Tetrahedron Vol. 50, No. 1, pp. 265-274, 1994
Printed in Great Britain

0040-4020/94 $6.00+.00

Total Syntheses of Phytosiderophores, 3-Epi-Hydroxymugineic Acid, Distichonic Acid A, and 2'-Hydroxynicotianamine

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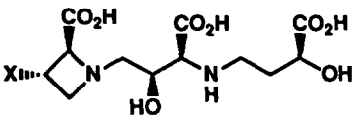
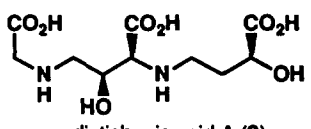
Abstract: First total syntheses of the unique phytosiderophores, 3-epi-hydroxymugineic acid (**2**), distichonic acid A (**3**), and 2'-hydroxynicotianamine (**5**), have been efficiently achieved from the same intermediates used for the synthesis of mugineic acid (**1**), the typical phytosiderophore.

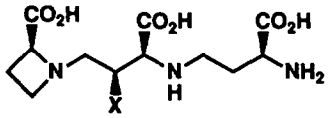
A series of iron-chelating amino acids has been isolated from some spieces of gramineous plants: mugineic acid (**1**)[1a] from barley (*Hordeum vulgare* L. var. minorimugi), 3-epi-hydroxymugineic acid (**2**)[1e] and distichonic acid A (**3**)[1e] from beer barley (*Hordeum vulgare* L. var. distichum), and nicotianamine (**4**)[1d] from leaves of *Nicotiana tabacum* L. They are called phytosiderophores which promote uptake and transport of iron required for the chlorophyll biosynthesis in higher plants. The most typical phytosiderophore is mugineic acid (**1**), which has been well investigated its structural feature as well as its iron transport mechanism,[1] and has been synthesized in our laboratory for the first time.[2,3]



mugineic acid (**1**) : X = H
3-epi-hydroxymugineic acid (**2**) : X = OH



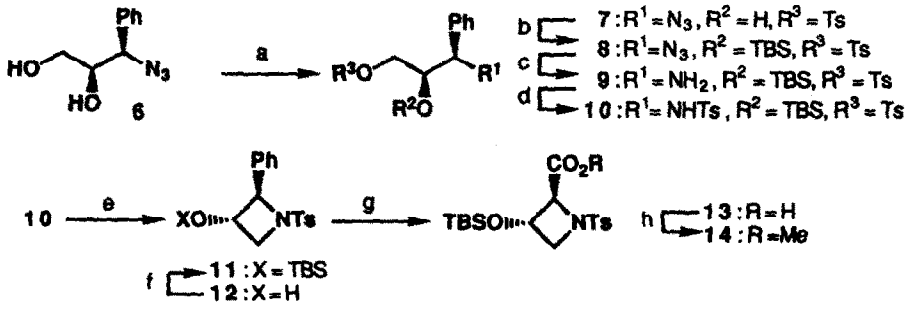
distichonic acid A (**3**)



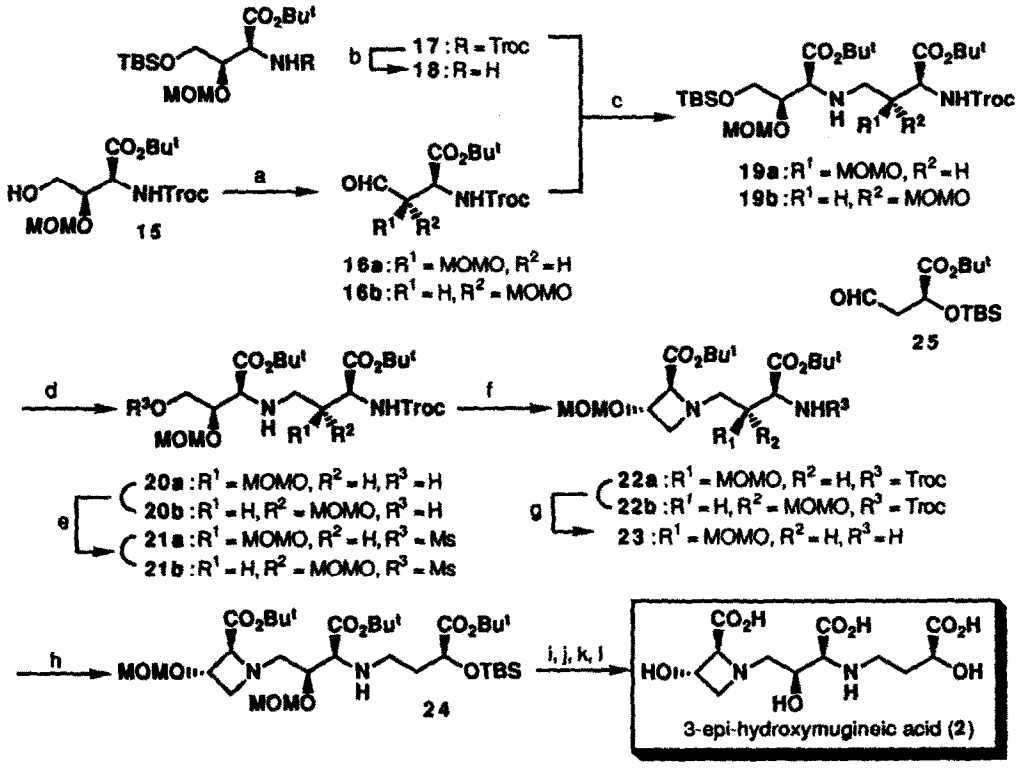
nicotianamine (**4**) : X = H
2'-hydroxynicotianamine (**5**) : X = OH

Recently, we have reported an efficient, improved synthesis of mugineic acid (**1**)[4] utilizing the phenyl group as the carboxyl synthon, which is much more suitable for the large scale production of **1**. We now wish to report the first total syntheses of 3-epi-hydroxymugineic acid (**2**), distichonic acid A (**3**), and their analog (2'-hydroxynicotianamine) (**5**) by employing the analogous procedure,[5] as they have the same skeleton as **1** except for the azetidine moiety.

