Pergamon

Tetrahedron Vol. 50, No. 31, pp. 9457-9470, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $7.00+0.00

0040-4020(94)00539-7

Total Synthesis of 2'-Deoxymugineic Acid and Nicotianamine

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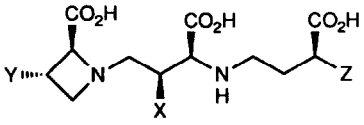
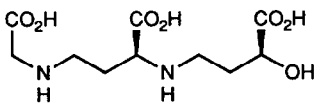
Abstract: Stereoselective total synthesis of the unique phytosiderophores, 2'-deoxymugineic acid (**4**) and nicotianamine (**5**), has been achieved from the β-tyrosine derivative **21** using its aryl groups as the carboxyl synthon.

We have recently achieved the efficient total synthesis of mugineic acid (**1**),[1] 3-epi-hydroxymugineic acid (**2**),[2] and distichonic acid A (**3**),[2] belonging to the phytosiderophores which are produced in higher plants as iron-chelating amino acids and promote uptake and transport of iron required for the chlorophyl biosynthesis.[3] The key feature of the synthesis has been the use of the phenyl group as the carboxyl synthon.[1b,1c,2,4,5]



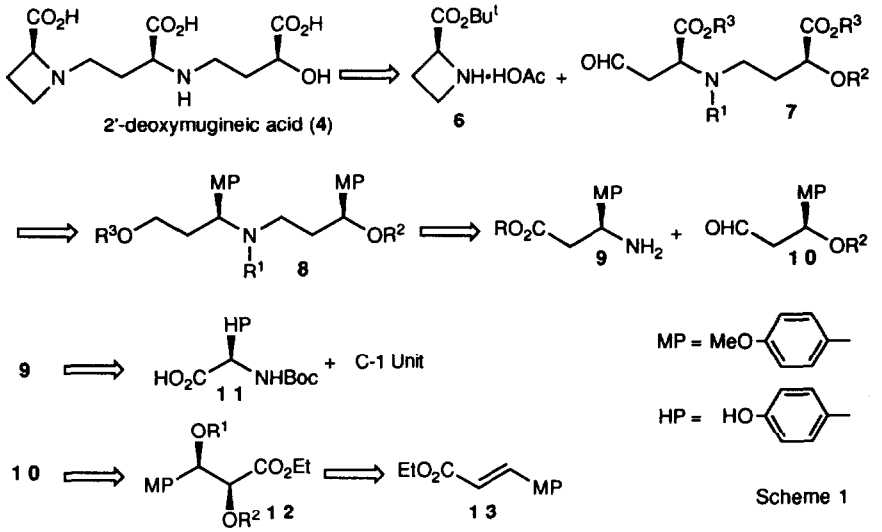
mugineic acid (**1**) : X = Z = OH, Y = H
3-epi-hydroxymugineic acid (**2**) : X = Y = Z = OH
2'-deoxymugineic acid (**4**) : X = Y = H, Z = OH
nicotianamine (**5**) : X = Y = H, Z = NH_2



distichonic acid A (**3**)

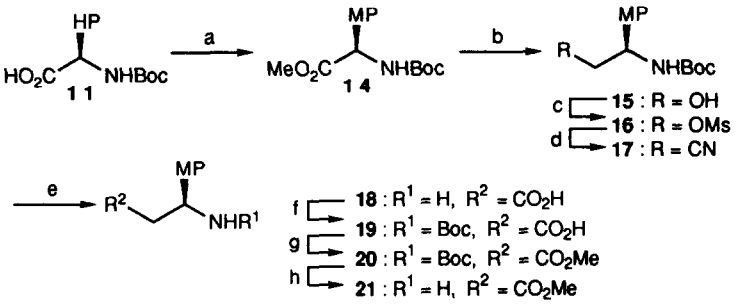
As an extension of the synthetic works on the phytosiderophores, we have now accomplished the total synthesis of 2'-deoxymugineic acid (**4**) and nicotianamine (**5**) by use of the p-methoxyphenyl group as the carboxyl synthon. The former phytosiderophore has been isolated from wheat (*Triticum aestivum* L.) [3,6] while the latter has been found in solanaceous plants, e.g. tobacco leaves (*Nicotiana tabacum*), and others.[3b,7,8]

Our retrosynthetic analysis for 2'-deoxymugineic acid (**4**) is illustrated in Scheme 1.[9] We thought that **4** would be prepared by coupling of tert-butyl azetidinecarboxylate (**6**) [1b,1c] with the aldehyde **7** obtained from **8** by the ruthenium catalyzed oxidation[10] of the p-methoxyphenyl(MP) group to the carboxyl one. The MP derivative **8** would be obtained by assembling the β-tyrosine derivative **9** and the aldehyde **10** which could be prepared from known tert-butoxycarbonyl(Boc)-p-hydroxyphenyl(HP)-glycine (**11**)[11] and ethyl p-methoxycinnamate (**13**),[12] respectively.



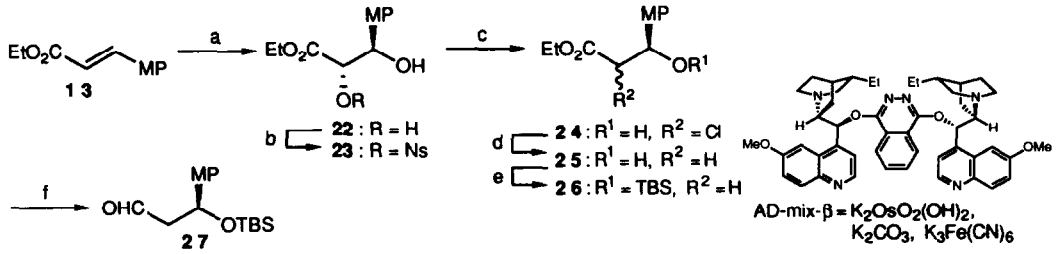
Scheme 1

First, we prepared the β-tyrosine derivative **21**,[13] the central fragment of 2'-deoxymugineic acid (**4**), utilizing our own method,[14] shown in Scheme 2. N-Boc-p-hydroxyphenylglycine (**11**) was methylated to give the MP ester **14**, which was efficiently converted to the cyanide **17** by successive treatment with lithium chloride-sodium borohydride, mesyl chloride, and potassium cyanide. Acidic hydrolysis of the cyanide **17**, followed by protection of the amino group with the Boc function and then the carboxyl group with the methyl ester function afforded the β-tyrosine derivative **20**, from which the Boc group was removed to give the required central fragment **21**. The overall yield of **21** was 57% from **11**.



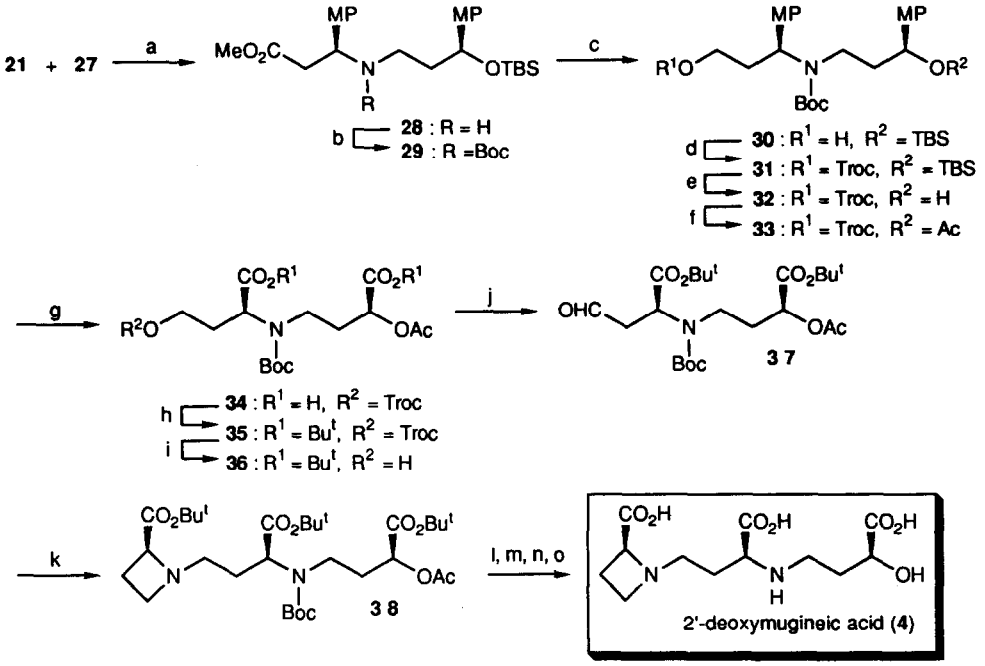
Scheme 2. (a) MeI, K_2CO_3, DMF, rt, 14 h. (b) LiCl, $NaBH_4$, THF, EtOH, rt, 16 h, 90% from **11**. (c) MsCl, Py, 0°C, 2 h, 94%. (d) KCN, 18-crown-6, DMSO, 50°C, 3 h, 83%. (e) conc. HCl, THF, 100°C, 12 h. (f) Boc_2O, 1N NaOH, THF, rt, 4 h. (g) MeI, K_2CO_3, DMF, rt, 11 h, 87% from **17**. (h) 10% HCl-MeOH, rt, 1 h, 94%.

