A NEW EFFICIENT SYNTHESIS OF NICOTIANAMINE AND 2'-DEOXYMUGINEIC ACID†

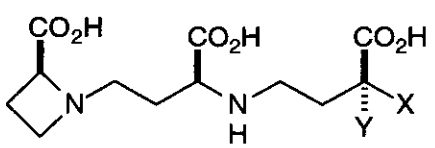
Takayuki Shioiri,*,[a] Naoko Irako,[a] Sachiko Sakakibara,[a] Fumiyoshi Matsuura,[a] and Yasumasa Hamada[b]

[a] Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

[b] Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba, Japan

Abstract – Nicotianamine and 2'-deoxymugineic acid, phytosiderophores, have been efficiently synthesized, which will be suitable for large scale production of these plant physiologically important compounds. The synthetic method for 2',3"-dideoxy-3"-oxomugineic acid was also investigated.

Both nicotianamine (**1**) and 2'-deoxymugineic acid (**2**) are important phytosiderophores by which uptake of iron from soil and its transport in plants are carried out. Although the synthetic methods for these phytosiderophores have been developed,[1] a more efficient method suitable for large scale production is still needed to develop since these are produced on a minute amount in nature and are an important tool for the investigation of plant physiology. We have been quite interested in the development of the synthetic method for phytosiderophores.[1] We now wish to report a new efficient synthesis of nicotianamine (**1**) and 2'-deoxymugineic acid (**2**) which is suitable for large scale production. In addition, the synthesis of 2',3"-

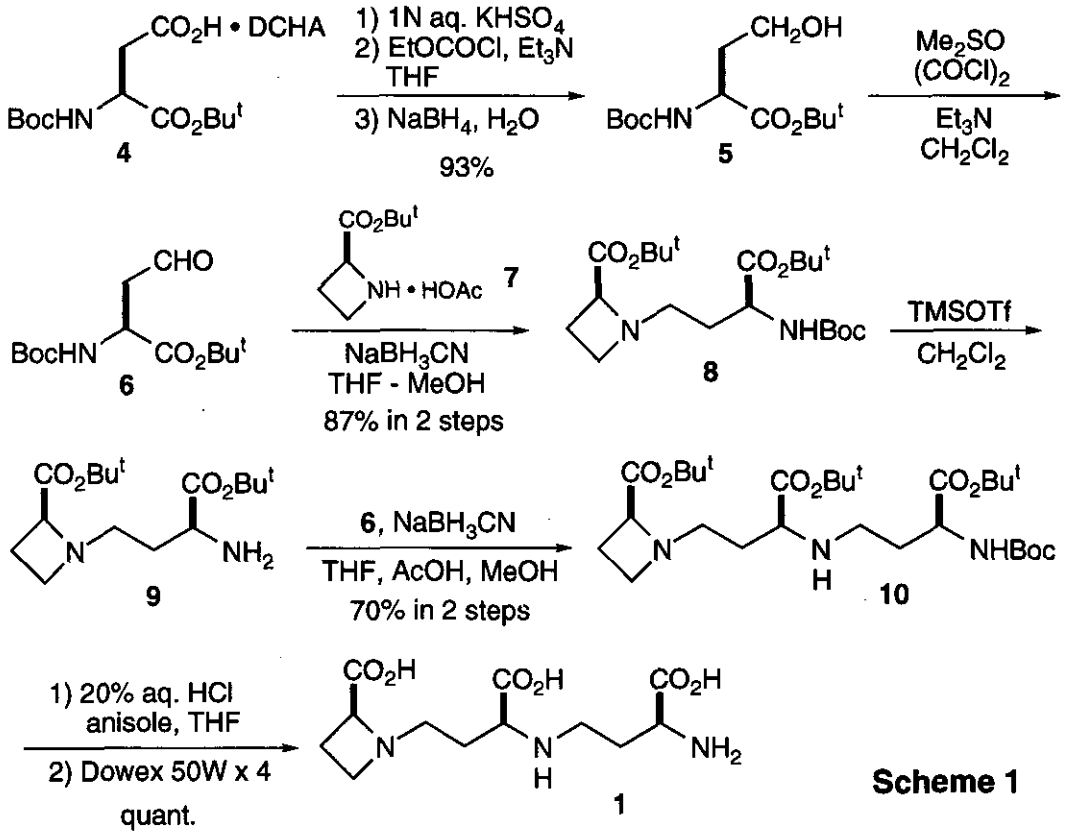


nicotianamine (**1**) : X=NH_2, Y=H
2'-deoxymugineic acid (**2**) : X=OH, Y=H
2',3"-dideoxy-3"-oxomugineic acid (**3**) : X, Y = O

† Dedicated to Professor Shigeru Oae on the occasion of his 77th birthday.

dideoxy-3"-oxomugineic acid (**3**), a presumed biosynthetic intermediate between **1** and **2**,[2] was also attempted.

