Novel Synthesis of Natural Pseudo-aminosugars, (+)-Valienamine and (+)-Validamine

Sir:

(+)-Valienamine (**1**) and (+)-validamine (**2**) have been found to be key components for biological activities in pseudo-aminosugars and pseudo-oligosaccharides such as validamycins, acarbose, and trestatines (Fig. 1).[1~3] Both pseudo-aminosugars **1** and **2** were also isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus* IFO 12703 to show some biological activities.[4,5]

Few syntheses of optically active compounds **1** and **2** have been reported by using L-quebrachitol,[6] (−)-quinic acid,[7] and D-glucose derivatives,[8] although the racemates of **1** and **2** have been synthesized in a variety of methodologies.[9]

We have extensively developed the one-step opening of a furanose ring containing a phenylsulfonylmethyl group followed by aldol condensation as a general method for the construction of optically active carbasugars (for an example: Fig. 2).[10,11]

Very recently, the total synthesis of pyralomicin 1c (**5**) was accomplished in our laboratories[12] using such strategies for the synthesis of the carbasugar moiety **4** from the L-arabinose derivative **3** (Fig. 2).

We now wish to demonstrate both the utility and the versatility of our method in the stereoselective synthesis of natural (+)-valienamine (**1**) and (+)-validamine (**2**) (Fig. 3). Furthermore, the anchor effect of an amino group[13] will be described in the stereoselective hydrogenation of the olefin of **1** to give **2**.

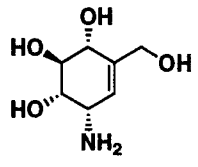
The starting compound **6**, which was prepared from D-xylose by bromine oxidation and tritylation,[14] was silylated and de-*O*-tritylated to provide the lactone **7** (Table 1).

Pfitzner-Moffatt oxidation of **7** followed by treatment with orthoformate gave the acetal **8**, which reacted with lithiated methyl phenyl sulfonate to give the furanose **9** in 94% yield. This was efficiently converted to the cyclohexenone **11** according to our methodologies[10~12] by ring-opening with TBSOTf and then ring-closing of the resulting enol silyl ether **10** with $SnCl_4$.

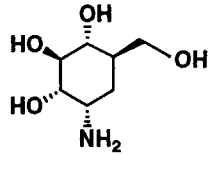
Compound **11** was subjected to the Michael reaction with tributylstannyl lithium followed by trapping of the produced anion with formaldehyde to incorporate the hydroxymethyl group. The α-hydroxymethyl-cyclohexenone **12** was thus obtained in 84% yield.

Stereoselective reduction of the carbonyl group in **12** was carried out by $Zn(BH_4)_2$ in ether to give the α-alcohol **13** in 80% yield with 10% of the β-alcohol. The configuration was confirmed by the ^{1}H-NMR studies of the corresponding penta-*O*-acetate **14**.[12]

Fig. 1. Structure of (+)-valienamine (**1**) and validamine (**2**).



1: (+)-Valienamine



2: (+)-Validamine

Fig. 2. Total synthesis of pyralomicin 1c.

