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A Synthesis of A γ-Azetidinyl-β-hydroxy-α-amino Acid Derivative, A Key Intermediate for the Synthesis of Mugineic Acid

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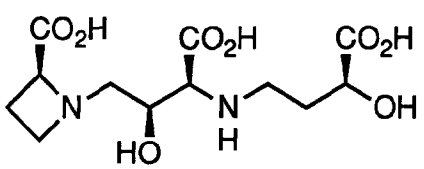
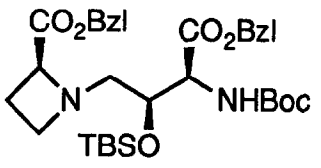
Abstract: The γ-azetidinyl-β-hydroxy-α-amino acid derivative **2**, a key intermediate for the total synthesis of mugineic acid (**1**), was stereoselectively prepared from readily available (2R,3R)-epoxysuccinic acid (**3**).

Mugineic acid (**1**) is a typical iron-chelating phytosiderophore and is required in quantities for the physiological studies of higher plants since it is produced in only a minute amount in Nature.[1] Although we have already succeeded in the total synthesis of mugineic acid (**1**),[2,3] we need a new, more convenient, synthetic method for its large scale production. We now report a new stereoselective synthesis of the γ-azetidinyl-β-hydroxy-α-amino acid derivative **2**, a key intermediate for the synthesis of mugineic acid,[2,3] suitable for the large scale production of 1 because of the ease of handling each synthetic reaction.

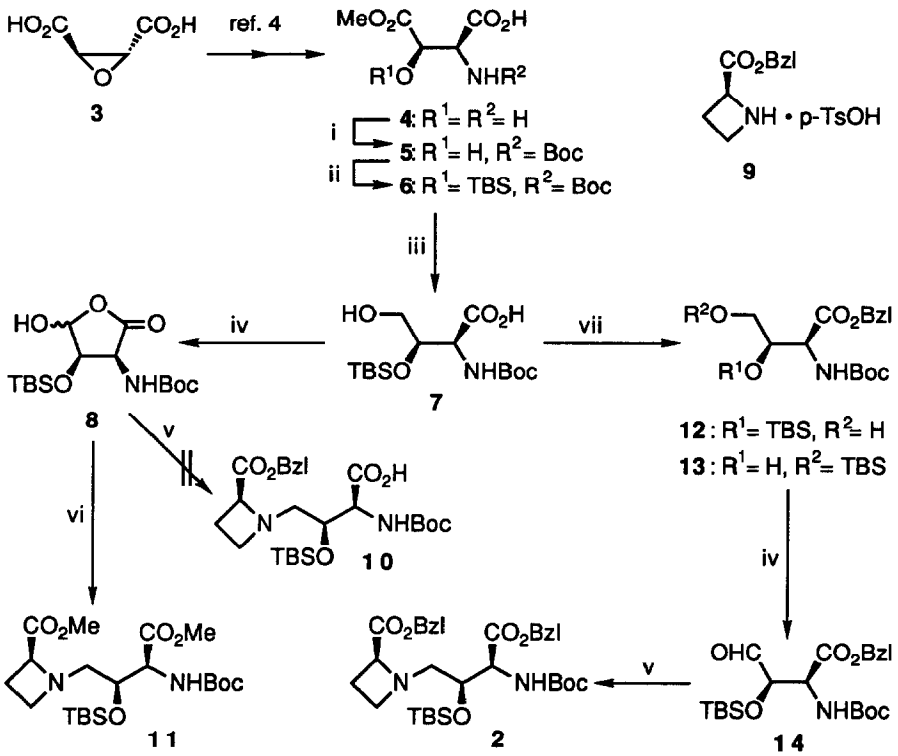


Mugineic Acid (**1**)