We first investigated a synthesis of the unknown (2S,3S)-hydroxyazetidinecarboxylic acid,[6] as shown in Scheme 1. The synthesis commenced from the known azido alcohol **6**,[7] which was synthesized from readily available (2S,3S)-2,3-epoxycinnamyl alcohol.[8] Sequential protection of the primary and secondary hydroxyl functions, reduction of the azido group, and tosylation of the resulting amino group afforded the N,O-ditosylate **10**. Construction of the azetidine ring was carried out by treatment of **10** with base to give the azetidine **11**[9] accompanied by its desilylated derivative **12**, the latter of which was easily reprotected to **11** under usual



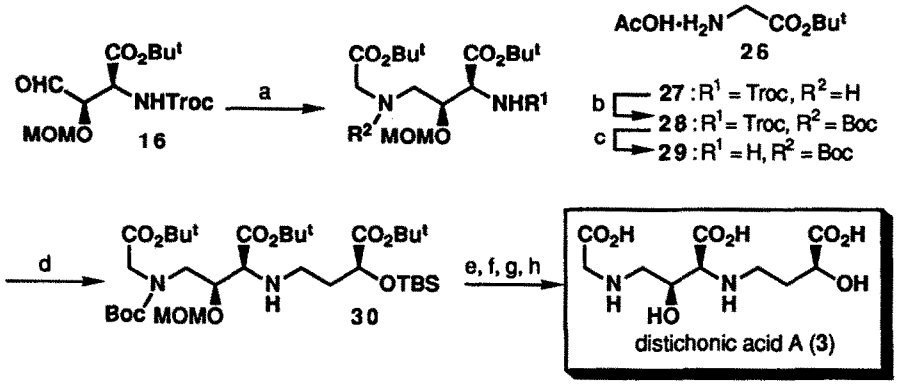
Scheme 1. (a) TsCl, Et_3N, CH_2Cl_2, rt, 4h. (b) TBSCl, imidazole, DMF, rt, 19h, 73% from **6**. (c) 5% Pd-C, HCO_2NH_4, MeOH, rt, 1h. (d) TsCl, DMAP, Et_3N, CH_2Cl_2, rt, 3h, 30% from **8**. (e) NaH, MeOH, rt, 11h, **11**: 75%; **12**: 18%. (f) TBSCl, imidazole, DMF, 50°C, 3h, 99%. (g) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 40h. (h) $TMSCHN_2$, benzene, MeOH, rt, 10min, 42% from **11**.



Scheme 2. (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C→0°C, 2h, 77%. (b) Zn, 1M aq. $AcONH_4$, THF, rt, 30h, 84%. (c) 1M $NaBH_3CN$ in THF, AcOH (1eq), MeOH, 0°C, 16h. (d) TBAF, AcOH, THF, rt, 17h, 99%. (e) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h, 99%. (f) $KHCO_3$, CH_3CN, 60°C, 42h, 85%. (g) Zn, AcOH, THF, rt, 13h, 93%. (h) **25**, 1M $NaBH_3CN$ in THF, AcOH (1eq), MeOH, 0°C, 14h, 85%. (i) 20% aqueous HCl, anisole, THF, rt, 24h. (j) Dowex 50W x 4 (H_2O then 15% aq. NH_3). (k) ODS silica gel, H_2O. (l) recrystallization from H_2O-EtOH, 93%.

silylation conditions. Oxidation of **11** with ruthenium trichloride-sodium metaperiodate,[4,10] followed by methyl esterification with trimethylsilyldiazomethane ($TMSCHN_2$)[11] gave the (2S,3S)-hydroxyazetidine-carboxylic acid as its protected form **14**.

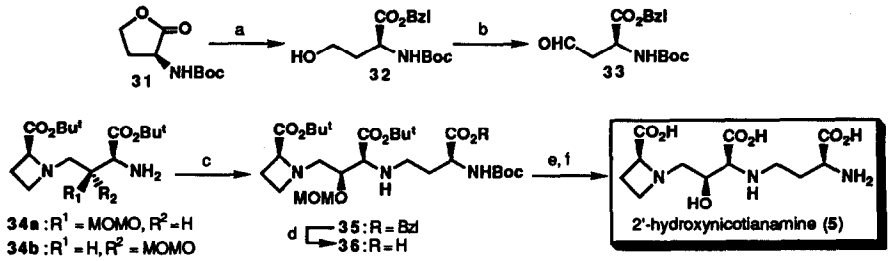
This successful formation of the azetidine ring prompted us to carry out the synthesis of 3-epi-hydroxymugineic acid (**2**), starting from the alcohol **15** and its O-tert-butyldimethylsilyl (TBS) derivative **17**, both of which have been utilized for the synthesis of mugineic acid (**1**).[4] After removal of the 2,2,2-trichloroethoxycarbonyl (Troc) group of **17**, the resulting amine **18** was coupled with the aldehyde **16a** containing a small amount of its C-2' epimer **16b** (13:1), obtained by oxidation of **15**, by employing the reductive N-alkylation procedure[12] to give a mixture of the amines **19a** and **19b** (10:1),[13] as shown in Scheme 2. Transformation of the TBS group to the methanesulfonyl (Ms) one was smoothly performed in 2 steps to give the mesylates **21a** and **21b** (10:1), which underwent the intramolecular cyclization[14] to give the azetidine carboxylic acid derivatives **22a** and **22b** (10:1). Deprotection of their Troc group, separation of the C-2' epimer by silica gel column chromatography, and then reductive N-alkylation with the known tert-butyl 2-tert-butyldimethylsiloxy-3-formylpropionate (**25**)[4] afforded the protected 3-epi-hydroxymugineic acid **24**. Removal of all of the protecting groups of **24** by acid treatment, followed by purification afforded 3-epi-hydroxymugineic acid (**2**) in 47 % yield in 8 steps from **15**, which was identical with the natural one by direct comparison of their ^1H NMR spectra (pH 6.3).[15]



Scheme 3. (a) **26**, 1M $NaBH_3CN$ in THF, MeOH, 0°C, 12h, 79% from **15**. (b) Boc_2O, i-Pr_2NEt (cat.), dioxane, rt, 1h, 100%. (c) Zn, AcOH, THF, rt, 3h. (d) **25**, 1M $NaBH_3CN$ in THF, AcOH (1eq), MeOH, 0°C, 3h→rt, 11h, 62% from **28**. (e) 20% aqueous HCl, anisole, THF, rt, 14h. (f) Dowex 50W x 4 (H_2O then 15% aq. NH_3). (g) ODS silica gel, H_2O. (h) recrystallization from H_2O, 85%.

Synthesis of distichonic acid A (**3**) was performed in a similar procedure to that of **2** (Scheme 3). The known tert-butyl glycinate acetic acid salt **26**[16] was coupled with the aldehydes **16a** and **16b** (15:1), and then treatment with Boc_2O afforded the intermediate **28**. Removal of the Troc group of **28**, followed by reductive condensation with the aldehyde **25** afforded the distichonic acid A as its protected form **30**. Deprotection of **30** was performed by the same procedure as that for 3-epi-hydroxymugineic acid (**2**) afforded distichonic acid A (**3**) in 42 % yield in 5 steps from **15**, which was identical with the natural one by comparison of their ^1H NMR spectra (1N DCl).

