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Total Syntheses of De-branched Nagstatin and Its Analogs Having Glycosidase Inhibiting Activities

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Abstract: De-branched nagstatin and its analogs have been synthesized from protected L-ribo- and xylo-furanoses through the inter- and intra-molecular nucleophilic reactions with the imidazole moieties.

An increasing awareness of the vital role played by carbohydrates in biological processes has stimulated interest in the syntheses of glycosidase inhibitors.[1] Nagstatin (**1**), which is an N-acetyl-β-D-glucosaminidase inhibitor isolated from fermentation broth of *Streptomyces amakusaensis*[2], attracted our attention because of our program in developing new glycosidase inhibitors.[3]

In this paper we describe the total syntheses of a variety of nagstatin analogs, which feature a general method of entry into the imidazole-having nitrogenous carbohydrates through the intermolecular and intramolecular nucleophilic reactions with the imidazole moieties.

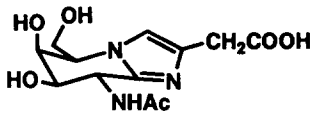
First of all, de-branched nagstatin **2** and its hydroxy analog **3** were effectively synthesized from methyl L-ribofuranoside.[4] O-Benzylation (BnBr, NaH, DMF, 0°C) followed by acid hydrolysis (0.05N HCl, dioxane, 105°C) gave the protected ribose **7** in 90% overall yield. Reaction of **7** (THF, 0°C, 0.5h) with lithiated N-tritylimidazole,[5] which was prepared from N-tritylimidazole and n-BuLi (THF,-5°C), gave the L-allose derivative **8**[6,7] [47%, mp 62~67°C(amorphous solid), $[\alpha]_D$ -111°(*c* 1.0, $CHCl_3$)] and L-altro derivative **9**[6,7] [40%; mp 132.5~133.5°C(EtOAc), $[\alpha]_D$ -31°(*c* 1.0, $CHCl_3$)]. The configurations of their C-2 positions[7] were determined by the NMR studies of the following cyclized compounds. Both compounds **8** and **9** were converted into **2** and **3** as follows. De-N-tritylation and the S_N2-type intramolecular cyclization of **8** were effectively realized in one-pot by reaction with $BnSO_2Cl$ in pyridine at -15°C for 1.5h to give preferentially the 5-O-sulfonylated compound followed by treatment with Ac_2O at 65°C for 1.5h to give the desired acetate **10**[6] [75%, oil, $[\alpha]_D$ -3.0°(*c* 1.0, $CHCl_3$)], which was de-O-acetylated (MeONa, MeOH, rt, 1.5h) to the nitrogenous D-talose analog **11**[6] [84%; mp 77~78°C(hexane-EtOAc), $[\alpha]_D$ -7.8°(*c* 1.0, $CHCl_3$)]. The effective de-N-tritylation seemed to be affected by the producing pyridinium acetate and was supported by the stepwise conversions of **13** and **20** into **14** and **21** as shown later. The inversion of the hydroxyl group in **11** with HN_3 (n-Bu_3P, DEAD, THF, PhMe, rt, 0.5h)[8] afforded the azido derivative **12** [68%, oil, $[\alpha]_D$ +98°(*c* 1.2, $CHCl_3$)], which was subjected to hydrogenolysis (H_2, Pd-C, AcOH) and N-acetylation (Ac_2O, MeOH) leading to the N-acetyl-D-galactosamine analog **2** [6] [65%, mp 210~212°C(decomp.), $[\alpha]_D$ +109°(*c* 1.3, H_2O)], which was corresponding to de-branched nagstatin. The optical rotation, the coupling constants of the ^{1}H-NMR, and

glycosidase inhibiting activities[9] of **2** were much the same as those of nagstatin (**1**), indicating that natural nagstatin has the D-galacto structure **1**[2].

