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TETRAHEDRON

Synthesis of Nectrisine and Related Compounds, and Their Biological Evaluation

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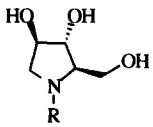
Abstract : An efficient and novel process is described for the synthesis of nectrisine **5** and its related derivatives **6**,**7** as potent glucosidase inhibitors *via* the corresponding lactams starting from D-(−)-diethyl tartrate. Also the results of biological evaluation of the synthesized compounds are described.

INTRODUCTION

During the past 10 years, some new and interesting compounds have been revealed that are potent inhibitors of glycosidase.[1] But these compounds generally suffer from lack of specificity and in some cases from low activity at cellular levels. In connection with a programme on the development of more effective glycosidase inhibitors, we have developed the versatile synthetic method of polyhydroxylated pyrrolidine compounds as potent α-glucosidase inhibitors.

Naturally occurring product DAB-1 **1**, isolated from *Angylocalyx boutiqueanus* and *Arachniodes standishii*[2] and its enantiomer LAB-1 **3** are powerful inhibitors of a range of α-glucosidases.[3] We have recently shown that DAB-1 and its *N*-protected derivative **2** and LAB-1 and its *N*-protected derivative **4** could be readily synthesized from optically active diethyl tartrate.[4]



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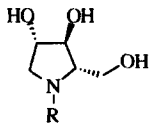

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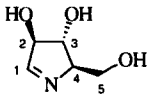

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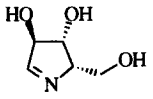

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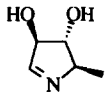

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Nectrisine **5**, a fungal metabolite isolated from *Nectria lucida*, is a potent α-glucosidase and α-mannosidase inhibitor.[5,6] Although 4-*epi*-nectrisine **6** has been reported to exist as a complex equilibrium mixture with dimerized and hydrated forms, its biological activities are not known.[7] In the previous

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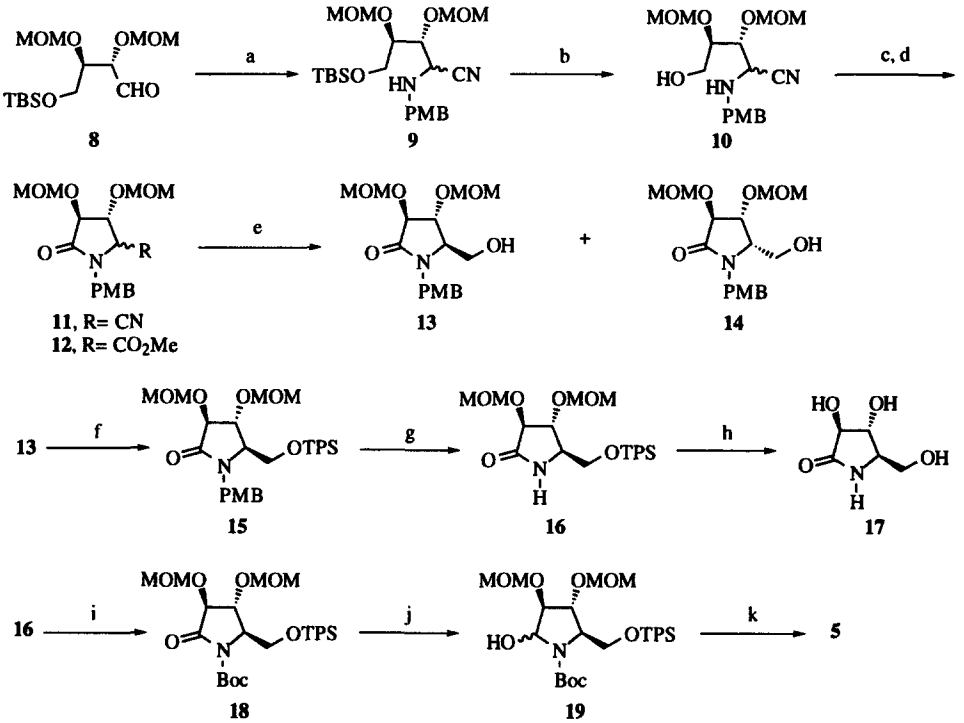
communication, we reported the synthesis of nectrisine and 4-*epi*-nectrisine.[8] We now present the details of this synthesis and the application of this synthetic method to produce various derivatives including 5-deoxynectrisine **7**. Furthermore, this paper presents the results of biological evaluation of the synthesized compounds in this programme using several glycosidases.

RESULTS AND DISCUSSION

1) Synthesis of Nectrisine

Our synthesis began with modified Strecker reaction[9] of the aldehyde **8**,[10] which was readily obtained from D-(−)-diethyl tartrate in good yield (4 steps, >90%) and is depicted in Scheme 1. Reaction of this aldehyde **4** with 2.4 eq. of *p*-methoxybenzylamine and 1.2 eq. of diethyl phosphorocyanidate (DEPC) in THF gave aminonitrile **9** (2 steps , 96%), as an inseparable diastereomeric mixture, the ratio of which was not determined because this stereocenter was epimerized concomitantly on the methanolysis of the nitrile **11** to the ester **12**. The aminonitrile **9** was subsequently deprotected with tetra-*n*-butylammonium fluoride (TBAF) in THF to the corresponding amino alcohol **10** in 87% yield.



Scheme 1: a) *p*-$(CH_3O)C_6H_4CH_2NH_2$, $(EtO)_2P(O)CN$, THF; 96%; b) TBAF, THF; 87%; c) TPAP, NMO, MS4A, CH_2Cl_2; d) NaOMe, MeOH, 0°C→ r.t. then 1N HCl ; 2 steps, 71%; e) $LiBH_4$, THF; 87%; f) TPSCl, imid., DMF; 96%; g) CAN, CH_3CN-H_2O (9:1); 84%; h) conc. HCl, MeOH-H_2O (2:1); 92%; i) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; quant.; j) $LiEt_3BH$, THF, −78°C; 93%; k) 6N HCl, THF, 50°C, 2h; >80%, then Dowex 1-X2 (OH^-), 90%

