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Novel and Versatile Synthesis of Pyrrolidine Type Azasugars, DAB-1 and LAB-1, Potent Glucosidase Inhibitors†

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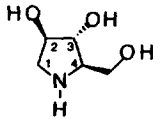
Abstract : Synthesis of glucosidase inhibitors, DAB-1 (1) and LAB-1 (2) from diethyl tartrate is described. The procedure afforded an epimerizable mixture of diastereomeric intermediates **8** and *ent.* **8**, and opened the door not only to the selective synthesis of DAB-1 and LAB-1 but for giving various related analogs. © 1997 Elsevier Science Ltd.

INTRODUCTION

Much attention has been paid to naturally occurring polyhydroxylated piperidines and pyrrolidines in view of their remarkable inhibitory activities against glucosidases and/or mannosidases and for their important role in a number of important biological processes.[1-2] At present, there are numerous known natural azasugars as a glucosidase inhibitor.[3]

Naturally occurring product DAB-1 (**1**), isolated from *Angylocalyx boutiqueanus* and *Arachniodes standishii*[4] and its enantiomer LAB-1 (**2**) are powerful inhibitors of a range of α-glucosidases.[5] Nectrisine **3**, a fungal metabolite isolated from *Nectria lucida*, is also a potent α-glucosidase and α-mannosidase inhibitor.[6] There are a variety of syntheses for **1**,[7] **2**[8] and **3**[9] which mostly start from sugars as chiral precursors. We have recently shown that netrisine and 4-*epi*-nectrisine could be readily synthesized from D-(-)-diethyl tartrate.[10] Herein we wish to describe a novel and versatile synthesis of enantiomeric DAB-1 (**1**) and LAB-1 (**2**) by employing an epimerizable mixture of diastereomeric intermediates, respectively.



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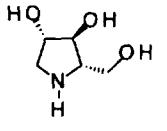

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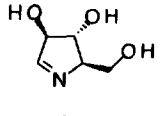

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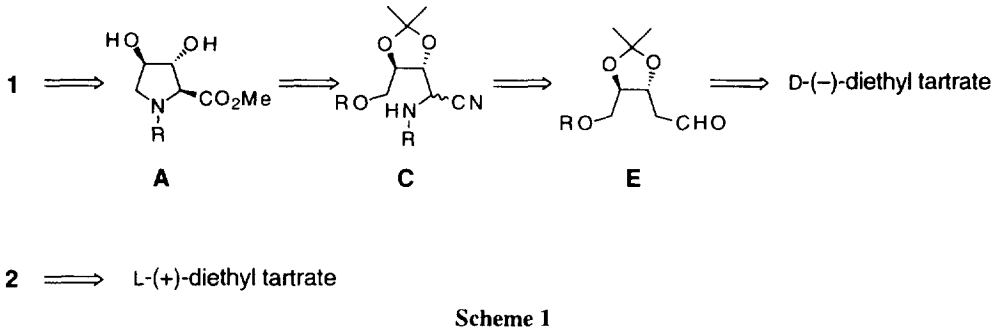
The synthesis of DAB-1 (**1**) and LAB-1 (**2**) could be planned according to the retrosynthetic paths

†Synthetic Studies on Enzyme Inhibitors. Part 5. For Part 4, see: Ishigami, K.; Kitahara, T. *Tetrahedron*, **1995**, *51*, 6431.

outlined in Scheme 1. It can be envisioned that DAB-1 (**1**) would be derived from the pyrrolidine **A** by reduction of the ester function, followed by deprotection of the *N*-protecting group. The pyrrolidine **A** can be generated from amino nitriles **C** by cyclization and methanolysis of nitrile. The diastereomeric mixture of amino nitrile **C** can be easily prepared by a modified Strecker reaction[11] with the known aldehyde **E**,[12] readily available from a chiral source, D-(−)-diethyl tartrate. LAB-1 (**2**) must be synthesized starting from L-(+)-diethyl tartrate in the same manner.