2

Our synthesis started from the β-hydroxyaspartic acid derivative **4** which was easily prepared from (2R,3R)-epoxysuccinic acid (**3**) according to the literature.[4] Treatment of **4** with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON) and triethylamine afforded the N-Boc derivative **5** in 88% yield. Silylation of the hydroxyl group of **5** was quantitatively performed with



Scheme 1. i, Boc-ON, Et_3N, dioxane; ii, TBS-Cl, imidazole, DMF; K_2CO_3, MeOH-H_2O; iii, $LiBH_4$; iv, pyridine·SO_3, DMSO, Et_3N, CH_2Cl_2; v, **9**, $NaBH_3CN$, MeOH; vi, (S)-2-azetidinecarboxylic acid, $NaBH_3CN$, MeOH, then $TMSCHN_2$, MeOH-benzene; vii, BzlBr, $KHCO_3$, DMF.

tert-butyldimethylsilyl chloride (TBS-Cl) to give the O-TBS derivative **6**. Selective reduction of its ester group with lithium borohydride smoothly proceeded to give the alcohol **7**.[5] The Parikh-Doering oxidation of **7** afforded the 4-hydroxy-γ-butyrolactone **8** in 67% yield. Although the reductive amination of **8** with the *p*-toluenesulfonate salt of benzyl (S)-2-azetidinecarboxylate **9** by use of sodium cyanoborohydride was unsuccessful to give the carboxylic acid **10**, analogous reductive amination with free (S)-2-azetidinecarboxylic acid, followed by treatment with trimethylsilyldiazomethane ($TMSCHN_2$)[6] furnished the desired methyl ester **11**, the methyl analogue of **2**, though in poor yield (Scheme 1).

Alternatively, the compound **7** was treated with benzyl bromide in the presence of potassium bicarbonate to give the desired alcohol **12** in 46% yield, accompanied with the silyl-migrated product **13** in 23% yield.[7] The Parikh-Doering oxidation of the alcohol **12** gave the aldehyde **14** in 51% yield. Reductive amination of **14** with **9** afforded the key intermediate **2**, which has previously been elabolated to mugineic acid (**1**),[2,3] in 43% yield.

Experimental

Melting points were uncorrected. IR spectra were recorded on a JASCO IRA-2 spectrometer. NMR spectra were recorded on a JEOL PMX-60, FX-100, EX-270, or GSX-400 spectrometer in $CDCl_3$ using tetramethylsilane standard. Mass spectra were obtained with a JEOL DX-300 spectrometer. Optical rotations were determined on a JASCO DIP-140 automatic polarimeter. Analytical TLC was performed on a silica gel plate (E. Merck Art. 5715). Normal column chromatography was carried out with silica gel BW-820 MH (Fuji Davison Co., Ltd.) and flash chromatography was performed with silica gel BW 200 (Fuji Davison Co., Ltd.).

(2S,3R)-3-Hydroxyaspartic acid β-methyl ester (4). Preparation of this compound was performed from (2R,3R)-epoxysuccinic acid (3) according to the reported procedure[4] in 62% overall yield as colorless crystals; mp 216-220°C (dec) (lit.[4] mp 226-229°C (dec)); $[\alpha]^{22}_D$ +66.1 (c 1.0, 1N HCl) (lit.[4] $[\alpha]^{25}_D$ +64.4(c 1.0, 1N HCl)); IR ν_{max} (KBr) 3150, 1765, 1750 cm^{-1}.