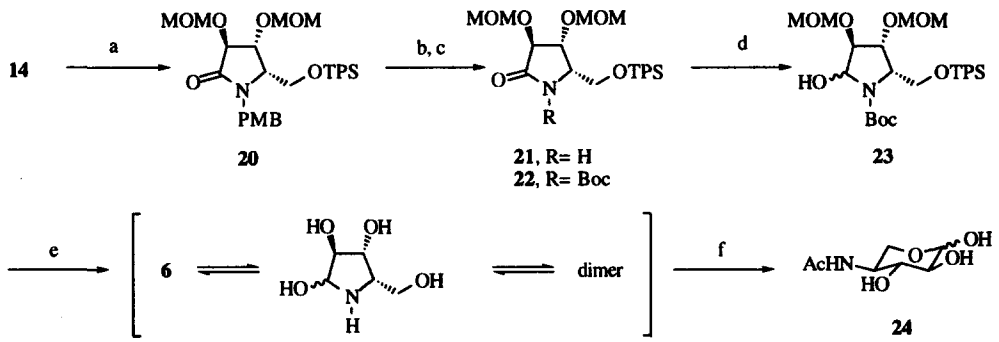
The amino alcohol **10** was oxidized by reaction with tetra-*n*-propylammonium perruthenate (TPAP)[11] and *N*-methylmorpholine-N-oxide (NMO) in CH_2Cl_2 at room temperature for 40 min, and cyclized to give the

lactam **11**. Without purification, the lactam was treated with 3 eq. of sodium methoxide in methanol at room temperature to give the methyl ester **12** (2 steps, 71%), which was reduced with $LiBH_4$ (lithium borohydride) in THF to form an alcohol and produced a chromatographically separable mixture of two diastereomers in 87% yield, *trans*-lactam **13** and *cis*-lactam **14**, in a ratio of 56:44. The latter was utilized for the synthesis of 4-*epi*-nectrisine **6**.

Protection of the primary alcohol of *trans*-lactam **13** with *t*-butyldiphenylsilyl chloride (TPSCl) and Et_3N gave the silyl ether **15** in 96% yield. At this juncture, the structure of compound **15** was further confirmed by a synthesis of (3*S*, 4*R*, 5*R*)-3,4-dihydroxy-5-hydroxymethyl-2-pyrrolidone **17**. Thus treatment of **15** with ceric ammonium nitrate (CAN)[12] in CH_3CN-H_2O (9:1) at 0℃ to afford lactam **16** in 84% yield and then the lactam was treated with conc. HCl in MeOH and H_2O (2:1) at 60℃ for 2h to furnish the corresponding pyrrolidone **17** in 92% yield which was identical in all respects with the literature.[6] The key step in this synthesis is the reduction of lactam to amino alcohol. Accordingly, we examined the reduction of **15** with various reducing reagents (DIBAL-H, $LiEt_3BH$, $NaBH_4$ etc), but reduction product was not obtained. Faced with this problem, we decided to replace the *N*-protecting group, -PMB, with the more electron-withdrawing and easily removable -Boc group. Thus lactam **16** was treated with di-*t*-Butyl dicarbonate (Boc_2O) and Et_3N in CH_2Cl_2 to give an imide **18** in quantitative yield. Thus, reduction of the imide **18** with $LiEt_3BH$ (Super Hydride®) in THF at –78℃ cleanly afforded amino alcohol **19** in 93% yield. The final task was the removal of the protecting groups. This was accomplished by treatment of 6N HCl in THF at 50℃ for 2h to give the amino sugar precursor[13] (>80% yield), followed by ion exchange column chromatography (Dowex resin, OH^-form) which afforded nectrisine **5** in 90% yield. Comparison of the specific optical rotation, ^1H and ^{13}C NMR data of our synthetic nectrisine **5** with those in the literature[5,6] completely confirmed the identity of them.

2) Synthesis of 4-*epi*-Nectrisine

The 4-*epi*-nectrisine **6** was then synthesized from **14**, following the set of reactions described above for the nectrisine **5**.



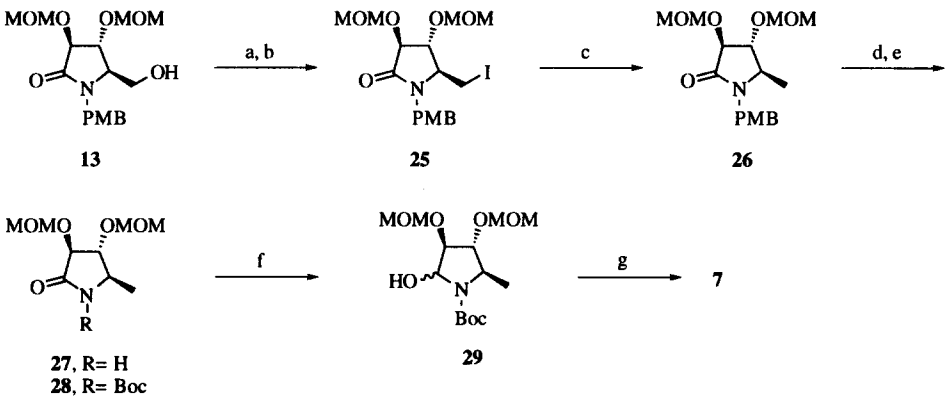
Scheme 2: a) TPSCl, imid., DMF; 92%; b) CAN, CH_3CN-H_2O (9:1), 0°C; 82% ; c) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; quant.; d) $LiEt_3BH$, THF, -78°C; 95%; e) 6N HCl, THF, 50°C, 2h, then Dowex 1-X2 (OH^-); >80%; f) Ac_2O, H_2O; Dowex 50W-X2 (H^+); quant.

Thus, as depicted in Scheme 2, protection of the primary hydroxyl function with TPSCl gave the silyl ether **20** in 92% yield. Removal of the protecting PMB group by CAN gave lactam **21** in 82% yield, which

was then treated with Boc_2O to give an imide **22** (quant. yield). The imide was reduced to amino alcohol **23** with Super Hydride® in THF at –78℃ in 95% yield. Finally, deprotection of **23** with 6N HCl in THF at 50℃ for 2h yielded a mixture of products (>80% yield). 4-*epi*-Nectrisine **6** was reported to exist as an equilibrium mixture of several forms.[7] For identification, we decided to acetylate the amino group. Treatment of the mixture of products with Ac_2O in H_2O gave **24** (quant. yield) which was identical in all respects with that in the literature.[7]

3) Synthesis of 5-Deoxynectrisine

We also looked into the synthesis of 5-deoxynectrisine **7** (Scheme 3). Thus esterification of **13** with *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine afforded the tosylate which was then converted into iodo compound **25** with sodium iodide ($NaHCO_3$, DMF) in 91% yield (based on the recovered tosylate). Hydrogenolysis of iodo compound **25** under palladium on carbon in EtOH gave the 5-deoxylactam **26** in quantitative yield. Removal of the -PMB protecting group in **26** with CAN provided lactam **27** (79% yield) which was treated with Boc_2O to give an imide **28** in quantitative yield. Reduction of the imide **28** with $LiEt_3BH$ (Super Hydride®) in THF at –78℃ cleanly afforded aminoalcohol **29** in 96% yield. The final task was the removal of the protecting groups. This was accomplished by treatment with 6N HCl in THF at 50℃ for 1h and successive purification with ion exchange column chromatography (H^+ form) to give the 5-deoxynectrisine **7** (>80% yield).