The synthesis of 2'-hydroxynicotianamine (**5**), an analog of nicotianamine (**4**),[1] was accomplished from a mixture of amines **34a** and **34b** (8:1), intermediate of our synthesis of mugineic acid (**1**),[4] and aldehyde **33**, which was easily prepared in 3 steps from the known lactone **31**.[12b] Reductive coupling of **34** with **33** afforded the protected 2'-hydroxynicotianamine **35**. Removal of all of the protecting groups of **35** followed by purification was performed in a similar manner with that of distichonic acid A (**3**), affording 2'-hydroxynicotianamine (**5**) in 41 % yield in 5 steps from **34** (Scheme 4).



Scheme 4. (a) KOH, DMF, H_2O, 0°C, 1h→rt, 2h, then 18-crown-6 (0.05 eq), BzlBr. (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C→0°C, 2h, 82% from **31**. (c) **33**, 1M $NaBH_3CN$ in THF, AcOH (1eq), i-PrOH,[16] 0°C, 12h→rt, 6h, 66%, (d) 5% Pd-C, H_2, THF, rt, 30min. (e) 20% aqueous HCl, anisole, THF, rt, 6h. (f) Dowex 50W x 4 (H_2O then 15% aq. NH_3), 76% from **35**.

The synthetic method for these phytosiderophores as described herein would be suitable for the large scale production because of the easy handling of the reactions and high yields of each reactions. Phytosiderophores produced in this laboratory can be supplied to those groups who wish to explore the phytopathological potentialities of these interesting compounds.

Experimental

Melting points were determined on a YAMATO MP-21 apparatus or a YANAGIMOTO micro melting point apparatus. Infrared spectra were measured with a JASCO IRA-2 or SHIMADZU FT IR-8100 spectrometer. ^1H NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on an EX-270 spectrometer with tetramethylsilane or chloroform as an internal standard. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. Silica gel (BW-200) was used for column chromatography.

(2R,3R)-3-Azido-2-tert-butyldimethylsiloxy-3-phenyl-1-p-toluenesulfonyloxypropane (8). To a stirred solution of **6**[4] (220 mg, 1.14 mM) in CH_2Cl_2 (2 ml) were added Et_3N (240 µl, 1.71 mM) and TsCl (230 mg, 1.20 mM) at 0°C. After being stirred at room temperature for 4 h, the mixture was treated with Et_2O (50 ml), washed with 1M aqueous $KHSO_4$ (20 ml x 2) and saturated brine (20 ml x 1), dried over Na_2SO_4, and concentrated in vacuo to give crude **7** (398 mg) as a colorless oil. This compound was used for the next reaction without further purification. Imidazole (120 mg, 1.71 mM) and TBSCl (210 mg, 1.37 mM) were added to a stirred solution of **7** (398 mg) in DMF (1ml) at room temperature. After being stirred at room temperature for 19 h, the mixture was treated with Et_2O (100 ml), washed with H_2O (50 ml x 1), 1M aqueous $KHSO_4$ (50 ml x 2), and saturated brine (50 ml x 1), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 55 g, hexane-Et_2O=14:1) to give **8** (382 mg, 73 %) as a colorless oil: IR ν_{max} (neat) 2107 cm^{-1}; ^1H NMR δ 0.00 (6H, s), 0.98 (9H, s), 2.67 (3H, s), 4.11-4.26 (3H, m), 4.76 (1H, d, J=5.6 Hz), 7.44-7.57 (7H, m), 7.97 (2H, d, J=8.3 Hz); Anal. calcd for $C_{22}H_{31}N_3O_4SSi$: C, 57.24; H, 6.77; N, 9.10. Found: C, 57.07; H, 6.70; N, 8.89.

(2R,3R)-2-tert-Butyldimethylsiloxy-3-phenyl-3-p-toluenesulfonylamino-1-p-toluenesulfonyloxypropane (10). To a stirred suspension of 5% Pd-C (500 mg) and **8** (1.72 g, 3.72 mM) in MeOH (30 ml) was added HCO_2NH_4 (590 mg, 9.31 mM) at 0°C. After being stirred at room temperature for 1h, the mixture was filtered through a pad of celite and concentrated in vacuo. Saturated aqueous $NaHCO_3$ (50 ml) was added to the residue and the mixture was extracted with EtOAc (50 ml x 3). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give **9** (1.33 g) as a yellow oil. After **9** was dissolved in CH_2Cl_2 (8 ml) at 0°C, Et_3N (780 µl, 5.58 mM), DMAP (25 mg, 0.20 mM), and TsCl (780 mg, 4.09 mM) were added successively. After being stirred at room temperature for 3 h, the mixture was treated with Et_2O, washed with 1M aqueous $KHSO_4$ (20 ml x 3) and saturated brine (20 ml x 1), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 80 g, hexane-Et_2O=3:2→4:3) to give **10** (650 mg, 30 %) as a colorless oil: $[\alpha]^{25}_D$ -15.2 (c 1.11, $CHCl_3$); IR ν_{max} (neat) 3304 cm^{-1}; ^1H NMR δ -0.01 (6H, s), 0.81 (9H, s), 2.34 (3H, s), 2.46 (3H, s), 3.61-3.72 (2H, m), 4.08-

4.14 (1H, m), 4.30 (1H, dd, J=4.3, 7.9 Hz), 4.98 (1H, d, J=7.6 Hz), 6.93 (2H, d, J=7.9 Hz), 7.05-7.18 (5H, m), 7.33 (2H, d, J=7.9 Hz), 7.46 (2H, d, J=8.3 Hz), 7.72 (2H, d, J=8.6 Hz); Anal. calcd for $C_{29}H_{39}NO_6S_2Si$: C, 59.05; H, 6.66; N, 2.37. Found: C, 59.17; H, 6.77; N, 2.07.

(2R,3S)-N-p-Toluenesulfonyl-3-tert-butyldimethylsiloxy-2-phenylazetidine (11) and (2R,3S)-N-p-Toluenesulfonyl-3-hydroxy-2-phenylazetidine (12). To a stirred solution of the ditosylate **10** (395 mg, 0.67 mM) in MeOH (5 ml) was added NaH (27 mg, 0.67 mM) at 0°C. After being stirred at room temperature for 11 h, the mixture was quenched with 1M aqueous $KHSO_4$ (1 ml), concentrated in vacuo, and extracted with ether (20 ml x 3). The combined organic extracts were washed with saturated brine (20 ml x 1), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 30 g, hexane-Et_2O=10:1→hexane-EtOAc=2:1) to give **11** (211 mg, 75 %) as a white solid and **12** (37 mg, 18 %) as a white solid. **11**: mp 103-108°C; $[\alpha]^{25}_D$ -145.7 (c 0.65, $CHCl_3$); IR ν_{max} (KBr) 1599, 1497 cm^{-1}; ^1H NMR δ -0.15 (3H, s), -0.14 (3H, s), 0.75 (9H, s), 2.43 (3H, s),3.45-3.50 (1H, m), 3.93-3.98 (1H, m), 4.13-4.20 (1H, m), 4.51 (1H, d, J=5.6 Hz) 7.27-7.37 (7H, m), 7.65 (2H, d, J=8.6 Hz); Anal. calcd for $C_{22}H_{31}NO_3SSi$: C, 63.27; H, 7.48; N, 3.35. Found: C, 63.45; H, 7.49; N, 3.16. **12**: mp 122-124°C; $[\alpha]^{25}_D$ -185.3 (c 0.36, $CHCl_3$); IR ν_{max} (KBr) 3430, 1597 cm^{-1}; ^1H NMR δ 1.67 (1H, br), 2.44 (3H, s), 3.51 (1H, t, J=7.3 Hz), 4.04 (1H, t, J=7.8 Hz), 4.27 (1H, dd, J=6.6, 12.2 Hz), 4.52 (1H, d, J=5.6 Hz), 7.27-7.41 (7H, m), 7.68 (2H, d, J=8.2 Hz); Anal. calcd for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.51; H, 5.81; N, 4.40.