Synthesis of the aldehyde **27**, the right fragment of **4**, started by catalytic dihydroxylation of ethyl p-methoxycinnamate (**13**) under the Sharpless conditions using AD-mix-β,[15] giving the diol **22** with more than 99%ee.[16] Removal of the C-2 hydroxyl group was performed in 3 steps (**22**→**25**): (1) transformation of the C-2 hydroxyl group to the p-nitrobenzenesulfonyl(Ns) one, (2) chlorination, and (3) transfer hydrogenation, as shown in Scheme 3. Protection of the C-3 hydroxyl group of the resulting mono alcohol **25** with tert-butyldimethylsilyl(TBS) chloride, followed by reduction of the ester group with diisobutylaluminum hydride (DIBAL) afforded the right fragment **27** in an overall yield of 50.5% from **13**.



Scheme 3. (a) AD-mix-β, $CH_3SO_2NH_2$, t-BuOH, H_2O, 4°C, 11 h→rt, 4 h, 92%, »99%ee. (b) NsCl, Py, 4°C, 18 h, 73%. (c) LiCl, DMF, 85°C, 14 h, 87%. (d) 5% Pd-C, HCO_2NH_4, MeOH, 0°C, 2 h, 91%. (e) TBSCl, imidazole, DMF, rt, 14 h, quant. (f) DIBAL, CH_2Cl_2, -78°C, 15 min, 95%.

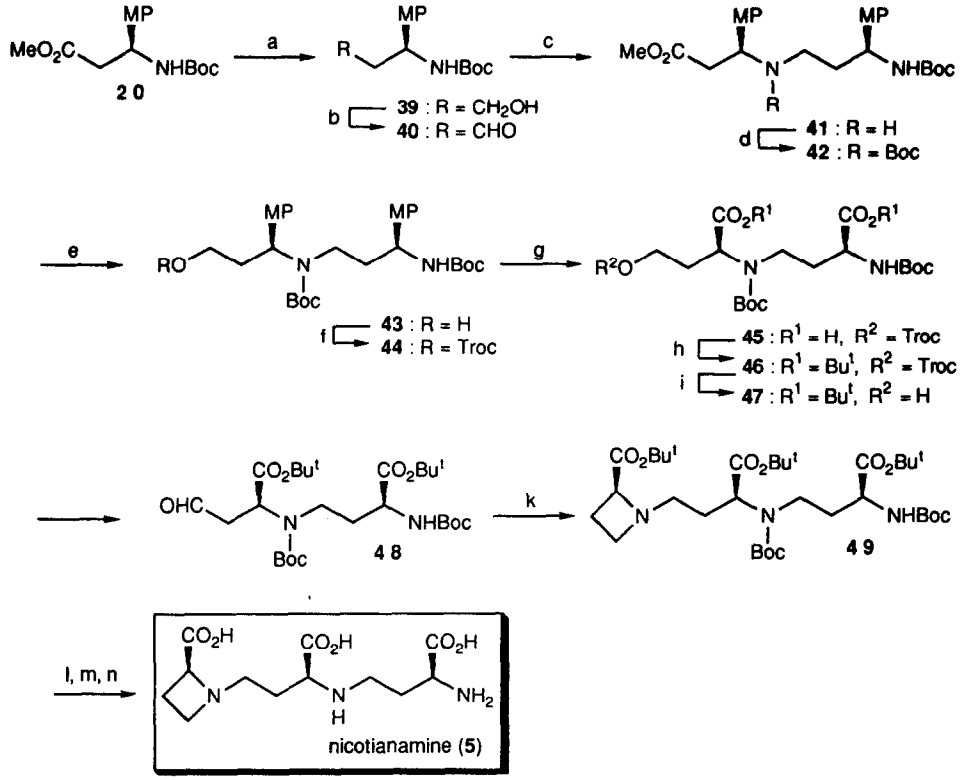
Assembling each fragment and the subsequent transformation to 2'-deoxymugineic acid (**4**) have been accomplished, as summarized in Scheme 4. Coupling of the amine **21** with the aldehyde **27** under the reductive N-alkylation conditions by use of sodium cyanoborohydride[1,2,9] afforded the di-MP derivative **28**, whose imino group was protected by the Boc function. Treatment of the resulting methyl ester **29** with lithium borohydride followed by 2,2,2-trichloroethoxycarbonyl(Troc) chloride afforded the TBS derivative **31**, whose TBS group was transformed to the acetyl one. Our previous work [2b] has already revealed that the electron-withdrawing group protecting the hydroxyl function more facilitates the ruthenium catalyzed oxidation. The



Scheme 4. (a) 1M $NaBH_3CN$ in THF, AcOH, MeOH, 0°C→10°C, 10 h, 74%. (b) Boc_2O, Et_3N (cat.), dioxane, 50°C, 14 h, quant. (c) 2M $LiBH_4$ in THF, Et_2O, THF, rt, 15 h. (d) TrocCl, DMAP, Py, rt, 20 h, 99% from **29**. (e) Ac_2O, TBAF, THF, rt, 3 h→50°C, 4 h→reflux, 11 h. (f) Ac_2O, Py, rt, 18 h, 94%. (g) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 5 h. (h) O-tert-butyl-N,N'-diisopropylisourea, t-BuOH, CH_2Cl_2, 50°C, 1 h, 61% from **33**. (i) Zn, AcOH, THF, rt, 3 h, 95%. (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C→0°C, 2 h, 94%. (k) **6**, 1M $NaBH_3CN$ in THF, MeOH, 0°C→7°C, 19 h, 88%. (l) 20% aqueous HCl, anisole, THF, rt, 24 h. (m) 1N NaOH, rt, 22 h. (n) Dowex 50W x 4 (H_2O then 15% aq. NH_3). (o) recrystallization from H_2O-EtOH, 89%.

acetyl derivative **33** thus obtained underwent the oxidation with ruthenium trichloride-sodium periodate followed by tert-butyl esterification, giving the amino acid derivative **35** in 61% yield. Removal of the Troc group followed by the Swern oxidation smoothly produced the aldehyde **37**, which underwent the reductive coupling with tert-butyl azetidinecarboxylate (**6**) to give the fully protected 2'-deoxymugineic acid **38**. Treatment of **38** under acidic and then alkaline conditions deprotected all of the protective groups to give 2'-deoxymugineic acid (**4**).

The same methodology as above was applied to the synthesis of nicotianamine (**5**)[17] having the 3"-amino function instead of the 3"-hydroxyl one in **4**, summarized in Scheme 5. The ester **20** was first converted to the aldehyde **40** through reduction with lithium borohydride followed by the Swern oxidation. Coupling of the aldehyde **40** with the amine **21** by use of sodium cyanoborohydride smoothly proceeded to give the imine **41**, which was converted to the Boc derivative **42**. Reduction of **42** followed by treatment with TrocCl afforded **44**, which underwent the ruthenium catalyzed oxidation and then the esterification to give the tert-butyl ester **46**. Although the difference of the oxidation substrates **33** and **44** was only the substituent at the C-3" position (**33**:AcO and **44**:BocNH), the efficiency of the oxidation of **44** was not high while the satisfactory result was obtained in the oxidation of **33**. Subsequent transformation of the tert-butyl ester **46** to nicotianamine (**5**) was analogously carried out as in the synthesis of **4**: (1) reductive removal of the Troc group, (2) the Swern oxidation, (3) attachment of the azetidine moiety, followed by (4) acidic removal of all the protective groups.



Scheme 5. (a) 2M $LiBH_4$ in THF, Et_2O, THF, rt, 11 h. (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C→0°C, 2 h, 97% from **20**. (c) **21**, 1M $NaBH_3CN$ in THF, AcOH, MeOH, 0°C→14°C, 15 h, 86%. (d) Boc_2O, dioxane, rt, 14 h, 94%. (e) 2M $LiBH_4$ in THF, Et_2O, rt, 13 h, 97%. (f) TrocCl, DMAP, Py, 0°C, 1 h→rt, 1 h, 98%. (g) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 8 h. (h) O-tert-butyl-N,N'-diisopropylisourea, t-BuOH, CH_2Cl_2, 40°C, 16 h, 35% from **44**. (i) Zn, AcOH, THF, rt, 2 h, 97%. (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C→0°C, 2 h, 94%. (k) **6**, 1M $NaBH_3CN$ in THF, MeOH, 4°C, 10 h, 93%. (l) 20% aqueous HCl, anisole, THF, rt, 36 h. (m) Dowex 50W x 4 (H_2O then 15% aq. NH_3), 94%.

Thus we could achieve the synthesis of 2'-deoxymugineic acid (**4**) and nicotianamine (**5**) utlizing the p-methoxyphenyl group as the carboxyl synthon. The methodology adopted here will have generality for the preparation of the other carboxylic acids.

Experimental

Melting points were determined on a YAMATO MP-21 apparatus or a YANAGIMOTO micro melting point apparatus. Infrared spectra were measured with a SHIMADZU FT IR-8100 spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on a JEOL 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-820MH or BW-200) was used for column chromatography.