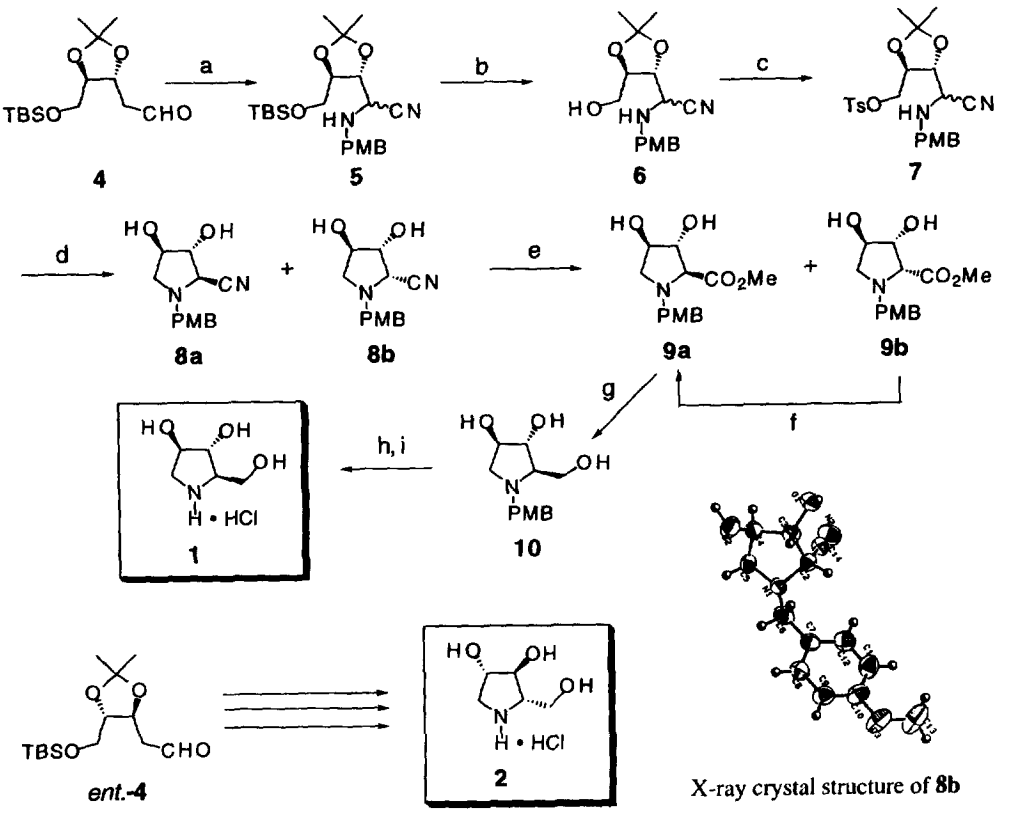


Scheme 1

RESULTS AND DISCUSSION

Our synthesis is illustrated in Scheme 2. Reaction of the aldehyde **4** with 2.4 eq. of *p*-methoxybenzylamine and 1.2 eq. of diethyl phosphorocyanidate (DEPC)[11] in THF gave aminonitrile **5** (86.7%), as an inseparable diastereomeric mixture, which was subsequently deprotected with tetra-*n*-butylammonium fluoride (TBAF) in THF to the corresponding amino alcohol **6** (quant.). Esterification of **6** with *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine afforded the tosylate **7** (84%), the precursor of the cyclization reaction. Cyclization was then examined under various basic conditions but proved unsuccessful. Because the 5-membered acetal ring could obstruct this cyclization, we decided to eliminate the acetonide protecting group. Thus, treatment of tosylate **7** with CF_3COOH-H_2O-THF (5:1:1) afforded cyclization products **8a** and **8b** in a ratio of 1:4 (74%). The configuration of the major product **8b** was confirmed by an X-ray structure analysis. Since the desired *trans*-product **8a** was a minor product, the epimerization of **8b** to **8a** was needed. Faced with this problem, we decided to convert the nitrile group into methyl ester under basic conditions. Thus, the diastereomeric mixture **8a** and **8b** was treated with 3eq. of sodium methoxide in MeOH at room temperature to give a chromatographically separable mixture of methyl ester **9a** (28%), **9b** (21%) and the recovered starting material (48.7%). Repeating this reaction with the recovered starting material under the same conditions, we obtained the desired *trans*-methyl ester **9a** (49%), as a slightly major product, and *cis*-methyl ester **9b** (38%) and the starting material (6%). In addition, treatment of **9b** with NaOMe in MeOH at 65-70°C for 2h afforded a 1:1 mixture of **9a**, **9b** in 75-80% yield. The configuration of **9a**, **9b** was assigned by ^{1}H NMR. The *trans* configuration of C-3 and C-4 in **9a** was evident from the observed coupling constant between *trans* protons H-3 and H-4, with $J_{3,4}$=2.8Hz, whereas the coupling constant of **9b** was in good agreement with that of the major *cis*-product **8b** ($J_{3,4}$=5.7Hz). Reduction of the methyl ester **9a** with sodium borohydride ($NaBH_4$) in ethanol gave the alcohol **10** (89%). Removal of the protecting PMB group in **10** by catalytic hydrogenolysis over Pearlman's catalyst ($Pd(OH)_2$-C) in ethanol provided DAB-1 (**1**) which was