(2R,3S)-N-p-Toluenesulfonyl-3-tert-butyldimethylsiloxy-2-phenylazetidine (11). To a stirred solution of **12** (121 mg, 0.399 mM) in DMF (3 ml) were added imidazole (130 mg, 1.60 mM) and TBSCl (180 mg, 1.20 mM) at room temperature. After being stirred at 50°C for 3 h, the mixture was quenched with 1M aqueous $KHSO_4$ (10 ml) and extracted with Et_2O (50 ml x 3). The combined organic extracts were washed with saturated brine (50 ml x 1), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 20 g, hexane-Et_2O=10:1→6:1) to give **11** (165 mg, 99 %) as a white solid.

Methyl (2S,3S)-N-p-toluenesulfonyl-3-tert-butyldimethylsiloxy-2-azetidinecarboxylate (14). To a stirred solution of **11** (45 mg, 0.11 mM) in EtOAc (0.5 ml), CH_3CN (0.5 ml), and H_2O (2.5 ml) were added $NaIO_4$ (576 mg, 2.69 mM) and $RuCl_3$ (1 mg, 2.69 μM) at room temperature. After being stirred at room temperature for 40 h, the mixture was extracted with EtOAc (20 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in Et_2O, filtered through a pad of celite, and concentrated in vacuo to give **13** (53 mg) as a yellow oil. The crude product **13** was dissolved in benzene (0.8 ml) and MeOH (0.2 ml) and treated with $TMSCHN_2$[10] (100 μl, 0.2 mM (2 M solution in hexane)). After being stirred at room temperature for 10 min, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 10 g, hexane-Et_2O=3:1) to give **14** (18 mg, 42 %) as a white solid: mp 67-69°C; $[\alpha]^{25}_D$ -56.2 (c 0.18, $CHCl_3$); IR ν_{max} (KBr) 1757 cm^{-1}; ^1H NMR δ -0.01 (3H, s), 0.00 (3H, s), 0.80 (9H, s), 2.44 (3H, s), 3.63 (1H, dd, J=5.9, 7.6 Hz), 3.73 (3H, s), 3.87-3.92 (1H, m), 4.33 (1H, d, J=5.3 Hz), 4.41-4.48 (1H, m), 7.35 (2H, d, J=8.6 Hz), 7.78 (2H, d, J=8.3 Hz); Anal. calcd for $C_{18}H_{29}NO_5SSi$: C, 54.11; H, 7.32; N, 3.51. Found: C, 54.24; H, 7.21; N, 3.10.

tert-Butyl (2S,3R)-2-amino-4-tert-butyldimethylsiloxy-3-methoxymethoxybutanoate (18). To a stirred solution of **17**[4] (393 mg, 0.75 mM) in THF (5 ml) and 1M aqueous $AcONH_4$ (2 ml) was added in one portion Zn powder (400 mg) at room temperature. After being stirred at room temperature for 20 h, Zn powder (1 g) and 1M aqueous $AcONH_4$ (4 ml) was added to the mixture. The mixture was stirred at room temperature for 10 h, filtered through a pad of celite, and concentrated in vacuo. The residue was neutralized with saturated aqueous $NaHCO_3$, and extracted with EtOAc (30 ml x 3). The extracts were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 30 g, hexane-EtOAc=2:1) to give **18** (219 mg, 84 %) as a colorless oil: $[\alpha]^{25}_D$ +32.9 (c 0.20, $CHCl_3$); IR ν_{max} (neat) 3387, 3336, 1736 cm^{-1}; ^1H NMR δ 0.06 (6H, s), 0.90 (9H, s), 1.48 (9H, s), 1.59 (2H, br), 3.39 (3H, s), 3.60 (1H, d, J=3.3 Hz), 3.73-3.86 (3H, m), 4.72 (2H, ABq, J=6.6 Hz); Anal. calcd for $C_{16}H_{35}NO_5Si$: C, 54.98; H, 10.09; N, 4.01. Found: C, 55.07; H, 9.99; N, 3.98.

tert-Butyl (2S,3R,2'S,3'S)-2-(3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl)amino-4-tert-butyldimethylsiloxy-3-methoxymethoxybutanoate (19a) and tert-Butyl (2S,3R,2'R,3'S)-2-(3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl)amino-4-tert-butyldimethylsiloxy-3-methoxymethoxybutanoate (19b). To a stirred solution of $(COCl)_2$ (183 μl, 0.95 mM) in CH_2Cl_2 (2 ml) was added a solution of DMSO (90 μl, 1.91 mM) in CH_2Cl_2 (1 ml) at -78°C. After the mixture was stirred for 10 min, a solution of **15** (261 mg, 0.64 mM) in CH_2Cl_2 (3 ml) and Et_3N (270 μl, 1.27 mM) were added. The mixture was allowed to warm to 0°C and stirred for 2 h. After being quenched with H_2O (10 ml), the mixture was extracted with CH_2Cl_2 (20 ml x 3), dried over Na_2SO_4, and concentrated in vacuo to give a mixture of the crude aldehydes **16a** and **16b** (13:1) (300 mg) as a pale yellow oil (The ratio of the epimers was determined by the integration of the methyne proton of the aldehyde group in its ^1H NMR spectrum). This mixture was used for the next reaction without further purification. A solution of the above crude aldehyde **16a** and **16b** (13:1) (300 mg) in MeOH (2.5 ml) and 1M $NaBH_3CN$ in THF (640 μl, 0.64 mM) were added to a stirred solution of **18** (316 mg, 0.90 mM) in AcOH (37 μl, 0.64 mM) and MeOH (1.3 ml) at 0°C. After being stirred at 0°C for 16 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (10 ml), extracted with $CHCl_3$ (50 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 60 g, hexane-EtOAc=7:1→6:1) to give **19a** and **19b** (10:1) (363 mg, 77 %): IR ν_{max} (neat) 3328, 1740 cm^{-1}; ^1H NMR δ 0.06 (6H, s), 0.89 (9H, s), 1.47 (9H, s), 1.48 (9H, s), 2.00-2.09 (1H, br), 2.70 (1H, dd, J=5.6, 12.2 Hz), 2.99 (1H, dd, J=5.9, 12.2 Hz), 3.39 (3H, s), 3.40 (4H, s), 3.66 (1H, dd, J=4.1, 10.1 Hz), 3.76-3.86 (2H, m), 3.98-4.03 (1H, m), 4.52 (1H, dd, J=2.8, 8.6 Hz), 4.69-4.79 (6H, m), 6.69, 7.00 (1H, each brd, J=6.3 Hz and J=8.6 Hz, respectively); Anal. calcd for $C_{29}H_{55}Cl_3N_2O_{11}Si$: C, 46.93; H, 7.47; N, 3.77. Found: C, 46.96; H, 7.31; N, 3.48. The ratio of the epimers was determined by the integration of the NH proton (6.69:7.00=1:10) in its ^1H NMR spectrum.