N-*tert*-Butoxycarbonyl-(2S,3R)-3-hydroxyaspartic acid β-methyl ester (5). To a stirred suspension of **4** (1.55 g, 9.7 mM) in H_2O (10 ml) at 0°C was added Et_3N (2 ml), followed by the addition of Boc-ON (2.70 g, 11.0 mM) in dioxane (10 ml) and the mixture was allowed to warm to ambient temperature. After being stirred for 15 hr, the reaction mixture was added to 1M aqueous $KHSO_4$ (4 ml) and concentrated *in vacuo*, and extracted three times with CH_2Cl_2 (each 20 ml). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo* to give **5** (2.24 g, 88%) as a pale brown oil: $[\alpha]^{22}_D$ + 18.6 (c 0.90, $CHCl_3$); IR ν_{max} (neat) 3350, 1710 cm^{-1}; ^1H NMR δ 1.46 (9H, s, $OC(CH_3)_3$), 3.84 (3H, s, OCH_3), 4.55 (1H, d, J=2.3 Hz, C_3-H), 4.89 (1H, brd, J=7.6 Hz, C_2-H), 5.06-5.43 (2H, br, disappeared with D_2O, OH, CO_2H), 5.61 (1H, brd, J=7.6 Hz, NHCO).

N-*tert*-Butoxycarbonyl-(2S,3R)-3-*tert*-butyldimethylsiloxyaspartic acid β-methyl ester (6). A mixture of **5** (2.22 g, 8.4 mM), TBS-Cl (3.8 g, 25.3 mM), and imidazole (2.3 g, 33.8 mM) in DMF (11 ml) was stirred at ambient temperature for 18 hr. The reaction mixture was added to 1M aqueous $KHSO_4$ (20 ml) and extracted three times with EtOAc (each 50 ml). The organic layer was washed with water (20 ml) and saturated brine (20 ml), dried over Na_2SO_4, and removed *in vacuo*. The residue was dissolved in 50 % aqueous MeOH, K_2CO_3 (1.1g) was added, and the mixture was stirred for 1.5 hr. After the mixture was concentrated *in vacuo*, the residue was extracted three times with EtOAc (each 50 ml). The organic layer was washed with saturated brine (20 ml), dried over Na_2SO_4, and removed *in vacuo* to give **6** (3.11 g, quant.) as a white solid: mp 106-110°C; $[\alpha]^{22}_D$ + 68.5 (c 1.04, $CHCl_3$); IR ν_{max} (KBr) 3300, 3100, 1750, 1650 cm^{-1}; ^1H NMR δ 0.06 (3H, s, $Si(CH_3)_2$), 0.10 (3H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.46 (9H, s, $OC(CH_3)_3$), 3.77 (3H, s, OCH_3), 4.63 (1H, d, J=2.2 Hz, C_3-H), 4.87 (1H, dd, J=2.4, 7.5 Hz, C_2-H), 5.40 (1H, brd, J=7.5 Hz, NHCO), 7.23 (1H, br, disappeared with D_2O, CO_2H). High resolution mass calcd for $C_{16}H_{31}NO_7Si$: 377.1870. Found: 377.1911.

N-*tert*-Butoxycarbonyl-(2S,3R)-3-*tert*-butyldimethylsiloxyhomoserine (7). To a stirred solution of **6** (1.90 g, 5.0 mM) in Et_2O (20 ml) under argon at 0°C was added dropwise $LiBH_4$ (2M solution in THF, 12.6 ml, 25.1 mM). After being stirred for 18 hr at room temperature, the mixture was quenched with 1M aqueous $KHSO_4$ (20 ml) and extracted three times with CH_2Cl_2 (each 50 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 7 (1.67 g, quant.) as a colorless oil: IR ν_{max} 3430, 1700 cm^{-1}; ^1H NMR δ 0.08 (6H, s, $Si(CH_3)_2$), 0.83 (9H, s, $SiC(CH_3)_3$), 1.38 (9H, s, $OC(CH_3)_3$), 3.66 (2H, brd, J=5.0 Hz, C_4-H, H), 3.95-4.12 (1H, m, C_3-H), 4.25-4.55 (1H, m, C_2-H), 5.35-6.05 (3H, m, 2H disappeared with D_2O, NHCO, OH, CO_2H).