conveniently isolated as its crystalline hydrochloride by treatment with conc. HCl (94%). Comparison of the melting point (m.p.= 114-115°C, lit.[5] m.p.= 113-115°C), specific optical rotation ($[\alpha]_D^{22}$ = +32.5°, c=0.5, H_2O, lit.[5] $[\alpha]_D^{20}$ = +37.9°, c=0.53, H_2O), ^1H and ^{13}C NMR data of synthetic **1** with those of the literature completely confirmed the identity of **1**.



Scheme 2. a) *p*-$(CH_3O)C_6H_4CH_2NH_2$, $(EtO)_2P(O)CN$, THF; 86.7%; b) TBAF, THF; quant.; c) *p*-TsCl, pyridine; 84%; d) CF_3COOH-H_2O-THF (5:1:1); 70-75%; e) NaOMe, MeOH then 2N HCl; 87%; f) NaOMe, MeOH, 65-70°C, 2h then 2N HCl; 78% ; g) $NaBH_4$, EtOH; 89%; h) H_2, 20% $Pd(OH)_2$-C, HCOOH, EtOH; i) conc. HCl; 94%

Alternatively, the enantiomeric LAB-1 (**2**) was then synthesized from L-(+)-diethyl tartrate, following the set of reactions previously described for the DAB-1 (**1**). LAB-1 (**2**) was most conveniently isolated as its hydrochloride by treatment with conc. HCl. Comparison of the melting point (m.p.= 109-111°C, lit.[5] m.p.= 107-111°C), specific optical rotation ($[\alpha]_D^{20}$ = –36.7°, c=0.37, H_2O, lit.[5] $[\alpha]_D^{20}$ = –34.6°, c=0.37, H_2O), ^1H and ^{13}C NMR of synthetic **2** with those of the literature completely confirmed the identity of LAB-1 (**2**).

In summary, the synthesis of DAB-1 (**1**) and LAB-1 (**2**) achieved in this work has permitted ready utilization of the nonsugar chiral pool, optically active diethyl tartrate, and an efficient and selective routes to

these glucosidase inhibitors has been developed. Because this procedure is simple and moreover, affords the related epimers, we anticipate that it may produce various synthetic intermediates and analogs. Further studies on the syntheses of analogs and thorough biochemical evaluations are in progress.

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 polarmeter. – Column chromatography: Merck Kieselgel 60 (Art. Nr. 7734). – melting points: uncorrected values.

(2R,3R)-2,3-Isopropylidenedioxy-4-[(t-butyldimethylsilyl)oxy]-1-cyano-N-(4-methoxybenzyl)butan amine (**5**). To a mixture of **4** (9.44g, 34.4mmol) and DEPC (6.73g, 41.3mmol) in THF (200ml) was added *p*-methoxybenzylamine (11.34g, 82.6mmol) in THF (30ml). The mixture was stirred at room temperature for 1h and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (EtOAc/Hexane, 1:6) to give 12.54g (86.7%) of **5** as an oil.; $[\alpha]_D^{20}$= +44.2 (c=1.0 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3270, 2920, 2220, 1620, 1520, 1460, 1380, 1250, 1090 and 840. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H,s), 0.81 (9H, d, *J*=3.2Hz), 1.39 (6H, d, *J*=4.9Hz), 2.17 (1H, bs), 3.58-3.68 (2H, m), 3.77 (3H, s), 3.81-4.21 (5H, m), 6.83 (2H, d, *J*=8.5Hz),7.26 (2H , d, *J*=8.5Hz). Anal. Cald. for $C_{22}H_{36}N_2O_4Si$: C, 62.82; H, 8.63; N, 6.66. Found: C, 62.34; H, 8.57; N, 6.56.