tert-Butyl (2S,3R,2'S,3'S)-2-(3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl)amino-4-hydroxy-3-methoxymethoxybutanoate (20a) and tert-Butyl (2S,3R,2'R,3'S)-2-(3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl)amino-4-hydroxy-3-methoxymethoxybutanoate (20b). To a stirred solution of **19a** and **19b** (10:1) (328 mg, 0.442 mM) in THF (3 ml) and AcOH (75 μl, 1.33 mM) was added TBAF (350 mg, 1.33 mM) at room temperature. After being stirred at room temperature for 17 h, the solvent was removed in vacuo. The residue was treated with Et_2O, washed with saturated aqueous $NaHCO_3$ (5 ml x 1), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 30 g, hexane-EtOAc=5:4) to give **20a** and **20b** (10:1) (275 mg, 99 %) as a colorless oil: IR ν_{max} (neat) 3432, 3337, 1748, 1732 cm^{-1}; ^1H NMR δ 1.48 (18H, s), 1.57 (1H, br), 1.94-2.27 (1H, br), 2.72 (1H, dd, J=5.3, 12.5 Hz), 3.00 (1H, dd, J=6.6, 12.5 Hz), 3.38 (1H, brd, J=3.6 Hz), 3.41 (3H, s), 3.42 (3H, s), 3.61-3.81 (3H, m), 3.90-3.98 (1H, m), 4.51 (1H, dd, J=2.8, 8.6 Hz), 4.60-4.79 (6H, m), 6.46, 6.75 (1H, brd and d, J=8.3 Hz and J=8.6 Hz, respectively); Anal. calcd for $C_{23}H_{41}Cl_3N_2O_{11}$: C, 43.99; H, 6.58; N, 4.46. Found: C, 44.02; H, 6.25; N, 4.05. The ratio of the epimers was determined by the integration of the NH proton (6.46:6.75=1:10) in its ^1H NMR spectrum.

tert-Butyl (2S,3R,2'S,3'S)-2-(3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl)amino-4-methanesulfonyloxy-3-methoxymethoxybutanoate (21a) and tert-Butyl (2S,3R,2'R,3'S)-2-(3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl)amino-4-methanesulfonyloxy-3-methoxymethoxybutanoate (21b). To a stirred solution of **20a** and **20b** (10:1) (165 mg, 0.26 mM) in CH_2Cl_2 (2.5 ml) were added Et_3N (55μl, 0.40 mM) and methanesulfonyl chloride (21 μl, 0.28 mM) at 0°C. After being stirred at 0°C for 1 h, the mixture was quenched with H_2O (5 ml) and extracted with Et_2O (20 ml x 3). The combined organic layer was washed with saturated brine (10 ml x 1), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 30 g, hexane-EtOAc=2.5:1) to give **21a** and **21b** (10:1) (184 mg, 99 %) as a colorless oil: IR ν_{max} (neat) 3328, 1732 cm^{-1}; ^1H NMR δ 1.49 (18H, s), 1.94 (1H, br), 2.70-2.73 (1H, m), 3.07-3.14 (1H, m), 3.11 (3H, s), 3.41 (3H,

s), 3.43 (3H, s), 4.07 (2H, brs), 4.20-4.24 (1H, m), 4.44 (1H, dd, J=6.3, 10.9 Hz), 4.56-4.60 (1H, m), 4.64-4.68 (1H, m), 4.70-4.81 (6H, m), 6.53, 6.76 (1H, each brd, J=6.3 Hz and J=9.3 Hz, respectively). The ratio of the epimers was determined by the integration of the NH proton (6.53:6.76=1:10) in its ^{1}H NMR spectrum.

tert-Butyl (2S,3S,2'S,3'S)-(3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl)-3-methoxymethoxy-2-azetidinecarboxylate (22a) and tert-Butyl (2S,3S,2'R,3'S)-(3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl)-3-methoxymethoxy-2-azetidinecarboxylate (22b). To a stirred solution of **21a** and **21b** (10:1) (116 mg, 0.16 mM) in CH_3CN (2 ml) was added $KHCO_3$ (165 mg, 1.64 mM) at room temperature. The mixture was allowed to warm to 60°C and stirred for 42 h. After cooling to room temperature, the solvent was removed in vacuo. The residue was treated with Et_2O (50 ml), washed with H_2O (10 ml x 1), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 11g, hexane-EtOAc=4:1) to give **22a** and **22b** (10:1) (85 mg, 85 %) as a colorless oil: IR ν_{max} (neat) 3320, 1740, 1732 cm^{-1}; ^{1}H NMR δ 1.46 (9H, s), 1.49 (9H, s), 2.81 (1H, dd, J=4.3, 12.9 Hz), 2.87-2.97 (2H, m), 3.35 (3H, s), 3.40 (3H, s), 3.47 (1H, d, J=5.6 Hz), 3.82 (1H, t, J=6.6 Hz), 3.96 (1H, dd, J=4.3, 7.6 Hz), 4.27 (1H, dd, J=6.3, 12.2 Hz), 4.52 (1H, dd, J=3.2, 8.9 Hz), 4.64 (2H, ABq, J=6.3 Hz), 4.66 (2H, ABq, J=6.3 Hz), 4.74 (2H, ABq, J=11.7 Hz), 7.10, 7.33 (1H, brd and d, J=9.2 Hz and J=8.9 Hz, respectively): Anal. calcd for $C_{23}H_{39}Cl_3N_2O_{10}$: C, 45.29; H, 6.44; N, 4.59. Found: C, 45.47; H, 6.41; N, 4.45.; High mass calcd for $C_{23}H_{39}Cl_3N_2O_{10}$: 608.1668. Found: 608.1657. The ratio of the epimers was determined by the integration of the NH proton (7.10:7.33=1:10) in its ^{1}H NMR spectrum.