(R)-2-tert-Butoxycarbonylamino-2-(4-methoxyphenyl)ethanol (15). To a stirred solution of **11**[11] (29.88 g, 0.11 M) in DMF (400 ml) at 0°C were added K_2CO_3 (37 g, 0.27 M) and MeI (16.7 ml, 0.27 M). After being stirred at room temperature for 14 h, the mixture was treated with Et_2O (1000 ml), washed with H_2O (500 ml x 2), 1M aq. $KHSO_4$ (500 ml x 2), and saturated brine (500 ml x 1), dried over Na_2SO_4, and concentrated in vacuo to give crude **14** (32.72 g, quant.) as a pale yellow oil. An analytical sample was purified by silica gel column chromatography (BW 200, hexane-Et_2O=3:2): $[\alpha]^{27}_D$ -97.4° (c 0.57, $CHCl_3$); IR ν_{max} (neat) 3380, 1748, 1710 cm^{-1}; ^{1}H NMR δ 1.43 (9H, s), 3.71 (3H, s), 3.80 (3H, s), 5.25 (1H, d, J=7.3 Hz), 5.47 (1H, br), 6.87 (2H, d, J=8.6 Hz), 7.28 (2H, d, J=8.3 Hz); Anal. calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.91; H, 7.13; N, 4.66.

To a stirred suspension of the above crude **14**, LiCl (9.5 g, 0.22 M), and $NaBH_4$ (8.5 g, 0.22 M) at 0°C was added dropwise EtOH (500 ml) over 50 min. After being stirred at room temperature for 16 h, the mixture was quenched under ice-cooling with 1M aq. $KHSO_4$ (200 ml) and concentrated in vacuo. The residue was treated with $CHCl_3$ and 1M aq. $KHSO_4$, and extracted with $CHCl_3$ (100 ml x 2). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from EtOH-EtOAc-hexane to give **15** (26.89 g, 90%) as colorless crystals: mp 130-132°C; $[\alpha]^{26}_D$ -38.1° (c 1.31, $CHCl_3$); IR ν_{max} (KBr) 3378, 1684 cm^{-1}; ^{1}H NMR δ 1.43 (9H, s), 2.28-2.36 (1H, br), 3.80 (3H, d, J=1.0 Hz), 3.82-3.85 (2H, m), 4.68-4.77 (1H, m), 5.06-5.16 (1H, br), 6.89 (2H, d, J=8.6 Hz), 7.22 (2H, d, J=8.6 Hz); Anal. calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.77; H, 7.87; N, 5.22.

(R)-2-tert-Butoxycarbonylamino-1-methanesulfonyloxy-2-(4-methoxyphenyl)ethane (16). To a stirred solution of **15** (1.05 g, 3.91 mM) in pyridine (5 ml) at 0°C was added MsCl (454 μl, 5.87 mM). After being stirred at 0°C for 2 h, the mixture was quenched with H_2O (2 ml), treated with Et_2O, washed with 1M aq. $KHSO_4$ (20 ml x 3), H_2O (20 ml x 1), and saturated brine (20 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 40 g, hexane-Et_2O=2:3→1:2) to give **16** (1.27 g, 94%) as a white solid. An analytical sample was recrystallized from EtOAc-Et_2O-hexane: mp 99-100°C; $[\alpha]^{23}_D$ -25.2° (c 0.44, $CHCl_3$); IR ν_{max} (KBr) 3380, 1682 cm^{-1}; ^{1}H NMR δ 1.43 (9H, s), 2.90 (3H, s), 3.80 (3H, s), 4.37 (1H, dd, J=5.9, 10.2 Hz), 4.44 (1H, dd, J=4.6, 10.2 Hz), 4.94-4.98 (1H, m), 5.06 (1H, br), 6.90 (2H, d, J=8.9 Hz), 7.24 (2H, d, J=8.6 Hz); Anal. calcd for $C_{15}H_{23}NO_6S$: C, 52.16; H, 6.71; N, 4.06. Found: C, 52.26; H, 6.57; N, 3.84.

(S)-2-tert-Butoxycarbonylamino-1-cyano-2-(4-methoxyphenyl)ethane (17). To a stirred solution of **16** (1.06 g, 3.07 mM) and 18-crown-6 (810 mg, 3.07 mM) in DMSO at 0°C was added KCN (1.00 g, 15.35 mM). The mixture was heated to 50°C and stirred for 3 h. After the mixture was treated with Et_2O, the ethereal solution was washed with H_2O (50 ml x 3) and saturated brine (50 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 50 g, hexane-Et_2O=3:2→5:4) to give **17** (707 mg, 83%) as a colorless solid. An analytical sample was recrystallized from Et_2O-hexane: mp 98-99°C; $[\alpha]^{23}_D$ -19.8° (c 0.78, $CHCl_3$); IR ν_{max} (KBr) 3368, 2249, 1682 cm^{-1}; ^{1}H NMR δ 1.45 (9H, s), 2.88 (1H, dd, J=4.8, 16.8 Hz), 2.98 (1H, dd, J=6.3, 16.8 Hz), 3.81 (3H, s), 4.90 (1H, dd, J=6.3, 11.1 Hz), 4.99 (1H, br), 6.92 (2H, d, J=8.9 Hz), 7.28 (2H, d, J=8.6 Hz);

Anal. calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.29; N, 10.14. Found: C, 65.16; H, 7.26; N, 10.18.

Methyl (S)-3-tert-butoxycarbonylamino-3-(4-methoxyphenyl)propionate (20). To a stirred solution of **17** (4.76 g, 17.2 mM) in THF (10 ml) at room temperature was added conc. HCl (100 ml). The mixture was heated to 100°C, stirred for 12 h, and concentrated in vacuo. The residue was purified by ion-exchange resin (Dowex 50W x 4, 100 ml, H_2O then 20% aq. pyridine) to give the amino acid **18** (3.7 g) as a colorless solid. The above crude amino acid **18** was dissolved in 1N NaOH (20 ml) and a solution of Boc_2O (4.5 g, 20.7 mM) in THF (20 ml) was added. After being stirred at room temperature for 4 h, the mixture was washed with Et_2O (10 ml x 3). The aqueous phase was acidified with 1M aq. $KHSO_4$, extracted with CH_2Cl_2 (50 ml x 3), dried over Na_2SO_4, and concentrated in vacuo to give crude **19** (4.75 g) as a white solid. K_2CO_3 (4.8 g, 34.5 mM) and MeI (2.15 ml, 34.5 mM) were added to a stirred solution of **19** in DMF (40 ml). After being stirred at room temperature for 11 h, the mixture was treated with Et_2O, washed with H_2O (100 ml x 2), 1M aq. $KHSO_4$ (100ml x 2), and saturated brine (100 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was recrystallized from Et_2O-hexane to give **20** (3.45 g). The filtrate was evaporated and the residue was purified by silica gel column chromatography (BW 820 MH, 40 g, hexane-Et_2O=1:1) to give **20** (1.20 g). The combined two crops were 4.65 g (87%) as a colorless solid: mp 90-91°C; $[\alpha]^{23}_D$ -38.9° (c 0.91, $CHCl_3$); IR ν_{max} (KBr) 3393, 1743, 1686 cm^{-1}; ^1H NMR δ 1.42 (9H, s), 2.78 (1H, dd, J=6.3, 15.2 Hz), 2.88 (1H, dd, J=5.9, 15.2 Hz), 3.61 (3H, s), 3.79 (3H, s), 5.05 (1H, br), 5.36 (1H, br), 6.86 (2H, d, J=8.9 Hz), 7.21 (2H, d, J=8.9 Hz); Anal. calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.82; H, 7.40; N, 4.59. [Lit.[13] data for the racemic **20**: mp 88-89°C (hexane-cyclohexane); ^1H NMR δ 1.45 (9H, s), 2.80 (2H, d, J=6 Hz), 3.60 (3H, s), 3.80 (3H, s), 5.00-5.30 (2H, m), 6.80-7.30 (4H, m).]

Methyl (S)-3-amino-3-(4-methoxyphenyl)propionate (21). The white solid **20** (7.41 g, 23.9 mM) was dissolved in 10% HCl-MeOH (60 ml). The mixture was stirred at room temperature for 1 h, and concentrated in vacuo. The residue was neutralized with saturated aq. $NaHCO_3$, and extracted with CH_2Cl_2 (50 ml x 3). The extracts were concentrated in vacuo to give **21** (4.68 g, 94%) as a pale yellow oil: IR ν_{max} (neat) 3368, 1738 cm^{-1}; ^1H NMR δ 2.64-2.77 (2H, br), 2.69 (2H, d, J=5.3 Hz), 3.66 (3H, s), 3.78 (3H, s), 4.39 (1H, t, J=6.8 Hz), 6.63 (2H, d, J=8.6 Hz), 7.29 (2H, d, J=8.9 Hz).

