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Novel Synthesis of Nectrisine and 4-*epi*-Nectrisine

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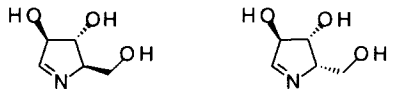
Abstract: *Nectrisine* **1**, *a potent glycosidase inhibitor, and 4-epi-Nectrisine* **2** *were synthesized from D-(−)- diethyl tartrate through the corresponding lactams. N-acyl protection was crucial to effect the reduction of the corresponding lactams to amino alcohols* © 1997 Elsevier Science Ltd.

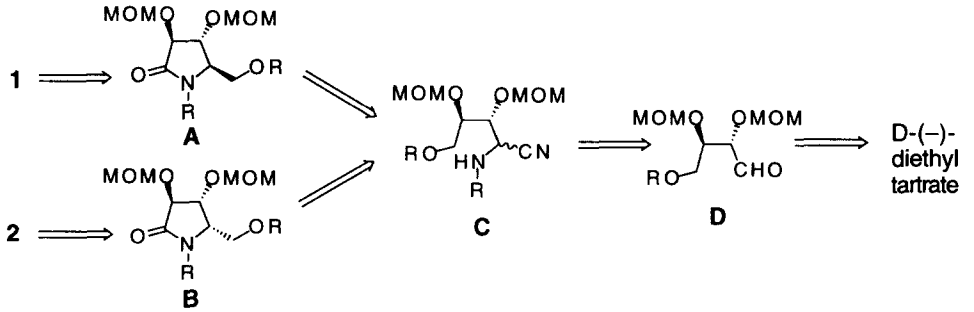
Much attention has been paid to polyhydroxylated pyrrolidines since they possess remarkable biological activities as inhibitors of glycosidases.[1-2] One such substance, nectrisine **1**, a fungal metabolite isolated from *Nectria lucida*, has attracted significant interest.[3] Syntheses of **1** have been published, mostly starting from sugars as chiral precursors.[4]

Herein we wish to describe the novel synthesis of nectrisine **1** and 4-*epi*-nectrisine **2** from D-(−)-diethyl tartrate *via* lactam intermediates **9a**, **9b** respectively. Although 4-*epi*-nectrisine **2** has been reported to exist as a complex equilibrium mixture with dimerized and hydrated forms, its biological activities are not known.[5]



1 **2**

Our synthetic strategy for a general approach to both diastereomers of nectrisine **1** and 4-*epi*-nectrisine **2** is illustrated in Scheme 1. **1** and **2** can be envisioned as being derived from the lactam precursors **A** and **B** by reduction of the carbonylfunctions, followed by hydrolytic deprotection of the protecting groups. Diastereomeric pyrrolidinones **A** and **B** can be generated from aminonitrile **C** by oxidative lactam formation and