2-*tert*-Butoxycarbonylamino-3-*tert*-butyldimethylsiloxy-4-hydroxy-D-lyxo-1,4-lactone (8). To a stirred solution of 7 (99 mg, 0.28 mM) and triethylamine (120 μl, 0.85 mM) in CH_2Cl_2 (2 ml) at 0°C was added in one portion sulfur trioxide-pyridine complex (140 mg, 0.85 mM) in DMSO (1 ml). After being stirred vigorously for 30 minutes at room temperature, the mixture was poured into ice-water (10 ml) and extracted three times with Et_2O (each 20 ml). The organic layer was washed with 1M aqueous $KHSO_4$ (10 ml) and saturated brine (10 ml), dried over Na_2SO_4, and removed *in vacuo* to give a pale yellow oil. Chromatographic purification of the residue (silica gel BW 200, 15 g, hexane-EtOAc=8:1) gave **10** (67 mg, 67%) as a colorless oil: IR ν_{max} (neat) 3350, 1790, 1710 cm^{-1}; ^1H NMR δ 0.12 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.46 (9H, s, $OC(CH_3)_3$), 2.84 (1H, br, disappeared with D_2O, OH), 4.39 (1H, d, J=4.0 Hz, C_3-H), 4.64-4.72 (1H, m, C_2-H), 5.00-5.08 (1H, br, C_4-H), 5.73 (1H, brd, J=2.8 Hz, NHCO).

Methyl N-[(2S,2'S,3'S)-3'-*tert*-butoxycarbonylamino-3'-methoxycarbonyl-2'-*tert*-butyldimethylsiloxypropyl]-2-azetidinecarboxylate (11). To a stirred solution of **8** (23 mg, 0.07 mM) in MeOH (1 ml) at 0°C was added (S)-azetidinecarboxylic acid (10 mg, 0.10 mM) and $NaBH_3CN$ (5 mg, 0.07 mM). After being stirred for 24 hr at room temperature, the mixture was poured into H_2O (10 ml) and extracted three times with $CHCl_3$ (each 20 ml). The organic layer was dried over Na_2SO_4 and removed *in vacuo* to give a pale yellow oil. The residue was dissolved in 20% MeOH-benzene (2 ml) and $TMSCHN_2$ (1.9 M in hexane, 200 μl) was added. After being stirred for 1 hr at room temperature, the mixture was concentrated *in vacuo* to give a pale yellow oil. The chromatographic purification (silica gel BW 200, 12 g, hexane-Et_2O=3:1) gave **11** (6 mg, 20%) as a colorless oil: $[\alpha]^{23}_D$ - 19.3 (c 0.42, $CHCl_3$); IR ν_{max} (neat) 3350, 1740, 1720 cm^{-1}; ^1H NMR δ 0.09 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.44 (9H, s, $OC(CH_3)_3$), 2.18-2.22 (1H, m, C_3-H), 2.23-2.39 (1H, m, C_3-H), 2.65 (1H, dd, J=4.8, 13.0 Hz, C_1'-H), 2.75 (1H, dd, J=3.3, 13.0 Hz, C_1'-H), 2.98 (1H, dd, J=7.7, 8.8 Hz, C_4-H), 3.51 (1H, br, C_2-H), 3.63 (1H, t, J=8.4 Hz, C_4-H), 3.71 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.04 (1H, brd, J=3.7 Hz, C_2'-H), 4.48 (1H, dd, J=3.7, 8.1 Hz, C_3'-H) 6.52 (1H, brd, J=8.6 Hz, NHCO). High resolution mass calcd for $C_{32}H_{62}N_2O_9Si$: 460.2605. Found: 460.2610.