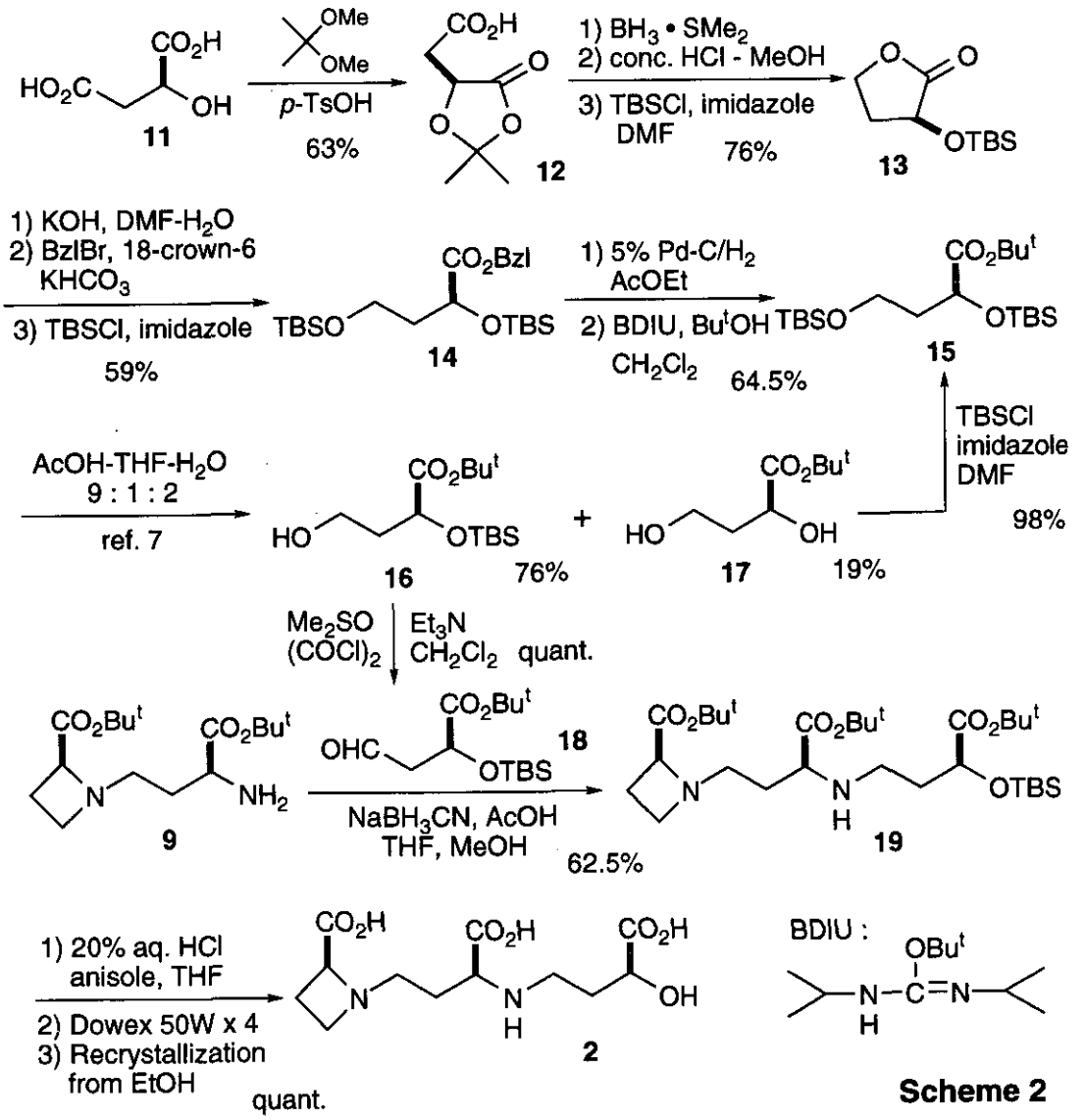
For the synthesis of nicotianamine, commercially available dicyclohexylamine(DCHA) salt of α-*tert*-butyl *N*-*tert*-butoxycarbonyl(Boc)-L-aspartic acid (**4**) was first converted to the corresponding β-aldehyde (**6**) *via* the known alcohol (**5**).[3] Reductive condensation of the aldehyde (**6**) with the salt (**7**) of (S)-azetidine-carboxylate[4] with sodium cyanoborohydride smoothly afforded the Boc-diester (**8**) which was selectively deprotected with trimethylsilyl triflate (TMSOTf) to give the amine (**9**). Reductive coupling of the amine (**9**) with the aldehyde (**6**) proceeded with sodium cyanoborohydride under analogous conditions to above, giving the protected nicotianamine (**10**). Acidic deprotection followed by purification afforded nicotianamine (**1**) in a good overall yield of 57% from the commercially available aspartic acid derivative (**4**).



Scheme 1

Next, our attention was turned to an efficient synthesis of 2'-deoxymugineic acid (**2**), a hydroxy analog of nicotianamine (**1**). The key feature of the synthesis is how to synthesize the right part of **2**. Thus, the