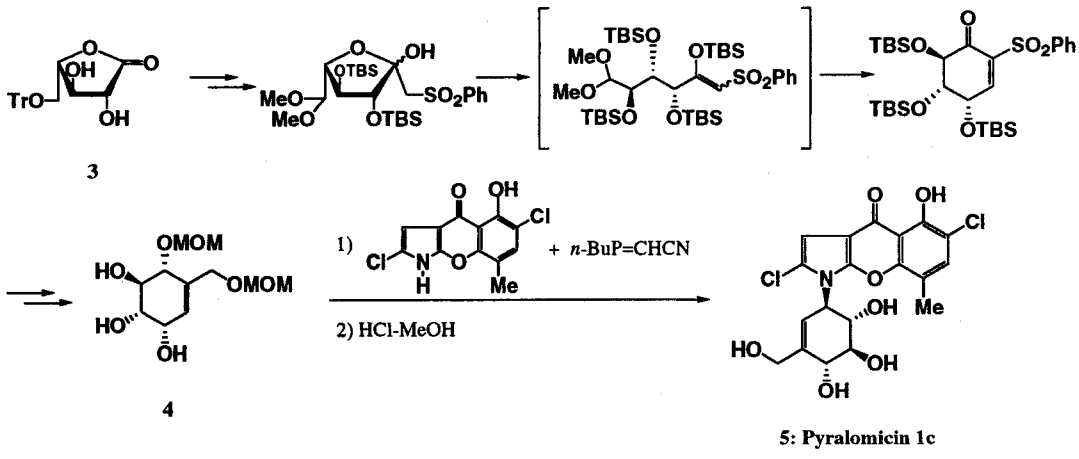
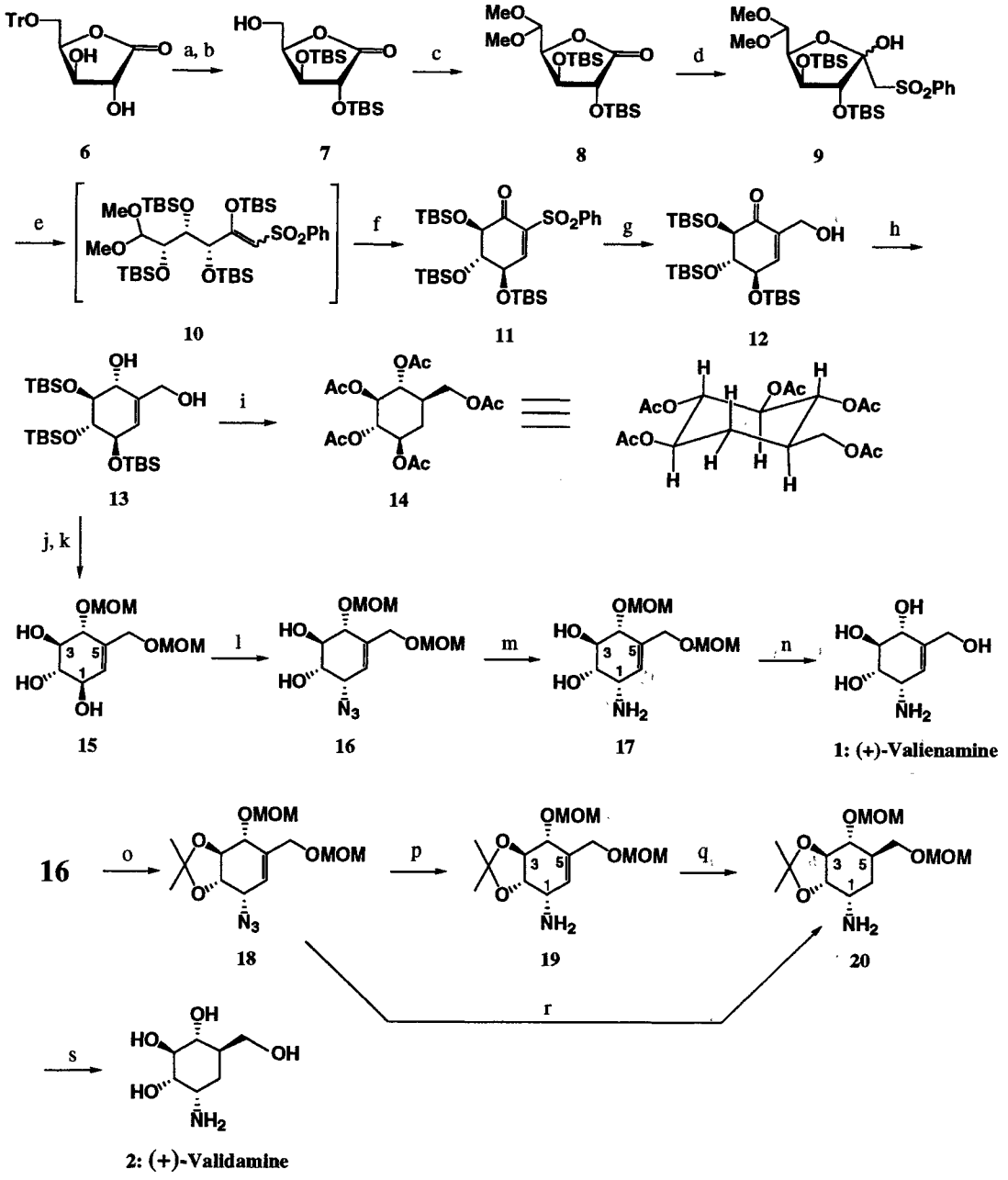


Fig. 3. Total synthesis of (+)-valienamine (1) and (+)-validamine (2).



