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Total Synthesis of Mugineic Acid. Efficient Use of the Phenyl Group as the Carboxyl Synthon†

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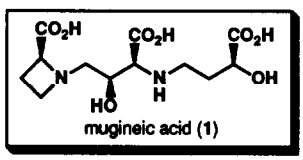
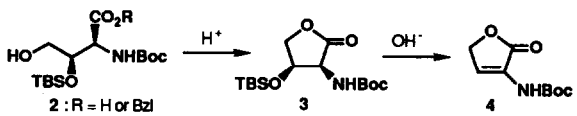
Abstract: Stereoselective total synthesis of mugineic acid (**1**), a unique phytosiderophore from roots of barley, has been achieved from readily available (2S,3S)- and (2R,3R)-2,3-epoxycinnamyl alcohols (**5**) and (**6**). The key step is the oxidation of the phenyl group to the carboxylic acid by use of the ruthenium trichloride-sodium metaperiodate system.

Mugineic acid (**1**) excreted from roots of barley (*Hordeum vulgare* L. var. minorimugi) has been identified as a typical phytosiderophore which promotes uptake and transport of iron in higher plants.[1] The first total synthesis of **1** was achieved by our group in 1986,[2] followed by its formal synthesis.[3] We now report a more efficient total synthesis of **1**, which will be suitable for the large scale production of **1**, an important tool in the studies of plant physiology. The key feature of our synthesis is the use of the phenyl group as the carboxyl synthon.[4]



mugineic acid (1)

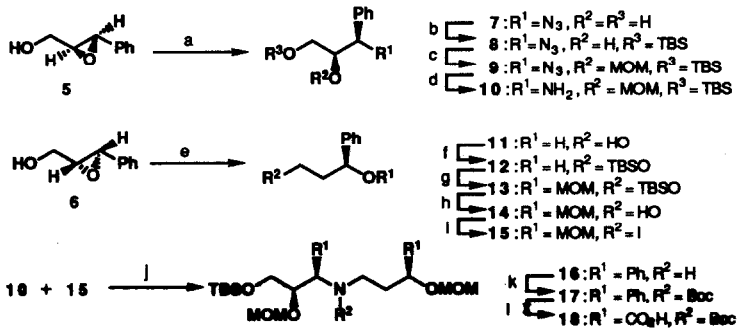
In our formal synthesis of **1**,[3b] we have found that the β-hydroxyhomoserine derivatives **2** easily undergo the cyclization to give the γ-lactone **3**. Attempted reconversion of **3** to **2** under alkaline conditions proved to give the β-elimination product **4**. This result will mainly cause the unsatisfactory overall yield of **1**. In order to prevent this unfavorable cyclization and elimination, we employed the phenyl group as a suitable substitute for the carboxyl group.



2 : R = H or Bzl　　3　　4　　**Scheme 1**

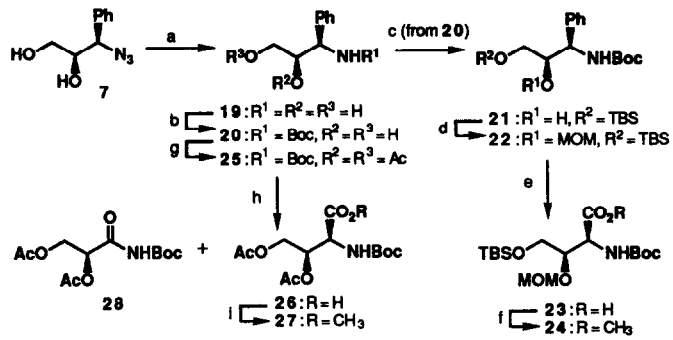
Our synthesis started from (2S,3S)- and (2R,3R)-2,3-epoxycinnamyl alcohols (**5**) and (**6**) which are readily available by the Sharpless epoxidation of cinnamyl alcohol.[5] After optical enrichment of **5** and **6** to 100% ee by recrystallization, **5** and **6** were converted to the azido alcohol **7** and the phenylpropanol **11**, respectively, according to the known procedures.[6,7] Conversion of **7** to the amine **10** was performed by protection of the primary and then secondary alcohols with the tert-butyldimethylsilyl (TBS) and methoxymethyl (MOM) groups, respectively, followed by reduction of the azido group. The phenylpropanol **11** was also converted to the iodide **15** by the analogous protection of the both alcohols with the TBS and MOM groups, deprotection of the TBS group, followed by iodination, as shown in Scheme 2. Coupling of **10** with **15** and then the N-protection with the tert-butoxycarbonyl (Boc) group afforded the diphenyl derivative **17**. Although the conversion of its two phenyl groups to the carboxyl function was tried through the ruthenium catalyzed oxidation using the ruthenium trichloride-sodium metaperiodate system,[8] the reaction did not occur at all and failed to give the dicarboxylic acid **18**.

† Dedicated with the greatest personal and professional respect to Professor Sir Derek Barton, the Giant in organic chemistry, on the occasion of his 75th birthday.



Scheme 2. (a) NaN_3, NH_4Cl, MeOH, H_2O, 70°C, 10h, quant. (b) TBSCl, DMAP, Et_3N, CH_2Cl_2, rt, 11h, 92%. (c) MOMCl, i-Pr_2NEt, CH_2Cl_2, rt, 22h, 94%. (d) 10% Pd-C, HCO_2NH_4, MeOH, rt, 2h, 92%. (e) Red-Al, DME, 0°C, 0.5h then rt, 4.5h, 83%. (f) TBSCl, Et_3N, CH_2Cl_2, rt, 17h, 93%. (g) MOMCl, i-Pr_2NEt, CH_2Cl_2, rt, overnight, 97%. (h) 46% aqueous HF, CH_3CN, rt, 15min, 100%. (i) I_2, PPh_3, imidazole, THF, CH_3CN, rt, 20min, 93%. (j) $NaHCO_3$, CH_3CN, reflux, 21h, 92%. (k) Boc_2O, i-Pr_2NEt (cat.), dioxane, 50°C, 20h, 98%. (l) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, rt.

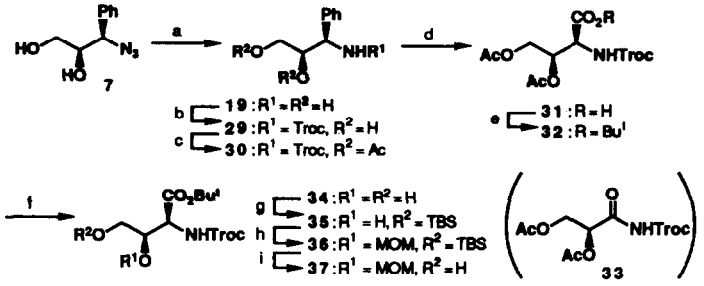
To investigate the reaction conditions of the ruthenium catalyzed oxidation, the Boc derivative **22** was prepared from **20** in 4 steps: reduction, N-protection, protection of primary and secondary alcohols. Oxidation of the phenyl derivative **22** afforded the carboxylic acid **23** which was smoothly transformed to the methyl ester **24**, as shown in Scheme 3. Various oxidation reaction conditions such as reaction solvents, temperatures, equivalents and concentration of the reactants were investigated, but the maximum yield of **24** was only 18% (23% conversion yield). Further investigations revealed that the acetyl derivative **25** prepared from the diol **7** could be transformed to the methyl ester **27** via the carboxylic acid **26** in 59% yield together with a small amount of the overoxidation product **28**[9] through the ruthenium catalyzed oxidation. These results have revealed that the protective group of the hydroxyl function in the ruthenium catalyzed oxidation should be an electron-withdrawing one, *e.g.*, Ac, which is superior to an electron-donating group, *e.g.*, TBS or MOM.[10]



Scheme 3. (a) 10% Pd-C, HCO_2NH_4, MeOH, rt, 2h, quant. (b) Boc_2O, saturated aqueous $NaHCO_3$, dioxane, rt, 8h, 93%. (c) TBSCl, DMAP, Et_3N, CH_2Cl_2, rt, 16h, 90%. (d) MOMCl, i-Pr_2NEt, CH_2Cl_2, 50°C, 20h, 92%. (e) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, rt, 48h. (f) $TMSCHN_2$, PhH, MeOH, rt, 30min, 18% (conversion 23%) from **22**. (g) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 12h, 98%. (h) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 24h. (i) $TMSCHN_2$, PhH, MeOH, rt, 15min, **27**: 59% from **25**; **28**: 8% from **25**.