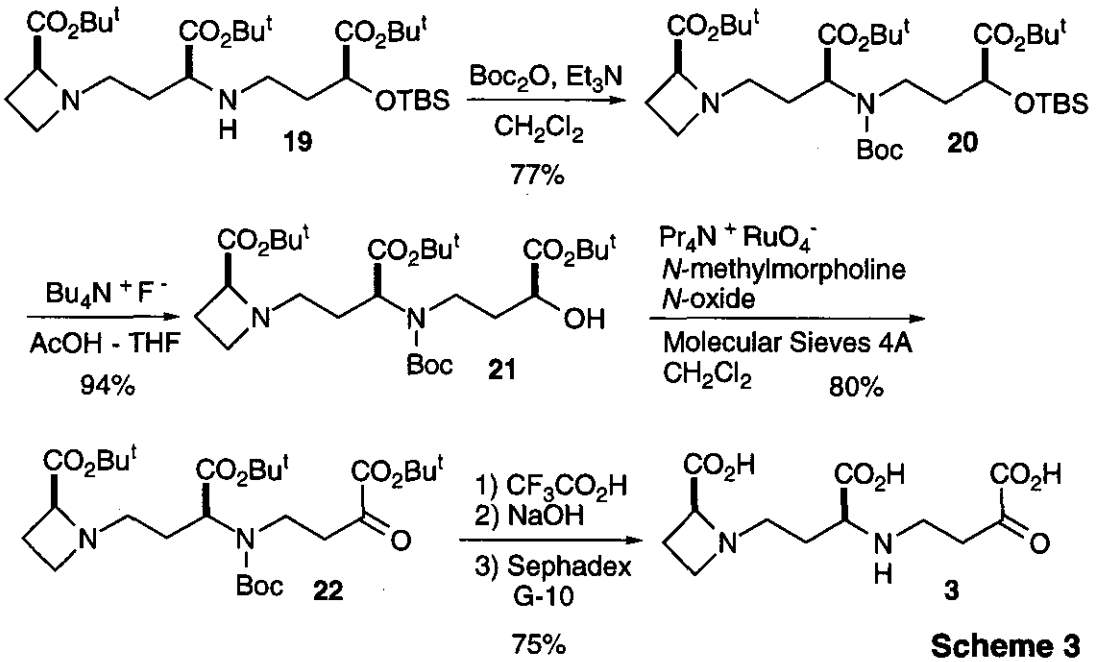
known acetal derivative (**12**) prepared from L-malic acid (**11**)[5,6] was converted to its *tert*-butyldimethylsilyl(TBS) derivative (**13**), which was converted to the benzyl ester (**14**) by alkaline treatment followed by benzylation and then silylation. The benzyl ester function of **14** was replaced with the *tert*-butyl one in two steps: catalytic removal of the benzyl ester followed by esterification with *O-tert*-butyl-*N,N'*-diisopropylisourea (BDIU). Although selective removal of the TBS group attached at the primary hydroxyl function from the *tert*-butyl ester (**15**) was achieved under acidic conditions to give the primary alcohol (**16**), the diol (**17**) was also formed though a small amount.[7] Since this by-product (**17**) was nearly quantitatively reconverted to the bis-TBS derivative (**15**), recycle use of **17** was easily realized.



Scheme 2

The alcohol (**16**) was oxidized under the Swern conditions to give the aldehyde (**18**).[7] Reductive coupling of the aldehyde (**18**) with the amine (**9**) was again achieved with sodium cyanoborohydride to give the tri-*tert*-butyl ester (**19**). 2'-Deoxymugineic acid (**2**) was finally obtained from **19** by acidic treatment followed by purification.

Incidentally, an attempted synthesis of 2',3"-dideoxy-3"-oxomugineic acid (**3**) was investigated since **3** was presumed to be a biosynthetic precursor of nicotianamine (**1**) from 2'-deoxymugineic acid (**2**).[2] The tri-*tert*-butyl ester (**19**) was converted to the Boc derivative (**20**) whose TBS group was selectively removed with tetra-n-butylammonium fluoride. Attempted oxidation of the alcoholic function of the resulting **21** failed by the Swern conditions or use of periodinane. However, use of tetra-n-propylammonium perruthenate for the oxidation afforded the α-keto ester (**22**). Although acidic removal of all the protective groups from **22** seemed to afford the desired α-keto acid (**3**), **3** was labile as expected and the complete identification of the structure (**3**) failed even as its salt.



Scheme 3

Thus, we have been able to develop a new efficient synthetic method for nicotianamine (**1**) and 2'-deoxymugineic acid (**2**), which will be suitable for large scale production of these plant physiologically important compounds.

EXPERIMENTAL

Melting points were determined on a YAMATO MP-21 apparatus. Infrared (Ir) spectra were measured with a SHIMADZU FT IR-8100 spectrophotometer. ^{1}H Nmr spectra were recorded on a JEOL EX-270 spectrometer with tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. Silica gel (BW-820MH or BW-200 purchased from Fuji Davison Co. Ltd.) was used for column chromatography. Tetrahydrofuran (THF) was dried by distillation from benzophenone ketyl. Other solvents were distilled and stored over molecular sieves (4A).