N-*tert*-Butoxycarbonyl-(2S,3R)-3-*tert*-butyldimethylsiloxyhomoserine benzyl ester (12) and N-*tert*-Butoxycarbonyl-O-*tert*-butyl-

dimethylsiloxy-(2R,3R)-3-hydroxyhomoserine benzyl ester (13). To a stirred solution of **6** (60 mg, 0.16 mM) in Et_2O-THF (1 ml-1.5 ml) under argon at 0°C was added dropwise $LiBH_4$ (2M solution in THF, 240 μl, 0.48 mM). After being stirred for 41 hr, the reaction mixture was quenched with 1M aqueous $KHSO_4$ (5 ml) and extracted three times with CH_2Cl_2 (each 30 ml). Triethylamine (1 ml) was added, and the mixture was dried over Na_2SO_4 and removed *in vacuo* to give the triethylammonium salt of **7** as a colorless oil. The salt was dissolved in DMF (1 ml), and $KHCO_3$ (15 mg, 0.16 mM) and benzyl bromide (23 μl, 0.19 mM) were added at 0°C. After being stirred for 18 hr, the mixture was diluted with EtOAc, washed with water (10 ml), and saturated brine (10 ml), dried over Na_2SO_4, and concentrated *in vacuo* to give a pale yellow oil. The chromatographic purification (silica gel BW 200, 15 g, hexane-Et_2O=6:1) gave **12** (32 mg, 46%) as a colorless oil and **13** (16 mg, 23%) as a colorless oil.[7]

12: IR ν_{max} (neat) 3400, 1740, 1710 cm^{-1}; ^1H NMR δ 0.12 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.45 (9H, s, $OC(CH_3)_3$), 1.67-2.27 (1H, m, disappeared with D_2O, OH), 3.63 (2H, d, J=5.0 Hz, C_4-H, H), 3.93-4.23 (1H, m, C_3-H), 4.40-4.60 (1H, m, C_2-H), 5.25 (2H, s, $C\underline{H}_2C_6H_5$), 5.10-5.30 (1H, m, NHCO), 7.26 (5H, s, $CH_2C_6\underline{H}_5$)

13: $[\alpha]^{22}_D$ + 17.9 (c 1.02, $CHCl_3$); IR ν_{max} (neat) 3450, 1720 cm^{-1}; ^1H NMR δ 0.03 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.43 (9H, s, $OC(CH_3)_3$), 3.32 (1H, brd, J=7.0 Hz, disapeared with D_2O, OH), 3.64 (2H, d, J=5.3 Hz, C_4-H, H), 4.02-4.06 (1H, m, C_3-H), 4.50-4.55 (1H, m, C_2-H), 5.19 (2H, AB q, J=12.5 Hz, $C\underline{H}_2C_6H_5$), 5.66 (1H, brd, J=7.3 Hz, NHCO), 7.32-7.36 (5H, m, $CH_2C_6\underline{H}_5$).

Benzyl (2R,3R)-2-*tert*-butoxycarbonylamino-3-*tert*-butyldimethylsiloxy-4-oxobutyrate (14). To a stirred solution of **12** (102 mg, 0.27 mM) and triethylamine (110 μl, 0.81 mM) in CH_2Cl_2 (2 ml) at 0°C was added in one portion sulfur trioxide-pyridine complex (175 mg, 0.81 mM) in DMSO (2.5 ml). After being stirred vigorously for 35 minutes at room temperature, the mixture was poured into ice-water (20 ml) and extracted three times with Et_2O (each 20 ml). The organic layer was washed with 1M aqueous $KHSO_4$ (20 ml) and saturated brine (10 ml), dried over Na_2SO_4, and concentrated *in vacuo* to give a pale yellow oil. The chromatographic purification of the residue (silica gel BW 200, 10 g, hexane-Et_2O=6:1) gave **14** (52 mg, 51%) as a colorless oil; $[\alpha]^{22}_D$ +26.5 (c 0.76, $CHCl_3$); IR ν_{max} (neat) 3500, 1730, 1710 cm^{-1}; ^1H NMR δ 0.05 (6H, s, $Si(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.45 (9H, s, $OC(CH_3)_3$), 4.43 (1H, s, C_3-H), 4.82 (1H, d, J=5.3 Hz, C_2-H), 5.18 (2H, AB q, J=12.2 Hz, $C\underline{H}_2C_6H_5$), 5.41 (1H, brd, J=6.9 Hz, NHCO), 7.29-7.39 (5H, m, $CH_2C_6\underline{H}_5$), 9.56 (1H, s, CHO). High resolution mass calcd for $C_{22}H_{35}NO_6Si$: 437.2232. Found: 437.2161.