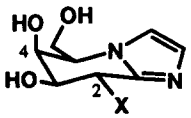
Alternatively, **12** was prepared from the other isomer **9**. Treatment of **9** with $BnSO_2Cl$ (Py, -10°C, 1h) to give **13** [6][86%; mp~60°C(amorphous solid), $[\alpha]_D$ -43°(*c* 1.4, $CHCl_3$)] followed by acetylation (Ac_2O, Py, 65°C, 1.5h) gave the cyclized compound **14** (90%; oil, $[\alpha]_D$ +75°(*c* 1.4, $CHCl_3$)] with de-N-tritylation as described above, which was de-O-acetylated (MeONa, MeOH) to **15** [95%; mp 112~113°C(hexane-EtOAc), $[\alpha]_D$ +38°(*c* 1.0, $CHCl_3$)]. Reaction of **15** with HN_3 (n-Bu_3P, DEAD, THF, PhMe, rt, 0.5h) gave **12** in 68% yield with retention of the C-2 configuration as expected. The S_N2 replacement of the C-2 equatorial group in carbohydrates has been hardly known to occur because of the ring oxygen, the anomeric substituent and dipolar effects.[10] This retention was confirmed by the fact that **15** was treated with benzoic acid, n-Bu_3P and DEAD (Et_2O, rt, 0.5h) to give the benzoate **16**[6] [75%. mp 97~98°C(EtOAc), $[\alpha]_D$ +98°(*c* 1.1, $CHCl_3$)], which was deacylated (MeONa, MeOH) to the starting **15**. Hydrogenolysis of **15** (H_2. Pd-C, AcOH, rt, 15h) afforded the nitrogenous D-galactose analog **3** [6][90%; mp~80°C(amorphous solid),$[\alpha]_D$ +29°(*c* 1.6, MeOH)]. Similarly, the enantiomeric N-acetyl-L-galactosamine analog **2'** and L-galactose analog **3'** were prepared from methyl D-ribofuranoside by the same procedures as mentioned above: **2'**[6]: mp 210~212°C(decomp.), $[\alpha]_D$ -104°(*c* 0.65, MeOH) ; **3'**[6]: mp~80°C(amorphous solid), $[\alpha]_D$ -32°(*c* 0.95, MeOH). Both compounds showed no significant glycosidase inhibiting activities[9].

Furthermore, nitrogenous N-acetyl-D-glucosamine, D-glucose and D-mannose analogs (**4**, **5** and **6**) were efficiently prepared from methyl L-xylofuranoside [4] by the similar fashion as described above. Successive O-benzylation (BnBr, NaH, DMF, 0°C) and hydrolysis (0.05N HCl, dioxane, 105°C) gave the protected xylofuranose **17** (92%), which reacted with lithiated N-tritylimidazole (THF, -10°C) to yield the L-gulose analog **18** [6][64%, mp 40~44°C(amorphous solid), $[\alpha]_D$ -55°(*c* 0.87, $CHCl_3$)] and L-idose analog **19** [6][16%; mp 43~46°C(amorphous solid), $[\alpha]_D$ +18°(*c* 1.2, $CHCl_3$)]. The approach of the imidazole moiety to the C-1 position[7] of **17** was reasonably controlled by the *cis* Li-chelation between the C-1 and C-2,[11] while the aforesaid reaction of **7** was not affected by such chelation controll probably because of the preferential formation of the *cis* Li-chelation between the C-2 and C-3. Benzylsulfonylation ($BnSO_2Cl$, Py, -10°C, 0.5 h) of **18** followed by acetylation with concomitant cyclization (Ac_2O, Py, 50°C, 8 h) gave the nitrogenous D-mannose analog **21**[6][84%, oil, $[\alpha]_D$ -50°(*c* 0.96, $CHCl_3$)], which was deacetylated (MeONa, MeOH) to the alcohol **22** [6][95%, mp 116.5~117.5°C(hexane-EtOAc), $[\alpha]_D$ -4.0°(*c* 0.95, $CHCl_3$)]. Hydrogenolysis (H_2, Pd-C, AcOH) of **22** gave the D-mannose analog **6**[6][91%, mp 111~114°C(amorphous solid), $[\alpha]_D$ -36°(*c* 1.0, MeOH)]. Mitsunobu inversion of the hydroxyl group of **22** was carried out with HN_3 by the aforesaid conditions to give **23**[6] [71%, oil, $[\alpha]_D$ +59°(*c* 1.0, $CHCl_3$)], which was converted into the nitrogenous N-acetyl-D-glucosamine analog **4** [6] [65%; mp 249~251°C(decomp.), $[\alpha]_D$ +52°(*c* 0.90, H_2O)] by hydrogenolysis and N-acetylation as described above. The azide **23** was also obtained from **24** with retention of the C-2 configuration as described in the preparation of **12** from **15**. The intermediate **24** was prepared from **19** by benzylsulfonylation and acetylation with cyclization followed by de-O-acetylation as described in the preparationn of **15** from **9**, and also derived from **22** in 85% overall yield by inversion (BzOH, n-Bu_3P, DEAD, THF, rt, 0.5h) and de-O-acylation (MeONa, MeOH). The D-glucose analog **5**[6] was prepared from **24** by hydrogenolysis (H_2, Pd-C, AcOH, rt, 15h): mp 169~174°C(amorphous solid), $[\alpha]_D$ -8.0°(*c* 0.97, MeOH).