Scheme 3: a) *p*-TsCl, pyr.; b) NaI, $NaHCO_3$, DMF; 91% in 2steps; c) H_2, Pd-C, EtOH; quant.; d) CAN, CH_3CN-H_2O (9:1), 0℃; 79%; e) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; quant.; f) $LiEt_3BH$, THF, –78℃; 96%; g) 6N HCl, THF, 50℃, 1h, then Dowex 50WX-2 (H^+); > 80%.

4) Glycosidase Inhibition[14]

Biological activities of synthesized compounds in this programme are shown in Table 1. The natural product DAB-1 **1** showed potent inhibitory activity towards wide range of glycosidases (α- and β-glucosidases and α-mannosidase) and in particular the potent competitive inhibition of yeast α-glucosidase with 50% inhibition (IC_{50}) of enzymic activity at 1.5×10^{-7}M which are comparable with those reported.[3] Interestingly, compound **2** and **4**, *N*-PMB protected form of **1** and **3**, showed comparatively potent inhibition activity against yeast α-glucosidase with 50% inhibition at 1.0×10^{-6}M and 4.0×10^{-6}M. Besides, they also showed some

specificity between α-glucosidase and α-mannosidase. It appears that the three hydroxy functionalities of DAB-1 and LAB-1 are important for their biological activities. On the other hand, nectrisine **5** was also powerful inhibitor of yeast α-glucosidase (IC_{50} 0.04×10^{-6}M) which are comparable with those reported.[5,6] 4-*epi*-Nectrisine **6** whose glycosidase inhibitor properties are unknown so far showed comparatively potent inhibition activity against yeast α-glucosidase with 50% inhibition at 8.0×10^{-6}M. 5-Deoxynectrisine **7** possessed a remarkably potent inhibitory activity (IC_{50} 1.9×10^{-6}M) against yeast α-glucosidase, showing that the hydroxyl group of C-5 in nectrisine has a little effect in the inhibition. However, pyrrolidone **17** showed a weak inhibition against yeast α-glucosidase (IC_{50} 40×10^{-6}M).

Table 1. Biological activities of pyrrolidine derivatives.

Inhibitors / Enzymes[b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**17**
α-Glu. (Yeast)	0.15[a]	1	15	4	0.04	8	1.9	40
β-Glu. (Almonds)	500	1000	2000	>2000	2.2	125	7.5	NI[c]
α-Man. (Jack Bean)	200	800	>2000	>2000	3	800	15	NI
β-Man. (Snail)	>2000	700	>2000	>2000	42	NI	–[d]	NI
β-Gal. (Jack Bean)	2000	800	>2000	>2000	–	–	–	NI

[a]IC_{50} ($\times10^{-6}$M) determined as described[14], [b]Glu.: Glucosidase, Man.: Mannosidase, Gal.: Galactosidase, [c]NI; no inhibition up to 1.0×10^{-3}M, [d]–: not tested.

In conclusion, we have developed a new type of oxidative lactam formation which has been successfully used in total synthesis of the nectrisine **5** and 4-*epi*-nectrisine **6**. Also this work could give access to an efficient method for the synthesis of pyrrolidone **17** and 5-deoxynectrisine **7** and some other derivatives. These pathways furnish various synthetic intermediates and analogs which may be helpful in evaluating structure-activity relationships of these glycosidase inhibitors. Further utilization of this methodology in the synthesis of other azasugars and related systems will be reported in due course.

EXPERIMENTAL

IR: Jasco A-102 spectrometer. – ^{1}H NMR (in $CDCl_3$, CD_3OD or D_2O): Jeol JNM EX-90 spectrometer (90

MHz), Bruker AC-300 spectrometer (300 MHz) or Jeol JNM– A 500 spectrometer (500MHz). – Optical rotations: Jasco DIP-371 polarimeter. – High resolution mass measurement: JEOL JMS-SX 102/SX102. – Column chromatography: Merck Kieselgel 60 (Art. Nr. 7734). – Melting points: uncorrected values.

Methods of biological evaluation were the same as described in reference.[14]

(1*RS*,2*S*,3*R*)-2,3-Bis(methoxymethyl)oxy-4-(*t*-butyldimethylsilyl)oxy-1-cyano-*N*-(4-methoxybenzyl)butanamine (9). To a cooled (0℃) solution of aldehyde **8** (26g, 80.6mmol) and DEPC (15.8g, 96.7mmol) in THF (150ml) was slowly added a solution of *p*-methoxybenzylamine (26.6g, 193mmol) in THF (50ml). The reaction mixture was then allowed to warm to room temperature and stirred for 1h. The solvents were removed under reduced pressure and the residue was purified by SiO_2 column chromatography (EtOAc/Hexane, 1:6) to give 36g (96%) of **9** as a colorless oil ; $[\alpha]_D^{21}$= +43.1 (*c* 1.5 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3320, 2930, 2210, 1510, 1460, 1250, 1030, 840 and 780. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, d, *J*=2.7Hz), 0.88 (9H, d, *J*=3.5Hz), 3.42 (6H, d, *J*=6.2Hz), 3.80 (3H, s), 3.66-3.85 (4H, m), 3.88-4.20 (4H, m), 4.74 (4H, d, *J*=4.9Hz), 6.86 (2H , d, *J*=8.6Hz) 7.27 (2H , d, *J*=8.6Hz). Anal. Calcd. for $C_{23}H_{40}N_2O_6Si$: C, 58.94; H, 8.60; N, 5.98. Found: C, 58.47; H, 8.57; N, 5.58.