tert-Butyl (2S,3S,2'S,3'S)-(3'-amino-3'-tert-butoxycarbonyl-2'-methoxymethoxypropyl)-3-methoxymethoxy-2-azetidinecarboxylate (23). To a stirred solution of **22a** and **22b** (10:1) (91 mg, 0.15 mM) in AcOH (1 ml) and THF (1.5 ml) was added in one portion Zn powder (300 mg) at room temperature. After being stirred at room temperature for 13 h, the mixture was filtered through a pad of celite, neutralized saturated aqueous $NaHCO_3$ (10 ml), extracted with EtOAc (30 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 10g, EtOAc-EtOH=15:1) to give **23** (60 mg, 93 %) as a colorless oil: $[\alpha]^{24}_D$ -32.5 (c 0.39, $CHCl_3$); IR ν_{max} (neat) 3388, 1732 cm^{-1}; ^{1}H NMR δ 1.47 (9H, s), 1.47 (9H, s), 1.67 (2H, br), 2.65 (1H, dd, J=3.3, 12.9 Hz), 2.82 (1H, t, J=6.9 Hz), 3.01 (1H, dd, J=6.3, 12.9 Hz), 3.35 (3H, s), 3.39 (3H, s), 3.48 (1H, d, J=5.9 Hz), 3.70-3.80 (3H, m), 4.27 (1H, dd, J=6.4, 12.4 Hz), 4.65 (2H, ABq, J=6.9 Hz), 4.69 (2H, ABq, J=6.6 Hz); Anal. calcd for $C_{20}H_{38}N_2O_8$: C, 55.28; H, 8.81; N, 6.45. Found: C, 54.85; H, 8.57; N, 6.43.

tert-Butyl (2S,3S,2'S,3'S,3"S)-3'-(3"-tert-butoxycarbonyl-3"-tert-butyldimethylsiloxypropylamino)-3'-tert-butoxycarbonyl-2'-methoxymethoxypropyl-3-methoxymethoxy-2-azetidinecarboxylate (24). To a stirred solution of **23** (162 mg, 0.37 mM) and AcOH (22 µl, 0.37 mM) in MeOH (1 ml) were added a solution of the aldehyde **25** (141 mg, 0.49 mM) in MeOH (2 ml) and 1M $NaBH_3CN$ in THF (370 µl, 0.37 mM) at 0°C. After being stirred at 0°C for 14 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (10 ml), extracted with $CHCl_3$ (30 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 30g, hexane-EtOAc=4:1) to give **25** (223 mg, 85 %) as a colorless oil: $[\alpha]^{24}_D$ -43.2 (c 0.74, $CHCl_3$); IR ν_{max} (neat) 3330, 1738, 1732 cm^{-1}; ^{1}H NMR δ 0.03 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.45 (9H, s), 1.46 (9H, s), 1.47 (9H, s), 1.63 (1H, br), 1.80-1.87 (2H, m), 2.54-2.74 (3H, m), 2.79 (1H, t, J=6.8 Hz), 2.95 (1H, dd, J=7.3, 12.9 Hz), 3.35 (3H, s), 3.47 (1H, d, J=5.6 Hz), 3.70-3.77 (2H, m), 4.12 (1H, t, J=6.1 Hz), 4.26 (1H, dd, J=6.6, 12.5 Hz), 4.64 (2H, ABq, J=6.6 Hz), 4.69 (2H, ABq, J=6.9 Hz); Anal. calcd for $C_{34}H_{66}N_2O_{10}Si$: C, 57.76; H, 9.41; N, 3.96. Found: C, 57.93; H, 9.20; N, 4.24.

3-epi-Hydroxymugineic acid (2). To a stirred solution of **24** (52 mg, 0.074 mM) in anisole (0.1 ml) and THF (0.1 ml) was added 20% aqueous HCl (1 ml) at room tempetature. After being stirred at room temperature for 24 h, the mixture was washed with Et_2O (10 ml x 3). The aqueous phase was concentrated in vacuo, purified by Dowex 50W x 4 (5 ml, H_2O then 15% aqueous NH_3) to give an orange solid (25 mg). Further purification was performed by ODS silica gel column chromatography (5 g, H_2O). The residue was

recrystallized from H_2O-EtOH to give 3-epi-hydroxymugineic acid (2) (23 mg, 93 %) as a white solid: mp 181-184°C (dec); $[\alpha]^{24}_D$ -33.2 (c 1.02, H_2O); ^1H NMR (D_2O, pH=6.3) δ 1.97-2.14 (1H, m), 2.16-2.26 (1H, m), 3.15-3.37 (2H, m), 3.47 (1H, dd, J=3.3, 13.5 Hz), 3.60 (1H, dd, J=8.9, 13.5 Hz), 3.83 (1H, dd, J=6.3, 9.9 Hz), 3.87 (1H, d, J=3.3 Hz), 4.17 (1H, dd, J=4.6, 7.3 Hz), 4.37 (1H, dd, J=6.3, 10.9 Hz), 4.47 (1H, dt, J=6.9, 13.2 Hz), 4.63 (1H, dd, J=6.9, 13.2 Hz), 4.68 (1H, d, J=6.9 Hz); FABMS m/z: 337 (M+1).

tert-Butyl (2'S,3'S)-2-(3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propylamino)acetate (27). To a stirred solution of $(COCl)_2$ (110 μl, 0.86 mM) in CH_2Cl_2 (2 ml) was added a solution of DMSO (125 μl, 1.72 mM) in CH_2Cl_2 (1 ml) at -78°C. After the mixture was stirred for 10 min, a solution of **15** (353 mg, 0.86 mM) in CH_2Cl_2 (3 ml) and Et_3N (360 μl, 2.58 mM) were added. The mixture was allowed to warm to 0°C and stirred for 2 h. After being quenched with H_2O (10 ml), the mixture was extracted with CH_2Cl_2 (20 ml x 3), dried over Na_2SO_4, and concentrated in vacuo to give a mixture of the crude aldehydes **16a** and **16b** (15:1) (370 mg) as a pale yellow oil (The ratio of the epimers was determined by the integration of the methyne proton of the aldehyde group in its ^1H NMR spectrum). This mixture was used for the next reaction without further purification. A solution of the above crude aldehydes **16a** and **16b** (15:1) (370 mg) in MeOH (4 ml) and 1M $NaBH_3CN$ in THF (860 μl, 0.86 mM) were added to a stirred solution of **26**[15] (330 mg, 1.72 mM) in MeOH (2 ml) at 0°C. After being stirred at 0°C for 12 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 ml), extracted with $CHCl_3$ (50 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 60 g, hexane-EtOAc=5:2→2:1) to give **27** (357 mg, 79 %): $[\alpha]^{24}_D$ +2.4 (c 0.43, $CHCl_3$); IR ν_{max} (neat) 3337, 1732 cm^{-1}; ^1H NMR δ 1.46 (9H, s), 1.47 (9H, s), 1.64 (1H, br); 2.82 (1H, dd, J=5.6, 12.5 Hz), 2.90 (1H, dd, J=5.3, 12.5 Hz), 3.30 (2H, d, J=5.3 Hz), 3.42 (3H, s), 3.98-4.00 (1H, m), 4.53 (1H, dd, J=3.3, 8.6 Hz), 4.66-4.75 (4H, m), 6.94 (1H, brd, J=8.6 Hz); Anal. calcd for $C_{19}H_{33}Cl_3N_2O_8$: C, 43.56; H, 6.35; N, 5.35. Found: C, 43.68; H, 6.24; N, 5.22.