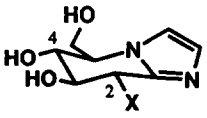
Details on the glycosidase inhibiting activities of the synthesized analogs (**2** - **6**) will be described in another paper[9].



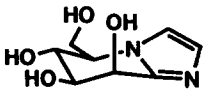
1 (Nagstatin)



2 : X=NHAc
3 : X=OH



4 : X=NHAc
5 : X=OH



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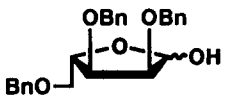

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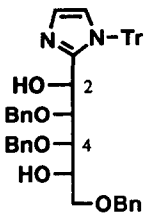

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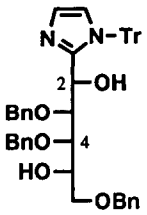

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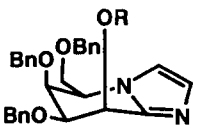
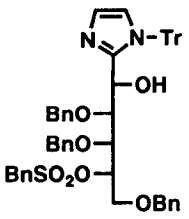


10 : R=Ac
11 : R=H



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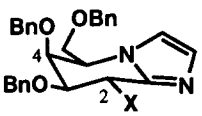
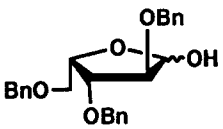


12 : X=N_3
14 : X=OAc
15 : X=OH
16 : X=OBz



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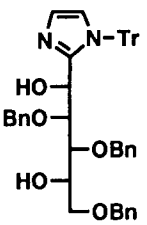

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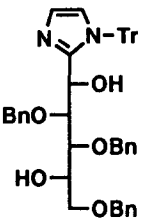

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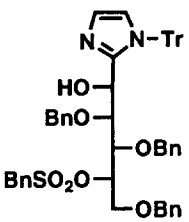

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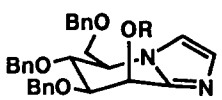
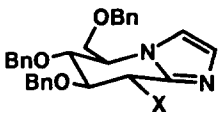