(*ent.* **5**). In the same manner as described for the preparation of **5**, *ent.* **4** (10g) yielded 13.4g (88%) of *ent.* **5** as an oil.; $[\alpha]_D^{22}$= –40.2 (c=0.6 in $CHCl_3$). The ^{1}H and IR spectral data were identical to those of **5**. Anal. Cald. for $C_{22}H_{36}N_2O_4Si$: C, 62.82; H, 8.63; N, 6.66. Found: C, 62.36; H, 8.53; N, 6.62.

(2R,3R)-2,3-Isopropylidenedioxy-4-hydroxy-1-cyano-N-(4-methoxybenzyl)butanamine (**6**). To a stirred solution of **5** (7.54g, 17.9mmol) in THF (100ml) cooled at 0℃ was added a solution of tetrabutylammonium fluoride (5.62g, 21.48mmol) in THF (30ml). The resulting mixture was allowed to warm to room temperature. After being stirred for 2h, water was added and the mixture was extracted with Et_2O. The extract was washed successively with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography (EtOAc/Hexane, 1:2) to give 5.5g (quant.) of **6** as an oil.; $[\alpha]_D^{20}$= +66.1 (c=2.0 in $CHCl_3$). IR (neat): ν_{max} (film)/cm^{-1}: 3440, 3270, 2920, 2220, 1620, 1520, 1460, 1380, 1250, 1170, 1090, 1040 and 840. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (6H ,s), 2.15 (1H, bs), 3.63-3.82 (3H, m), 3.78 (3H, s), 3.99-4.25 (5H, m), 6.83 (2H, d, *J*=8.5Hz),7.23 (2H, d, *J*=8.5Hz). Anal. Cald. for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.6; H, 7.45; N, 8.72.

(*ent.* **6**). In the same manner as described for the preparation of **6**, *ent.* **5** (12g) yielded 8.74g (quant.) of *ent.* **6** as an oil.; $[\alpha]_D^{20}$= –67.6 (c=1.7 in $CHCl_3$). The ^{1}H and IR spectral data were identical to those of **6**. Anal. Cald. for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.40; H, 7.18; N, 8.89.

(2R, 3R)-2,3-Isopropylidenedioxy-4-(p-toluenesulfonyl)oxy-1-cyano-N-(4-methoxybenzyl)butanamine (**7**). *p*-TsCl (4.1g, 21.5mmol) was added to a solution of **6** (5.5g, 17.9mmol) in pyridine (40ml) at room temperature. The resulting reaction mixture was stirred for 4h. After concentration *in vacuo*, the residue was dissolved in Et_2O (50ml) and washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (EtOAc/Hexane, 1:4) to give (6.95g, 84%) **7** as an oil.; $[\alpha]_D^{20}$= +43.4 (c=0.8 in $CHCl_3$). IR ($CHCl_3$): ν_{max} (film)/cm^{-1}: 3270, 2940, 2220, 1620, 1520, 1360, 1250, 1180, 1100, 980, 820 and 760. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (6H, d, *J*=4.9Hz), 1.88 (1H, bs), 2.45 (3H, s), 3.54-3.65 (1H, m), 3.81 (3H, s), 4.0-4.39 (6H, m), 6.88 (2H, d, *J*=8.5Hz), 7.28 (4H, t, *J*=8.0Hz), 7.72 (2H, d, *J*=8.5Hz). Anal. Cald. for $C_{23}H_{28}N_2O_6S$: C, 59.98; H, 6.13; N, 6.08. Found: C, 59.82; H, 6.13; N, 5.86.

(*ent.* **7**). In the same manner as described for the preparation of **7**, *ent.* **6** (7g) yielded 9.05g (86%) of *ent.* **7** as an oil.; $[\alpha]_D^{20}$= −58.3 (c=1.0 in $CHCl_3$). The ^{1}H and IR spectral data were identical to those of **7**. Anal. Cald. for $C_{23}H_{28}N_2O_6S$: C, 59.98; H, 6.13; N, 6.08. Found: C, 59.60; H, 5.97; N, 5.63.