***tert*-Butyl (S)-2-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate (5).** *N*-Boc-L-aspartic acid α-*t*-butyl ester dicyclohexylamine salt (**4**) (10.0 g, 21.8 mmol) was dissolved in AcOEt-benzene (4:1, 100 ml). The solution was washed with 1M aqueous $KHSO_4$ (50 ml), and dried over Na_2SO_4. Concentration in vacuo gave the β-free acid as a white solid. Triethylamine (4.6 ml, 33 mmol) and then a solution of ethyl chloroformate (3.20 ml, 33.5 mmol) in THF (10 ml) was dropwise added to a stirred solution of the β-free acid in THF (30 ml) at -10°C under argon. The mixture was stirred at -10°C for 1 h. Triethylammonium chloride was removed by filtration and washed with THF (10 ml × 2). A solution of $NaBH_4$ (1.65 g, 43.6 mmol) in H_2O (15 ml) was added dropwise to the filtrate at 0°C. After being stirred at 0°C for 0.5 h and then at room temperature for 3.5 h, the mixture was acidified with 1N aqueous $KHSO_4$ (40 ml), then basified with saturated aqueous $NaHCO_3$, and extracted with Et_2O (50 ml × 3). The extracts were washed with saturated aqueous NaCl, and dried over Na_2SO_4. Concentration in vacuo gave an oily residue, which was purified by silica gel column chromatography with hexane-AcOEt (2:1) to give **5** (5.60 g, 93%) as a colorless oil. Ir ν_{max} (film): 3386, 2978, 1717, 1700, 1507, 1368, 1252, 1156, 1055 cm^{-1}. ^{1}H Nmr ($CDCl_3$) δ: 1.45 and 1.47 (s × 2, 18H), 1.47-1.50 (m, 1H), 2.04-2.16 (m, 1H), 3.00-3.50 (br, 1H, disappeared with D_2O), 3.60-3.69 (m, 2H), 4.32-4.38 (m, 1H), 5.30-5.35 (m, 1H).

***tert*-Butyl (S)-2-*tert*-butoxycarbonylamino-3-formylpropionate (6).** To a solution of oxalyl chloride (0.53 ml, 6.08 mmol) in CH_2Cl_2 (6 ml) was added a solution of DMSO (0.58 ml, 8.17 mmol) in CH_2Cl_2 (3 ml) at -78°C under argon, and the mixture was stirred at -78°C for 5 min. A solution of the alcohol (**5**) (1.11 g, 4.03 mmol) in CH_2Cl_2 (10 ml) was added at -78°C, and the mixture was stirred at -78°C for 15 min, and then a solution of triethylamine (1.70 ml, 12.2 mmol) in CH_2Cl_2 (6 ml) was added. After the mixture was stirred at -78°C for 0.5 h and then at 0°C for 2 h, water (40 ml) was added, and the mixture was extracted with CH_2Cl_2 (40 ml × 3). The extracts were washed with saturated aqueous NaCl,

and dried over Na_2SO_4. Concentration in vacuo gave the crude aldehyde (**6**) (1.24 g) as a pale yellow oil, which was used for the next reaction without further purification. Ir ν_{max}(film): 3376, 2980, 1738, 1717, 1504, 1368, 1252, 1156, 1055, 847 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.42 and 1.44 (s × 2, 18H), 2.91-3.14 (m, 2H), 4.49-4.51 (m, 1H), 5.35-5.37 (br s, 1H), 9.74 (s, 1H).

***tert*-Butyl (2S,3'S)-3'-*tert*-butoxycarbonyl-3'-(*tert*-butoxycarbonylamino)propyl-2-azetidenecarboxylate (8).** To a stirred solution of the above crude aldehyde (**6**) (4.867 g, 15.5 mmol) and the salt (**7**) of (S)-azetidinecarboxylate[4] (3.326 g, 16.3 mmol) in MeOH (35 ml) was added dropwise 1M $NaBH_3CN$ in THF (15.4 ml, 15.4 mmol) at 0°C. After the mixture was stirred at 0°C for 20 h, saturated aqueous $NaHCO_3$ (50 ml) was added, and the mixture was concentrated in vacuo. Water (50 ml) was added to the residue, and the mixture was extracted with CH_2Cl_2 (100 ml × 2). After the extracts were dried over Na_2SO_4, concentration in vacuo gave the residue, which was purified by silica gel column chromatography with hexane-AcOEt (2:1 → 1:1) to give **8** (5.60 g, 87%) as a pale yellow oil, $[\alpha]_D^{26}$ -39.5° (c 1.21, $CHCl_3$). Ir ν_{max}(film): 3353, 2979, 1732, 1717, 1505, 1368, 1250, 1156, 849 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.44, 1.45 and 1.48 (s × 3, 27H), 1.67-1.70 (m, 1H), 1.82-1.87 (m, 1H), 2.14-2.18 (m, 1H), 2.25-2.33 (m, 1H), 2.40-2.46 (m, 1H), 2.69-2.80 (m, 2H), 3.36-3.40 (m, 1H), 3.43-3.52 (m, 1H), 4.08-4.16 (m, 1H), 5.62 (d, 1H, J=7.6 Hz). Anal. Calcd for $C_{21}H_{38}N_2O_6$: C, 60.85; H, 9.24; N, 6.76. Found: C, 60.82; H, 9.37; N, 6.65.

***tert*-Butyl (2S,3'S)-3'-amino-3'-*tert*-butoxycarbonylpropyl-2-azetidinecarboxylate (9).** To a stirred solution of **8** (4.62 g, 11.5 mmol) in CH_2Cl_2 (130 ml) under argon was added dropwise TMSOTf (2.80 ml, 14.5 mmol) at 0°C. After the mixture was stirred at 0°C for 0.5 h, saturated aqueous $NaHCO_3$ (100 ml) was added, and the mixture was extracted with CH_2Cl_2 (60 ml, 120 ml). The extracts were dried over Na_2SO_4, and concentrated in vacuo to give the crude amine (**9**) (4.09 g) as a pale yellow oil, which was used for the next reaction without further purification. Some of **9** was purified by silica gel column chromatography with AcOEt-ethanol (1:1) to give a pale yellow oil, $[\alpha]_D^{26}$ -4.94° (c 1.26, $CHCl_3$). Ir ν_{max}(film): 3380, 3305, 2977, 1732, 1368, 1248, 1157, 849 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.46 and 1.47 (s × 2, 18H), 1.51-1.61 (m, 1H), 1.81-1.91 (m, 1H), 1.99 (brs, 2H, disappeared with D_2O). 2.14-2.19 and 2.21-2.35 (m × 2, 2H), 2.47-2.55 (m, 1H), 2.72-2.82 (m, 2H), 3.36-3.52 (m, 3H).