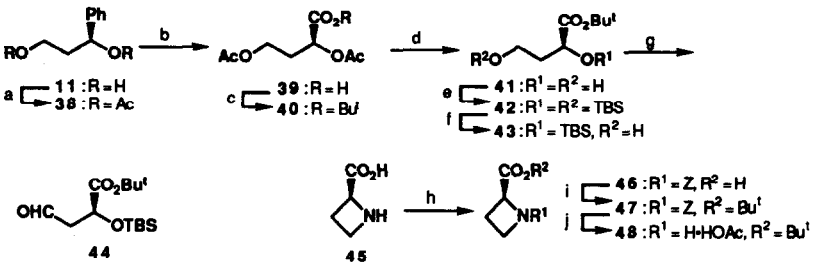
Based on these preliminary results, we now focused our attention on an alternative approach to mugineic acid (**1**), in which the transformation of the phenyl function to the carboxylic acid was performed as the O-acetyl derivative before condensation of each fragment. We selected the tert-butyl ester as the protective group of the carboxyl function and the 2,2,2-trichloroethoxycarbonyl (Troc) group for protection of the amino function. Thus, the azide **7** was efficiently converted to the fully protected phenylamine **30** by catalytic reduction of the azido group, protection of the amino group with TrocCl, and acetylation of the hydroxyl functions, as shown in Scheme 4. After the ruthenium catalyzed oxidation of **30**, esterification of the resulting

carboxyl function with O-tert-butyl-N,N'-diisopropylisourea[11] afforded the β-hydroxyhomoserine derivative **32** together with a small amount of the overoxidation product **33**.[9] Conversion of **32** to the required alcohol **37** was smoothly accomplished by deacetylation with triethylamine in aqueous methanol, sequential protection of primary and secondary alcohols with the TBS and MOM groups, followed by selective removal of the TBS group.



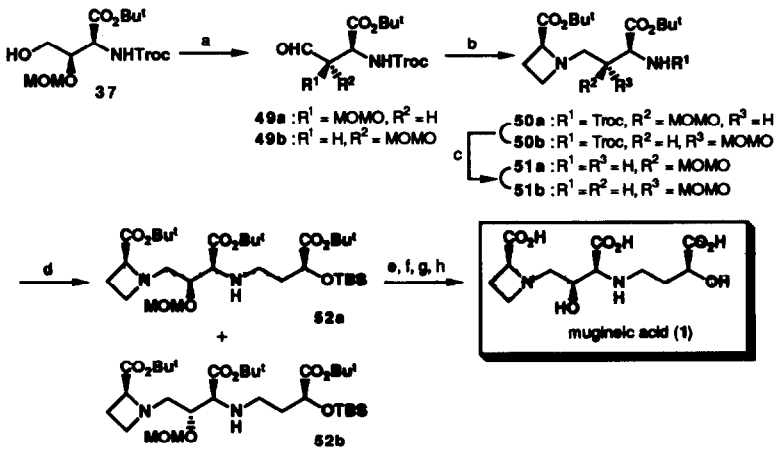
Scheme 4. (a) 10% Pd-C, HCO_2NH_4, MeOH, rt, 1h, quant. (b) TrocCl, $KHCO_3$, EtOAc, H_2O, rt, 1h, 99%. (c) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 19h, 94%. (d) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 24h. (e) O-tert-butyl-N,N'-diisopropylisourea, Bu^tOH, CH_2Cl_2, 50°C, 6h, **32**: 76%, **33**: 14%. (f) Et_3N, MeOH, H_2O, -20°C, 3h then 0°C, 2h, 72%. (g) TBSCl, DMAP, Et_3N, CH_2Cl_2, rt, 20h, 98%. (h) MOMCl, i-Pr_2NEt, CH_2Cl_2, reflux, 17h, 95%. (i) AcOH, H_2O, rt, 24h, 99%.

Preparation of the aldehyde fragment **44**, the right-hand constituent of **1**, was achieved by employing the similar procedures as described above. After acetylation of the diol functions of **11**, the ruthenium catalyzed oxidation of the acetate **38** followed by esterification smoothly afforded the tert-butyl ester **40**. Deacetylation of **40**, silylation, selective desilylation, followed by the Swern oxidation furnished the aldehyde **44**, as shown in Scheme 5. (*S*)-Azetidinecarboxylic acid (**45**) was converted to the acetic acid salt of tert-butyl ester **48**, the left-hand constituent **1**, according to the literature.[12]



Scheme 5. (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 6h, 99%. (b) $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 22h. (c) O-tert-butyl-N,N'-diisopropylisourea, CH_2Cl_2, rt, 18h, 80% from **38**. (d) Et_3N, MeOH, H_2O, -20°C, 8h, 77%. (e) TBSCl, imidazole, DMF, 50°C, 40h, 97%. (f) AcOH : THF : H_2O = 9:1:2, rt, 20h, **43**:76% (conversion 94%), **41**:19%. (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C → 0°C, 2h, 92%. (h) carbobenzoxy chloride (ZCl), $NaHCO_3$, dioxane, H_2O, rt, 16h. (i) O-tert-butyl-N,N'-diisopropylisourea, CH_2Cl_2, reflux, 8h, 86%. (j) 10% Pd-C, H_2, EtOAc, rt, 1h, then addition of AcOH (1 eq.), 99%.

Assembling each fragment (**37**, **44**, and **48**) was accomplished as outlined in Scheme 6. Treatment of the alcohol **37** under the Swern oxidation conditions gave the aldehyde **49a** and its C-2' epimer **49b** in a ratio of 15:1. Condensation of the mixture of the crude aldehydes **49** with the tert-butyl ester **48** by use of sodium cyanoborohydride[13] afforded an inseparable mixture of **50a** and its C-2' epimer **50b** in a ratio of 8:1. Deprotection of the Troc group with zinc in acetic acid followed by reductive N-alkylation with the aldehyde **44** afforded the protected mugineic acid **52a** and its C-2' epimer **52b**, which were separated by column chromatography. Removal of all the protecting groups of **52a** under acidic conditions yielded mugineic acid (**1**), which was identical with the natural one by comparison of their ^{1}H-NMR spectra at pH 4.5.[1b]



Scheme 6. (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78° C → 0°C, 2h. (b) **48**, 1M $NaBH_3CN$ in THF, MeOH, 0°C, 16h, **50a** and **50b**: 81% (conversion 91%), 37:12%. (c) Zn, AcOH, THF, rt, 4h, 95%. (d) **44**, 1M $NaBH_3CN$ in THF, AcOH (1 eq), MeOH, 0°C, 3h then rt, 8h, **52a**: 78%, **52b**: 10%. (e) 20% aqueous HCl, anisole, THF, rt, 40h. (f) Dowex 50W x 4 (H_2O then 15% aqueous pyridine). (g) ODS silica gel, H_2O. (h) recrystallization from H_2O-EtOH, 92%.

Our synthesis of mugineic acid (**1**) consists of 15 steps from readily available (2S,3S)-2,3-epoxycinnamyl alcohol (**5**) in an overall yield of 29%, which will be suitable for the large scale production of **1**. Our strategy using the phenyl group as the carboxyl synthon will have a generality for preparation of the other carboxylic acids.[14]

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 a JEOL PMX-60, FX-100, EX-270, or GSX-400 spectrometer with tetramethylsilane or chloroform as 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.

(2R,3R)-3-Azido-1-tert-butyldimethylsilyloxy-2-hydroxy-3-phenylpropane (8). To a stirred solution of **7**[6] (705 mg, 3.65 mM) in CH_2Cl_2 (2 ml) at room temperature was added Et_3N (1.02 ml, 7.30 mM), DMAP (45 mg, 0.37 mM), and TBSCl (605 mg, 4.01 mM). After being stirred at room temperature for 11 h, the mixture was treated with EtOAc (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. The residue was purified by silica gel column chromatography (BW 200, 130 g, hexane-Et_2O=8:1) to give **8** (1.04 g, 92 %) as a colorless oil: IR ν max (neat) 3437, 2105 cm^{-1}; ^1H NMR δ -0.04 (6H, s), 0.82 (9H, s), 2.22-2.40 (1H, m), 3.40-3.82 (3H, m), 4.32-4.52 (1H, m), 7.02-7.32 (5H, m).