*(2R,3R)-N-(4-Methoxybenzyl)-2,3-dihydroxy-4-cyano*pyrrolidine (**8a, b**). A solution of **7** (2g, 4.3mmol) in 20ml of CF_3COOH-H_2O-THF (8:1:1) was stirred for 20h at room temperature. The reaction mixture was concentrated *in vacuo* and 50ml of EtOAc was added to the residue and the mixture was poured into saturated aqueous $NaHCO_3$ (100ml) and extracted with EtOAc (three times). The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography (EtOAc/Hexane, 2:1) to give 0.16g (15%) of **8a** as an oil and 0.61g (57%) of **8b** as a white crystalline solid; **8a**; $[\alpha]_D^{21}$= −33.4 (c=0.5 in MeOH). IR (neat): ν_{max} (film)/cm^{-1}: 3400, 2940, 2220, 1680, 1520, 1250, 1180 and 760. ^{1}H-NMR ($CDCl_3$) δ: 2.65 (1H, dd, *J*=2.8Hz, 8.0Hz), 3.15 (1H, dd, *J*=6.5Hz), 3.47 (1H, d, *J*= 2.4Hz), 3.62 (1H, d, *J*=12.8Hz), 3.80 (3H, s), 3.90 (1H, d, *J*=12.8Hz), 4.15 (1H, m), 4.35 (1H, bs), 6.87 (2H, d, *J*=8.5Hz), 7.24 (2H, d, *J*=8.5 Hz). Anal. Cald. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.57; H, 6.40; N, 11.25.; **8b**; m.p.= 110-113℃; $[\alpha]_D^{21}$= +34.2 (c=0.5 in MeOH). IR ($CHCl_3$): ν_{max} (film)/cm^{-1}: 3400, 2940, 2220, 1680, 1520, 1250, 1180 and 760. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (1H, br), 2.73 (1H, dd, *J*=2.8Hz, 8.0Hz), 3.09 (1H, dd, *J*=6.5Hz), 3.62 (1H, d, *J*=12.8Hz), 3.80 (3H, s), 3.84 (1H, d, *J*=12.8Hz), 3.93 (1H, d, *J*=5.6Hz), 4.22-4.27 (2H, m), 6.87 (2H, d, *J*=8.5Hz), 7.24 (2H, d, *J*=8.5Hz). Anal. Cald. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.5; N, 11.28. Found: C, 62.47; H, 6.50; N, 11.28.

X-ray analysis of **8b**: Crystal size 0.5 × 1.0 × 1.0 mm. All data were obtained Rigaku AFC-5S automated four-circle diffractometer with graphite-monochromated Mo *K*α radiation. Final lattice parameters were obtained from a least-squares refinement using 25 reflections. Crystal data: $C_{13}H_{16}N_2O_3$, *Mr*=248.28, monoclinic, space group P2$_1$, a=7.383(5)Å, b=6.534(4)Å, c=13.723(3)Å, β=104.26(3)°, V=641.6(5) Å^3, *Z*=2, *Dx*=1.285 g/cm^3, F(000)=264, and μ(Mo*K*α)=0.86cm^{-1}. The intensities were measured using ω/2θ scan up to 50°. Three standard reflections were monitored every 150 measurements. The data were corrected for Lorentz and

polarization factors. Decay and absorption corrections were applied. Of the 1348 independent reflections which were collected, 1248 reflections with $I > 3.0\sigma(I)$ were used for structure determination and refinement. The structure was solved by direct method using TEXSAN crystallographic software package.[13] All non-H atoms were found in Fourier map. All H atoms were calculated at geometrical positions and refined isotropically. The refinement of atomic parameters was carried out by the full matrix least-squares refinement, using anisotropically temperature factors for all non-H atoms. The final refinement converged with R=0.036 and Rw=0.041 for 226 parameters. The minimum and maximum peaks in the final difference Fourier map were –0.14 and 0.23 eÅ^{-3}. Atomic scattering factors were taken from "International Tables for X-ray Crystallography."[14]

(*ent.* **8a, b**). In the same manner as described for the preparation of a mixture of **8a, b**, *ent.* **7** (6g) yielded 2.4g (74.7%) of a mixture of *ent.* **8a, b** as an oil. Further purification was not occurred.