tert-Butyl (2'S,3'S)-2-(N-tert-butoxycarbonyl-3'-tert-butoxycarbonyl-2'-methoxymethoxy-3'-(2,2,2-trichloroethoxycarbonylamino)propylamino)acetate (28). To a stirred solution of **27** (272 mg, 0.52 mM) in dioxane were added i-Pr_2NEt (1 drop, cat.) and Boc_2O (340 mg, 1.59 mM) at 0°C. After being stirred at room temperature for 2 h, the mixture was treated with Et_2O, washed with 1M aqueous $KHSO_4$ (10 ml x 1) and saturated brine (10 ml x 1), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 30 g, hexane-Et_2O=5:2) to give **28** (323 mg, 100 %): $[\alpha]^{25}_D$ +13.9 (c 0.55, $CHCl_3$); IR ν_{max} (neat) 1732 cm^{-1}; ^1H NMR δ 1.43, 1.46, 1.47, 1.48, 1.50 (27H, each s), 3.37-3.49 (1H, m), 3.41, 3.42 (3H, each s), 3.57-3.68 (1H, m), 3.75-3.94 (2H, m), 4.02-4.14 (1H, m), 4.35-4.40 (1H, m), 4.59-4.80 (4H, m), 6.33, 6.60 (1H, each brd, J=8.6 Hz and J=8.9 Hz, respectively). (Two rotamers were detected in its ^1H NMR spectrum.); Anal. calcd for $C_{24}H_{41}Cl_3N_2O_{10}$: C, 46.20; H, 6.62; N, 4.49. Found: C, 46.21; H, 6.43; N, 4.41.

tert-Butyl (2'S,3'S,3"S)-2-(N-tert-butoxycarbonyl-3'-(3"-tert-butoxycarbonyl-3"-tert-butyldimethylsiloxypropylamino)-3'-tert-butoxycarbonyl-2'-methoxymethoxypropylamino)-acetate (30). To a stirred solution of **28** (315 mg, 0.51 mM) in AcOH (1 ml) and THF (6 ml) was added in one portion Zn powder (700 mg) at room temperature. After being stirred at room temperature for 3 h, the mixture was filtered through a pad of celite. Saturated aqueous $NaHCO_3$ (10 ml) was added, and the mixture was extracted with EtOAc (30 ml x 3). The extracts were dried over Na_2SO_4, and concentrated in vacuo to give crude **29** (270 mg) as a pale yellow oil: IR ν_{max} (neat) 3391, 3385, 1742, 1705 cm^{-1}; ^1H NMR δ 1.42, 1.45, 1.46, 1.47, 1.48, (27H, each s), 1.60 (2H, brs), 3.37, 3.37 (3H, each s), 3.39-3.60 (3H, m), 3.84-4.02 (3H, m), 4.62-4.69 (2H, m). (Two rotamers were detected in its ^1H NMR spectrum.) This mixture was used for the next reaction without further purification. A solution of **25** in MeOH (2 ml) and 1M $NaBH_3CN$ in THF (500 μl, 0.50 mM) were added to a stirred solution of the crude amine **29** (270 mg) in AcOH (28 ml, 0.51 mM) and MeOH (1.5 ml) at 0°C. After being stirred at 0°C for 3h, the mixture was allowed to warm to room temperature, stirred for 11 h, quenched with saturated aqueous $NaHCO_3$ (5 ml), extracted with $CHCl_3$ (30 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 40 g, hexane-Et_2O=4:1→3.5:1→3:1) to give **30** (226 mg, 62 %): $[\alpha]^{24}_D$ -17.5 (c

0.43, $CHCl_3$); IR ν_{max} (neat) 3339, 1748, 1707 cm^{-1}; ^1H NMR δ 0.03, 0.07, 0.08 (6H, each s), 0.89 (9H, s), 1.45 (9H, s), 1.46 (9H, s), 1.47 (9H, s), 1.48 (9H, s), 1.62 (1H, br), 1.83 (1H, dd, J=7.6, 13.4 Hz), 2.55-2.78 (2H, m), 3.20-3.26 (1H, m), 3.34, 3.36 (3H, each s), 3.40-3.57 (2H, m), 3.78-4.01 (3H, m), 4.07-4.15 (1H, m), 4.59-4.69 (2H, m). (Two rotamers were detected in its ^1H NMR spectrum.); Anal. calcd for $C_{35}H_{68}N_2O_{11}Si$: C, 58.30; H, 9.51; N, 3.89. Found: C, 58.25; H, 9.26; N, 3.75.

Distichonic acid A (3). To a stirred solution of **30** (26 mg, 0.036 mM) in anisole (0.1 ml) and THF (0.1 ml) was added 20% aqueous HCl (1 ml) at room tempetature. After being stirred at room temperature for 14 h, the mixture was washed with Et_2O (5 ml x 3). The aqueous phase was concentrated in vacuo, purified by Dowex 50W x 4 (5 ml, H_2O then 15% aqueous NH_3) to give an orange solid (10 mg). Further purification was performed by ODS silica gel column chromatography (5 g, H_2O). The residue was recrystallized from H_2O to give distichonic acid A (3) (9 mg, 85 %) as a white solid: mp 200-201°C (dec); $[\alpha]^{24}_D$ +3.2 (c 0.68, 1N HCl); CD $\Delta\varepsilon_{213nm}$+2.62 (c 4.0 x 10^{-4}, 1N HCl); ^1H NMR (1N DCl) δ 1.93-1.98 (1H, m), 2.12-2.14 (1H, m), 3.13-3.22 (2H, m), 3.27-3.34 (2H, m), 3.88 (2H, s), 4.14 (1H, d, J=2.6 Hz), 4.26 (1H, dd, J=4.6, 7.9 Hz), 4.46-4.49 (1H, m).