***tert*-Butyl (2S,3'S,3"S)-3'-(3"-*tert*-butoxycarbonyl-3"-*tert*-butoxycarbonylaminopropyl-amino-3'-*tert*-butoxycarbonylpropyl)-2-azetidinecarboxylate (10).** To a stirred solution of

the crude amine (**9**) (4.08 g, 10.6 mmol) and acetic acid (0.61 ml, 10.6 mmol) in MeOH (50 ml) were added a solution of the crude aldehyde (**6**) (3.36 g, 10.6 mmol) in MeOH (50 ml) and 1M $NaBH_3CN$ in THF (11.0 ml, 11.0 mmol) at 0°C. After being stirred at 0°C for 16 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (100 ml), and concentrated in vacuo. Water (50 ml) was added to the residue, and the mixture was extracted with CH_2Cl_2 (125 ml × 2). The extracts were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane-AcOEt (1:6 → 0:1) to give **10** (4.25 g, 70%) as a colorless oil, $[\alpha]_D^{24.5}$ -40.8° (c 1.00, $CHCl_3$). Ir ν_{max}(film): 3362, 2998, 1728, 1368, 1250, 1156 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.44 and 1.457 and 1.462 (s × 3, 36H), 1.55-1.77 (m, 3H), 1.90-1.91 (m, 1H), 2.05-2.31 (m, 2H), 2.45-2.55 (m, 2H), 2.65-2.80 (m, 3H), 3.00-3.10 (m, 1H), 3.15-3.40 (m, 1H), 3.50 (t, 1H, J=8.3 Hz), 4.08-4.20 (m, 2H), 5.68 (d, 1H, J=7.3 Hz). HRms Calcd for $C_{29}H_{53}N_3O_8$: 571.3832. Found: 571.3852.

Nicotianamine (1). To a stirred solution of **10** (4.20 g, 7.35 mmol) in THF (9 ml) and anisole (9 ml) was added 20% aqueous HCl (165 ml) at room temperature. After being stirred at room temperature for 17 h, the mixture was washed with Et_2O (50 ml × 2) and concentrated in vacuo. The residue was purified by ion-exchange resin (Dowex 50W × 4, 20 ml, H_2O then 15% aqueous NH_3) to give nicotianamine (**1**) (2.31 g, quantitative) as a white solid, mp >> 245°C $[\alpha]_D^{28.5}$ -43.4° (c 0.37, H_2O) [lit.,[8] mp >> 240°C, $[\alpha]_D^{24}$ -51.7° (c 0.37, H_2O)]. Ir ν_{max}(nujol): 3413, 2924, 1601, 1574, 1464, 1375, 1297, 801, 764 cm^{-1}. ^1H Nmr (D_2O, TMSP, pH=6.3, HMG of HOD) δ: 1.97-2.34 (m, 4H), 2.46-2.61 (m, 1H), 2.68-2.81 (m, 1H), 3.20-3.31 (m, 2H), 3.33-3.47 (m, 2H), 3.78 (dd, 1H, J=4.6, 8.3 Hz), 3.86 (dd, 1H, J=6.3, 5.3 Hz), 3.95 (t, 1H, J=9.6 Hz), 4.10 (dd, 1H, J=4.6, 9.9 Hz), 4.77 (t, 1H, J=9.2 Hz). The spectral data (ir, nmr) were identical with those of the authentic sample.[8]

(S)-α-*tert*-Butyldimethylsiloxy-γ-butyrolactone (13). To a stirred solution of L-malic acid (**11**) (30.2 g, 255 mmol) in 2,2'-dimethoxypropane (150 ml) was added *p*-TsOH·H_2O (350 mg, 1.84 mmol) at 0°C. After the mixture was stirred at room temperature for 23 h, triethylamine (0.26 ml, 1.86 mmol) was added. The mixture was concentrated in vacuo, and extracted with Et_2O (200 ml). The organic extracts were washed with H_2O (100 ml × 2) and saturated aqueous NaCl (100 ml), and dried over Na_2SO_4. Concentration in vacuo gave a pale yellow solid (**12**, 24.8 g, 63%), which was recrystallized with Et_2O-CCl_4 to give a white solid (**12**). Ir ν_{max}(nujol): 3268, 2924, 1763, 1734, 1281, 1129, 926, 824 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.57 and 1.63 (s × 2, 6H), 2.85 (dd, 1H, J=6.6, 17.1 Hz), 3.00 (dd, 1H, J=17.2, 4.0 Hz), 4.72 (dd, 1H, J=4.0, 6.6 Hz), 8.7 (br, 1H). To a stirred solution of **12** (22.0 g, 126 mmol) in