(2R,3R)-N-(4-Methoxybenzyl)-2,3-dihydroxy-4-methoxycarbonylpyrrolidine (**9a,b**). Sodium (0.19g, 8.3mmol) was dissolved in 15ml of MeOH. To this solution was added a mixture of **8a** and **8b** (0.7g, 2.8mmol) in 10ml of MeOH. After 5h at room temperature, the ice-cooled reaction mixture was acidified to pH5 with 2M HCl. Then 30ml of saturated aqueous NH_4Cl and 30ml of EtOAc were added. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (EtOAc/Hexane, 2:1) to give 0.34g (48.7%) of recovered **8**, and 0.22g (27.8%) of **9a** as an oil and 0.17g (21%) of **9b** as a solid.; **9a**; $[\alpha]_D^{21}$= –27.4 (c=0.9 in MeOH). IR (neat): ν_{max} (film)/cm^{-1}: 3360, 2920, 1740, 1520, 1460, 1380, 1250, 1040 and 910. ^{1}H-NMR ($CDCl_3$) δ: 2.89 (1H, dd, *J*=4.5Hz, 10.5Hz), 2.98 (1H, d, *J*=10.5Hz), 3.22 (1H, d, *J*= 2.8Hz), 3.66 (1H, d, *J*=12.9Hz), 3.67 (3H, s), 3.80 (3H, s), 3.78-3.87 (3H, m), 3.97 (1H, d, *J*=4.4 Hz), 4.22 (1H, br, s), 6.84 (2H, d, *J*=8.5Hz), 7.22 (2H, d, *J*=8.5 Hz). Anal. Cald. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.40; H, 6.83; N, 5.09.; **9b**; m.p.=134-137℃; $[\alpha]_D^{21}$= +15.1 (c=0.42 in MeOH). IR ($CHCl_3$): ν_{max} (film)/cm^{-1}: 3400, 2220, 1518, 1250, 1180 and 760. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (1H, dd, *J*=4.5Hz), 3.40 (1H, d, *J*=3.5Hz, 6.0Hz), 3.52 (2H, d, *J*= 12.8Hz), 3.62 (1H, d, *J*=5.7Hz), 3.73 (3H, s), 3.80 (3H, s), 3.87 (1H, d, *J*=12.8Hz), 4.20 (2H, m), 6.85 (2H, d, *J*=8.5Hz), 7.22 (2H, d, *J*=8.5 Hz). Anal. Cald. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 60.05; H, 6.75; N, 5.06.

Epimerization of **9b** *to* **9a.** Sodium (0.06g, 2.6mmol) was dissolved in 10ml of MeOH. To this solution was added a solution of **9b** (0.25g, 0.89mmol) in 5ml of MeOH. After the mixture was heated under 65-70℃ for 2h, the ice-cooled reaction mixture was acidified to pH5 with 2M HCl. Then 30ml of saturated aqueous NH_4Cl and 30ml of EtOAc were added. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (EtOAc/Hexane, 2:1) to give 0.10g (40%) of **9a**, 0.09g (38%) of **9b**

(*ent.* **9a, 9b**). In the same manner as described for the preparation of **9a** and **9b**, *ent.* **8** (2.2g) yielded 1.03g (46.8%) of recovered *ent.* **8** and 0.72g (29%) of *ent.* **9a** as an oil, 0.57g (23%) of *ent.* **9b** as a solid.;

ent. **9a**; $[\alpha]_D^{21}$= +25.4 (c=0.9 in MeOH). The ^{1}H and IR spectral data were identical to those of **9a**. Anal. Cald. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.47; H, 6.82; N, 5.10. *ent.* **9b**; m.p.=142-143℃; $[\alpha]_D^{21}$= −17.3 (c=0.42 in MeOH). The ^{1}H and IR spectral data were identical to those of **9b**. Anal. Cald. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.50; H, 6.78; N, 5.02.