21 : R=Ac
22 : R=H



23 : X=N_3
24 : X=OH

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REFERENCES AND NOTES

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6. All compounds were purified by silica-gel column chromatography and/or recrystallization, and were fully characterized by spectroscopic means. Optical rotations were measured using a 0.5 dm tube at 22°C. Significant ^{1}H-NMR spectral data (270 and 400 MHz, $CDCl_3$, δ; TMS=0, unless otherwise noted) are the following. **2**(CD_3OD): δ 2.05(3H,s), 3.94(1H,dd,J=9&2Hz), 4.15(1H,ddd,J=6&6& 3Hz), 4.32(1H,dd,J=3&2Hz),5.14(1H,d,J=9Hz), 6.95(1H,d,J=1.5Hz), 7.35(1H,d,J=1.5Hz). **3**(CD_3OD): δ 3.87(1H,dd,J=7&2Hz), 4.23(1H,dt,J=5&4Hz), 4.38(1H,dd,J=4&2Hz), 4.76(1H,d, J=7Hz), 7.05(1H,d,J=1Hz), 7.36(1H,d,J=1Hz). **4**(pyridine-d_5): δ 2.11(3H,s), 4.34(1H,ddd,J=9&5& 2.5Hz), 4.44(1H,dd,J=9&9Hz), 4.57(1H,dd,J=9&9Hz), 5.85(1H,dd,J=9&9Hz), 7.35(1H,d, J=1.5Hz), 7.68(1H,d,J=1.5Hz). **5**(D_2O): δ 3.85(1H,dd,J=10&9Hz), 3.98(1H,dd,J=10&9Hz), 4.12(1H,m), 4.72(1H,d,J=9Hz), 7.30(1H,d,J=1.5Hz), 7.43(1H,d,J=1.5Hz). **6**(pyridine-d_5): δ 4.40(1H,dd,J=7.5&4Hz), 4.76(1H,ddd,J=9&4&4Hz), 5.04(1H,dd,J=9&7.5Hz), 5.66(1H,d,J=4Hz), 7.39(1H,d,J=1.5Hz), 7.78(1H,d,J=1.5Hz). **8** : δ 3.83(1H,dd), 3.92(1H,ddd), 4.00(1H,dd), 4.53 (1H,dd), 6.83(1H,d), 7.09(1H,d). **9** : δ 1.86(1H,dd), 3.50(1H,dd), 3.82(1H,ddd), 4.50(1H,dd). **10** : δ 4.09(1H,dd), 4.21(1H,dd), 4.35(1H,ddd), 6.25(1H,d), 7.18(1H,d), 7.20(1H,d). **11** : δ 3.97(1H, dd,J=4&2Hz), 4.24(1H,dd,J=5&2Hz), 4.30(1H,dt,J=6&5Hz), 5.02(1H,d,J=4Hz), 7.07(1H,d, J=2Hz), 7.11(1H,d,J=2Hz). **12** : δ 3.81(1H,dd), 4.24(1H,dd), 4.28(1H,dt), 5.00(1H,d), 7.07(1H,d), 7.11(1H,d). **13** : δ 1.50(1H,d), 3.73(1H,dd), 4.46(1H,s), 5.08(1H,ddd). **14**: δ 3.98(1H,dd), 4.21 (1H,dd), 4.45(1H,ddd), 6.22(1H,d), 7.08(1H,d), 7.15(1H,d). **15** : δ 4.02(1H,dd,J=5.5&2Hz), 4.35 (1H,dd,J=5&2Hz), 4.39(1H,ddd,J=7.5&5&3Hz), 5.17(1H,d,J=5.5Hz), 6.98(1H,d,J=1.5Hz), 7.10 (1H,d,J=1.5Hz). **16** : δ 4.12(1H,dd), 4.29(1H,dd), 4.50(1H,ddd), 6.49(1H,d), 7.11(1H,d). **18** : δ 3.74(1H,dd), 3.98(1H,dt), 4,15(1H,dd), 4.51(1H,br.dd), 6.85(1H,d). **19**(acetone-d_6): δ 3.19(1H,dd), 3.25(1H,dd), 3.54(1H,m), 4.34(1H,dd), 6.82(1H,d), 7.05(1H,d). **20** : δ 4.04(1H,dd), 4.19(1H,dd), 4.54(1H,dd), 5.04(1H,ddd), 6.82(1H,d). **21**(acetone-d_6): δ 4.16(1H,dd), 4.24(1H,ddd), 4.29(1H, dd), 6.50(1H,d), 6.98(1H,d). **22** : δ 3.96(1H,dd,J=8&4Hz), 4.15(1H,ddd,J=6&6&3.5Hz), 4.20(1H, dd,J=8&6Hz), 5.13(1H,d,J=4Hz), 7.01(1H,d,J=1.5Hz), 7.10(1H,d,J=1.5Hz). **23** : δ 3.88(1H,dd), 3.96(1H,dd), 4.15(1H,ddd), 4.73(1H,d), 7.02(1H,d), 7.13(1H,d). **24**(acetone-d_6): δ 3.97(1H,dd, J=7.5&6Hz), 4.06(1H,dd,J=7.5&7.5Hz), 4.30(1H,m),4.79(1H,d,J=6Hz), 6.95(1H,s), 7.19(1H,s).
7. The carbon-numbering protocol and nomenclature conveniently parallel those of carbohydrates.
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9. The glycosidase inhibiting activities were kindly assayed by Dr. Shokichi Ohuchi, Meiji Seika Kaisha, Ltd.. For examples, compounds **2** and **4** showed the strong inhibiting activities against N-acetyl-β-D-glucosaminidase at IC_{50} 0.0015 and 0.0017 μg/ml, respectively. Their details will be reported in J. Antibiotics.
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