(2R,3R)-3-Azido-1-tert-butyldimethylsilyloxy-2-methoxymethyloxy-3-phenylpropane (9). To a stirred solution of **8** (968 mg, 3.15 mM) in CH_2Cl_2 (6 ml) was added i-Pr_2NEt (3.3 ml, 18.89 mM) and MOMCl (960 µl, 12.60 mM). After the mixture was refluxed for 22 h with stirring, the mixture was treated with Et_2O (100 ml), washed with 1M aqueous $KHSO_4$ (50 ml x 4) 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, 90 g, hexane-Et_2O=19:1) to give **9** (1.04 g, 94 %) as a colorless oil: IR ν max (neat) 2105 cm^{-1}; ^1H NMR δ 0.04 (6H, s), 0.90 (9H, s), 3.14 (3H, s), 3.40-3.96 (3H, m), 4.36-4.80 (3H, m), 7.36 (5H, s).

(2R,3R)-3-Amino-1-tert-butyldimethylsilyloxy-2-methoxymethyloxy-3-phenylpropane (10). To a stirred solution of the azide **9** (1.03 g, 2.92 mM) and 10% Pd-C (200 mg) in MeOH (20 ml) at room temperature was added a solution of HCO_2NH_4 (740 mg, 11.68 mM) in MeOH (10 ml). After being stirred at room temperature for 2 h, the mixture was filtered through the pad of celite and concentrated in vacuo.

The residue was purified by silica gel column chromatography (BW 200, 100 g, hexane-EtOAc=3:4) to give **10** (974 mg, 96 %) as a colorless oil: IR ν_{max} (neat) 3384, 3320 cm^{-1}; ^1H NMR δ 0.01 (6H, s), 0.90 (9H, s), 1.68 (2H, brs), 3.21 (3H, s), 3.36-3.84 (3H, m), 4.04-4.24 (1H, m), 4.40-4.76 (2H, m), 7.08-7.44 (5H, m).

(S)-1-tert-Butyldimethylsilyloxy-3-hydroxy-3-phenylpropane(12). To a stirred solution of **11**[7] (295 mg, 1.94 mM) in CH_2Cl_2 (2ml) was added Et_3N (811µl, 5.82 mM) and TBSCl (440 mg, 2.91 mM). After being stirred at room temperature for 17 h, the mixture was treated with EtOAc (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. The residue was purified by silica gel column chromatography (BW 200, 60 g, hexane-EtOAc=14:1) to give **12** (485 mg, 93 %) as a colorless oil: IR ν_{max} (neat) 3440 cm^{-1}; ^1H NMR δ 0.09 (3H, s), 0.10 (3H, s), 0.93 (9H, s), 1.87-2.04 (2H, m), 3.75-3.77 (1H, m), 3.86 (2H, t, J=5.3 Hz), 4.93-4.98 (1H, m), 7.22-7.39 (5H, m).

(S)-1-tert-Butyldimethylsilyloxy-3-methoxymethyloxy-3-phenylpropane (13). To a stirred solution of **12** (400 mg, 1.49 mM) in CH_2Cl_2 (3 ml) was added i-Pr_2NEt (1.56 ml, 8.94 mM) and MOMCl (453 µl, 5.96 mM). After being stirred at room temperature overnight, the mixture was treated with Et_2O (30 ml), washed with 1M aqueous $KHSO_4$ (10 ml x 3) 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, 50 g, hexane-Et_2O=14:1) to give **13** (453 mg, 97 %) as a colorless oil: IR ν_{max} (neat) 2930, 1470 cm^{-1}; ^1H NMR δ 0.05 (3H, s), 0.06 (3H, s), 0.92 (9H, s), 1.82-1.92 (1H, m), 2.02-2.12 (1H, m), 3.36 (3H, s), 3.58-3.66 (1H, m), 3.72-3.81 (1H, m), 4.45 (2H, s), 4.76-4.82 (1H, m), 7.30-7.39 (5H, m).

(S)-1-Hydroxy-3-methoxymethyloxy-3-phenylpropane (14). To a stirred solution of **13** (1.87 g, 6.00 mM) in CH_3CN (21 ml) at 0°C was added 46% aqueous HF (1.00 ml). After being stirred at room temperature for 15 min, the mixture was treated with CH_2Cl_2 (20 ml) and H_2O (20 ml), 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, 150 g, hexane-Et_2O=3:2) to give **14** (1.18 g, 100 %) as a colorless oil: IR ν_{max} (neat) 3420 cm^{-1}; ^1H NMR δ 1.75-2.25 (3H, m), 3.33 (3H, s), 3.73 (2H, t, J=5.0 Hz), 4.43 (2H, s), 4.47 (1H, t, J=7.0 Hz), 7.22 (5H, s).

(S)-1-Iodo-3-methoxymethyloxy-3-phenylpropane (15). To a stirred solution of **14** (472 mg, 2.38 mM) in THF (4.5 ml) and CH_3CN (1.5 ml) at 0°C was added PPh_3 (1.25 g, 4.76 mM), imidazole (405 mg, 5.95 mM), and I_2 (1.33 g, 5.24 mM). After being stirred at room temperature for 20 min, the mixture was quenched with 5% aqueous $Na_2S_2O_3$ (10 ml), extracted with Et_2O (50 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 90 g, hexane-Et_2O=14:1) to give **15** (685 mg, 93 %) as a colorless oil: IR ν_{max} (neat) 2948, 1493 cm^{-1}; ^1H NMR δ 1.97-2.43 (2H, m), 3.03-3.53 (2H, m), 3.32 (3H, s), 4.37-4.77 (1H, m), 4.40 (2H, s), 7.17 (5H, s).

(2R,3R,3'S)-1-tert-Butyldimethylsilyloxy-2-methoxymethyloxy-3-(3'-methoxymethyloxy-3'-phenylpropylamino)-3-phenylpropane (16). To a stirred solution of **10** (509 mg, 1.56 mM) and $NaHCO_3$ (190 mg, 2.26 mM) in CH_3CN (6 ml) was added a solution of **15** (525 mg, 1.70mM) in CH_3CN (4ml). After being stirred at reflux for 21 h, the mixture was treated with Et_2O (50 ml), washed with H_2O (20 ml x 1) 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, 90 g, hexane-EtOAc=6:1) to give **16** (730 mg, 92 %) as a colorless oil: IR ν_{max} (neat) 3341 cm^{-1}; ^1H NMR δ -0.04 (3H, s), -0.02 (3H, s), 0.85 (9H, s), 1.62 (3H, brs), 1.77-1.85 (1H, m), 1.96-2.05 (1H, m), 2.47-2.59 (2H, m), 3.25 (3H, s), 3.26 (3H, s), 3.45-3.51 (1H, m), 3.63-3.67 (1H, m), 3.78-3.84 (2H, m), 4.47 (2H, ABq, J=6.7 Hz), 4.61-4.65 (1H, m), 4.67 (2H, ABq, J=6.7 Hz), 7.20-7.33 (10H, m).

(2R,3R,3'S)-3-(N-tert-Butoxycarbonyl-3'-methoxymethyloxy-3'-phenylpropylamino)-1-tert-butyldimethylsilyloxy-2-methoxymethyloxy-3-phenylpropane (17). To a stirred solution of **16** (378 mg, 0.75 mM) and i-Pr_2NEt (13 µl, 0.08 mM) in dioxane (2 ml) was added Boc_2O (380 mg, 1.73 mM). After being stirred at 50°C for 20 h, the mixture was treated with Et_2O (50 ml), washed with 1M aqueous $KHSO_4$ (10 ml x 1), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 50 g, hexane-Et_2O=6:1) to give **17** (444 mg, 98 %) as a colorless oil: $[\alpha]^{27}_D$ -72.3 (c 1.39, $CHCl_3$); IR ν_{max} (neat) 1694 cm^{-1}; ^1H NMR δ 0.01 (3H, s), 0.02 (3H, s), 0.89 (9H, s), 1.45 (9H, s), 1.75-1.83 (1H, m), 3.02 (3H, s), 3.10-3.19 (2H, br), 3.28 (3H, s), 3.73-3.77 (2H,

m), 4.33-4.44 (2H, m), 4.42 (2H, s), 4.47 (1H, d, J=6.4 Hz), 4.72 (1H, d, J=6.6 Hz), 4.89 (1H, d, J=8.6 Hz), 7.10-7.17 (2H, m), 7.21-7.31 (6H, m), 7.46 (2H, d, J=6.6 Hz); High mass calcd for $C_{33}H_{53}NO_7Si$: 603.8697. Found: 603.3590.