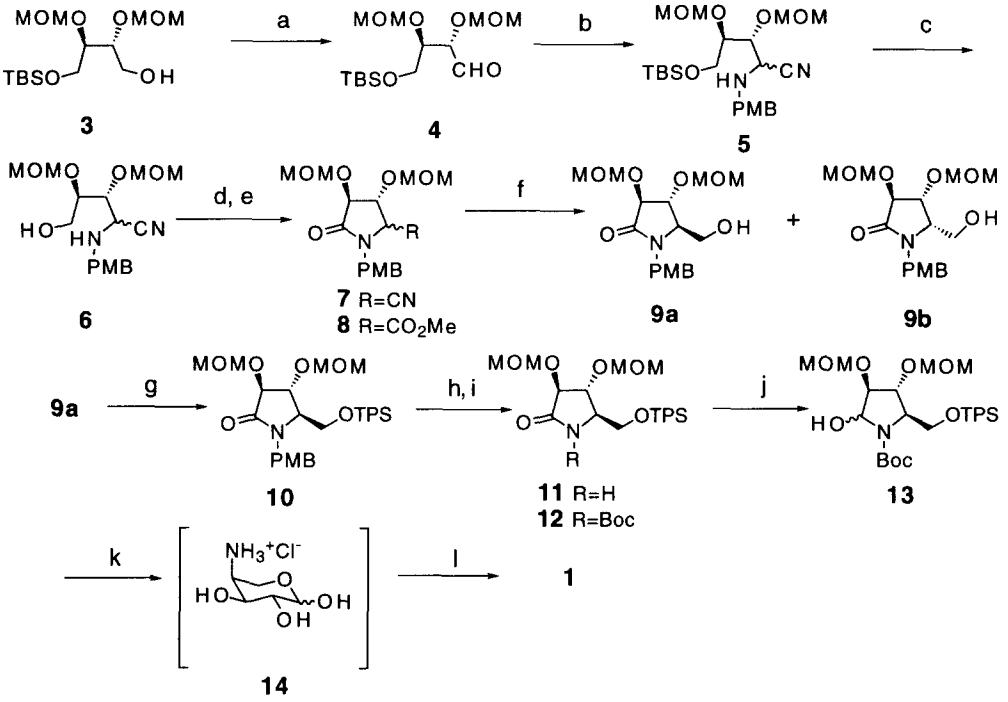


Scheme 1

reduction of the nitrile. The diastereomeric mixture of amino nitriles **C** can be easily prepared by a modified Strecker reaction[6] with aldehyde **D** provided from the starting material D-(−)-diethyl tartrate.

Our synthesis began with Swern oxidation of the known alcohol **3**,[7] which was obtained from D-(-)-diethyl tartrate in good yield (3steps, >90%) and is depicted in Scheme 2. Reaction of this aldehyde **4** with 2.4 eq. of *p*-methoxybenzylamine and 1.2 eq. of diethyl phosphorocyanidate (DEPC)[6] in THF gave aminonitrile **5** (2steps , 96%), as an inseparable diastereomeric mixture which was subsequently deprotected with tetra-*n*-butylammonium fluoride (TBAF) in THF to the corresponding amino alcohol **6** in 87% yield. The amino alcohol **6** was oxidized by reaction with tetra-*n*-propylammonium perruthenate (TPAP)[8] and *N*-methylmorpholine-N-oxide (NMO) in dichloromethane at room temperature for 40 min to give the lactam **7**.

Without purification, the lactam was treated with 3 eq. of sodium methoxide in methanol at room temperature to give methyl ester **8** (2steps, 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 **9a** and *cis*-lactam **9b**, in a ratio of 56:44. Protection of the primary alcohol of *trans*-lactam **9a** with *t*-butyldiphenylsilylchloride (TPSCl) and Et_3N gave the silyl ether **10** in 96% yield.

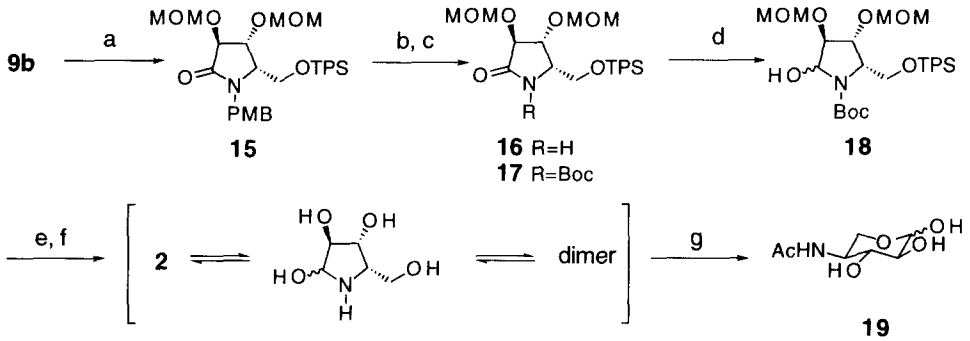


a) Swern oxidation; b) *p*-$(CH_3O)C_6H_4CH_2NH_2$, $(EtO)_2P(O)CN$, THF; 2 steps, 96%; c) TBAF, THF; 87%; d) TPAP, NMO, MS4A, CH_2Cl_2; e) NaOMe, MeOH, 0°C→ r.t. then 1N HCl ; 2 steps, 71%; f) $LiBH_4$, THF, 0°C→ r.t.; 87%; g) imidazole, TPSCl, DMF; 96%; h) $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O (9:1), 0°C; 84%; i) Et_3N, $(Boc)_2O$, DMAP, CH_2Cl_2; quant.; j) $LiEt_3BH$, THF, -78°C; 93%; k) 6N HCl, THF, 50°C, 2h; >80%, l) Dowex 1-X2 (OH^-), 90%