Ethyl (2S,3R)-2,3-dihydroxy-3-(4-methoxyphenyl)propionate (22). To a stirred suspension of AD-mix-β (17.84 g) and $CH_3SO_2NH_2$ (1.21 g, 12.74 mM) in t-BuOH (60 ml) and H_2O (60 ml) at 0°C was added **13** (2.63 g, 12.74 mM). After being stirred at 4°C for 11 h, the mixture was warmed to room temperature and stirred for 4 h. The mixture was quenched with $Na_2S_2O_3$ (20 g), concentrated in vacuo, and extracted with CH_2Cl_2 (100 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 820 MH, 150 g, hexane-EtOAc=3:2→2:3) to give **22** (2.83 g, 92%, »99%ee[16]) as a colorless solid. An analytical sample was recrystallized from EtOAc-hexane: 91-92°C; $[\alpha]^{23}_D$ -6.0° (c 0.84, $CHCl_3$); IR ν_{max} (KBr) 3453, 1732 cm^{-1}; ^1H NMR δ 1.26 (3H, t, J=7.3 Hz), 2.79 (1H, d, J=6.6 Hz), 3.19 (1H, d, J=5.9 Hz), 3.80 (3H, s), 4.25 (2H, q, J=7.3 Hz), 4.31 (1H, dd, J=3.3, 5.9 Hz), 4.94 (1H, dd, J=3.3, 6.6 Hz), 6.90 (2H, d, J=8.6 Hz), 7.33 (2H, d, J=8.6 Hz); Anal. calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.15; H, 6.62.

Ethyl (2S,3R)-3-hydroxy-3-(4-methoxyphenyl)-2-(4-nitrobenzenesulfonyloxy)-propionate (23). To a stirred solution of **22** (185 mg, 0.77 mM) in pyridine (2.5 ml) at 0°C was added NsCl (205 mg, 0.92 mM). After being stirred at 4°C for 18 h, the mixture was quenched with H_2O (1 ml), treated with Et_2O, washed with 1M aq. $KHSO_4$ (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 820 MH, 20 g, hexane-EtOAc=2.2:1→2:1) to give **23** (240 mg, 73%) as a yellow solid. An analytical sample was recrystallized from EtOAc-hexane: 123-123.5°C; $[\alpha]^{23}_D$ -49.4° (c 0.56, $CHCl_3$); IR ν_{max} (KBr) 3573, 1742 cm^{-1}; ^1H NMR δ 1.21 (3H, t, J=7.3 Hz), 2.41 (1H, d, J=5.3 Hz), 3.76 (3H, s), 4.19 (2H, q, J=7.3 Hz),

4.98 (1H, d, J=4.0 Hz), 5.18 (1H, d, J=4.6 Hz), 6.73 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.6 Hz), 7.85 (2H, d, J=8.9 Hz), 8.22 (2H, d, J=8.9 Hz); Anal. calcd for $C_{18}H_{19}NO_9S$: C, 50.82; H, 4.50; N, 3.29. Found: C, 50.79; H, 4.60; N, 3.05.

Ethyl (2RS,3R)-2-chloro-3-hydroxy-3-(4-methoxyphenyl)propionate (24). To a stirred solution of **23** (4.56 g, 10.7 mM) in DMF was added LiCl (910 mg, 21.4 mM). The mixture was heated to 85°C and stirred for 14 h. After the mixture was treated with Et_2O, the ethereal solution was washed with 1M aq. $KHSO_4$ (50 ml x 3) and saturated brine (50 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 150 g, hexane-Et_2O=3:1) to give **24** (2.41 g, 87%) as a colorless oil: IR ν_{max} (neat) 3496, 1743 cm^{-1}; ^1H NMR δ 1.15 (1.5H, t, J=7.3 Hz), 1.29 (1.5H, t, J=7.3 Hz), 2.88 (0.5H, d, J=3.6 Hz), 2.91 (0.5H, d, J=5.0 Hz), 4.11 (1H, q, J=7.3 Hz), 4.26 (1H, q, J=7.3 Hz), 4.35 (0.5H, d, J=7.9 Hz), 4.41 (0.5H, d, J=6.9 Hz), 5.01 (0.5H, dd, J=4.6, 7.9 Hz), 5.07 (0.5H, dd, J=3.3, 6.6 Hz), 6.89 (1H, d, J=8.9 Hz), 6.91 (1H, d, J=8.6 Hz), 7.31 (1H, d, J=8.9 Hz), 7.33 (1H, d, J=8.9 Hz). (The ratio of the epimers was 1:1); Anal. calcd for $C_{12}H_{15}ClO_4$: C, 55.71; H, 5.84. Found: C, 55.76; H, 5.85.

Ethyl (S)-3-hydroxy-3-(4-methoxyphenyl)propionate (25). To a stirred suspension of **24** (2.08 g, 8.02 mM) and 5% Pd-C (1.00 g) in MeOH (40 ml) at 0°C was added HCO_2NH_4 (2.53 g, 40.10 mM). After being stirred at 0°C for 2 h, the mixture was filtered through the pad of celite and concentrated in vacuo. The residue was treated with Et_2O, washed with saturated aq. $NaHCO_3$ (50 ml x 2), H_2O (50 ml x 1), and saturated brine (50 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 75 g, hexane-Et_2O=7:4→5:4) to give **25** (1.64 g, 91%) as a colorless oil: $[\alpha]^{25}_D$ -40.4° (c 1.06, $CHCl_3$); IR ν_{max} (neat) 3496, 1732 cm^{-1}; ^1H NMR δ 1.27 (3H, t, J=7.3 Hz), 2.67 (1H, dd, J=4.0, 16.5 Hz), 2.76 (1H, dd, J=8.9, 16.5 Hz), 3.15 (1H, br), 3.80 (3H, s), 4.18 (2H, q, J=7.3 Hz), 5.09 (1H, dd, J=4.0, 8.6 Hz), 6.89 (2H, d, J=8.6 Hz), 7.30 (2H, d, J=8.6 Hz); Anal. calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.24.

Ethyl (S)-3-tert-butyldimethylsiloxy-3-(4-methoxyphenyl)propionate (26). To a stirred solution of **25** (1.62 g, 7.23 mM) in DMF (10 ml) were added imidazole (983 mg, 14.46 mM) and TBSCl (1.63 g, 10.85 mM). After being stirred at room temperature for 14 h, the mixture was treated with Et_2O, washed with 1M aq. $KHSO_4$ (50 ml x 3) and saturated brine (50 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 80 g, hexane-Et_2O=14:1) to give **25** (2.44 g, 99.6%) as a colorless oil: $[\alpha]^{25}_D$ -60.1° (c 0.62, $CHCl_3$); IR ν_{max} (neat) 1738 cm^{-1}; ^1H NMR δ -0.19 (3H, s), 0.00 (3H, s), 0.83 (9H, s), 1.25 (3H, t, J=7.3 Hz), 2.51 (1H, dd, J=4.3, 14.5 Hz), 2.71 (1H, dd, J=9.2, 14.5 Hz), 3.80 (3H, s), 4.05-4.18 (2H, m), 5.10 (1H, dd, J=4.3, 8.9 Hz), 6.84 (2H, d, J=8.6 Hz), 7.26 (2H, d, J=8.6 Hz); Anal. calcd for $C_{18}H_{30}O_4Si$: C, 63.87; H, 8.93. Found: C, 63.87; H, 9.00.

(S)-2-tert-Butyldimethylsiloxy-2-(4-methoxyphenyl)-1-formylethane (27). To a stirred solution of **26** (2.44 g, 7.20 mM) in CH_2Cl_2 (19 ml) at -78°C was added 1.5M DIBAL in toluene (5.04 ml, 7.56 mM). The mixture was stirred for 15 minutes, quenched with 1M aq. $KHSO_4$, and warmed to room temperature. After being extracted with CH_2Cl_2 (30 ml x 3), the mixture was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 80 g, hexane-Et_2O=19:1→14:1) to give **27** (2.02 g, 95%) as a colorless oil: $[\alpha]^{25}_D$ -76.7° (c 0.40, $CHCl_3$); IR ν_{max} (neat) 1727 cm^{-1}; ^1H NMR δ -0.16 (3H, s), 0.03 (3H, s), 0.85 (9H, s), 2.60 (1H, ddd, J=2.0, 4.3, 15.5 Hz), 2.84 (1H, ddd, J=2.6, 8.2, 15.5 Hz), 3.81 (3H, s), 5.16 (1H, dd, J=4.3, 8.2 Hz), 6.86 (2H, d, J=8.9 Hz), 7.25 (2H, d, J=8.6 Hz), 9.78 (1H, t, J=2.5 Hz); Anal. calcd for $C_{16}H_{26}O_3Si$: C, 65.26; H, 8.91. Found: C, 65.46; H, 8.93.