Benzyl N-[(2S,2'S,3'S)-3'-*tert*-butoxycarbonylamino-3'-benzyloxycarbonyl-2'-*tert*-butyldimethylsiloxypropyl]-2-azetidinecarboxylate (2). To a stirred solution of **14** (44 mg, 0.10 mM) in MeOH (0.5 ml) at 0°C was added a solution of **9** (37 mg, 0.11 mM) in MeOH (0.5 ml) and $NaBH_3CN$ (7 mg, 0.11 mM). After being stirred for 12 hr, the mixture was poured into saturated aqueous $NaHCO_3$ (5 ml) and extracted three times with Et_2O (each 20 ml). The

organic layer was washed with saturated brine (10 ml), dried over Na_2SO_4, and concentrated *in vacuo* to give a pale yellow oil. The chromatographic purification (silica gel BW 200, 10 g, hexane-EtOAc=6:1) gave **2** (24 mg, 43%) as a colorless oil; IR ν_{max} (neat) 3450, 1740, 1720 cm^{-1}; ^1H NMR δ 0.03 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$), 0.85 (9H, s, $SiC(CH_3)_3$), 1.43 (9H, s, $OC(CH_3)_3$), 2.13-2.24 (1H, m, C_3-H), 2.31-2.40 (1H, m, C_3-H), 2.64 (1H, dd, J=5.3, 12.8 Hz, $C_{1'}$-H), 2.74 (1H, dd, J=3.9, 12.8 Hz, $C_{1'}$-H), 2.94 (1H, dd, J=7.8, 8.4 Hz, C_4-H), 3.47 (1H, brt, J=7.0 Hz, C_2-H), 3.63 (1H, t, J=8.2 Hz, C_4-H), 4.02 (1H, brd, J=3.8 Hz, $C_{2'}$-H), 4.54 (1H, dd, J=3.2, 8.7 Hz, $C_{3'}$-H), 5.11 (2H, AB q, J=12.4 Hz, $C\underline{H}_2C_6H_5$), 5.12 (2H, AB q, J=12.4 Hz, $C\underline{H}_2C_6H_5$), 6.37 (1H, d, J=8.6 Hz, NHCO), 7.27-7.37 (10 H, m, $CH_2C_6\underline{H}_5$). High resolution mass calcd for $C_{33}H_{48}N_2O_7Si$: 612.3231. Found: 612.3201. Identical with the sample prepared before.[2,3]

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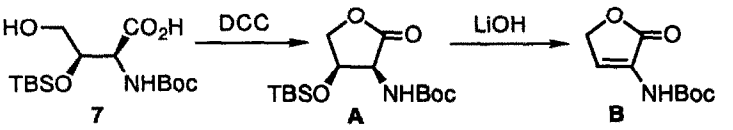
5 The alcohol **7** was easily lactonized with DCC in the presence of DMAP in CH_2Cl_2 at room temperature for 45 min. The lactone **A** thus obtained in 83% yield easily underwent the elimination under alkaline conditions (LiOH, THF-H_2O, 0°C, 1 h) to give 2-Boc-tetrone **B** in quantitative yield. Cf. Hamada, Y.; Kawai, A.; Matsui, T.; Hara, O.; Shioiri, T. *Tetrahedron* **1990**, *46*, 4823.



7 A B

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7 The primary OH function of **12** is recognized by OH multiplet in its ^1H NMR spectra while the secondary OH function of **13** is done by the OH doublet. Cf. Mulzer, J.; Schöllhorn, B. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 431.