THF (400 ml) was added $BH_3 \cdot SMe_2$ (19.0 ml, 200 mmol) at -10°C → 0°C under an argon atmosphere. After being stirred at -10°C → 0°C for 8 h, and then at -10°C → 23°C for 14.5 h, the mixture was cooled to 0°C and quenched with MeOH (50 ml). The solvent was removed in vacuo and the residue was dissolved in MeOH (30 ml) and then conc. HCl (10 ml) was added at 0°C. After the mixture was stirred at room temperature for 1.5 h, benzene-EtOH (1:1, 100 ml) was added. Concentration in vacuo gave the residue, which was purified by silica gel column chromatography with AcOEt to give α-hydroxy-γ-butyrolactone (11.6 g, 91%) as a pale yellow oil. The lactone was dissolved in DMF (160 ml), and imidazole (12.6 g, 185 mmol) and TBSCl (22.0 g, 146 mmol) were added to the mixture. After being stirred at room temperature for 16 h, the mixture was quenched with 1M aqueous $KHSO_4$ (100 ml) and extracted with Et_2O (400 ml). The combined ethereal solution was washed with saturated aqueous NaCl (100 ml), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane-Et_2O (4:1 → 2:1) to give **13** (20.7 g, 76%) as a colorless oil. Ir ν_{max}(film): 2930, 1788, 1474, 1254, 1154, 1022, 999, 839, 781, cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 0.150 and 0.176 (s × 2, 6H), 0.916 (s, 9H), 2.22 (ddd, 1H, J=8.6, 8.9, 12.5 Hz), 2.40-2.51 (m, 1H), 4.19 (dt, 1H, J=6.3, 9.2 Hz), 4.35-4.44 (m, 2H).

Benzyl (S)-2,4-di-(*tert*-butyldimethylsiloxy)butanoate (14). To a stirred solution of **13** (7.93 g, 36.7 mmol) in DMF (110 ml) at 0°C was added a solution of KOH (2.47 g, 37.5 mmol) in H_2O (25 ml). After being stirred at 0°C for 1.5 h, $KHCO_3$ (3.78 g, 37.0 mmol), 18-crown-6 (987 mg, 3.73 mmol), and BzlBr (6.60 ml, 55.5 mmol) were added to the mixture. The mixture was stirred at 0°C for 0.5 h and then at room temperature for 15 h, and extracted with $CHCl_3$ (200 ml × 3). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give a solution of the benzyl butanoate in DMF. Imidazole (7.04 g, 103 mmol) and TBSCl (12.7 g, 84.5 mmol) were added to the above solution, and the mixture was stirred at room temperature for 20.5 h. After dilution with Et_2O (400 ml), the mixture was washed with 1M aqueous $KHSO_4$ (100 ml), H_2O (100 ml), and saturated aqueous NaCl (100 ml), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane-Et_2O (22:1) to give **14** (9.53 g, 59%) as a colorless oil. Ir ν_{max}(film): 2955, 1754, 1258, 1136, 1103, 837, 777 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 0.028 and 0.042 (s × 2, 12H), 0.878 and 0.882 (s × 2, 18H), 1.85-1.97 (m, 2H), 3.65-3.78 (m, 2H), 4.41 (dd, 1H, J=4.3, 7.9 Hz), 5.15 (ABq, 2H, J=12.2 Hz), 7.31-7.37 (m, 5H).

***tert*-Butyl (S)-2,4-di-(*tert*-butyldimethylsiloxy)butanoate (15).** (i) To a stirred suspension of 5% Pd-C (1.83 g) in AcOEt (125 ml) under a H_2 atmosphere was added a solution of **14** (7.94 g, 18.1 mmol) in AcOEt (40 ml). After being stirred at room temperature under a H_2 atmosphere for 1 h, the mixture was filtered though the pad of celite and the filtrate was concentrated in vacuo to give the crude carboxylic acid (6.45 g) as a white solid. Ir ν_{max}(nujol): 2928, 1723, 1471, 1256, 1102, 837, 777 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 0.051, 0.056, and 0.135 (s × 3, 12H), 0.889 and 0.933 (s × 2, 18H), 1.93-2.00 (m, 2H), 3.67-3.83 (m, 2H), 4.41 (t, 1H, J=5.6 Hz). After this crude compound was dissolved in *t*-BuOH (70 ml) and CH_2Cl_2 (20 ml), BDIU (14 ml, 58.6 mmol) was added to the mixture. The mixture was stirred at room temperature for 1.5 h, and then filtered through the pad of celite, which was washed with CH_2Cl_2 (80 ml). The combined filtrate and washings were concentrated in vacuo to give the residue, which was purified by silica gel column chromatography with hexane-Et_2O (24:1) to give **15** (4.72 g, 64.5%) as a colorless oil. Ir ν_{max}(film): 2930, 1752, 1477, 1256, 1136, 1103, 837, 777 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 0.045, 0.053, and 0.092 (s × 3, 12H), 0.893 and 0.908 (s × 2. 18H), 1.46 (s, 9H), 1.69-1.98 (m, 2H), 3.64-3.79 (m, 2H), 4.22 (dd, 1H, J=4.1, 8.3 Hz). [lit.,[7] Ir ν_{max}(film): 1752 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 0.05 (s, 6H), 0.09 (s, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 1.46 (s, 9H), 1.69-1.98 (m, 2H), 3.64-3.79 (m, 2H), 4.22 (dd, 1H, J=4.0, 8.6 Hz).] This compound was identified with the authentic one by comparison of its spectra.[7]

(ii) To a stirred solution of **17** (1.81 g, 10.3 mmol) in DMF (30 ml) was added imidazole (2.20 g, 32.3 mmol) and TBSCl (4.16 g, 27.6 mmol). The mixture was stirred for 23.5 h at room temperature, and quenched with 1M aqueous $KHSO_4$ (50 ml). After extraction with Et_2O (100 ml), the extracts were washed with saturated aqueous NaCl (50 ml), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane-Et_2O (24:1) to give **15** (4.05 g, 98%).