Methyl (3S,3'S)-3-(3'-tert-butyldimethylsiloxy-3'-(4-methoxyphenyl)propylamino)-3-(4-methoxyphenyl)propionate (28). To a stirred solution of **21** (51 mg, 0.24 mM) and **27** (81 mg, 0.28 mM) in MeOH (1.2 ml) and AcOH (14 µl, 0.24 mM) at 0°C was added 1M $NaBH_3CN$ in THF (245 µl, 0.24 mM). The stirred mixture was warmed to 10°C over 10 h, then quenched with saturated aq. $NaHCO_3$, and extracted with $CHCl_3$ (20 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 820 MH, 11 g, hexane-EtOAc=4:1→3:1) to give **28** (88 mg, 74%) as a colorless oil: $[\alpha]^{23}_D$ -62.9° (c 2.33, $CHCl_3$); IR ν_{max} (neat) 3346, 1738 cm^{-1}; ^1H NMR δ -0.20 (3H, s), -0.05 (3H, s), 0.81 (9H, s), 1.54-1.89 (3H, m), 2.41-2.50 (2H, m), 2.58 (1H, dd, J=6.3, 15.3 Hz), 2.70 (1H, dd, J=7.9, 15.3 Hz), 3.62 (3H, s), 3.79 (6H, s), 3.98 (1H, dd, J=6.3, 7.9 Hz), 4.68 (1H, dd, J=5.0, 7.3 Hz), 6.81 (2H, d, J=8.6 Hz), 6.84 (2H, d, J=8.6 Hz), 7.16 (2H, d, J=8.9 Hz), 7.19 (2H, d, J=8.9 Hz); Anal. calcd for $C_{27}H_{41}NO_5Si$: C, 66.49; H, 8.47; N, 2.87. Found: C, 66.24; H, 8.36; N, 2.82.

Methyl (3S,3'S)-3-(N-tert-butoxycarbonyl-3'-tert-butyldimethylsiloxy-3'-(4-methoxyphenyl)propylamino)-3-(4-methoxyphenyl)propionate (29). To a stirred solution of **28** (334 mg, 0.69 mM) in dioxane (1.7 ml) at 0°C were added Boc_2O (300 mg, 1.37 mM) and Et_3N (1 drop, cat.). After being stirred at 50°C for 14 h, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 25 g, hexane-Et_2O=3:1) to give **29** (401 mg, 99.6%) as a colorless oil: $[\alpha]^{23}_D$ -74.9° (c 0.52, $CHCl_3$); IR ν_{max} (neat) 1744, 1694 cm^{-1}; ^1H NMR δ -0.23 (3H, s), -0.04 (3H, s), 0.85 (9H, s), 1.42 (9H, s), 1.65-1.78 (1H, m), 2.87-3.01 (4H, m), 3.62 (3H, s), 3.79 (3H, s), 3.80 (3H, s), 4.44-4.50 (1H, m), 5.49-5.68 (1H, m), 6.79 (2H, d, J=8.6 Hz), 6.81 (2H, d, J=8.9 Hz), 7.06 (2H, d, J=8.3 Hz), 7.13 (2H, d, J=8.6 Hz); Anal. calcd for $C_{32}H_{49}NO_7Si$: C, 65.39; H, 8.40; N, 2.38. Found: C, 65.34; H, 8.49; N, 2.33.

(3S,3'S)-3-(N-tert-butoxycarbonyl-3'-tert-butyldimethylsiloxy-3'-(4-methoxyphenyl)-propylamino)-3-(4-methoxyphenyl)-1-(2,2,2-trichloroethoxycarbonyloxy)propane (31). To a stirred solution of **29** (234 mg, 0.40 mM) in Et_2O (2 ml) and THF (0.5 ml) under an argon atomosphere at 0°C was added 2M $LiBH_4$ in THF (400 µl, 0.80 mM). After being stirred at room temperature for 15 h, the mixture was quenched with 1M aq. $KHSO_4$, and extracted with CH_2Cl_2 (20 ml x 3). The extracts were dried over Na_2SO_4, and concentrated in vacuo to give crude **30** (245 mg) as a colorless oil. An analytical sample was purified by silica gel column chromatography (BW 820 MH, hexane-EtOAc=3:1): $[\alpha]^{23}_D$ -71.4° (c 1.42, $CHCl_3$); IR ν_{max} (neat) 3453, 1688 cm^{-1}; ^1H NMR δ -0.26 (3H, s), -0.10 (3H, s), 0.81 (9H, s), 1.18-1.39 (1H, m), 1.44 (9H, s), 1.64-1.75 (1H, m), 1.81-2.07 (2H, m), 2.76 (2H, t, J=8.6 Hz), 3.44-3.53 (1H, m), 3.67-3.77 (2H, m), 3.79 (3H, s), 3.82 (3H, s), 4.29-4.33 (1H, m), 5.44-5.49 (1H, m), 6.78 (2H, d, J=8.6 Hz), 6.82 (2H, d, J=8.9 Hz), 6.98 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz); Anal. calcd for $C_{31}H_{49}NO_6Si$: C, 66.51; H, 8.82; N, 2.50. Found: C, 66.27; H, 8.74; N, 2.55.

The above crude alcohol **30** was dissolved in pyridine (1.5 ml), and DMAP (2.4 mg, 0.02 mM) and TrocCl (82 µl, 0.60 mM) were added. After being stirred at room temperature for 20 h, the mixture was quenched with H_2O (2ml), treated with Et_2O, washed with 1M aq. $KHSO_4$ (20 ml x 3) and saturated brine (20 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 25 g, hexane-Et_2O=3:1) to give **31** (289 mg, 99%) as a colorless oil: $[\alpha]^{23}_D$ -49.6° (c 1.18, $CHCl_3$); IR ν_{max} (neat) 1761, 1687 cm^{-1}; ^1H NMR δ -0.24 (3H, s), -0.05 (3H, s), 0.85 (9H, s), 1.43 (10H, s), 1.64-1.77 (1H, m), 2.24 (2H, dd, J=6.9, 14.2 Hz), 2.84-3.02 (2H, m), 3.79 (3H, s), 3.81 (3H, s), 4.17-4.31 (2H, m), 4.42 (1H, t, J=6.9 Hz), 4.74 (2H, ABq, J=11.9 Hz), 5.25-5.34 (1H, m), 6.79 (2H, d, J=8.9 Hz), 6.82 (2H, d, J=8.9 Hz), 7.03 (2H, d, J=8.9 Hz), 7.14 (2H, d, J=8.9 Hz).

(3S,3'S)-3-(N-tert-butoxycarbonyl-3'-hydroxy-3'-(4-methoxyphenyl)propylamino)-3-(4-methoxyphenyl)-1-(2,2,2-trichloroethoxycarbonyloxy)propane (32). To a stirred solution of **31** (159 mg, 0.22 mM) and Ac_2O (82 µl, 0.87 mM) in THF (1 ml) at room temperature was added TBAF (226

mg, 0.87 mM). After being stirred at room temperature for 3 h, at 50°C for 4 h, and then at 75°C for 11 h, the mixture was treated with Et_2O. The ethereal solution was washed with saturated aq. $NaHCO_3$ (20 ml x 1), H_2O (20 ml x 1), and saturated brine (20 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 10 g, hexane-EtOAc=3:1→2:1) to give **32** (134 mg, quant) as a colorless oil: $[\alpha]^{23}_D$ -74.9° (c 0.84, $CHCl_3$); IR ν_{max} (neat) 3453, 1761, 1687 cm^{-1}; ^1H NMR δ 1.13-1.43 (3H, m), 1.52 (9H, s), 2.31-2.39 (2H, m), 2.94-3.03 (1H, m), 3.51-3.65 (1H, m), 3.78 (3H, s), 3.81 (3H, s), 4.28-4.40 (3H, m), 4.74 (2H, ABq, J=11.9 Hz), 5.34 (1H, t, J=7.8 Hz), 6.81 (2H, d, J=8.3 Hz), 6.87 (2H, d, J=8.6 Hz), 7.08 (2H, d, J=8.6 Hz), 7.23 (2H, d, J=8.6 Hz); Anal. calcd for $C_{28}H_{36}Cl_3NO_8$: C, 54.16; H, 5.84; N, 2.26. Found: C, 53.85; H, 5.82; N, 2.09.

(3S,3'S)-3-(3'-acetoxy-N-tert-butoxycarbonyl-3'-(4-methoxyphenyl)propylamino)-3-(4-methoxyphenyl)-1-(2,2,2-trichloroethoxycarbonyloxy)propane (33). To a stirred solution of **32** (122 mg, 0.20 mM) in pyridine (0.4 ml) at room temperature was added Ac_2O (55 µl, 0.59 mM). After being stirred at room temperature for 18 h, the mixture was quenched with H_2O (1 ml). After the mixture was treated with Et_2O, the ethereal solution was washed with 1M aq. $KHSO_4$ (20 ml x 3) and saturated brine (20 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 10 g, hexane-Et_2O=2:1) to give **33** (123 mg, 94%) as a colorless oil: $[\alpha]^{23}_D$ -65.3° (c 0.77, $CHCl_3$); IR ν_{max} (neat) 1761, 1738, 1694 cm^{-1}; ^1H NMR δ 1.47 (9H, s), 1.55-1.70 (1H, m), 1.80-1.93 (1H, m), 2.00 (3H, s), 2.20-2.29 (2H, m), 2.90 (2H, brs), 3.79 (3H, s), 3.82 (3H, s), 4.24-4.29 (2H, m), 4.74 (2H, ABq, J=11.9 Hz), 5.30 (1H, br), 5.48 (1H, dd, J=5.9, 7.6 Hz), 6.83 (2H, d, J=8.6 Hz), 6.85 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz); Anal. calcd for $C_{30}H_{38}Cl_3NO_9$: C, 54.35; H, 5.78; N, 2.11. Found: C, 54.62; H, 5.88; N, 2.26.