Conditions; (a) TBSOTf, 2,6-lutidine/CH_2Cl_2, rt, 4 hours; 90% (b) H_2, Pd-C/$CHCl_3$, rt, 12 hours; 87% (c) 1) DCC, Py•TFA, DMSO/Et_2O, rt, 30 minutes 2) CSA, $HC(OMe)_3$/MeOH, 50°C, 15 hours; 73% (d) $MeSO_2Ph$, *n*-BuLi/THF, -78°C, 30 minutes; 94% (e) TBSOTf, 2,6-lutidine/CH_2Cl_2, 40°C, 2 days; 92% (f) $SnCl_4$/CH_2Cl_2, -78°C, 3 hours; 70% (g) *n*-Bu_3SnLi, HCHO/THF, -78°C to 40°C, 3 days; 84% (h) $Zn(BH_4)_2$/Ether, 0°C, 1 hour; 80% (i) 1) 3atm H_2, Raney Ni/EtOH, rt, 12 hours; 77% 2) 3%HCl-MeOH, 50°C, 2 hours; quant 3) Ac_2O, AcONa, 70°C, 24 hours; 82% (j) MOMCl, *n*-Bu_4NI, DIPEA CH_2ClCH_2Cl, 50°C, 24 hours; 85% (k) TBAF/THF, rt, 3 hours; 97% (l) HN_3, Ph_3P, DEAD/THF, rt, 1 hour; 81% (m) H_2, Raney Ni/H_2O/1,4-dioxane, rt, 3 hours; quant (n) 3%HCl-MeOH, 50°C, 3 hours; quant (o) $Me_2C(OMe)_2$, CSA/DMF, 90°C, 3 hours; 90% (p) H_2, Raney Ni/H_2O/1,4-dioxane, rt, 2 hours; quant (q) 3atm H_2, Raney Ni/H_2O/1,4-dioxane, rt, 10 hours; quant (r) 3atm H_2, Raney Ni/H_2O/1,4-dioxane, rt, 24 hours; quant (s) 3%HCl-MeOH, 50°C, 3 hours; quant

Table 1. Physico-chemical properties of compounds.