(2R,3R)-3-tert-Butoxycarbonylamino-1,2-dihydroxy-3-phenylpropane (20). To a stirred solution of **7** (459 mg, 2.38 mM) and 10% Pd-C (110 mg) in MeOH (5 ml) at 0°C was added a solution of HCO_2NH_4 (600 mg, 9.50 mM) in MeOH (5ml). After being stirred at room temperature for 2 h, the mixture was filtered through the pad of celite and concentrated in vacuo to give **19** (864 mg) as a yellow oil. The compound **19** was dissolved in dioxane (5 ml), and saturated aqueous $NaHCO_3$ (5 ml) and Boc_2O (623 mg, 2.85 mM) were added. After being stirred at room temperature for 8 h, the mixture was concentrated in vacuo, extracted with EtOAc (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=4:5) to give **20** (590mg, 93%) as a white solid, which was recrystallized from EtOAc-hexane: mp 109-112°C; $[\alpha]^{22}_D$ -42.4 (c 1.02, $CHCl_3$); IR ν_{max} (KBr) 3378, 1684 cm^{-1}; ^1H NMR δ 1.43 (9H, s), 2.46 (1H, d, J=7.3 Hz), 3.02 (1H, br), 3.48 (2H, brd, J=7.3 Hz), 3.68-3.87 (1H, m), 4.66-4.71 (1H, m), 5.19 (1H, br), 7.28-7.42 (5H, m); Anal calcd for $C_{14}H_{21}NO_4$: C, 62.9; H, 7.92; N, 5.24. Found: C, 62.96; H, 7.99; N, 4.91.

(2R,3R)-3-tert-Butoxycarbonylamino-1-tert-butyldimethylsilyloxy-2-hydroxy-3-phenylpropane (21). To a stirred solution of **20** (326 mg, 1.22 mM) in CH_2Cl_2 at room temperature was added Et_3N (680 mg, 4.88 mM), DMAP (3 mg, 0.22 mM), and TBSCl (550 mg, 3.66 mM). After being stirred at room temperature for 16 h, the mixture was treated with Et_2O (50 ml), washed with 1M aqueous $KHSO_4$ (20 ml x 3), 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=2:1) to give **21** (418 mg, 90%) as a colorless oil: $[\alpha]^{24}_D$ -27.9 (c 1.10, $CHCl_3$); IR ν_{max} (neat) 3422, 1700 cm^{-1}; ^1H NMR δ 0.04 (3H, s), 0.06 (3H, s), 0.92 (9H, s), 2.55 (1H, d, J=7.3 Hz), 3.45 (1H, dd, J=4.3, 10.6 Hz), 3.54-3.59 (1H, m), 3.82-3.90 (1H, m), 4.86-4.88 (1H, m), 6.03 (1H, d, J=5.6 Hz), 7.22-7.37 (5H, m); Anal. calcd for $C_{20}H_{35}NO_4Si$: C, 62.95; H, 9.24; N, 3.67. Found: C, 62.82; H, 9.18; N, 3.30.

(2R,3R)-3-tert-Butoxycarbonylamino-1-tert-butyldimethylsilyloxy-2-methoxymethyloxy-3-phenylpropane (22). To a stirred solution of **21** (79 mg, 0.21 mM) in CH_2Cl_2 (3 ml) was added i-Pr_2NEt (220 µl, 1.24 mM) and MOMCl (63 µl, 0.83mM). After the mixture was warmed at 50°C for 20 h with stirring, the mixture was dissolved in Et_2O (50 ml). The ethereal solution was washed with 1M aqueous $KHSO_4$ (20 ml x 3), 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=3:1) to give **22** (81 mg, 92%) as a colorless oil: $[\alpha]^{24}_D$ -32.5 (c 1.20, $CHCl_3$); IR ν_{max} (neat) 3295, 1719 cm^{-1}; ^1H NMR δ -0.02 (6H, s), 0.88 (9H, s), 1.36 (9H, s), 3.12-3.56 (2H, m), 3.33 (3H, s), 3.60-3.84 (1H, m), 4.68 (2H, s), 4.74-5.00 (1H, m), 6.04-6.40 (1H, m), 7.04-7.44 (5H, m); Anal. calcd for $C_{22}H_{39}NO_5Si$: C, 62.08; H, 9.23; N, 3.29. Found: C, 62.31; H, 9.33; N, 3.30.

Methyl (2S,3R)-2-tert-butoxycarbonylamino-4-tert-butyldimethylsilyloxy-3-methoxymethyloxybutanoate (24). To a stirred solution of **22** (228 mg, 0.54 mM) in CCl_4 (2 ml), CH_3CN (2 ml), and H_2O (3 ml) was added $NaIO_4$ (1.72 g, 8.04mM) and $RuCl_3$ (3 mg, 0.013 mM). After being stirred for 48 h, the mixture was extracted with CH_2Cl_2 (30 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in Et_2O, filtered through the pad of celite, and concentrated in vacuo to give **23** (80 mg) as a red oil. The crude product **23** was dissolved in benzene (1.6 ml) and MeOH (0.4 ml). $TMSCHN_2$[15] (280 µl, 0.56 mM (2M solution in hexane)) was added and the mixture was stirred at room temperature for 30 min, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 20 g, hexane-Et_2O=2:1) to give the starting material **22** (44 mg, 19.3%) and **24** (20 mg, 18% (conv. 23%)) as a colorless oil: $[\alpha]^{27}_D$ +17.5 (c 1.03, $CHCl_3$); IR ν_{max} (neat) 3431, 1749, 1722 cm^{-1}; ^1H NMR δ 0.07 (6H, s), 0.88 (9H, s), 1.37 (9H, s), 3.33 (3H, s), 3.55-3.92 (3H, m), 3.62 (3H, s), 4.25-4.45 (1H, m), 4.60 (2H, s), 5.32-5.42 (1H, br); Anal. calcd for $C_{18}H_{37}NO_7Si$: C, 53.04; H, 9.15; N, 3.44. Found: C, 53.13; H, 9.08; N, 3.33.

(2R,3R)-3-tert-Butoxycarbonylamino-1,2-diacetoxy-3-phenylpropane (25). To a stirred solution of **20** (145 mg, 0.54 mM) and Et_3N (190 µl, 1.36 mM) in CH_2Cl_2 (3 ml) at room temperature was added DMAP (3 mg, 0.03 mM) and Ac_2O (110 µl, 1.19 mM). After being stirred at room temperature for 12

h, the mixture was treated with Et_2O (50 ml), 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, 20 g, hexane-Et_2O=1:1) to give **25** (187 mg, 98%) as a white solid, which was recrystallized from Et_2O-petroleum ether: mp 84-88°C; $[\alpha]^{22}_D$ -37.6 (c 0.99, $CHCl_3$); IR ν_{max} (KBr) 3399, 1736, 1686 cm^{-1}; ^1H NMR δ 1.42 (9H, s), 1.98 (3H, s), 2.04 (3H, s), 4.02-4.08 (1H, m), 4.23 (1H, dd, J=4.0, 12.2 Hz), 5.00 (1H, br), 5.15 (1H, br), 5.33-5.39 (1H, m), 7.29-7.38 (5H, m); Anal. calcd for $C_{18}H_{25}NO_6$: C, 61.53; H, 7.17; N, 3.99. Found: C, 61.33; H, 7.30; N, 3.69.

Methyl (2S,3R)-2-tert-butoxycarbonylamino-3,4-diacetoxybutanoate (27) and (S)-2-(N-tert-Butoxycarbonylcarbamoyl)-1,2-diacetoxyethane (28). To a stirred solution of **25** (101 mg, 0.33 mM) in EtOAc (1 ml), CH_3CN (1 ml) and H_2O (8 ml) was added $NaIO_4$ (2.0 g, 9.5 mM) and $RuCl_3$ (4.3 mg, 0.019 mM). After being stirred at room temperature for 27 h, the mixture was extracted with EtOAc (50 ml x 3), and dried over Na_2SO_4. The solvent was removed in vacuo and the mixture was dissolved in Et_2O, filtered through the pad of celite, and concentrated in vacuo. The residue was dissolved in saturated aqueous $NaHCO_3$ and extracted with Et_2O (30 ml x 2). The organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 10 g, hexane-Et_2O=1:1) to give **28** (8 mg, 8%) as a colorless oil: $[\alpha]^{26}_D$ -15.6 (c 0.31, $CHCl_3$); IR ν_{max} (neat) 3288, 1792, 1750, 1717 cm^{-1};^1H NMR δ 1.42 (9H, s), 2.08 (3H, s), 2.19 (3H, s), 4.47-4.56 (2H, m), 5.72-5.75 (1H, m), 7.64 (1H, brs); ^{13}C NMR δ 20.67, 20.72, 27.94, 62.37, 71.68, 83.68, 149.52, 166.95, 169.68, 170.53; High mass calcd for $C_{12}H_{19}NO_7$: 289.1161. Found: 290.1163 (M+1).