(1*RS*,2*R*,3*R*)-2,3-Bis(methoxymethyl)oxy-4-hydroxy-1-cyano-*N*-(4-methoxybenzyl)butanamine (10). To a cold (0℃) solution of **9** (8.8g, 18.8mmol) in THF (50ml) was added a solution of TBAF (6.2g, 22.6mmol) in THF (15ml). The resulting mixture was allowed to warm to room temperature. After being stirred for 2h, H_2O (20ml) was added and the mixture was extracted with Et_2O (50ml, 3times). The extract was washed successively with H_2O, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography (EtOAc/Hexane, 1:3) to give 5.8g (87%) of **10** as a pale yellow oil ; $[\alpha]_D^{25}$= +20.2 (*c* 1.0 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3480, 3320, 2940, 2210, 1610, 1510, 1460, 1250, 1030, 830 and 730. ^{1}H-NMR ($CDCl_3$) δ: 3.40 (6H, dd, *J*=2.3, 3.5Hz), 3.79 (3H, s), 3.72-3.94 (6H, m), 3.96 (1H, d, *J*=2.2Hz), 4.13 (1H, d, *J*=4.0Hz), 4.60 (1H, s), 4.75 (4H, dd, *J*=2.7, 5.3Hz), 6.87 (2H , d, *J*=8.6Hz) 7.26 (2H , d, *J*=8.6Hz). Anal. Calcd. for $C_{17}H_{26}N_2O_6$: C, 57.61; H, 7.39; N, 7.90. Found: C, 57.23; H, 7.26; N, 7.63.

(3*S*,4*R*,5*RS*)-*N*-(4-Methoxybenzyl)-3,4-bis(methoxymethyl)oxy-5-cyano-2-pyrrolidinone (11). The alcohol **10** (2.5g, 7.0mmol) was dissolved in CH_2Cl_2 (30ml) containing both the powdered 4A molecular sieves and NMO (2.5g, 21mmol). After stirring the mixture for 10min, solid TPAP (0.25g, 0.7mmol) was added in one portion at room temperature under argon atmosphere. This reaction was exothermic and thus the reaction mixture was allowed to reflux. After being stirred for 1h, the reaction mixture was filtered through SiO_2 under pressure, eluting with EtOAc. The filtrate was concentrated *in vacuo* to give 2.5g (quant.) of crude pyrrolidinone **11** as an oil ; IR (neat): ν_{max} (film)/cm^{-1}: 2960, 2840, 2210, 1720, 1620, 1510, 1440, 1250, 1050, 830 and 730. ^{1}H-NMR ($CDCl_3$) δ: 3.44 (6H, s), 3.80 (3H, s), 3.84-3.92 (1H, m), 4.01-4.34 (3H, m), 4.55 (1H, d, *J*=7.5Hz), 4.80 (2H, d, *J*=8.0Hz), 5.05 (2H, dd, *J*=3.6, 6.6Hz), 6.87 (2H , d, *J*=8.6Hz) 7.20 (2H , d, *J*=8.6Hz). This compound was used for the next step without further purification.

(3*S*,4*R*,5*RS*)-*N*-(4-Methoxybenzyl)-3,4-bis(methoxymethyl)oxy-5-methoxycarbonyl-2-pyrrolidinone (12). Sodium (0.5g, 21.3mmol) was dissolved in 25ml of MeOH. To this solution a dropwise solution of **11** (2.5g, 7.1mmol) in MeOH (10ml) was added and stirred for 30min. The reaction mixture was cooled (0℃) and acidified to pH 4 with 2M HCl. The reaction mixture was then allowed to warm to

room temperature and the mixture was stirred for 3h. The solvents were evaporated and the residue was partitioned with H_2O (15ml) and EtOAc (30ml). The aqueous layer was extracted with EtOAc (30ml, 3times) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (EtOAc/Hexane, 1:2) to give 1.9g (71%) of **12** as an oil ; $[\alpha]_D^{25}$= –78.2 (*c* 1.3 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 2950, 1760, 1710, 1610, 1510, 1440, 1040, 820 and 730. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (3H, d, *J*=5.8Hz), 3.43 (3H, d, *J*=2.3Hz), 3.66 (3H, d, *J*=9.3Hz), 3.77 (3H, s), 3.82-4.13 (2H, m), 4.24-4.44 (2H, m), 4.58 (1H, d, *J*=3.1Hz), 4.65 (2H, d, *J*=2.3Hz), 4.71-4.92 (1H, m), 5.07 (1H, dd, *J*=5.2, 6.7Hz), 6.82 (2H, d, *J*=8.6Hz), 7.15 (2H, dd, *J*=3.0, 8.6Hz). Anal. Calcd. for $C_{18}H_{25}NO_8$: C, 57.39; H, 6.57; N, 3.65. Found: C, 57.25; H, 6.51; N, 3.78.

(3*S*,4*R*)-*N*-(4-Methoxybenzyl)-3,4-bis(methoxymethyl)oxy-5-hydroxymethyl-2-pyrrolidinone (13, 14). To a stirred and cooled (0℃) solution of the methylester **12** (2g, 5.2mmol) in THF(30ml) $LiBH_4$ (4ml of 2M THF solution, 7.8mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 20h. After quenching the reaction by addition of H_2O (10ml), the reaction mixture was thoroughly extracted with EtOAc (30ml, 5times). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the resulting residue by SiO_2 column chromatography (EtOAc/Hexane, 1:1) gave 0.85g (46%) of (*5R*)-isomer **13** and 0.76g (41%) of (*5S*)-isomer **14** as solid ; **13**; m.p.= 56-57℃. $[\alpha]_D^{27}$= 3.0 (*c* 0.82 in $CHCl_3$). IR (neat): ν_{max} (nujol)/cm^{-1}: 3460, 2920, 2850, 1680, 1610, 1510, 1450, 1380, 1250, 1160, 1030, 980, 840 and 740. ^{1}H-NMR ($CDCl_3$) δ: 3.34 (3H, s), 3.35 (1H, m), 3.50 (3H, s), 3.69 (1H, dt, *J*=3.0, 5.5Hz), 3.78 (1H, m), 3.79 (3H, s), 4.18 (1H, dd, *J*=5.0, 10Hz), 4.24 (1H, d, *J*=15.0Hz), 4.36 (1H, d, *J*=5.0Hz), 4.66 (1H, d, *J*=7.0Hz), 4.72 (1H, d, *J*=15.0Hz), 4.79 (2H, dd, *J*=6.5, 9.5Hz), 5.12 (1H, d, *J*=6.5Hz), 6.86 (2H, d, *J*=8.5Hz), 7.20 (2H, d, *J*=8.5Hz). Anal. Calcd. for $C_{17}H_{25}NO_7$: C, 57.45; H, 7.09; N, 3.94. Found: C, 57.44; H, 7.04; N, 3.97. **14**; m.p.= 64-66℃. $[\alpha]_D^{27}$= –138.1 (*c* 0.82 in $CHCl_3$). IR (neat): ν_{max} (nujol)/cm^{-1}: 3440, 2940, 2840, 1700, 1610, 1510, 1440, 1370, 1250, 1150, 1040, 920, 830 and 760. ^{1}H-NMR ($CDCl_3$) δ: 3.38 (3H, s), 3.45 (3H, s), 3.50 (1H, m), 3.69 (1H, dt, *J*=3.4, 5.5Hz), 3.75 (1H, dd, *J*=2.2, 6.4Hz), 3.79 (3H, s), 4.04 (1H, d, *J*=14.7Hz), 4.30 (1H, dd, *J*=7.9, 15.6Hz), 4.59 (1H, d, *J*=7.6Hz), 4.70 (1H, d, *J*=4.3Hz), 4.79 (2H, dd, *J*=3.9, 6.7Hz), 6.84 (2H, d, *J*=8.5Hz), 7.17 (2H, d, *J*=8.5Hz). Anal. Calcd. for $C_{17}H_{25}NO_7$: C, 57.45; H, 7.09; N, 3.94. Found: C, 57.49; H, 7.09; N, 4.05.