No.	$[\alpha]_D$ Mp (°C)	^{1}H-NMR (400,500 or 600MHz; δ ppm; *J* Hz)
1 · HCl	+73°(*c* 0.25, 1N HCl) Hygroscopic	(CD_3OD and DCl): δ 3.72(1H, dd, *J*=6.4&8.8), 3.86(1H, dd, *J*=5.2&8.8), 3.95(1H, m), 4.03(1H, d, *J*=6.4), 4.18(1H, d, *J*=14.8), 4.25(1H, d, *J*=14.8), 5.74(1H, ddd, *J*=1.0, 1.0&5.2)
1 · base	+90°(*c* 0.43, H_2O) 69-71	(D_2O): δ 3.57(1H, br s), 3.70(2H, br s), 4.11(1H, br s), 4.13(1H, d, *J*=12.8), 4.24(1H, d, *J*=12.8), 5.82(1H, br d, *J*=3.0)
2 · HCl	+60°(*c* 0.52, 1N HCl) 228-229	(D_2O and DCl): δ 1.38(1H, ddd, *J*=4.0, 14.0&14.0), 1.40-1.47(1H, m), 1.70(1H, ddd, *J*=2.4, 2.6&14.0), 2.99(1H, dd, *J*=10.4&10.4), 3.16(1H, dd, *J*=10.4&10.4), 3.32(1H, dd, *J*=5.8&11.4), 3.39-3.43(2H, m), 3.41(1H, dd, *J*=4.0&11.4)
2 · base	+56°(*c* 0.38, H_2O) Syrup	(D_2O): δ 1.37(1H, ddd, *J*=4.0, 14.0&14.0), 1.67-1.78(2H, m), 3.13-3.19(2H, m), 3.40(1H, dd, *J*=5.0&10.4), 3.46(1H, dd, *J*=10.4&10.4), 3.55(1H, dd, *J*=6.0&11.6), 3.64(1H, dd, *J*=4.0&11.6)
6	+73°(*c* 1.10, $CHCl_3$) Foam	($CDCl_3$): δ 3.00(2H, br s), 3.31(1H, dd, *J*=3.0&11.0), 3.68(1H, dd, *J*=3.0&11.0), 4.49(1H, dd, *J*=7.8&7.8), 4.58(1H, ddd, *J*=3.0, 3.0&7.8), 4.78(1H, d, *J*=7.8), 7.20-7.43(15H, m)
7	+64°(*c* 0.60, $CHCl_3$) 169-172	($CDCl_3$): δ 0.09(3H, s), 0.12(6H, s), 0.17(3H, s), 0.90(18H, s), 1.98(1H, dd, *J*=4.4&9.0), 3.84(1H, ddd, *J*=3.6, 9.0&12.8), 3.93(1H, ddd, *J*=4.4, 4.4&12.8), 4.41(1H, dd, *J*=6.0&6.0), 4.43(1H, d, *J*=6.0), 4.44-4.50(1H, m)
8	+55°(*c* 0.67, $CHCl_3$) Syrup	($CDCl_3$): δ 0.08(3H, s), 0.09(3H, s), 0.12(3H, s), 0.13(3H, s), 0.87(9H, s), 0.88(9H, s), 3.38(3H, s), 3.46(3H, s), 4.13(1H, d, *J*=4.6), 4.19(1H, dd, *J*=4.6&4.6), 4.47(1H, dd, *J*=4.6&4.6), 4.61(1H, d, *J*= 4.6)
11	-76°(*c* 1.16, $CHCl_3$) 136-142	($CDCl_3$): δ -0.18(3H, s), -0.03(3H, s), 0.02(3H, s), 0.04(3H, s), 0.17(3H, s), 0.19(3H, s), 0.77(18H, s), 0.93(9H, s), 3.82-3.87(2H, m), 4.41(1H, dd, *J*=3.6&3.6), 7.49(2H, t, *J*=8.0), 7.58(1H, t, *J*=8.0), 7.74(1H, dd, *J*=1.0&3.6), 7.98(2H, d, *J*=8.0)
12	-60°(*c* 1.05, $CHCl_3$) 124-125	($CDCl_3$): δ 0.04(3H, s), 0.08(9H, s), 0.14(3H, s), 0.15(3H, s), 0.89(9H, s), 0.93(9H, s), 0.94(9H, s), 2.24(1H, dd, *J*= 6.0&6.0), 3.79(1H, dd, *J*=6.0&8.6), 3.96(1H, d, *J*=8.6), 4.21-4.36(3H, m), 6.61(1H, s)
13	-58°(*c* 0.94, $CHCl_3$) Syrup	($CDCl_3$): δ 0.07(3H, s), 0.08(3H, s), 0.09(3H, s), 0.10(3H, s), 0.14(3H, s), 0.15(3H, s), 0.86(9H, s), 0.88(18H, s), 2.06(1H, br s), 3.10(1H, d, *J*=11.0), 3.83(1H, br d, *J*=11.0), 3.95(1H, ddd, *J*=1.0, 1.0&4.0), 4.03(1H, dd, *J*=3.0&4.0), 4.02-4.06(1H, m), 4.19(1H, dd, *J*=4.0&13.0), 4.31(1H, d, *J*=13.0), 5.73(1H, ddd, *J*=1.0, 1.0&4.0)
14	+10°(*c* 0.56,$CHCl_3$) Syrup	($CDCl_3$): δ 1.56(1H, ddd, *J*=12.4, 12.4&12.4), 1.98-2.12(1H, m), 1.99(3H, s), 2.02(3H, s), 2.04(6H, s), 2.06(3H, s), 2.19(1H, ddd, *J*=5.0, 5.0&12.4), 3.95(1H, dd, *J*=3.0&11.0), 4.08(1H, dd, *J*=5.0&11.0), 4.93(1H, ddd, *J*=5.0, 10.0&12.4), 5.02(1H, dd, *J*=10.0&11.6), 5.09(1H, dd, *J*=11.6&11.6), 5.16(1H, dd, *J*=10.0&10.0)
15	-92°(*c* 0.87, $CHCl_3$) 66	(C_6D_6 and D_2O): δ 2.96(3H, s), 3.13(3H, s), 3.60(1H, dd, *J*=5.0&10.0), 3.71(1H, br d, *J*=7.8), 3.81(1H, dd, *J*=5.0&6.0), 3.95(1H, d, *J*=12.8), 3.98(1H, dd, *J*=7.8&10.0), 4.06(1H, d, *J*=12.8), 4.38(1H, d, *J*=7.0), 4.39-4.43(3H, m), 5.55(1H, dd, *J*=1.0&6.0)
16	+129°(*c* 0.90, $CHCl_3$) Syrup	(dioxane-d_8 and D_2O): δ 3.60(3H, s), 3.67(3H, s), 3.98(1H, dd, *J*=4.0&10.4), 4.02(1H, dd, *J*=7.0&10.4), 4.26(1H, d, *J*=7.0), 4.34(1H, d, *J*=13.0), 4.42(1H, d, *J*=13.0), 4.48(1H, dd, *J*=4.0&6.0), 4.88(1H, d, *J*=6.4), 4.90(1H, d, *J*=6.4), 5.00(1H, d, *J*=6.4), 5.15(1H, d, *J*=6.4), 6.14(1H, dd, *J*=1.0&6.0)