tert-Butyl (2S,3'S)-2-(3'-acetoxy-N-tert-butoxycarbonyl-3'-tert-butoxycarbonylpropylamino)-4-(2,2,2-trichloroethoxycarbonyloxy)butanoate (35). To a stirred solution of **33** (128 mg, 0.19 mM) in EtOAc (0.5 ml), CH_3CN (0.5 ml), and H_2O (17 ml) were added $NaIO_4$ (4.13 g, 19.30 mM) and $RuCl_3$ (2.2 mg, 9.65 µM). After being stirred at room temperature for 5 h, the mixture was extracted with EtOAc (30 ml x 3). The extracts were dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in Et_2O, and filtered through the pad of celite. The filtrate was concentrated in vacuo to give the crude carboxylic acid **34** (90 mg) as a pale red oil. The crude product **34** was dissolved in a mixture of CH_2Cl_2 (0.5 ml) and t-BuOH (0.5 ml), followed by treatment with O-tert-butyl-N,N'-diisopropylisourea (460 µl, 1.93 mM). After being stirred at 50°C for 1 h, the mixture was filtered through the pad of silica gel (BW 820 MH, 10g, hexane-Et_2O) and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 10 g, hexane-Et_2O=3:1) to give **35** (76 mg, 61%) as a colorless oil: $[\alpha]^{24}_D$ -43.2° (c 0.66, $CHCl_3$); IR ν_{max} (neat) 1759, 1705, 1699 cm^{-1}; ^1H NMR δ 1.47 (27H, s), 2.02-2.27 (3H, m), 2.14 (3H, s), 2.41-2.54 (1H, m), 3.05-3.15 (1H, m), 3.40-3.66 (1H, m), 3.77-3.94 (1H, m), 4.19-4.28 (1H, m), 4.31-4.42 (1H, m), 4.78 (2H, s), 4.92 (1H, dd, J=3.3, 9.2 Hz); Anal. calcd for $C_{26}H_{42}Cl_3NO_{11}$: C, 47.97; H, 6.50; N, 2.15. Found: C, 47.80; H, 6.40; N, 1.94.

tert-Butyl (2S,3'S)-2-(3'-acetoxy-N-tert-butoxycarbonyl-3'-tert-butoxycarbonylpropylamino)-4-hydroxybutanoate (36). To a stirred solution of **35** (256 mg, 0.39 mM) in AcOH (450 µl, 7.87 mM) and THF (6 ml) at room temperature was added Zn powder (750 mg). After being stirred at room temperature for 3 h, the mixture was neutralized with pyridine (640 µl, 7.87 mM) and filtered through the pad of celite. The filtrate was treated with Et_2O, washed with H_2O (20 ml x 1), saturated aq. $NaHCO_3$ (20 ml x 1), 1M aq. $KHSO_4$ (20 ml x 1), and saturated brine (20 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 12 g, hexane-EtOAc=5:2→3:2) to give **36** (178 mg, 95%) as a colorless oil: $[\alpha]^{24}_D$ -43.5° (c 0.10, $CHCl_3$); IR ν_{max} (neat) 3496, 1738, 1734, 1700 cm^{-1}; ^1H NMR δ 1.47 (27H, s), 1.88-2.29 (4.5H, m), 2.13 (3H, s), 2.49-2.53 (0.5H, m), 3.19-3.51 (2H, m), 3.52-3.80 (2H, m), 3.86-3.95 (0.5H, m), 4.33-4.38 (0.5H, m), 4.87-4.91

(1H, m). (Two rotamers were detected); Anal. calcd for $C_{23}H_{41}NO_9$: C, 58.09; H, 8.69; N, 2.95. Found: C, 57.93; H, 8.61; N, 2.87.

tert-Butyl (2S,3'S)-2-(3'-acetoxy-N-tert-butoxycarbonyl-3'-tert-butoxycarbonylpropylamino)-4-oxobutanoate (37). To a stirred solution of $(COCl)_2$ (47 μl, 0.54 mM) in CH_2Cl_2 (0.5 ml) under an argon atomosphere at -78°C was added a solution of DMSO (50 μl, 0.72 mM) in CH_2Cl_2 (0.5 ml). After the mixture was stirred for 10 min, a solution of **36** (171 mg, 0.36 mM) in CH_2Cl_2 (2 ml) and Et_3N (151 μl, 1.08 mM) were added. The mixture was allowed to warm to 0°C and stirred for 2 h. After being quenched with H_2O, the mixture was extracted with CH_2Cl_2 (20 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, 12 g, hexane-Et_2O=5:3) to give **37** (160 mg, 94%) as a colorless oil: $[\alpha]^{24}_D$ -66.1° (c 0.24, $CHCl_3$); IR ν_{max} (neat) 1742, 1700 cm^{-1}; ^1H NMR δ 1.45, 1.47 (27H, each s), 1.99-2.00 (2H, m), 2.15 (3H, s), 2.73-2.96 (1H, m), 3.23-3.50 (3H, m), 4.20-4.30 (1H, m), 4.92 (1H, dd, J=3.8, 9.1 Hz), 9.82 (1H, s); Anal. calcd for $C_{23}H_{39}NO_9$: C, 58.34; H, 8.30; N, 2.96. Found: C, 58.70; H, 8.20; N, 2.97.

tert-Butyl (2S,3'S,3"S)-3'-(3"-acetoxy-N-tert-butoxycarbonyl-3"-tert-butoxycarbonylpropylamino)-3'-tert-butoxycarbonylpropyl-2-azetidinecarboxylate (38). To a stirred solution of **6** (106 mg, 0.49 mM) and **37** (154 mg, 0.33 mM) in MeOH (1.2 ml) at 0°C was added 1M $NaBH_3CN$ in THF (325 μl, 0.33 mM). The stirred mixture was warmed to 7°C over 19 h, then quenched with saturated aq. $NaHCO_3$, 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, 10 g, hexane-EtOAc-benzene=6:2:1) to give **38** (176 mg, 88%) as a colorless oil: $[\alpha]^{24}_D$ -86.2° (c 0.17, $CHCl_3$); IR ν_{max} (neat) 1738, 1732, 1700 cm^{-1}; ^1H NMR δ 1.45, 1.47 (36H, each s), 1.81-1.90 (1H, m), 1.92-2.30 (5H, m), 2.13 (3H, s), 2.34-2.42 (1H, m), 2.65-2.79 (2H, m), 3.14-3.25 (1H, m), 3.33-3.38 (1H, m), 3.49 (1H, t, J=8.4 Hz), 3.55-3.60 (0.5H, m), 3.66-3.76 (0.5H, m), 3.81-3.88 (0.5H, m), 3.94-3.99 (0.5H, m), 4.93 (1H, dd, J=3.5, 9.7 Hz); Anal. calcd for $C_{31}H_{54}N_2O_{10}$: C, 60.57; H, 8.85; N, 4.56. Found: C, 60.34; H, 8.63; N, 4.49.

2'-Deoxymugineic acid (4) To a stirred solution of **38** (59 mg, 0.096 mM) in THF (0.1 ml) and anisole (0.1 ml) at room temperature was added 20% aq. HCl (2 ml). After being stirred at room temperature for 24 h, the mixture was washed with Et_2O (5 ml x 3) and concentrated in vacuo. The residue was dissolved in 1N NaOH (1.2 ml) and stirred for 22 h. After being acidified to about pH 7, the mixture was purified by ion-exchange resin (Dowex 50W x 4, 20 ml, H_2O then 15% aq. NH_3) to give crude **4** (32 mg). Recrystallization of **4** from aqueous EtOH afforded pure **4** (26 mg, 89%) as a white solid: mp 200-202°C; $[\alpha]^{24}_D$ -62.3° (c 0.31, H_2O); ^1H NMR (D_2O, TMSP, pH 7.6, HMG of HOD, at 50°C) δ 1.95-2.26 (4H, m), 2.53 (1H, ddd, J=9.2, 12.2, 18.5 Hz), 2.69-2.82 (1H, m), 3.15-3.27 (2H, m), 3.32-3.52 (2H, m), 3.76 (1H, dd, J=4.6, 8.6 Hz), 3.95 (1H, q, J=9.7 Hz), 4.10 (1H, dt, J=4.6, 9.6 Hz), 4.14 (1H, dd, J=4.6, 7.3 Hz), 4.72 (1H, t, J=9.6 Hz); FABMS m/z: 305 (M+1). [lit.[6,9] mp 198.4-200.5°C; $[\alpha]_D$ -70.5° (H_2O); ^1H NMR δ 2.17 (4H, m), 2.62 (2H, m), 3.27 (2H, t, J=7.5 Hz), 3.45 (2H, m), 3.84 (1H, dd, J=6, 8 Hz), 4.04 (2H, m), 4.36 (1H, dd, J=5, 7.5 Hz), 4.75 (1H, t, J=9.5 Hz).]