(3*S*,4*R*,5*R*)-*N*-(4-Methoxybenzyl)-3,4-bis(methoxymethyl)oxy-5-(*t*-butyldiphenylsiloxymethyl)-2-pyrrolidinone (15). To a stirred solution of the alcohol **13** (0.7g, 1.97mmol), imidazole (0.16g, 2.4mmol) in DMF (15ml) was added dropwise a solution of TPSCl (0.77g, 3mmol) in DMF (5ml) at room temperature. After stirring for an additional 6h, H_2O (10ml) was added and the mixture was extracted with Et_2O (50ml, 3times). The ether extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography (EtOAc/Hexane, 1:4) to give 1.12g (96%) of **15** as an oil ; $[\alpha]_D^{27}$= +21.6 (*c* 0.71 in $CHCl_3$). IR (neat): ν_{max} (nujol)/cm^{-1}: 2930, 1710, 1610, 1510, 1430, 1250, 1150, 1110, 920, 860 and 710. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (9H, s), 3.25 (4H, s), 3.46 (3H, s), 3.62 (1H, d, *J*=15.3Hz), 3.68 (1H, dd, *J*=4.0, 11.3Hz), 3.74 (3H, s), 3.75 (1H, dd, *J*=4.0, 11.3Hz), 4.35 (2H, d, *J*=4.3Hz), 4.61 (1H, d, *J*=6.7Hz), 4.74 (1H, d, *J*=7.0Hz), 4.80 (1H, d, *J*=6.4Hz), 4.97 (1H, d,

J=15.0Hz), 5.13 (1H, d, *J*=6.7Hz), 6.73 (2H, d, *J*=8.3Hz), 6.84 (2H, d, *J*=8.5Hz), 7.44 (6H, m), 7.66 (4H, dd, *J*=6.7, 14Hz). Anal. Calcd. for $C_{33}H_{43}NO_7Si$: C, 66.75; H, 7.30; N, 2.36. Found: C, 66.54; H, 7.31; N, 2.42.

(3*S*,4*R*,5*R*)-3,4-Bis(methoxymethyl)oxy-5-(*t*-butyldiphenylsiloxymethyl)-2-pyrrolidinone (16). To a precooled (0℃) solution of **15** (0.7g, 1.2mmol) in CH_3CN-H_2O (9:1, 15ml) a solution of CAN (1.9g, 3.6mmol) in CH_3CN-H_2O (9:1, 10ml) was added dropwise. After stirring for 30min at 0℃, the reaction mixture was allowed to warm to room temperature and stirred for an additional 3h. The reaction mixture was diluted with 10ml of H_2O and thoroughly extracted with EtOAc (30ml, 5times). The organic extracts were washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (EtOAc/Hexane, 1:2) to give 0.47g (84%) of **16** as a white crystalline solid ; m.p.= 89-91℃. $[\alpha]_D^{20}$= +7.0 (*c* 0.63 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3250, 2920, 2860, 1730, 1680, 1460, 1110, 1060, 920, 820 and 710. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (9H, s), 3.16 (3H, s), 3.40 (3H, s), 3.55 (1H, dt, *J*=3, 5.5Hz), 3.58 (1H, dd, *J*=7.9, 9.8Hz), 3.86 (1H, dd, *J*=2.4, 7.3Hz), 3.93 (1H, dd, *J*=5.8, 11.9Hz), 4.36 (1H, d, *J*=7.0Hz), 4.54 (1H, d, *J*=6.7Hz), 4.67 (1H, d, *J*=6.4Hz), 4.74 (1H, d, *J*=6.4Hz), 5.03 (1H, d, *J*=6.2Hz), 5.82 (1H, bs), 7.39 (6H, m), 7.61 (4H, d, *J*=6.7Hz). Anal. Calcd. for $C_{25}H_{35}NO_6Si$: C, 63.40; H, 7.45; N, 2.96. Found: C, 63.54; H, 7.42; N, 2.90.

(3*S*, 4*R*, 5*R*)-3,4-Dihydroxy-5-hydroxymethyl-2-pyrrolidone (17). Conc. HCl (1ml) was added to a stirred solution of compound **16** (0.05g, 0.1mM) in MeOH (6ml) and H_2O (3ml). The reaction mixture was stirred at 60℃ for 2h and concentrated *in vacuo*. The resulting residue was then purified by SiO_2 flash column chromatography ($CHCl_3$/MeOH/28% aq.NH_4OH, 5:3:1) to give **17**, as a white crystalline solid (0.018g, 92%) ; m.p.= 135-138℃. $[\alpha]_D^{21}$= +15.2 (*c* 0.4 in H_2O). IR (KBr): ν_{max} (film)/cm^{-1}: 3200, 2910, 2850, 1658, 1340, 1314, 1278, 1090 and 1060. ^{1}H-NMR (D_2O) δ: 3.36 (1H, ddd, *J*=8.0, 5.0, 4.0Hz), 3.51 (1H, dd, *J*=12.5Hz), 3.70 (1H, dd, *J*=12.4Hz), 3.91 (1H, t, *J*=8.0Hz), 4,21 (1H, d, *J*=8.0Hz). Anal. Calcd. for $C_5H_9NO_4$: C, 40.82; H, 6.17; N, 9.52. Found: C, 40.48; H, 6.02; N, 9.03.