Scheme 2

The key step in this synthesis is the reduction of lactam to amino alcohol. Accordingly, we examined the reduction of **10** with various reducing reagents, but our attempts were unsuccessful. Faced with this problem, we decided to replace the *N*-protecting group, PMB, with the more electron-withdrawing and easily removable Boc group. Removal of the PMB protecting group in **10** by ceric ammonium nitrate (CAN)[9] in CH_3CN-H_2O (9:1) at 0℃ provided lactam **11** in 84% yield, which was treated with di-*t*-Butyl dicarbonate (Boc_2O) and Et_3N in CH_2Cl_2 to give an imide **12** in quantitative yield. Thus, reduction of the imide **12** with $LiEt_3BH$ (Super Hydride®)[10] in THF at -78℃ cleanly afforded amino alcohol **13** 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 **14**[11] (>80% yield), followed by ion exchange chromatography (Dowex resin, OH^-form) which afforded nectrisine **1** in 90% yield. Comparison of the specific optical rotation, ^1H and ^{13}C NMR data of our synthetic nectrisine **1**[12] with those in the literature[3,4b] completely confirmed the identity of nectrisine.

The 4-*epi*-nectrisine **2** was then synthesized from **9b**, following the set of reactions previously described for the nectrisine **1**. Thus, as depicted in Scheme 3, protection of the primary hydroxyl function with TPSCl and Et_3N gave the silyl ether **15** in 92% yield. Removal of the protecting PMB group by CAN in CH_3CN-H_2O (9:1) at 0℃ gave lactam **16** in 82% yield, which was then treated with Boc_2O and Et_3N in CH_2Cl_2 to give an imide **17**(quant. yield). The imide was reduced to amino alcohol **18** by Super Hydride® in THF at -78℃ in 95% yield. Finally, deprotection of **18** with 6N HCl in THF at 50℃ for 2h yielded a mixture of products (>80% yield). 4-*epi*-Nectrisine **2** was reported to exist as an equilibrium mixture of several forms.[5] For identification, we decided to acetylate the amino group. Treatment of the mixture of products with Ac_2O in H_2O gave **19**[13] (quant. yield) which was identical in all respects with that in the literature.[5a]



a) imidazole, TPSCl, DMF; 92%; b) $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O(9:1), 0°C; 82% ; c) Et_3N, $(Boc)_2O$, DMAP, CH_2Cl_2; quant.; d) $LiEt_3BH$, THF, -78°C; 95%; e) 6N HCl, THF, 50°C, 2h; f) Dowex 1-X2 (OH^-); >80%, g) Ac_2O, H_2O; Dowex 50W-X2 (H^+); quant.

Scheme 3

In summary, a new route to **1** and **2** *via* lactam intermediates **9a**, **9b** has been developed. These pathways produce various synthetic intermediates and analogs which may be helpful in evaluating structure-activity relationships of this glucosidase inhibitor. A thorough biochemical evaluation of **2** and related derivatives is in progress and will be reported elsewhere.

Acknowledgments

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12. Physical data for **1**: $[\alpha]_D^{20}$ = +19.6°(c=0.5, H_2O), lit : $[\alpha]_D$ = +21.8°(c=0.6, H_2O),[4b] lit : $[\alpha]_D^{23}$ = +22.0°(c=0.55, H_2O),[3] IR (KBr): 3300, 2900, 1640, 1560, 1400, 1040, 850 cm^{-1}, ^1H NMR (300 MHz, D_2O) δ 7.67 (1H, bs), 3.09-4.08 (5H, m), ^{13}C NMR (300 MHz, D_2O) δ 170.7, 83.6, 78.5, 77.0, 61.4.
13. Physical data for **19**: $[\alpha]_D^{20}$ = –47.7°(c=0.9, H_2O), lit : $[\alpha]_D^{24}$ = –53°- –49°(c=3.3, H_2O),[5a] IR (Nujol): 3330, 2920, 2850, 1710, 1640, 1560, 1460, 1380, 1070 cm^{-1}, ^1H NMR (500 MHz, 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 (500 MHz, 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.

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