Table 1. Continued

No.	$[\alpha]_D$ Mp (°C)	^{1}H-NMR (400,500 or 600MHz; δ ppm; *J* Hz)
17	+103°(*c* 0.42, MeOH) Syrup	(dioxane-d_8 and D_2O): δ 3.45(3H, s), 3.56(3H, s), 3.64(1H, dd, *J*=4.4&4.4), 3.77(1H, dd, *J*=4.4&8.4), 3.92(1H, dd, *J*=6.0&8.4), 4.11(1H, d, *J*=6.0), 4.15(1H, d, *J*=12.0), 4.28(1H, d, *J*=12.0), 4.74(1H, d, *J*=7.0), 4.77(1H, d, *J*=7.0), 4.87(1H, d, *J*=7.0), 4.99(1H, d, *J*=7.0), 5.98(1H, d, *J*=4.4)
18	+204°(*c* 1.01, $CHCl_3$) 54-55	(dioxane-d_8 and D_2O): δ 1.68(3H, s), 1.69(3H, s), 3.56(3H, s), 3.62(3H, s), 3.98(1H, dd, *J*=4.2&10.0), 4.17(1H, dd, *J*=8.0&10.0), 4.33(1H, d, *J*=13.0), 4.42(1H, d, *J*=13.0), 4.57(1H, d, *J*=8.0), 4.78(1H, dd, *J*=4.2&5.8), 4.85(1H, d, *J*=7.0), 4.87(1H, d, *J*=7.0), 4.92(1H, d, *J*=6.4), 5.11(1H, d, *J*=6.4), 6.15(1H, dd, *J*=1.0&5.8)
19	+178°(*c* 0.52, MeOH) Syrup	(dioxane-d_8 and D_2O): δ 1.54(3H, s), 1.56(3H, s), 3.45(3H, s), 3.50(3H, s), 3.78(1H, dd, *J*=5.0&10.0), 3.94(1H, dd, *J*=5.0&5.8), 4.02(1H, dd, *J*=8.0&10.0), 4.19(1H, d, *J*=12.0), 4.33(1H, d, *J*=12.0), 4.48(1H, d, *J*=8.0), 4.74(1H, d, *J*=7.0), 4.76(1H, d, *J*=7.0), 4.83(1H, d, *J*=7.0), 5.00(1H, d, *J*=7.0), 6.06(1H, d, *J*=5.8)
20	+101°(*c* 0.89, MeOH) Syrup	(C_6D_6): δ 1.37(3H, s), 1.38(3H, s), 1.45(1H, ddd, *J*=3.6, 13.0&15.0), 1.62(1H, ddd, *J*=3.0, 5.0&15.0), 2.22-2.32(1H, m), 3.19(3H, s), 3.27(3H, s), 3.28(1H, dd, *J*=6.0&10.0), 3.31(1H, ddd, *J*=3.6, 5.0&6.0), 3.64(1H, dd, *J*=3.0&9.0), 3.73(1H, dd, *J*=6.0&9.0), 3.86(1H, dd, *J*=10.0&10.0), 4.34(1H, dd, *J*=10.0&10.0), 4.49(1H, d, *J*=6.0), 4.54(1H, d, *J*=6.0), 4.69(1H, d, *J*=6.0), 5.29(1H, d, *J*=6.0)

The alcohol **13** was transformed to the properly protected alcohol **15**. Although **15** possessed three hydroxy groups, the allyl hydroxy group at C-1 was expected to be more reactive than others.[12]

As expected, Mitsunobu inversion of the allyl alcohol **15** using HN_3 gave predominantly the α-azide **16**. Mild hydrogenation of **16** with 1 atm of hydrogen over Raney Ni produced the corresponding amino compound **17** in a quantitative yield without any significant reduction of the olefin.