The aqueous phase was acidified with $KHSO_4$, and extracted with EtOAc (50 ml x 3). The extracts were dried over Na_2SO_4 and concentrated in vacuo to give **26** (79 mg) as a red oil. The crude product **26** was dissolved in benzene (1.6 ml) and MeOH (0.4 ml), treated with $TMSCHN_2$[15] (100 μl, 0.20 mM (2M solution in hexane)). After being stirred for 15 min, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 10g, hexane-EtOAc=6:1) to give **27** (63 mg, 59%) as a colorless oil: $[\alpha]^{26}_D$ +21.6 (c 1.23, $CHCl_3$); IR ν_{max} (neat) 3368, 1750, 1717 cm^{-1}; ^1H NMR δ 1.45 (9H, s), 2.06 (3H, s), 2.07 (3H, s), 3.79 (3H, s), 4.15-4.31 (2H, m), 4.71-4.75 (1H, m), 5.28-5.36 (2H, m); Anal calcd for $C_{14}H_{23}NO_8$: C, 50.45; H, 6.95; N, 4.20. Found: C, 50.44; H, 7.16; N, 4.15.

(2R,3R)-1,2-Dihydroxy-3-(2,2,2-trichloroethoxycarbonylamino)-3-phenylpropane (29). To a stirred solution of 7[6] (4.8 g, 25.0 mM) and 10% Pd-C (1 g) in MeOH (100 ml) at 0°C was added HCO_2NH_4 (4.7 g, 74.9 mM). After being stirred at room temperature for 1 h, the mixture was filtered through the pad of celite and concentrated in vacuo to give the amine **19** (5.2 g, quant.) as a yellow oil. After **19** was dissolved in EtOAc (30 ml) and H_2O (30 ml) at 0°C, $KHCO_3$ (5 g, 50 mM) and TrocCl (3.78 ml, 27.4 mM) were added. After being stirred at room temperature for 1 h, the mixture was extracted with EtOAc (100 ml x 3). The organic extracts were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 200 g, hexane-EtOAc=5:7) to give **29** (8.4 g, 99%) as a colorless oil: $[\alpha]^{26}_D$ -41.9 (c 1.10, $CHCl_3$); IR ν_{max} (neat) 3388, 1713 cm^{-1}; ^1H NMR δ 2.32-2.40 (1H, m), 2.49-2.55 (1H, m), 3.53-3.74 (2H, m), 3.94-4.02 (1H, m), 4.72 (2H, ABq, J=11.9 Hz), 4.84-4.87 (1H, m), 6.02 (1H, brd, J=1.3 Hz), 7.29-7.42 (5H, m); Anal calcd for $C_{12}H_{14}Cl_3NO_4$: C, 42.07; H, 4.12; N, 4.09. Found: C, 42.16; H, 4.20; N, 3.70.

(2R,3R)-1,2-Diacetoxy-3-(2,2,2-trichloroethoxycarbonylamino)-3-phenylpropane (30). To a stirred solution of **29** (7.63 g, 22.3 mM) in CH_2Cl_2 (50 ml) at room temperature was added pyridine (7.2 ml, 89.1 mM) and Ac_2O (6.3 ml, 66.8 mM). After being stirred at room temperature for 19 h, the mixture was treated with Et_2O (200 ml), and the ethereal solution was washed with 10% aqueous citric acid (50 ml x 3) and saturated brine (20 ml x 1), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (BW 200, 200 g, hexane-Et_2O = 5:4) to give **30** (8.9 g, 94%) as a colorless oil: $[\alpha]^{25}_D$ -34.0 (c 1.19, $CHCl_3$); IR ν_{max} (neat) 3341, 1748, 1717 cm^{-1}; ^1H NMR δ 2.00 (3H, s), 2.06 (3H, s), 4.04 (1H, dd, J= 5.9, 10.9 Hz), 4.25-4.31 (1H, m), 4.72 (2H, ABq, J=11.9 Hz), 5.07-5.13 (1H, m), 5.40 (1H, dd, J=5.6, 9.9 Hz), 7.29-7.41 (5H, m); Anal. calcd for $C_{16}H_{18}Cl_3NO_6$: C, 45,04; H, 4.25; N, 3.28 Found: C, 44.76; H, 4.27; N, 3.00.

tert-Butyl (2S,3R)-3,4-diacetoxy-2-(2,2,2-trichloroethoxycarbonylamino)butanoate (32) and (S)-1,2-Diacetoxy-2-(N-2,2,2-trichloroethoxycarbonylcarbamoyl)ethane (33). To a

stirred solution of **30** (1.39 g, 3.25 mM) in EtOAc (6 ml),CH_3CN (6 ml), and H_2O (70 ml) were added $NaIO_4$ (17.4 g, 81.3 mM) and $RuCl_3$ (37 mg, 0.16 mM). After being stirred at room temperature for 24 h, the mixture was extracted with EtOAc (200 ml x 3). The 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. The residue was dissolved in saturated aqueous $NaHCO_3$, and the mixture was extracted with Et_2O (50 ml x 3). The organic 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-Et_2O=1:1) to give **33** (162 mg, 14%) as a colorless oil: $[\alpha]^{26}_D$ -13.4 (c 1.10, $CHCl_3$); IR ν_{max} (neat) 3287, 1717 cm^{-1}; ^1H NMR δ 2.08 (3H, s), 2.20 (3H, s), 4.51 (2H, d, J=4.0 Hz), 4.82 (2H, ABq, J=11.9 Hz), 5.71 (1H, t, J=4.0 Hz), 8.23 (1H, brs); Anal. calcd for $C_{10}H_{12}Cl_3NO_7$: C, 33.22; H, 3.35; N, 3.87. Found: C, 33.22; H, 3.44; N, 3.44.

The aqueous phase was acidified with $KHSO_4$, and extracted with EtOAc (100 ml x 3). The organic extracts were dried over Na_2SO_4, and concentrated in vacuo to give **31** (1.32 g) as a red oil. The crude product **31** was dissolved in a mixture of CH_2Cl_2 (1.5 ml) and t-BuOH (6 ml), followed by treatment with O-t-butyl-N,N'-diisopropylisourea (1.55 ml, 6.5 mM). After being stirred at 50°C for 6 h, the mixture was filtered through the pad of celite and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 160 g, hexane-Et_2O=3:1) to give **32** (1.11 g, 76%) as a colorless oil: $[\alpha]^{26}_D$ +8.2 (c 0.80, $CHCl_3$); IR ν_{max} (neat) 3388, 1755, 1732 cm^{-1}; ^1H NMR δ 1.50 (9H, s), 2.06 (3H, s), 2.07 (3H, s), 4.22 (1H, dd, J=6.9, 11.9 Hz), 4.32 (1H, dd, J=5.0, 11.9 Hz), 4.61-4.80 (1H, m), 4.73 (2H, ABq, J=12.0 Hz), 5.32-5.38 (1H, m), 5.85 (1H, d, J=8.3 Hz); Anal calcd for $C_{15}H_{22}Cl_3NO_8$: C, 39.97; H, 4.92; N, 3.11. Found: C, 40.18; H, 5.10; N, 2.83.