(3*S*,4*R*,5*R*)-*N*-(*t*-Butoxycarbonyl)-3,4-bis(methoxymethyl)oxy-5-(*t*-butyldiphenylsiloxymethyl)-2-pyrrolidinone (18). To a stirred solution of **16** (0.5g, 1.1mmol), Et_3N (0.14g, 1.4mmol) and DMAP (catalytic amount) in CH_2Cl_2 (15ml) was added a solution of $(Boc)_2O$ (0.32g, 1.5mmol) in CH_2Cl_2 (5ml) at room temperature. After being stirred for overnight, the solvents were removed under reduced pressure. The residue was then partitioned with H_2O (10ml) and EtOAc (20ml). The aqueous layer was extracted with EtOAc (30ml, 3times) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (EtOAc/Hexane, 1:4) to give 0.6g (quant.) of **18** as an oil ; $[\alpha]_D^{21}$= –42.4 (*c* 0.71 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 2930, 1800, 1770, 1720, 1470, 1370, 1310, 1150, 1110, 1040, 920, 820, 740 and 704. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (9H, s), 1.42 (9H, s), 3.34 (3H, s), 3.42 (3H, s), 3.86 (2H, m), 4.04 (1H, m), 4.23 (1H, d, *J*=3.4Hz), 4.37 (1H, dd, *J*=2.8, 5.5Hz), 4.67 (2H, dd, *J*=1.8, 6.7Hz), 4.72 (1H, d, *J*=6.7Hz), 4.96 (1H, d, *J*=6.7Hz), 7.38 (6H, m), 7.64 (4H, dd, *J*=6.5, 10.5Hz). Anal. Calcd. for $C_{30}H_{43}NO_8Si$: C, 62.80; H, 7.55; N, 2.44. Found: C, 62.44; H, 7.50; N, 2.85.

(3*S*,4*R*,5*R*)-*N*-(*t*-Butoxycarbonyl)-2-hydroxy-3,4-bis(methoxymethyl)oxy-5-(*t*-

butyldiphenylsiloxymethyl) pyrrolidine (19). To a precooled (–78°C) solution of **18** (0.32g, 0.56mmol) in THF (10ml) under argon atmosphere $LiEt_3BH$ (0.7ml of a 1M THF solution, 0.73mmol) was slowly added. After being stirred at –78°C for 30min, the solution was quenched at this temperature with methanol (5ml) and subsequently with 10ml of saturated aqueous $NaHCO_3$ solution. The resulting foamy slurry was allowed to warm to room temperature and then it was vigorously extracted with EtOAc (20ml, 3times). The extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (EtOAc/Hexane, 1:3) to give 0.3g (93%) of **19** as an oil ; $[\alpha]_D^{21}$= –29.1 (*c* 0.3 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3450, 2930, 1700, 1470, 1430, 1380, 1150, 1110, 1040, 920, 820, 740 and 704. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s), 1.31 (4.5H, bs), 1.51 (4.5H, bs), 3.28 (3H, bs), 3.42 (3H, s), 3.69-4.11 (4H, m), 4.44-4.70 (1H, m), 4.74 (4H, s), 5.36 (0.5H, bs), 5.51 (0.5H, bs), 7.38 (6H, m), 7.62 (4H, m). Anal. Calcd. for $C_{30}H_{45}NO_8Si$: C, 62.58; H, 7.88; N, 2.43. Found: C, 62.30; H, 7.83; N, 2.44.

Synthesis of nectrisine (5). To a stirred solution of **19** (0,1g, 0,17mmol) in THF (3ml) was added dropwise a solution of 6N HCl in THF (1:1 v/v, 2ml) at room temperature. The reaction mixture was stirred at 50°C for 2h and concentrated *in vacuo*. The resulting residue was then purified by SiO_2 flash column chromatography ($CHCl_3$/MeOH/28% aq. NH_4OH, 5:3:1) to give the 4-amino-4-deoxy-D-arabinose which was subjected to ion exchange chromatography purification (Dowex 1-X2, OH^-) to obtain pure nectrisine **5** (0,02g, 91%) ; $[\alpha]_D^{20}$= +19.6 (*c* 0.5 in H_2O), [lit[5] : $[\alpha]_D^{20}$= +21.8 (*c* 0.6 in H_2O)]. IR (KBr): ν_{max} (film)/cm^{-1}: 3300, 2900, 1640, 1560, 1400, 1040 and 850. ^{1}H-NMR (D_2O) δ: 7.67 (1H, bs), 3.09-4.08 (5H, m), ^{13}C NMR (D_2O) δ: 170.7, 83.6, 78.5, 77.0, 61.4.13. HRFABMS m/z: 131.0591 $[M]^+$ (Calcd. for $C_5H_9NO_3$ 131.0582)

(3*S*,4*R*,5*S*)-*N*-(4-Methoxybenzyl)-3,4-bis(methoxymethyl)oxy-5-(*t*-butyldiphenylsiloxymethyl)-2-pyrrolidinone (20). In the same manner as described for the preparation of **15**, **14** (1.3g, 3.68mmol) yielded 2.0g (92%) of **20** as an oil.; $[\alpha]_D^{27}$= –74.0 (*c* 0.67 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 1710, 1610, 1510, 1370, 1250, 1150, 1110, 1040, 920, 860 and 710. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s), 3.24 (3H, s), 3.36 (1H, d, *J*=11.9Hz), 3.43 (3H, s), 3.59 (1H, d, *J*=14.5Hz), 3.62 (1H, dd, *J*=2.5, 11.5Hz), 3.75 (3H, s), 3.78 (1H, dd, *J*=2.5, 11.5Hz), 4.15 (1H, dd, *J*=7.9, 16.2Hz), 4.59 (1H, d, *J*=6.7Hz), 4.71 (1H, d, *J*=6.5Hz), 4.85 (2H, d, *J*=6.5Hz), 5.04 (1H, d, *J*=15.0Hz), 5.12 (1H, d, *J*=6.7Hz), 6.76 (2H, d, *J*=8.3Hz), 7.01 (2H, d, *J*=8.5Hz), 7.39 (6H, m), 7.64 (4H, dd, *J*=6.7, 14Hz). Anal. Calcd. for $C_{33}H_{43}NO_7Si$: C, 66.75; H, 7.30; N, 2.36. Found: C, 66.30; H, 7.38; N, 2.38.