Epimerization of ent. **9b** to *ent.* **9a** In the same manner as described for the epimerization of **9b** to **9a**, *ent.* **9b** (0.3g) yielded 0.11g (38%) of *ent.* **9a** and 0.12g (41%) of *ent.* **9b**.

(2R,3R,4R)-N-(4-Methoxybenzyl)-2,3-dihydroxy-4-hydroxymethylpyrrolidine (**10**). To a stirred solution of **9a** (0.25g, 0.89mmol) in 10ml of EtOH was added $NaBH_4$ (0.067g, 1.78mmol). After the addition, the mixture was heated under reflux and vigorously stirred for 1h under Ar. After cooling, the reaction mixture was evaporated, diluted with water, and extracted with EtOAc. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2($CHCl_3$/MeOH, 5:2) to give 0.2g (89%) of **10** as an oil.; $[\alpha]_D^{21}$= −52.3 (c=0.5 in MeOH). IR ($CHCl_3$): ν_{max} (film)/cm^{-1}: 3360, 2960, 1610, 1520, 1460, 1250, 1040 and 820. ^{1}H-NMR (CD_3OD) δ: 2.50 (1H, dd, *J*=4.5Hz), 2.64 (1H, dd, *J*=5.0Hz , 10.5Hz), 2.78 (1H, d, *J*=10.5Hz), 3.29 (1H, m), 3.38 (1H, d, *J*=11Hz), 3.64 (2H, m), 3.76 (3H, s), 3.86 (1H, m), 3.91 (1H, m), 3.96 (1H, d, *J*=12.8 Hz), 6.85 (2H, d, *J*= 8.5Hz), 7.25 (2H, d, *J*= 8.5Hz). Anal. Cald. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.85; H, 7.78; N, 5.50.

(*ent.* **10**). In the same manner as described for the preparation of **10**, *ent.* **9a** (0.3g) yielded 0.24g (89%) of *ent.* **10** as an oil.; $[\alpha]_D^{22}$= +52.1 (c=0.5 in MeOH). The ^{1}H and IR spectral data were identical to those of **10**. Anal. Cald. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.30; H, 7.73; N, 5.39.

Synthesis of DAB-1 (**1**). **10** (0.1g, 0.39mmol) dissolved in EtOH (5ml) was stirred under a hydrogen atmosphere in the presence of 20% $Pd(OH)_2$-C (0.01g) and HCOOH (catalytic amount) for 1h. The catalyst was removed by filtration and the reaction mixture was concentrated, removing residual water by azeotroping with toluene. The residue was purified by flash chromatography using $CHCl_3$-MeOH-28% aq. NH_4OH (5:3:1) as the eluent. The appropriate fractions were combined and concentrated *in vacuo* to provide the free amine as an oil. This oil was dissolved in MeOH (5ml) and aqueous hydrochloric acid (12N, 0.2ml) was slowly added. After cooling to 5℃, the solid was collected by filtration and dried in a vacuum oven to give hydrogen chloride of DAB-1 (**1**), (0.063g, 94%) as a white solid.; m. p.=114-115℃; $[\alpha]_D^{22}$= +32.5 (c=0.5 in H_2O). IR ($CHCl_3$): ν_{max} (film)/cm^{-1}: 3360, 2960, 1580, 1400, 1260, 1080, 1010 and 960; ^{1}H-NMR (D_2O) δ: 3.21 (1H, dd, *J*=12.5Hz, 2.6Hz), 3.46 (2H, m), 3.69 (1H, dd, *J*=12.2Hz, 8.1Hz), 3.81 (1H, dd, *J*=4.7Hz), 3.95 (1H, m), 4.19 (1H, m). ^{13}C NMR (D_2O) d 50.90 (t, CH_2N), 59.83 (t, CH_2OH), 67.53 (d, CHN), 75.18 (d, CHOH), 76.56 (d, CHOH).

Synthesis of LAB-1 (**2**). In the same manner as described for the preparation of DAB-1 (**1**), *ent.* **10** (0.1g) yielded 0.61g (91%) of hydrogen chloride of LAB-1 (**2**) as a white solid; m. p.=109-111℃; $[\alpha]_D^{20}$= −36.5 (c=0.37 in H_2O). The ^{1}H and IR spectral data were identical to those of hydrogen chloride of DAB-1 (**1**).

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