tert-Butyl (2S,3R)-3,4-dihydroxy-2-(2,2,2-trichloroethoxycarbonylamino)butanoate (34). To a stirred solution of **32** (927 mg, 2.06 mM) in MeOH (8 ml) and H_2O (3 ml) at -20°C was added Et_3N (860 µl, 6.17 mM) dropwise. After the mixture was stirred at -20°C for 3 h, Et_3N (200 µl, 1.43 mM) and H_2O (1 ml) were added, and the mixture was allowed to warm to 0°C, and stirred for 2 h. After being treated with 1 M aqueous $KHSO_4$ (10 ml), the mixture was concentrated in vacuo, 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, 70 g, hexane-EtOAc=9:8) to give **34** (541 mg, 72%) as a white solid, which was recrystallized from Et_2O-hexane: mp 76-81°C; $[\alpha]^{25}_D$ +7.08 (c 1.07, $CHCl_3$); IR ν_{max} (KBr) 3440, 1738, 1713 cm^{-1}; ^1H NMR δ 1.50 (9H, s), 2.19 (2H, brs), 3.73 (2H, d, J=2.0 Hz), 3.95-4.04 (1H, m), 4.36 (1H, dd, J=5.4, 8.3 Hz), 4.75 (2H, ABq, J=12.0 Hz), 5.94 (1H, brd, J=7.3 Hz); Anal. calcd for $C_{11}H_{18}Cl_3NO_6$: C, 36.04; H, 4.95; N, 3.82. Found: C, 36.04; H, 5.04; N, 3.69.

tert-Butyl (2S,3R)-4-tert-butyldimethylsilyloxy-3-hydroxy-2-(2,2,2-trichloroethoxycarbonylamino)butanoate (35). To a stirred solution of **34** (1.33 g, 3.62 mM) in CH_2Cl_2 (10 ml) at 0°C was added Et_3N (2.0 ml, 14.5 mM), DMAP (22 mg, 0.18 mM), and TBSCl (1.09 g, 7.23 mM). After being stirred at room temperature for 20 h, the mixture was dissolved in Et_2O (100 ml), 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, 150 g, hexane-Et_2O=5:2) to give secondary alcohol **35** (1.70 g, 98%) as a colorless oil: $[\alpha]^{25}_D$ -7.96 (c 1.02, MeOH); IR ν_{max} (KBr) 3338, 1744, 1732 cm^{-1}; ^1H NMR δ 0.09 (3H, s), 0.093 (3H, s), 0.92 (9H, s), 1.48 (9H, s), 2.88 (1H, brd, J=6.6 Hz), 3.75 (2H, d, J=4.3 Hz), 4.03 (1H, br), 4.43 (1H, dd, J=4.0, 8.6 Hz), 4.73 (2H, ABq, J=12.0 Hz), 6.15 (1H, brd, J=7.9 Hz); Anal. calcd for $C_{17}H_{32}Cl_3NO_6Si$: C, 42.46; H, 6.71; N, 2.91. Found: C, 42.58; H, 7.00; N, 2.75.

tert-Butyl (2S,3R)-4-tert-butyldimethylsilyloxy-3-methoxymethyloxy-2-(2,2,2-trichloroethoxycarbonylamino)butanoate (36). To a stirred solution of **35** (1.97 g, 4.09 mM) in CH_2Cl_2 (20 ml) was added i-Pr_2NEt (4.3 ml, 24.5 mM) and MOMCl (1.24 ml, 16.4 mM). After being stirred at reflux for 17 h, the mixture was diluted with Et_2O (100 ml). The ethereal solution was washed with 1M aqueous $KHSO_4$ (50 ml x 3) 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, 150 g, hexane-Et_2O=8:1) to give fully protected amino acid **36** (2.05 g, 95%) as a colorless oil: $[\alpha]^{26}_D$ +15.0 (c 0.48, $CHCl_3$); IR ν_{max} (neat) 3443, 1744 cm^{-1}; ^1H NMR δ 0.08 (3H, s), 0.09 (3H, s), 0.92 (9H, s), 1.48 (9H, s), 3.41 (3H, s), 3.81-3.84 (2H, m), 3.86-3.93 (1H, m), 4.49 (1H, dd, J=3.0, 8.6 Hz), 4.69 (2H, s), 4.72 (2H, s), 6.48 (1H, brd, J=8.3

Hz); Anal. calcd for $C_{19}H_{36}Cl_3NO_7Si$: C, 43.47; H, 6.91; N, 2.67. Found: C, 43.67; H, 7.17; N, 2.57.

tert-Butyl (2S,3R)-4-hydroxy-3-methoxymethyloxy-2-(2,2,2-trichloroethoxycarbonylamino)butanoate (37). To a stirred solution of **36** (695 mg, 1.32 mM) in AcOH (5 ml) at room temperature was added H_2O (2 ml). After being stirred at room temperature for 24 h, the mixture was diluted with Et_2O (50 ml), washed with satutated aqueous Na_2CO_3 (20 ml x 3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 70 g, hexane-Et_2O=1:1) to give **37** (537 mg, 99%) as a colorless oil: $[\alpha]^{26}_D$ -47.9 (c 0.89, $CHCl_3$); IR ν_{max} (neat) 3422, 1738, 1728 cm^{-1}; ^1H NMR δ 1.49 (9H, s), 2.74 (1H, br), 3.43 (3H, s), 3.79 (2H, brs), 3.87-3.90 (1H, m), 4.45 (1H, dd, J=3.5, 8.6 Hz), 4.69-4.79 (4H, m), 6.14 (1H, brd, J=8.1 Hz); Anal. calcd for $C_{13}H_{22}Cl_3NO_7$: C, 38.30; H, 5.44; N, 3.44. Found: C, 38.39; H, 5.69; N, 3.21.

(S)-1,3-Diacetoxy-3-phenylpropane (38). To a stirred solution of **11** (219 mg, 1.44 mM) and Et_3N (600 µl, 3.60 mM) in CH_2Cl_2 (2 ml) at room temperature were added DMAP (9 mg, 0.07 mM) and Ac_2O (340 µl, 4.32 mM). After being stirred at room temperature for 6 h, the mixture was treated with Et_2O (100 ml), washed with 1M aqueous $KHSO_4$ (30 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, 30 g, hexane-Et_2O=4:1) to give **38** (332 mg, 98%) as a colorless oil: $[\alpha]^{22}_D$ -54.1 (c 0.55, $CHCl_3$); IR ν_{max} (neat) 1740 cm^{-1}; ^1H NMR δ 2.03 (3H, s), 2.07 (3H, s), 2.11-2.30 (2H, m), 3.94-4.30 (2H, m), 5.86 (1H, dd, J=5.9, 7.8 Hz), 7.33 (5H, m); Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83;. Found: C, 65.75; H, 6.94.

tert-Butyl (S)-2,4-diacetoxybutanoate (40). To a stirred solution of **38** (1.03 g, 4.37 mM) in EtOAc (10 ml), CH_3CN (10 ml), and H_2O (95 ml) were added $NaIO_4$ (23.3 g, 109.2 mM) and $RuCl_3$ (49 mg, 0.22 mM). After being stirred at room temperature for 22 h, the mixture was extracted with EtOAc (200 ml x 3) and dried over Na_2SO_4. The solvent was removed in vacuo and the mixture was dissolved in Et_2O, filtered through the pad of celite, and concentrated in vacuo to give **39** (1.32 g) as a red oil. The crude product **39** was dissolved in CH_2Cl_2 (20 ml), and O-tert-Butyl-N,N'-diisopropylisourea (1.56 ml, 6.55 mM) was added. The mixture was stirred at room tempetature for 18 h, filtered through the pad of celite, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 100 g, hexane-Et_2O=6:1) to give **40** (906 mg, 80%) as a colorless oil: $[\alpha]^{25}_D$ -39.4 (c 1.11, $CHCl_3$); IR ν_{max} (neat) 1747, 1744 cm^{-1};^1H NMR δ 1.47 (9H, s), 2.06 (3H, s), 2.13 (3H, s), 2.03-2.26 (2H, m), 4.10-4.17 (2H, m), 4.95-5.00 (1H, m); Anal. calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.44. Found: C, 55.22; H, 8.62.

tert-Butyl (S)-2,4-dihydroxybutanoate (41). To a stirred solution of **40** (698 mg, 2.68 mM) in MeOH (5 ml) and H_2O (5 ml) at 0°C was added Et_3N (3.8 µl, 26.8 mM) dropwise. After being stirred at -20°C for 8 h, the mixture was concentrated in vacuo, and extracted with Et_2O (30 ml x 3). The ethereal solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 40 g, hexane-EtOAc=1:1) to give **41** (366 mg, 77%) as a white solid, which was recrystallized from Et_2O-hexane: mp 61-63°C; $[\alpha]^{25}_D$ -16.3 (c 0.47, $CHCl_3$); IR ν_{max} (KBr) 3441, 1732 cm^{-1}; ^1H NMR δ 1.49 (9H, s), 1.81-1.91 (1H, m), 2.01-2.12 (1H, m), 2.38 (1H, br), 3.20 (1H, d, J=4.6 Hz), 3.82-3.86 (2H, m), 4.21-4.28 (1H, m); Anal. calcd for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.34; H, 9.20.