Benzyl (S)-2-tert-butoxycarbonylamino-3-formylpropionate (33). To a stirred solution of the amino lactone **31**[12b] (1.45 g, 7.21 mM) in DMF (20 ml) was added a solution of KOH (405 mg, 7.21 mM) in H_2O (5 ml) at 0°C. After being stirred at 0°C for 1 h, the mixture was allowed to warm to room temperature and stirred for 2h. A solution of KOH (80 mg, 0.14 mM) in H_2O (1 ml) was added, the mixture was stirred at 0°C for 30 min, and 18-crown-6 (95 mg, 0.36 mM) and benzyl bromide (1.29 ml, 10.81 mM) were added. After being stirred at room temperature for 18 h, the mixture was treated with benzene and EtOAc, washed with H_2O (50 ml x 2) and saturated brine (50 ml x 1), dried over Na_2SO_4, and concentrated in vacuo to give crude **32** (2.63 g) as a colorless oil: ^1H NMR δ 1.44 (9H, s), 1.56-1.69 (1H, m), 2.11-2.23 (1H, m), 2.98-3.21 (1H, br), 3.60-3.75 (2H, m), 4.54-4.58 (1H, m), 5.14-5.24 (2H, m), 5.39 (1H, brd, J=7.3 Hz), 7.29-7.41 (5H, m). A solution of DMSO (1 ml, 14.41 mM) in CH_2Cl_2 (5 ml) was added to a stirred solution of $(COCl)_2$ (940 µl, 10.81 mM) in CH_2Cl_2 (30 ml) at -78°C. After the mixture was stirred for 10 min, a solution of crude **32** (2.63 g) in CH_2Cl_2 (15 ml) and Et_3N (3 ml, 21.62 mM) were added. The mixture was allowed to warm to 0°C and stirred for 2 h. After being quenched with H_2O (20 ml), the mixture was extracted with CH_2Cl_2 (50 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 120 g, hexane-Et_2O=4:3→1:1→2:3) to give **33** (1.82 g, 82 %): $[\alpha]^{24}_D$ +3.3 (c 0.95, $CHCl_3$); IR ν_{max} (neat) 3337, 1738, 1700 cm^{-1}; ^1H NMR δ 1.43 (9H, s), 2.97-3.16 (2H, m), 4.60-4.67 (1H, m), 5.17 (2H, s), 5.40 (1H, brd, J=7.6 Hz), 7.26-7.36 (5H, m), 9.72 (1H, s).

tert-Butyl (2S,2'S,3'S,3"S)-3'-(3"-benzyloxycarbonyl-3"-tert-butoxycarbonylamino-propylamino)-3'-tert-butoxycarbonyl-2'-methoxymethoxypropyl-2-azetidinecarboxylate (35). To a stirred solution of **34a** and **34b** (8:1) (1.71 g, 4.57 mM) in i-PrOH[17] (30 ml) and AcOH (390 µl, 6.85 mM) were added a solution of **33** (1.68 g, 5.48 mM) in i-PrOH (10 ml) and 1M $NaBH_3CN$ in THF (4.6 ml, 4.57 mM) at 0°C. After being stirred at 0°C→17°C for 12 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (20 ml), extracted with $CHCl_3$ (50 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 200 g, hexane-Et_2O=1:1→1:2), (BW 200, 150 g, hexane-EtOAc=2:1→3:2→1:1), (BW 200, 30 g, hexane-EtOAc=3:2) to give **35** (2.00 g, 66 %) as a colorless oil: $[\alpha]^{24}_D$ -27.6 (c 1.35, $CHCl_3$); IR ν_{max} (neat) 3368, 1732, 1717 cm^{-1}; ^1H NMR δ 1.43, 1.44, 1.45, 1.46 (27H, each s), 1.63 (1H, br), 1.88-1.97 (2H, m), 2.12-2.28 (2H, m), 2.51-2.61 (2H, m), 2.70-2.89 (3H, m), 3.36 (3H, s), 3.40-3.59 (3H, m), 3.68-3.76 (1H, m), 4.35-4.40 (1H, m), 4.68 (2H, ABq, J=6.9 Hz), 5.09-5.20 (2H, m), 6.09, 6.27 (1H, each brd, J=9.9 Hz and J=8.9 Hz, respectively), 7.28-7.36 (5H, m); Anal. calcd for $C_{34}H_{55}N_3O_{10}$: C, 61.33; H, 8.33; N, 6.31. Found: C, 61.20; H, 8.17; N, 6.27. (Two rotamers were detected in its ^1H NMR spectrum.)

(2S,2'S,3'S,3"S)-3'-(3"-amino-3"-carboxylpropylamino)-3'-carboxyl-2'-hydroxy-propyl-2-azetidinecarboxylate (2'-Hydroxynicotianamine) (5). To a stirred suspension of 5% Pd-C (160 mg) in THF (5 ml) under hydrogen atmosphere was added a solution of **35** (798 mg, 1.20 mM) in THF (5 ml) at room temperature. After being stirred at room temperature for 6 h, the mixture was filtered through a

pad of celite and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 50 g, hexane-EtOAc=1:1→EtOH) to give **36** (592 mg, 86 %) as a colorless oil. Aqueous HCl (20%, 5 ml) was added to a stirred solution of **36** (592 mg) in anisole (1 ml) and THF (1 ml) at room tempetature. After being stirred at room temperature for 24 h, the mixture was washed with Et_2O (20 ml x 3). The aqueous phase was concentrated in vacuo, and the residue was purified by Dowex 50W x 4 (20 ml, H_2O then 15% aqueous NH_3) to give a white solid (292 mg, 76 % from **35**): mp 212-215°C (dec); $[\alpha]^{26}_D$ -41.5 (c 0.75, 1N HCl); ^1H NMR (1N DCl) δ 2.37-2.60 (2H, m), 2.77-2.86 (2H, m), 3.43-3.61 (2H, m), 3.65-3.82 (2H, m), 4.20-4.31 (3H, m), 4.39 (1H, d, J=2.3 Hz), 4.58-4.81 (1H, m), 5.35 (1H, t, J=9.7 Hz); ^{13}C NMR (67.8 MHz, 1N DCl) δ 22.22, 27.20, 44.72, 51.15, 52.28, 56.83, 63.75, 65.22, 66.90, 167.97, 170.65, 171.22; FABMS (glycerin) m/z: 320 (M+1).

Acknowledgments. We are grateful to the Japan Research Foundation for Optically Active Compounds, Foundation for the Promotion of Research on Medicinal Resources, the Ministry of Education, Science and Culture, and the Sasagawa Scientific Research Grant from The Japan Science Society for financial support of this work. F. M. gratefully acknowledges the postgraduate fellowship from the Japan Society for the Promotion of Science. We thank Dr. K. Nomoto of Suntory Institute for Bioorganic Research for the sample of **2**, spectra of **2** and **3**, and helpful discussions.

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(*Received in UK* 16 *August* 1993; *revised* 5 *October* 1993; *accepted* 8 *October* 1993)