(S)-3-tert-Butoxycarbonylamino-3-(4-methoxyphenyl)-1-oxopropane (40). To a stirred solution of **20** (693 mg, 2.45 mM) in Et_2O (5 ml) and THF (2 ml) under an argon atomosphere at 0°C was added 2M $LiBH_4$ in THF (1.84 ml, 3.68 mM). After being stirred at room temperature for 11 h, the mixture was quenched with 1M aq. $KHSO_4$, and extracted with CH_2Cl_2 (50 ml x 3). The extracts were dried over Na_2SO_4, and concentrated in vacuo to give the crude alcohol **39** (693 mg) as a white solid: IR ν_{max} (neat) 3384, 1682 cm^{-1}; ^1H NMR δ 1.44 (9H, s), 1.49-1.68 (1H, br), 1.76-1.86 (1H, m), 2.00-2.08 (1H, m), 3.69 (2H, dd, J=3.6, 7.6 Hz), 3.80 (3H, s), 4.81-4.90 (2H, m), 6.88 (2H, d, J=8.9 Hz), 7.22 (2H, d, J=8.6 Hz).

To a stirred solution of $(COCl)_2$ (320 μl, 3.68 mM) in CH_2Cl_2 (5 ml) under argon atomosphere at -78°C was added a solution of DMSO (350 μl, 4.91 mM) in CH_2Cl_2 (1 ml). After the mixture was stirred for 10

min, a solution of **39** (693 mg) in CH_2Cl_2 (11 ml) and Et_3N (1.03 ml, 7.36 mM) were added. The mixture was allowed to warm to 0°C and stirred for 2 h. After being quenched with H_2O, the mixture was extracted with CH_2Cl_2 (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 820 MH, 30 g, hexane-Et_2O=1:1→1:2) to give **40** (607 mg, 97%) as a white solid. An analytical sample was recrystallized from Et_2O-hexane: mp 105-107°C; $[\alpha]^{23}_D$ -34.7° (c 0.49, $CHCl_3$); IR ν_{max} (KBr) 3370, 1725, 1689 cm^{-1}; ^1H NMR δ 1.42 (9H, s), 2.88 (1H, ddd, J=1.3, 6.3, 16.5 Hz), 2.99 (1H, ddd, J=2.1, 7.1, 16.5 Hz), 3.79 (3H, s), 5.02 (1H, brd, J=4.6 Hz), 5.12-5.16 (1H, m), 6.87 (2H, d, J=8.9 Hz), 7.23 (2H, d, J=8.9 Hz), 9.74 (1H, t, J=2.0 Hz); Anal. calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.20; H, 7.49; N, 4.85.

Methyl (3S,3'S)-3-(3'-tert-butoxycarbonylamino-3'-(4-methoxyphenyl)propylamino)-3-(4-methoxyphenyl)propionate (41). To a stirred solution of **21** (100 mg, 0.48 mM) and **40** (96 mg, 0.34 mM) in MeOH (1.2 ml) and AcOH (30 μl, 0.52 mM) at 0°C was added 1M $NaBH_3CN$ in THF (345 μl, 0.35 mM). The stirred mixture was warmed to 14°C over 15 h, then quenched with saturated aq. $NaHCO_3$, and extracted with $CHCl_3$ (20 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 , 20 g, hexane-EtOAc=5:4→1:1) to give **41** (140 mg, 86%) as a colorless oil: $[\alpha]^{23}_D$ -47.9° (c 1.57, $CHCl_3$); IR ν_{max} (neat) 3343, 1734, 1697 cm^{-1}; ^1H NMR δ 1.42 (9H, s), 1.75 (2H, br), 1.81-1.91 (1H, m), 2.41-2.46 (2H, m), 2.59 (1H, dd, J=5.6, 15.8 Hz), 2.72 (1H, dd, J=8.4, 15.8 Hz), 3.65 (3H, s), 3.76 (3H, s), 3.81 (3H, s), 3.93 (1H, dd, J=5.6, 8.3 Hz), 4.67 (1H, brd, J=1.0 Hz), 5.91 (1H, d, J=7.3 Hz), 6.76 (2H, d, J=8.6 Hz), 6.86 (2H, d, J=8.6 Hz), 7.02 (2H, d, J=8.6 Hz), 7.21 (2H, d, J=8.9 Hz).

Methyl (3S,3'S)-3-(N-tert-butoxycarbonyl-3'-tert-butoxycarbonylamino-3'-(4-methoxyphenyl)propylamino)-3-(4-methoxyphenyl)propionate (42). To a stirred solution of **41** (82 mg, 0.17 mM) in dioxane (0.3 ml) at room temperature was added Boc_2O (42 mg, 0.19 mM). After being stirred at room temperature for 14 h, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 11 g, hexane-Et_2O=5:4) to give **42** (93 mg, 94%) as a colorless oil: $[\alpha]^{23}_D$ -65.4° (c 0.43, $CHCl_3$); IR ν_{max} (neat) 3368, 1740, 1692 cm^{-1}; ^1H NMR δ 1.40 (10H, s), 1.46 (9H, s), 1.85 (1H, br), 2.87 (2H, d, J=7.9 Hz), 2.98 (2H, m), 3.63 (3H, s), 3.78 (3H, s), 3.81 (3H, s), 4.36 (2H, br), 5.64 (1H, br), 6.82 (2H, d, J=8.9 Hz), 6.86 (2H, d, J=8.6 Hz), 7.05 (2H, d, J=6.3 Hz), 7.16 (2H, d, J=8.3 Hz); Anal. calcd for $C_{31}H_{44}N_2O_8$: C, 65.02; H, 7.74; N, 4.89. Found: C, 65.30; H, 7.63; N, 4.99.

(3S,3'S)-3-(N-tert-Butoxycarbonyl-3'-tert-butoxycarbonylamino-3'-(4-methoxyphenyl)propylamino)-3-(4-methoxyphenyl)-1-propanol (43). To a stirred solution of **42** (149 mg, 0.26 mM) in Et_2O (2 ml) under an argon atomosphere at 0°C was added 2M $LiBH_4$ in THF (195 μl, 0.39 mM). After being stirred at room temperature for 13 h, the mixture was quenched with 1M aq. $KHSO_4$, and extracted with CH_2Cl_2 (20 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 820 MH, 11 g, hexane-EtOAc=2:1→1:1) to give **43** (137 mg, 97%) as a colorless oil: $[\alpha]^{23}_D$ -59.8° (c 0.17, $CHCl_3$); IR ν_{max} (neat) 3301, 1682, 1661 cm^{-1}; ^1H NMR δ 1.05 (1H, br), 1.41 (9H, s), 1.49 (9H, s), 1.72-2.02 (3H, m), 2.75 (1H, m), 2.94 (1H, m), 3.46-3.51 (1H, m), 3.70 (2H, br), 3.78 (3H, s), 3.83 (3H, s), 4.25 (2H, br), 5.49 (1H, brd, J=10.2 Hz), 6.80 (2H, d, J=8.6 Hz), 6.89 (2H, d, J=8.6 Hz), 6.96 (2H, d, J=8.3 Hz), 7.22 (2H, d, J=9.2 Hz); Anal. calcd for $C_{30}H_{44}N_2O_7$: C, 66.15; H, 8.14; N, 5.14. Found: C, 65.72; H, 7.79; N, 5.29.

(3S,3'S)-3-(N-tert-Butoxycarbonyl-3'-tert-butoxycarbonylamino-3'-(4-methoxyphenyl)propylamino)-3-(4-methoxyphenyl)-1-(2,2,2-trichloroethoxycarbonyloxy)propane (44). The alcohol **43** (556 mg, 1.02 mM) was dissolved in pyridine (2.5 ml) at 0°C, and DMAP (6 mg, 0.051 mM) and TrocCl (170 μl, 1.23 mM) were added. After being stirred at 0°C for 1 h, TrocCl (42 μl, 0.31

mM) was added to the mixture. The mixture was stirred for 1 h, quenched with H_2O (1 ml), treated with Et_2O, washed with 1M aq. $KHSO_4$ (20 ml x 3), H_2O (20 ml x 1), and saturated brine (20 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 40 g, hexane-Et_2O=3:2→1:1) to give **44** (719 mg, 98%) as a colorless solid. An analytical sample was recrystallized from Et_2O-hexane: mp 108-110°C; $[\alpha]^{23}_D$ -53.4° (c 0.81, $CHCl_3$); IR ν_{max} (neat) 3411, 1757, 1694, 1678 cm^{-1}; ^1H NMR δ 1.40 (10H, s), 1.48 (9H, s), 1.83 (1H, br), 2.24-2.26 (2H, m), 2.97 (2H, m), 3.78 (3H, s), 3.82 (3H, s), 4.26 (4H, br), 4.75 (2H, ABq, J=11.9 Hz), 5.34 (1H, br), 6.81 (2H, d, J=8.9 Hz), 6.88 (2H, d, J=8.9 Hz), 7.03 (2H, d, J=7.2 Hz), 7.18 (2H, d, J=8.3 Hz); Anal. calcd for $C_{33}H_{45}Cl_3N_2O_9$: C, 55.04; H, 6.30; N, 3.89. Found: C, 55.01; H, 6.31; N, 3.83.