***tert*-Butyl (S)-2-*tert*-butyldimethylsiloxy-4-hydroxybutanoate (16).** Prepared from **15** according to the literature.[7] A small amount of the diol (**17**) was also formed.

***tert*-Butyl (S)-2-*tert*-butyldimethylsiloxy-4-oxobutanoate (18).** Prepared from **16** according to the literature.[7] The crude yellow oil (**18**) was used for the next reaction without further purification.

***tert*-Butyl (2S,3'S,3"S)-3'-(3"-*tert*-butyldimethylsiloxy-3"-*tert*-butoxycarbonylpropyl-amino)-3'-*tert*-butoxycarbonylpropyl-2-azetidinecarboxylate (19).** To a stirred solution of the crude amine (**9**) (4.17 g, 12.0 mmol) and AcOH (0.63 ml, 11.0 mmol) in MeOH (40 ml) were added a solution of the crude aldehyde (**18**) (3.70 g, 1.10 mmol) in MeOH (10 ml) and 1M $NaBH_3CN$ in THF

(11.0 ml, 11.0 mmol) at 0°C. After being stirred at 0°C for 19.5 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (100 ml), and concentrated in vacuo. Water (50 ml) was added to the residue, which was extracted with CH_2Cl_2 (100 ml × 2), and the extracts were dried over Na_2SO_4. Concentration in vacuo followed by silica gel column chromatography with hexane-AcOEt (2:1 → 0:1) gave **19** (4.03 g, 62.5%) as a colorless oil, $[\alpha]_D^{26}$ -55.1° (c 0.99, $CHCl_3$). Ir ν_{max}(film): 2982, 1732, 1368, 1252, 1152, 839, 779 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 0.036 and 0.078 (s × 2, 6H), 0.897 (s, 9H), 1.46 (s, 29H), 1.57 (s, 1H), 1.67-1.85 (m, 2H), 2.12-2.18 (m, 1H), 2.25-2.32 (m, 1H), 2.44-2.58 (m, 2H), 2.63-2.81 (m, 3H), 3.08 (t, 1H, J=6.6 Hz), 3.34-3.38 (m, 1H), 3.47 (t, 1H, J=8.9 Hz), 4.08-4.16 (m, 1H). Anal. Calcd for $C_{30}H_{57}N_2O_7Si$: C, 61.40; H, 9.81; N, 4.76. Found: C, 61.23; H, 10.10; N, 5.03.

2'-Deoxymugineic acid (2). To a stirred solution of **19** (4.65 g, 7.91 mmol) in THF (10 ml) and anisole (10 ml) at room temperature was added 20% aqueous HCl (175 ml). After being stirred at room temperature for 17 h, the mixture was washed with Et_2O (100 ml) and concentrated in vacuo. The residue was purified by ion-exchange resin (Dowex 50W × 4, 25 ml, H_2O then 15% aqueous NH_3) to give a yellow oil. Crystallization and recrystallization of the yellow oil from EtOH afforded **2** (2.47 g, quant.) as a white solid, mp 190-192°C (decomp.), $[\alpha]_D^{23.5}$ -61.1° (c 0.30, H_2O) [lit.,[8] mp 200-202°C, $[\alpha]_D^{24}$ -62.3° (c 0.31, H_2O)]. Ir ν_{max}(nujol): 3409, 2924, 1649, 1615, 1592, 1421, 1377, 1100. ^1H Nmr (D_2O, TMSP, pH=7.6, HMG of HOD at 50°C) δ: 1.94-2.17 (m, 4H), 2.45-2.56 (m, 1H), 2.68-2.72 (m, 1H), 3.09-3.17 (m, 2H), 3.28-3.39 (m, 2H), 3.66 (dd, 1H, J=5.3, 7.6 Hz), 3.85 (q, 1H, J=9.2 Hz), 4.04 (dt, 1H, J=4.3, 9.6 Hz), 4.13 (dd, 1H, J=4.6, 6.9 Hz), 4.60 (t, 1H, J=9.0 Hz).

***tert*-Butyl (2S,3'S,3"S)-3'-(3"-*tert*-butyldimethylsiloxy-*N*-*tert*-butoxycarbonyl-3"-*tert*-butoxycarbonylpropylamino)-3'-*tert*-butoxycarbonylpropyl-2-azetidinecarboxylate (20).** To a stirred solution of **19** (480 mg, 0.82 mmol) in CH_2Cl_2 (5 ml) were added Et_3N (5.7 μl, 0.041 mmol) and Boc_2O (446 mg, 2.04 mmol) at 0°C. After being stirred at room temperature for 15 h, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 50 g, hexane:EtOAc=7:1) to give **20** (435 mg, 77%) as a colorless oil, $[\alpha]_D^{26}$ -64.8°(c 0.755, $CHCl_3$). Ir ν_{max}(film) 2977, 1740-1698 (br.), 1368, 1157 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 0.05 and 0.08 (s × 2, 6H), 0.91 (s, 9H), 1.42, 1.44, 1.45, and 1.46 (s × 4, 27H), 1.63 (m, 1H), 1.86-2.41 (6H, m), 2.70-2.79 (2H, m), 3.00-3.30 (1H, m), 3.35 (1H, m), 3.51-3.59 (2H, m), 4.00-4.10 (2H, m). Anal. Calcd for. $C_{35}H_{65}N_2O_9Si$: C, 61.28; H, 9.55; N, 4.08, Found: C, 61.24; H, 9.52; N, 4.01.