tert-Butyl (S)-2,4-di-tert-butyldimetylsilyloxybutanoate (42). To a stirred solution of **41** (325 mg, 1.84 mM) in DMF (2 ml) was added imidazole (500 mg, 7.38 mM) and TBSCl (830 mg, 5.53 mM). The mixture was heated to 50°C, stirred for 40 h, and quenched with 1M aqueous $KHSO_4$ (20 ml). After extraction with Et_2O (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 820MH, 80 g, hexane-Et_2O=22:1) to give **42** (724 mg, 97%) as a colorless oil: $[\alpha]^{24}_D$ -21.35 (c 0.43, $CHCl_3$); IR ν_{max} (neat) 1752 cm^{-1}; ^1H NMR δ 0.05 (6H, s), 0.09 (6H, s), 0.89 (9H, s), 0.90 (9H, s), 1.46 (9H, s), 1.69-1.98 (2H, m), 3.64-3.79 (2H, m), 4.22 (1H, dd, J=4.0, 8.6 Hz); Anal. calcd for $C_{20}H_{44}O_4Si_2$: C, 59.35; H, 10.96. Found: C, 59.43; H, 10.95.

tert-Butyl (S)-2-tert-butyldimethylsilyloxy-4-hydroxybutanoate (43). After **42** (204 mg, 0.504 mM) was dissolved in AcOH (1.8 ml), THF (0.2 ml), and H_2O (0.4 ml), the mixture was stirred at room tempetature for 20 h. After dilution with Et_2O (50 ml), the mixture was washed with saturated aqueous K_2CO_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, 20 g, hexane-Et_2O=2:1→1:1) to give **43** (111 mg, 76% (conversion 94%)) as a

colorless oil and **41** (17 mg, 19%) as a white solid: **43**: $[\alpha]^{24}_D$ -41.1 (c 0.37, $CHCl_3$); IR ν_{max} (neat) 3493, 1750 cm^{-1}; ^1H NMR δ 0.08 (3H, s), 0.09 (3H, s), 0.92 (9H, s), 1.47 (9H, s), 1.54-1.80 (1H, m), 1.91-2.04 (2H, m), 3.77-3.81 (2H, m), 4.28-4.32 (1H, m); Anal. calcd for $C_{14}H_{30}O_4Si$: C, 57.89; H, 10.41. Found: C, 57.77; H, 10.51.

tert-Butyl (S)-2-tert-butyldimethylsilyloxy-4-oxobutanoate (44). To a stirred solution of $(COCl)_2$ (145 μl, 1.65 mM) in CH_2Cl_2 (3 ml) at -78°C was added a solution of DMSO (195 μl, 2.76 mM) in CH_2Cl_2 (2 ml). After the mixture was stirred for 10 min, a solution of **43** (320 mg, 1.10 mM) in CH_2Cl_2 (5 ml) and Et_3N (460 μl, 3.31 mM) were added. The mixture was allowed to warm to room temperature, and stirred for 2 h. After being quenched with H_2O (5 ml), the mixture was extracted with CH_2Cl_2 (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-Et_2O=8:1) to give **44** (291mg, 92%) as a colorless oil: $[\alpha]^{24}_D$ -37.1 (c 0.59, $CHCl_3$); IR ν_{max} (neat) 1750, 1735 cm^{-1}; ^1H NMR δ 0.08 (3H, s), 0.12 (3H, s), 0.88 (9H, s), 1.46 (9H, s), 2.74-2.77 (2H, m), 4.55 (1H, t, J=5.9 Hz), 9.78 (1H, t, J=2.0 Hz); Anal. calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.17; H, 9.92.

tert-Butyl (S)-N-benzyloxycarbonylazetidinecarboxylate (47). To a stirred solution of **45** (2.0 g, 19.8 mM) in dioxane (10 ml) and saturated aqueous $NaHCO_3$ (30 ml) was added ZCl (3.1 ml, 21.8 mM). After being stirred at room temperature for 16 h, the mixture was concentrated in vacuo and extracted with Et_2O (20 ml x 1). The aqueous phase was acidified with $KHSO_4$ and extracted with EtOAc (100 ml x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give **46** (4.64 g) as a colorless oil. The residue **46** was dissolved in CH_2Cl_2 (60 ml), and O-tert-butyl-N,N'-diisopropylisourea (9.45 ml, 39.6 mM) was added. After being stirred at 50°C for 8 h, the mixture was filtered through the pad of celite and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW 200, 170 g, hexane-Et_2O=3:2) to give **47** (4.95 g, 86%) as a colorless oil: $[\alpha]^{25}_D$ -92.2 (c 0.70, $CHCl_3$); IR ν_{max} (neat) 1740, 1717 cm^{-1}; ^1H NMR δ 1.43 (9H, s), 1.90-2.67 (2H, m), 3.77-4.20 (2H, m), 4.50 (1H, dd, J=7.5, 13.5 Hz), 5.03 (2H, s), 7.23 (5H, s); Anal. calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 66.20; H, 7.46; N, 4.86.

tert-Butyl (S)-azetidinecarboxylate acetic acid salt (48). To a stirred solution of **47** (2.02 g, 6.93 mM) in EtOAc (70 ml) was added 10% Pd-C (400 mg). After the mixture was stirred at room temperature for 1 h under H_2 atmosphere, AcOH (400 μl, 6.99 mM) was added. The mixture was filtered through the pad of celite, and concentrated in vacuo to give **48** (1.49 g, 99%) as a pale yellow oil: $[\alpha]^{24}_D$ -37.9 (c 0.56, $CHCl_3$); IR ν_{max} (neat) 3456-2463 (br), 1738 cm^{-1}; ^1H NMR δ 1.50 (9H, s), 2.03 (3H, s), 2.27-2.41 (1H, m), 2.76-2.90 (1H, m), 3.78 (2H, t, J=7.9 Hz), 4.51 (1H, dd, J=6.3, 9.6 Hz), 7.90 (1H, br), 8.13 (1H, br).

tert-Butyl (2S,3R)-3-methoxymethyloxy-4-oxo-2-(2,2,2-trichloroethoxycarbonylamino) butanoate (49a) and tert-Butyl (2S,3S)-3-methoxymethyloxy-4-oxo-2-(2,2,2-trichloroethoxycarbonylamino)butanoate (49b). To a stirred solution of $(COCl)_2$ (70 μl, 0.80 mM) in CH_2Cl_2 (1 ml) was added a solution of DMSO (76 μl, 1.07 mM) in CH_2Cl_2 (1 ml) at -78°C. After the mixture was stirred for 10 min, a solution of **37** (220 mg, 0.54 mM) in CH_2Cl_2 (3 ml) and Et_3N (230 μl, 1.61 mM) were added. The mixture was allowed to warm to room temperature, and stirred for 2 h. The mixture was 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 **49a** and **49b** (246 mg, 15:1) as a pale yellow oil. This mixture was used for the next reaction without further purification. IR ν_{max} (neat) 3337, 1748, 1732 cm^{-1}; ^1H NMR δ 1.46 (9H, s), 3.44 (3H, s), 4.33 (1H, d, J=2.4 Hz), 4.69-4.85 (5H, m), 6.08 (1H, brd, J=11.0 Hz), 9.65, 9.68 (1H, s); Anal. calcd for $C_{13}H_{26}Cl_3NO_7$: C, 38.21; H, 4.93; N, 3.43. Found: C, 38.11; H, 5.14; N, 3.16. The ratio of the epimers was determined by the integration of the methyne proton of the aldehyde group in its ^1H NMR spectrum.

tert-Butyl (2S,2'S,3'S)-3'-tert-butoxycarbonyl-2'-methoxymethyloxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl-2-azetidinecarboxylate (50a) and tert-Butyl (2S,2'R,3'S)-3'-tert-butoxycarbonyl-2'-methoxymethyloxy-3'-(2,2,2-trichloroethoxycarbonylamino)propyl-2-azetidinecarboxylate (50b). To a stirred solution of **48** (175 mg, 0.80 mM) in MeOH (1.5 ml) at 0°C was added dropwise a solution of the above aldehydes **49a** and **49b** (246 mg) in MeOH (2 ml) and 1M $NaBH_3CN$ (in THF) (540 μl, 0.54 mM). After the mixture was stirred at 0°C for 16 h,

saturated aqueous $NaHCO_3$ (5 ml) was added. The mixture was 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, 40 g, hexane-EtOAc=4:1→2:1) to give **50a** and **50b** (8:1) (239 mg, 81% (conversion 91%)) and the reduced alcohol **37** (27 mg, 12%) as a colorless oil, respectively.