(3*S*,4*R*,5*S*)-3,4-Bis(methoxymethyl)oxy-5-(*t*-butyldiphenylsiloxymethyl)-2-pyrrolidinone (21). In the same manner as described for the preparation of **16**, **15** (0.7g, 1.2mmol) yielded 0.46g (82%) of **21** as colorless needles ; m.p.= 143-145°C. $[\alpha]_D^{27}$= –71.5 (*c* 0.62 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3250, 2920, 2860, 1730, 1680, 1460, 1110, 1060, 920, 820 and 710. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (9H, s), 3.23 (3H, s), 3.41 (3H, s), 3.66 (1H, d, *J*=7.6Hz), 3.74 (2H, m), 4.36 (1H, dd, *J*=7.3, 14.7Hz), 4.52 (1H, d, *J*=7.6Hz), 4.58 (1H, d, *J*=6.7Hz), 4.70 (1H, d, *J*=6.7Hz), 4.77 (1H, d, *J*=6.4Hz), 5.04 (1H, d, *J*=6.4Hz), 5.88 (1H, bs), 7.42 (6H, m), 7.66 (4H, dd, *J*=6.4, 10.1Hz). Anal. Calcd. for $C_{25}H_{35}NO_6Si$: C, 63.40; H, 7.45; N, 2.96. Found: C, 63.54; H, 7.42; N, 2.90.

(3*S*,4*R*,5*S*)-*N*-(*t*-Butoxycarbonyl)-3,4-bis(methoxymethyl)oxy-5-(*t*-butyldiphenylsiloxymethyl)-2-pyrrolidinone (22). In the same manner as described for the preparation

of **18, 21** (0.32g, 0.67mmol) yielded 0.39g (quant.) of **22** as an oil ; $[\alpha]_D^{21}$= –30.1 (*c* 0.62 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 2930, 1790, 1770, 1720, 1470, 1430, 1360, 1310, 1150, 1110, 1030, 920, 870, 820, 760 and 704. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (9H, s), 1.48 (9H, s), 3.33 (3H, s), 3.44 (3H, s), 3.91 (2H, d, *J*=1.8Hz), 4.17 (1H, d, *J*=8.2Hz), 4.32 (1H, dd, *J*=8.6, 17.4Hz), 4.71 (1H, d, *J*=6.4Hz), 4.82 (2H, dd, *J*=6.7, 13.7Hz), 5.05 (1H, d, *J*=9.2Hz), 5.09 (1H, d, *J*=6.4Hz), 7.38 (6H, m), 7.62 (2H, d, *J*=7.9Hz), 7.74 (2H, d, *J*=6.7Hz). Anal. Calcd. for $C_{30}H_{43}NO_8Si$: C, 63.80; H, 7.55; N, 2.44. Found: C, 62.60; H, 7.51; N, 2.59.

(3*S*,4*R*,5*S*)-*N*-(*t*-Butoxycarbonyl)-2-hydroxy-3,4-bis(methoxymethyl)oxy-5-(*t*-butyldiphenylsiloxymethyl) pyrrolidine (23). In the same manner as described for the preparation of **19, 22** (0.26g, 0.45mmol) yielded 0.25g (95%) of **23** as an oil ; $[\alpha]_D^{21}$= –3.3 (*c* 0.50 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3470, 2930, 1690, 1390, 1110, 920, 870, 820, 740 and 704. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (9H, s), 1.34 (4.5H, bs), 1.51 (4.5H, bs), 3.28 (3H, bs), 3.42 (3H, s), 3.75-3.97 (3H, m), 4.17 (1H, bs), 4.46 (1H, br), 4.73-4.83 (4H, m), 5.16 (0.5H, bs), 5.25 (0.5H, bs), 7.39 (6H, m), 7.69 (2H, bs), 7.76 (2H, d, *J*=6.0Hz). Anal. Calcd. for $C_{30}H_{45}NO_8Si$: C, 62.58; H, 7.88; N, 2.43. Found: C, 62.15; H, 7.84; N, 2.88.

Synthesis of 4-*epi*-nectrisine (6). To a stirred solution of **23** (0.1g, 0.17mmol) in THF (3ml) was added dropwise a solution of 6N HCl in THF (1:1 v/v, 2ml) at room temperature. The reaction mixture was stirred at 50℃ for 2h and concentrated *in vacuo*. The resulting residue was then subjected to ion exchange chromatography purification (Dowex 1-X2, OH^-) to give a mixture of products, including dimeric form and 4-*epi*-nectrisine **6** (0.03g, 80%). This compound was used for the next step and for bioassay without further purification.

4-Acetoamido-4-deoxy-L-xylose (24). To a stirred solution of a mixture of products **6** (0.03g, 0.2mmol) in H_2O (5ml) was added Ac_2O (0.12g, 1mmol). The reaction mixture was stirred at room temperature for overnight and concentrated *in vacuo*. The resulting residue was then subjected to ion exchange chromatography purification (Dowex 50WX-2, H^+) to give 0.21g (quant.) of **24** as an oil ; $[\alpha]_D^{20}$= –47.7 (*c* 0.9 in H_2O), [lit[7a] : $[\alpha]_D^{24}$= –53-49 (*c* 3.3 in H_2O)]. IR (neat): ν_{max} (film)/cm^{-1}: 3330, 2920, 2850, 1710, 1640, 1560, 1460, 1380, 1070. ^{1}H-NMR (D_2O) δ: 5.24 (α- anomer, 0.4H, d, *J*=3.5Hz), 4.57 (β-anomer, 0.6H, d, *J*=7.5Hz), 3.89 (2H, m), 3.67 (2H, m), 3.31 (1H, m), 2.02 (3H, s), ^{13}C NMR (D_2O) δ: 175.3, 97.3, 93.1, 75.4, 74.1, 72.7, 70.9, 64.2, 60.0, 51.8(2C), 22.7. HRFABMS m/z: 192.0858 [M+H] (Calcd. for $C_7H_{13}NO_5$ 191.0793)