***tert*-Butyl (2S,3S',3"S)-3'-(3"-hydroxy-*N*-*tert*-butoxycarbonyl-3"-*tert*-butoxycarbonyl-propylamino)-3'-*tert*-butoxycarbonylpropyl-2-azetidinecarboxylate (21).** To a stirred solution of **20** (125 mg, 0.182 mmol) and AcOH (63 μl, 1.092 mmol) in THF (2 ml) was added $Bu_4N^+F^-\cdot 3H_2O$ (285 mg, 0.903 mmol) at 0°C. After being stirred at 65°C for 12 h, the mixture was diluted with CH_2Cl_2 (20 ml) and washed with saturated aqueous $NaHCO_3$ (5 ml), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 10 g, hexane:EtOAc=1:1) to give **21** (91 mg, 94%) as a colorless oil, $[\alpha]_D^{23}$ -64.4° (c 0.61, $CHCl_3$). Ir ν_{max}(film): 3495, 2979, 1700-1738 (br), 1159 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.49, 1.46, 1.44, and 1.43 (s × 4, 36H), 1.83-1.86 (m, 2H), 2,11-2.30 (m, 4H), 2.35-2.44 (m, 1H), 2.68-2.77 (m, 2H), 3.20-3.36 (m, 3H; 2H after addition of D_2O), 3.47-3.64 (m, 2H), 3.91-4.12 (m, 2H).

***tert*-Butyl (2S,3S',3"S)-3'-(3"-oxo-*N*-*tert*-butoxycarbonyl-3"-*tert*-butoxycarbonyl-propylamino)-3'-*tert*-butoxycarbonylpropyl-2-azetidinecarboxylate (22).** The alcohol (**21**) (1.127 g, 1.970 mmol) was dissolved in CH_2Cl_2 (20 ml) containing both molecular sieves 4Å (985 mg) and *N*-methylmorpholine *N*-oxide (462 mg, 3.944 mmol) at 0°C. After the mixture was stirred for 10 min, $Pr_4N^+RuO_4^-$ (34 mg, 0.10 mmol) was added and the mixture was stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2, and filtered through the pad of celite. The filtrate was washed with saturated sodium sulfite solution, brine, and saturated copper (II) sulfate solution. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820MH, 50 g, hexane:Et_2O=4:1) to give **22** (903 mg, 80%) as a colorless oil, $[\alpha]_D^{26}$ -28.76° (c 1.573, $CHCl_3$). Ir ν_{max}(film): 2979, 1770-1738 (br), 1159, 756 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.40, 1.42, 1.44, and 1.45 (s × 4, 36H), 1.84-1.91 (1H, m), 2.01-2.05 (1H, m), 2.11-2.16 (1H, m), 2.38-2.39 (1H, m), 2.67-2.77 (2H, m), 3.06-3.14 (1H, m), 3.17-3.23 (1H, m), 3.35-3.43 (2H, m), 3.46-3.49 (1H, m), 3.66-3.81 (1H, m), 3.99-4.15 (1H, m). ^{13}C Nmr ($CDCl_3$, 50°C) δ: 21.1, 27.2, 27.8, 28.0, 28.1, 28.3, 38.9-39.1, 42.0-43.5, 50.7, 55.3, 59.6-60.0, 65.9, 80.3, 80.7, 81.1, 83.5, 154.8, 160.2, 170.5, 171.8, 193.8. Anal. Calcd for $C_{29}H_{50}N_2O_9$: C, 61.03; H, 8.83; N, 4.91. Found C, 61.19; H, 9.05; N, 5.04. HRms Calcd for $C_{29}H_{50}N_2O_9$: 570.3516. Found: 570.3557.

2',3"-Dideoxy-3"-oxomugineic acid (3). The α-keto ester (**22**) (35 mg, 0.0613 mmol) was dissolved in trifluoroacetic acid (470 μl, 7.53 mmol) and the mixture was stirred at room temperature for 1 h. After being treated with CH_2Cl_2 (1 ml, distilled), the mixture was evaporated in vacuo. The residue was treated with CH_2Cl_2 and dried in vacuo again. This procedure was repeated 7 times. The residue

was dried over P_2O_5 in vacuo for 12 h. After addition of 1N NaOH aq (123 μl), the mixture was stirred at room temperature for 1 h and then purified by Sephadex G-10 (ca. 100 ml H_2O). Currented water solution was collected, and then dried by evaporation and freeze-drying to give a yellow amorphous solid of **3** (28 mg, 75%). HR FABms Calcd for $C_{12}H_{19}O_7N_2$ (MH^+): 303.1192. Found: 303.1180.

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