tert-Butyl (2S,3'S)-2-(N-tert-butoxycarbonyl-3'-tert-butoxycarbonyl-3'-tert-butoxycarbonylaminopropylamino)-4-(2,2,2-trichloroethoxycarbonyloxy)butanoate (46). To a stirred solution of **44** (2.84 g, 3.94 mM) in EtOAc (11 ml), CH_3CN (11 ml), and H_2O (340 ml) were added $NaIO_4$ (84.3 g, 394.15 mM) and $RuCl_3$ (44 mg, 0.20 mM). After being stirred at room temperature for 8 h, the mixture was extracted with EtOAc (100 ml x 3). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in Et_2O, and the mixture was filtered through the pad of celite, and concentrated in vacuo to give the crude carboxylic acid **45** (1.23 g) as a red oil. The crude product **45** was dissolved in a mixture of CH_2Cl_2 (10 ml) and t-BuOH (10 ml) followed by treatment with O-tert-butyl-N,N'-diisopropylisourea (9.4 ml, 39.41 mM). After being stirred at 40°C for 16 h, the mixture was filtered through the pad of SiO_2 (BW 820 MH, 50g, hexane-Et_2O) and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 100 g, hexane-Et_2O=2.5:1→2:1) to give **46** (980 mg, 35%) as a colorless oil: $[\alpha]^{24}_D$ -22.4° (c 0.75, $CHCl_3$); IR ν_{max} (neat) 3389, 1767, 1738, 1732, 1715, 1705 cm^{-1}; ^1H NMR δ 1.43, 1.46 (36H, each s), 1.78-1.92 (1H, m), 2.05-2.27 (2H, m), 2.37-2.50 (1H, m), 2.94-3.11 (1H, m), 3.34-3.66 (1H, m), 3.87-4.14 (2H, m), 4.18-4.38 (2H, m), 4.78 (2H, s), 5.00-5.13 (1H, m).

tert-Butyl (2S,3'S)-2-(N-tert-butoxycarbonyl-3'-tert-butoxycarbonyl-3'-tert-butoxycarbonylaminopropylamino)-4-hydroxybutanoate (47). To a stirred solution of **46** (70 mg, 0.099 mM) in AcOH (283 μl, 4.95 mM) and THF (1.5 ml) at room temperature was added Zn powder (200 mg). After being stirred at room temperature for 6 h, Zn powder (200 mg) was added to the mixture, which was stirred for 2 h, and neutralized with pyridine (400 μl, 4.95 mM). The mixture was filtered through the pad of celite, treated with EtOAc, washed with H_2O (20 ml x 1), 1M aq. $KHSO_4$ (20 ml x 2), saturated aq. $NaHCO_3$ (20 ml x 2), and saturated brine (20 ml x 1), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 7 g, hexane-EtOAc=3:1) to give **47** (51 mg, 97%) as a colorless oil: $[\alpha]^{24}_D$ -12.2° (c 1.11, $CHCl_3$); IR ν_{max} (neat) 3492, 1738, 1732, 1717, 1700 cm^{-1}; ^1H NMR δ 1.44, 1.46, 1.47, 1.48 (36H, each s), 1.81-1.99 (2H, m), 2.04-2.29 (2H, m), 2.68-2.72 (1H, br), 3.10-3.19 (2H, m), 3.44-3.59 (1H, m), 3.63-3.79 (1H, m), 3.98-4.16 (1H, m), 4.47-4.53 (1H, m), 5.05-5.17 (1H, m); Anal. calcd for $C_{26}H_{48}N_2O_9$: C, 58.63; H, 9.08; N, 5.25. Found: C, 58.49; H, 9.15; N, 4.94.

tert-Butyl (2S,3'S)-2-(N-tert-butoxycarbonyl-3'-tert-butoxycarbonyl-3'-tert-butoxycarbonylaminopropylamino)-4-oxobutanoate (48). To a stirred solution of $(COCl)_2$ (74 μl, 0.85 mM) in CH_2Cl_2 (1 ml) under an argon atomosphere at -78°C was added a solution of DMSO (80 μl, 1.13 mM) in CH_2Cl_2 (0.5 ml). After the mixture was stirred for 10 min, a solution of **47** (302 mg, 0.57 mM) in CH_2Cl_2 (2 ml) and Et_3N (237 μl, 1.70 mM) were added. The mixture was allowed to warm to 0°C and stirred for 2 h. After being quenched with H_2O, the mixture was extracted with CH_2Cl_2 (20 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 820 MH, 20 g, hexane-Et_2O=5:4) to give **48** (283 mg, 94%) as a colorless oil: $[\alpha]^{24}_D$ -24.4° (c 0.96, $CHCl_3$); IR ν_{max} (neat) 3389, 1738, 1732, 1717, 1684 cm^{-1}; ^1H NMR δ 1.44, 1.46, 1.48 (36H, each s), 1.76-1.86 (1H, m), 2.09-2.19 (1H, m), 2.73-2.96 (1H, m), 3.21-3.30 (1H, m), 3.40 (1H, dd, J=6.3, 18.1 Hz), 3.47-3.62 (1H,

m), 4.11-4.20 (1H, m), 4.28-4.37 (1H, m), 5.03-5.13 (1H, m), 9.80 (1H, s); Anal. calcd for $C_{26}H_{46}N_2O_9$: C, 58.85; H, 8.74; N, 5.28. Found: C, 58.53; H, 8.53; N, 5.03.

tert-Butyl (2S,3'S,3"S)-3'-(N-tert-butoxycarbonyl-3"-tert-butoxycarbonyl-3"-tert-butoxycarbonylaminopropylamino-3'-tert-butoxycarbonylpropyl)-2-azetidinecarboxylate (49). To a stirred solution of **6** (147 mg, 0.686 mM) and **48** (239 mg, 0.45 mM) in MeOH (2 ml) at 0°C was added 1M $NaBH_3CN$ in THF (450 µl, 0.45 mM). After being stirred at 4°C for 10 h, the mixture was quenched with saturated aq. $NaHCO_3$, and extracted with $CHCl_3$ (50 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=4:1→2:1) to give **49** (281 mg, 93%) as a colorless oil: $[\alpha]^{24}_D$ -55.5° (c 0.37, $CHCl_3$); IR ν_{max} (neat) 3391, 1748, 1734, 1717, 1700 , 1684 cm^{-1}; ^1H NMR δ 1.43, 1.47 (36H, each s), 1.81-1.91 (2H, m), 2.01-2.41 (4H, m), 2.63-2.78 (2H, m), 3.13-3.68 (5H, m), 3.88-4.16 (2H, m), 5.29-5.39 (1H, m); Anal. calcd for $C_{34}H_{61}N_3O_{10}$: C, 60.78; H, 9.15; N, 6.25. Found: C, 60.47; H, 9.05; N, 5.96.

Nicotianamine (5) To a stirred solution of **49** (61 mg, 0.091 mM) in THF (0.1 ml) and anisole (0.1 ml) at room temperature was added 20% aq. HCl (2 ml). After being stirred at room temperature for 36 h, the mixture was washed with Et_2O (5 ml x 3) and concentrated in vacuo. The residue was purified by ion-exchange resin (Dowex 50W x 4, 10 ml, H_2O then 15% aq. NH_3) to give **5** (26 mg, 94%) as a white solid: mp »240°C; $[\alpha]^{24}_D$ -51.7° (c 0.37, H_2O); ^1H NMR (D_2O, TMSP, pH=6.3, HMG of HOD) δ 2.05-2.34 (4H, m), 2.47-2.61 (1H, m), 2.68-2.81 (1H, m), 3.24-3.29 (2H, m), 3.35-3.46 (2H, m), 3.80 (1H, dd, J=4.6, 8.3 Hz), 3.89 (1H, dd, J=5.9, 7.3 Hz), 3.99 (1H, t, J=9.6 Hz), 4.10 (1H, dt, J=4.5, 9.8 Hz), 4.78 (1H, t, J=9.6 Hz); FABMS m/z: 304 (M+1). [lit.[1e,f] mp »240°C; $[\alpha]^{23}_D$ -60.5° (c 2.7, H_2O); ^1H NMR δ 2.22 (4H, m), 2.62 (2H, m), 3.27 (2H, t, J=7.5 Hz), 3.41 (2H, m), 3.80 (1H, dd, J=6. 8 Hz), 3.89 (1H, dd, J=4, 7.5 Hz), 4.02 (2H, m), 4.76 (1H, t, J=9.5 Hz).]

Acknowledgements Our works have been supported in part by the Japan Research Foundation for Optically Active Compounds, the Japan Science Foundation, Ministry of Education, Science and Culture, Japan, to which our thanks are due. We thank Dr. K. Nomoto of Suntory Institute for Bioorganic Research for the sample of 2'-deoxymugineic acid (**4**), spectra of **4**, and nicotianamine (**5**). F. M. gratefully acknowledges the postgraduate fellowship from the Japan Society for the Promotion of Science.

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16. The enatiomeric excess of **22** was determined by HPLC analysis (Sumichiral OA-4100, hexane-dichloroethane-EtOH = 100 : 19 : 1).
17. For the former synthesis of **5**, see (a) Ripperger, H.; Faust, J.; Scholz, G. *Phytochemistry* **1982**, *21*, 1786. (b) Fushiya, S.; Nakatsuyama, S.; Sato, Y.; Nozoe, S. *Heterocycles* **1981**, *15*, 819.

(*Received in UK* 9 *May* 1994; *accepted* 17 *June* 1994)