50a and **50b**: IR ν_{max} (neat) 3320, 1736, 1730 cm^{-1}; ^1H NMR δ 1.46, 1.47, 1.47, 1.48 (18H, s), 2.10-2.28 (2H, m), 2.69-2.98 (3H, m) 3.39, 3.40 (3H, s), 3.53-3.63 (2H, m), 3.94 (1H, br), 4.50-4.90 (5H, m), 7.51 (1H, br). Anal. calcd for $C_{21}H_{35}Cl_3N_2O_8$: C, 45.87; H, 6.42; N, 5.09. Found: C, 46.23; H, 6.48, N, 4.94. The ratio of the epimers was determined by the integration of methyl signal of the methoxymethyl group in its ^1H NMR spectrum.

tert-Butyl (2S,2'S,3'S)-3'-amino-3'-tert-butoxycarbonyl-2'-methoxymethyloxypropyl-2-azetidinecarboxylate (51a) and tert-Butyl (2S,2'R,3'S)-3'-amino-3'-tert-butoxycarbonyl-2'-methoxymethyloxypropyl-2-azetidinecarboxylate (51b). To a stirred solution of **50a** and **50b** (68 mg, 0.12 mM) in THF (1 ml) and AcOH (0.8 ml) at room tempetature was added Zn powder (20 mg) in one portion. After being stirred at room temperature for 2 h, the mixture was filtered through the pad of celite, and concentrated in vacuo. After neutralization with saturated aqueous $NaHCO_3$, the mixture was 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=14:1) to give a mixture of amines **51a** and **51b** (8:1) (44 mg, 95%) as a pale yellow oil: IR ν_{max} (neat) 3405, 1732 cm^{-1}; ^1H NMR δ 1.45, 1.46, 1.47 (18H, s), 1.78 (2H, br), 2.11-2.39 (2H, m), 2.54-2.67 (1H, m), 2.76-2.95 (2H, m), 3.33-3.50 (1H, m), 3.38, 3.39 (3H, s), 3.56 (1H, t, J=8.3 Hz), 3.65-3.81 (2H, m), 4.70, 4.72 (2H, ABq, J=6.9 Hz); Anal. calcd for $C_{18}H_{34}N_2O_6$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.56; H, 9.26; N, 7.41. The ratio of the epimers was determined by the integration of methyl signal of the methoxymethyl group in its ^1H NMR spectrum.

tert-Butyl (2S,2'S,3'S,3"S)-3'-(3"-tert-butoxycarbonyl-3"-tert-butyldimetylsilyloxypropylamino)-3'-tert-butoxycarbonyl-2'-methoxymethyloxypropyl-2-azetidinecarboxylate (52a) and tert-Butyl (2S,2'R,3'S,3"S)-3'-(3"-tert-butoxycarbonyl-3"-tert-butyldimetylsilyloxypropylamino)-3'-tert-butoxycarbonyl-2'-methoxymethyloxypropyl-2-azetidinecarboxylate (52b). To a stirred solution of **51a** and **51b** (97 mg, 0.26 mM) and AcOH (15 μl, 0.26 mM) in MeOH (0.2 ml) at 0°C was added dropwise a solution of the aldehyde **44** (117 mg, 0.41 mM) in MeOH (0.8 ml). After being stirred at 0°C for 3 h, the mixture was allowed to warm to room temperature, and stirred for 8 h. After being quenched with saturated aqueous $NaHCO_3$, the mixture was 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 300, 25 g hexane-EtOAc=4:1) to give **52a** (130 mg, 78 %) as a colorless oil and **52b** (17 mg, 10%) as a colorless oil, respectively. **52a**: $[\alpha]^{24}_D$ -47.2 (c 0.90, $CHCl_3$); IR ν_{max} (neat) 3337, 1732 cm^{-1}; ^1H NMR δ 0.03 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.45 (18H, s), 1.47 (9H, s), 1.72 (1H, br), 1.80-1.88 (2H, m), 2.08-2.33 (2H, m), 2.54-2.90 (5H, m), 3.32-3.38 (2H, m), 3.37 (3H, s), 3.55 (1H, t, J=8.4 Hz), 3.71-3.77 (1H, m), 4.12 (1H, t, J=6.1 Hz), 4.71 (2H, ABq, J=6.6 Hz); Anal. calcd for $C_{32}H_{62}N_2O_9Si$: C, 59.41; H, 9.66; N, 4.33. Found: C, 59.32; H, 9.78; N, 4.09. High mass calcd for $C_{32}H_{62}N_2O_9Si$: 646.4224. Found: 646.4209. **52b**: $[\alpha]^{25}_D$ +12.8 (c 0.69, $CHCl_3$); IR ν_{max} (neat) 3320, 1732 cm^{-1}; ^1H NMR δ 0.03 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.44 (9H, s), 1.45 (9H, s), 1.47 (9H, s), 1.81-1.89 (3H, m), 2.12-2.18 (2H, m), 2.60-2.92 (5H, m), 3.33-3.41 (2H, m), 3.37 (3H, s), 3.52 (1H, t, J=8.6 Hz), 3.75-3.77 (1H, m), 4.10-4.15 (1H, m), 4.69 (2H, ABq, J=6.6 Hz).

Mugineic acid (1). To a stirred solution of **52a** (160 mg, 0.25 mM) in anisole (0.1 ml) and THF (0.2 ml) at room tempetature was added 20% aqueous HCl (2 ml). After being stirred at room temperature for 40 h, the mixture was washed with Et_2O (20 ml x 3). The aqueous phase was concentrated in vacuo, purified by Dowex 50W x 4 (5 ml) to give an orange solid (79 mg). Further purification was performed by ODS silica gel column chromatography (20 g, H_2O) to give a pale yellow solid (78 mg, quant.). The residue was recrystallized from H_2O-EtOH to give mugineic acid (**1**) (73 mg, 92 %) as a white solid: mp 200-203°C (dec); $[\alpha]^{24}_D$ -64.6 (c 0.43, H_2O); ^1H NMR (D_2O, pH=4.5 adjusted by the addition of 1N-DCl) δ 1.99-2.08 (1H, m), 2.15-2.24 (1H, m), 2.53-2.63 (1H, m), 2.67-2.76 (1H, m), 3.16-3.23 (1H, m), 3.28-3.34 (1H, m), 3.41 (1H, dd, J=2.7, 13.5 Hz), 3.55 (1H, dd, J=9.4, 13.5 Hz), 3.85 (1H, d, J=3.3 Hz), 4.03 (1H, q, J=9.7 Hz), 4.17 (1H, dd, J=4.6, 7.3 Hz), 4.44 (1H, dt, J=3.1, 9.5 Hz), 4.88 (1H, t, J=9.7 Hz). [lit.[1a] mp 210-212°C

(dec); $[\alpha]_D$ -70.7 (H_2O); ^1H NMR[1b] (D_2O, pH=4.5) δ 2.04, 2.18, 2.57, 2.71, 3.20, 3.28, 3.42 (1H, dd, J=2.6, 13.4 Hz), 3.54 (1H, dd, J=9.4, 13.4 Hz), 3.84 (1H, t, J=3.2 Hz), 4.03 (1H, q, J=9.7 Hz), 4.09 (1H, dd, J=4.5, 9.7 Hz), 4.18 (1H, dd, J=4.6, 7.3 Hz), 4.44 (1H, dt, J=3.2, 9.4 Hz), 4.88 (1H, t, J=9.7 Hz).]

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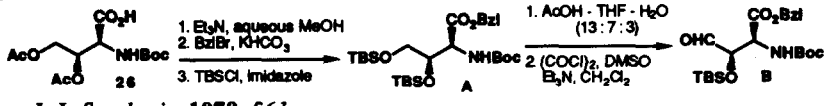
10. The crude carboxylic acid **26** successively underwent deacetylation, benzyl esterification, and tert-butyldimethylsilylation to give the amino acid derivative **A** in 51% overall yield. Deprotection at the primary alcohol function of **A** followed by the Swern oxidation, resulted in the formation of the aldehyde **B** in only 25% yield. However, this constitutes a formal synthesis of mugineic acid (**1**) since **B** was already converted to **1**.[3b]



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