(3*S*,4*R*,5*R*)-*N*-(4-Methoxybenzyl)-3,4-bis(methoxymethyl)oxy-5-iodo-methyl-2-pyrrolidinone (25). To a stirred solution of the alcohol **13** (0.25g, 0.7mM) in pyridine (7ml) was added *p*-toluenesulfonyl chloride (0.27g, 1.4mM) and a catalytic amount of DMAP. The solution was stirred for overnight and H_2O (10ml) was added to the reaction mixture. It was then partitioned between Et_2O and H_2O. The aqueous layer was separated and extracted with Et_2O (30ml, 3 times). The combined ether layers were washed with a solution of $CuSO_4$ (30ml, 3times), brine, dried ($MgSO_4$), and concentrated in *vacuo*. To a stirred solution of crude tosylate in DMF (10ml) was slowly added NaI (0.19g, 1.2mM) and $NaHCO_3$ (0.17g, 2.0mM). The reaction mixture was heated to 65-70℃ for 2h and then cooled to room temperature. Et_2O (30ml) and H_2O (20ml) were added and the layers were separated. The aqueous phase was extracted with ether (30ml, 3times) and the combined organic phases were washed with H_2O, brine, dried ($MgSO_4$) and concentrated in

vacuo. The resulting residue was purified by SiO_2 column chromatography (EtOAc/Hexane, 1:2) to afford 0.24g (74%) of **25** and 0.07g (19%) of recovered starting tosylate compound ; $[\alpha]_D^{19}$= –12.8 (*c* 0.5 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 2940, 1710, 1610, 1510, 1440, 1250, 1150, 1110, 1040, 920 and 830. ^{1}H-NMR ($CDCl_3$) δ: 3.10-3.25 (2H, m), 3.35 (3H, s), 3.47 (3H, s), 3.40-3.75 (1H, m), 3.80 (3H, s), 3.90-4.15 (2H, m), 4.45 (1H, d, *J*=5.7Hz), 4.65-4.82 (3H, m), 4.95-5.20 (2H, m), 6.82 (2H, d, *J*=8.6Hz), 7.21 (2H, d, *J*=8.6Hz). Anal. Calcd. for $C_{17}H_{24}INO_6$: C, 43.88; H, 5.20; N, 3.01. Found: C, 44.22; H, 5.19; N, 3.00.

(3*S*,4*R*,5*R*)-*N*-(4-Methoxybenzyl)-3,4-bis(methoxymethyl)oxy-5-methyl-2-pyrrolidinone (26). A solution of **25** (0.2g, 0.43mM) in EtOH (5ml) was hydrogenated over 10% palladium on carbon (0.1g) and $NaHCO_3$ (0.3g) at atmospheric pressure for 3h. After filtration, the catalyst was washed with EtOH (10ml) and the resulting EtOH solution was evaporated in *vacuo*. The resulting residue was purified by SiO_2 column chromatography (EtOAc/Hexane, 1:2) to afford 0.14g (quant.) of **26** as a colorless oil ; $[\alpha]_D^{20}$= +32.7 (*c* 0.4 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 2940, 1703, 1610, 1510, 1440, 1380, 1250, 1150, 1040, 920, 840, 810 and 760. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, *J*=6.2Hz), 3.16-3.37 (1H, m), 3.34 (3H, s), 3.43 (3H, s), 3.78 (3H, s), 3.83-4.00 (2H, m), 4.32 (1H, d, *J*=5.7Hz), 4.60-4.83 (3H, m), 5.02-5.19 (2H, m), 6.84 (2H, d, *J*=8.6Hz), 7.15 (2H, d, *J*=8.6Hz). Anal. Calcd. for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.13; H, 7.40; N, 4.13.

(3*S*,4*R*,5*R*)-3,4-Bis(methoxymethyl)oxy-5-methyl-2-pyrrolidinone (27). In the same manner as described for the preparation of **16**, **26** (0.21g, 0.61mmol) yielded 0.11g (79%) of **27** as a white crystalline solid ; m.p.= 46-48℃. $[\alpha]_D^{19}$= –15.2 (*c* 0.08 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3320, 2920, 1720, 1670, 1460, 1380, 1120, 1050, 990 and 920. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, d, *J*=6.2Hz), 3.41 (3H, s), 3.45 (3H, s), 3.89 (1H, m), 4.30-4.38 (1H, m), 4.34 (1H, d, *J*=65.7Hz), 4.74-4.88 (3H, m), 5.06-5.13 (1H, m), 6.56 (1H, bs, -NH). Anal. Calcd. for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.61; H, 7.87; N, 6.37.

(3*S*,4*R*,5*R*)-*N*-(t-Butoxycarbonyl)-3,4-bis(methoxymethyl)oxy-5-methyl-2-pyrrolidinone (28). In the same manner as described for the preparation of **18**, **27** (0.1g, 0.46mmol) yielded 0.15g (quant.) of **28** as a crystalline solid ; m.p.= 46-48℃. $[\alpha]_D^{20}$= –132.1 (*c* 0.21 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 2980, 2830, 1790, 1720, 1460, 1370, 1310, 1210, 1150, 1110, 1040, 990, 920, 850, 760 and 670. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, d, *J*=6.5Hz), 1.53 (9H, s), 3.24-3.57 (1H, m), 3.39 (3H, s), 3.42 (3H, s), 3.78-4.05 (1H, m), 4.19 (1H, d, *J*=3.5Hz), 4.72 (3H, m), 5.01 (1H, d, *J*=6.7Hz). Anal. Calcd. for $C_{14}H_{25}NO_7$: C, 52.65; H, 7.89; N, 4.39. Found: C, 52.68; H, 7.84; N, 4.39.

(3*S*,4*R*,5*R*)-*N*-(t-Butoxycarbonyl)-2-hydroxy-3,4-bis(methoxymethyl)oxy-5-methylpyrrolidine (29). In the same manner as described for the preparation of **19**, **28** (0.024g, 0.08mmol) yielded 0.023g (96%) of **29** as an oil ; $[\alpha]_D^{20}$= –9.2 (*c* 0.08 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3440, 2930, 1700, 1390, 1050 and 920. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, d, *J*=6.5Hz), 1.53 (9H, s), 3.39 (3H, s), 3.42 (3H, s), 3.78-4.05 (2H, m), 4.72 (5H, m), 5.20 (1H, br). Anal. Calcd. for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36. Found: C, 51.87; H, 8.51; N,4.04.

Synthesis of 5-deoxynectrisine (7). To a stirred solution of **29** (0.05g, 0.16mmol) in THF (2ml) was added dropwise a solution of 6N HCl in THF (1:1 v/v, 1ml) at room temperature. The reaction mixture was stirred at 50℃ for 2h and concentrated *in vacuo*. The resulting residue was then purified by SiO_2 flash column

chromatography ($CHCl_3$/MeOH, 5:1) and then ion exchange chromatography (Dowex 1-X2, OH^-) to give 0.014g (80%) of **7** ; $[\alpha]_D^{20}$= –6.5 (*c* 1.0 in H_2O). IR (neat): ν_{max} (nujol)/cm^{-1}: 3390, 2920, 1650, 1460, 1380, 1040 and 720. ^{1}H-NMR (D_2O) δ: 1.16 (3H, d, *J*= 7Hz), 3.01-3.89 (3H, m), 7.47 (1H, s). HRFABMS m/z: 115.0662 $[M]^+$ (Calcd. for $C_5H_9NO_2$ 115.0633)

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