Deprotection of **17** with methanolic hydrogen chloride gave the hydrochloride of (+)-valienemine (**1**), which was chromatographed on Dowex 1X2 (OH-type) with water to give, after evaporation of the eluates, a syrup. This was gradually crystallized to provide the free base of **1** as a monohydrate. Both the hydrochloride and the free base of **1** were identical in all respects with the authentic samples of the natural product.[2]

On the final stage to synthesize validamine (**2**), extensive efforts were directed toward stereoselective hydrogenation of the olefin **17** that would ensure the configuration of the hydroxymethyl group at C-5.

Unfortunately, catalytic hydrogenation of **17** either on Raney Ni or Pd-C gave an approximately 1 : 1 mixture of the diastereomers due to the C-5.

The ^{1}H-NMR studies of **16** and **17** indicated that their conformations were different as shown in Fig. 4. Compound **16** adopts the usual half-chair form with the *quasi*-axial azido group, while the amino compound **17** exists in the boat-like form with the *quasi*-equatorial amino group. The latter form **17** might be due to the interaction such as hydrogen bonding between the C-1 amino and C-2 hydroxy groups.

The *quasi*-axial amino group or hydroxy group of methylcyclohex-2-enylamines or 2-enols has been known to act as the anchor toward the surface of Raney Ni on catalytic hydrogenation to give preferentially the *trans* isomer.[13]

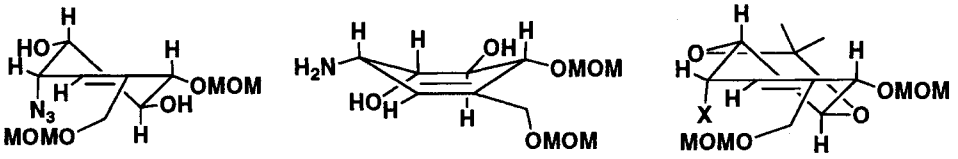
Accordingly, the *quasi*-equatorial amino group of **17** could not participate in the anchor effect for stereoselective hydrogenation.[13]

We expected that the conformation of the acetonated derivatives **18** and **19** would be much more rigid than **17** to keep the half-chair form having the *quasi*-axial amino group (Fig. 4 and 5).

Mild catalytic hydrogenation of **18** gave quantitatively the corresponding amino compound **19**.

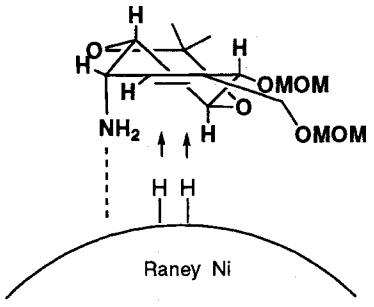
As a mixture of dioxane and H_2O was used for catalytic

Fig. 4. Conformations of key intermediates **16**~**19**.



16 **17** **18: X = N_3**
19: X = NH_2

Fig. 5. The anchor effect of the amino group in **19** over Raney Ni.



hydrogenation, the ^{1}H-NMR spectra of **17** and **19** were measured in dioxane-d_6 and D_2O to support that **19** existed in the half-chair form with the *quasi*-axial amino group (Fig. 4).

The *quasi*-axial amino group of **19** was expected to assist the anchor effect giving the desired 1,5-*trans* isomer **20** (Fig. 5).[13]

As expected, catalytic hydrogenation of **19** over Raney Ni in a mixture of dioxane and H_2O gave, after evaporation of the solvent, the *trans* isomer **20** as a single product in a quantitative yield.

Direct hydrogenation of **18** to **20** was also achieved in a quantitative yield with 3 atm of hydrogen on Raney Ni.

Acidic deprotection of **20** gave quantitatively the hydrochloride of (+)-validamine (**2**), which was chromatographed on Dowex 1X2 (OH-type) with water to yield the free base of **2**. Both the hydrochloride and the free base of **2** were identical in all respects with the authentic samples of the natural product.[3]

In summary, the novel synthesis of (+)-valienamine and (+)-validamine has been accomplished by our synthetic strategies for the construction of carbasugars. The absolutely stereoselective hydrogenation of **18** and **19** to give (+)-validamine is particularly noteworthy.

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