37$ (dd, $J_{3,4} = 2.4$ Hz), respectively, confirming the assigned structure.
9. ^{1}H NMR (300 MHz, D_2O) data: $\delta = 0.92$ (d, $J = 6.8$ Hz, 3H, Me), 1.30 [ddd, $J_{1,5a(ax)} = J_{5,5a(ax)} = J_{5agem} = 12.7$ Hz, 1H, 5a(ax)-H], 1.62 [ddd, $J_{1,5a(eq)} = J_{5,5a(eq)} = 4.0$ Hz, 1H, 5a(eq)-H], 1.71 (m, 1H, 5-H), 2.78 (m, 1H, 1-H), 3.40 (m, 2H, 2-H, 3-H), 3.77 (br s, 1H, 4-H).
10. Ogawa, S.; Hattori, H.; Toyokuni, T.; Suami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2077.
11. ^{1}H NMR (300 MHz, D_2O) data: **5**: $\delta = 1.63$ (s, 3H, Me), 3.49 (br dd, $J_{1,2} = 4.8$, $J_{1,5a} = 1.3$ Hz, 1H, 1-H), 3.73 (dd, $J_{2,3} = 9.6$, $J_{3,4} = 4.1$ Hz, 1H, 3-H), 3.81 (dd, 1H, 2-H), 3.97 (d, 1H, 4-H), 5.36 (br d, 1H, 5a-H); **6**: $\delta = 1.63$ (s, 3H, Me), 3.04 (br dd, $J_{1,2} = 8.5$, $J_{1,5a} = 1.2$ Hz, 1H, 1-H), 3.27 (dd, $J_{2,3} = 10.9$ Hz, 1H, 2-H), 3.41 (dd, $J_{3,4} = 4.0$ Hz, 1H, 3-H), 3.90 (d, 1H, 4-H), 5.23 (br d, 1H, 5a-H).
12. ^{1}H NMR (300 MHz, $CDCl_3$) data: **33α**: $\delta = 1.72$ (br s, 3H,

Me), 2.05, 2.08, and 2.10 (3 s, each 3H, 3 × OAc), 4.23 (dd, $J_{1,2}=5.0$, $J_{2,3}=9.3$ Hz, 1H, 2-H), 4.84 (m, 1H, 1-H), 5.17 (dd, $J_{3,4}=4.0$ Hz, 1H, 3-H), 5.56 (br d, $J_{1,5a}=2.2$ Hz, 1H, 5a-H), 5.60 (d, 1H, 4-H); **33β** δ = 1.73 (t, $J=\sim 1.7$ Hz, 3H, Me), 1.99, 2.11, and 2.13 (3 s, each 3H, 3 × OAc), 3.42 (br dd, $J_{1,2}=7.5$, $J_{1,5a}=2.1$ Hz, 1H, 1-H), 5.05 (dd, $J_{2,3}=11.2$, $J_{3,4}=3.9$ Hz, 1H, 3-H), 5.14 (dd, 1H, 2-H), 5.54 (d, 1H, 4-H), 5.57 (br d, 1H, 5a-H).

13. Biological assays were carried out as described earlier.[2] The α-L-fucosidase (bovine kidney) used in this study was purchased from CALBIOCHEM.