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SYNTHESIS OF TETRASUBSTITUTED PYRROLIDINE DERIVATIVES EMPLOYING β-LACTAM AS A CHIRAL BUILDING BLOCK

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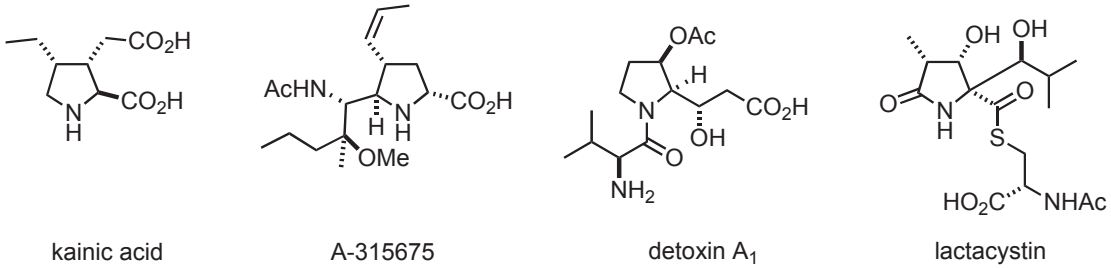
Abstract – A new method for constructing tetrasubstituted pyrrolidine derivatives using the known β-lactam as a chiral building block was developed. After construction of a carbapenem skeleton, the β-lactam moiety was cleaved to afford a multi-substituted pyrrolidine. The present method was employed for the synthesis of A-315675 analogs.

INTRODUCTION

Multi-substituted pyrrolidines are widely found as a substructure of natural and non-natural biologically active compounds. For example, kainic acid is known as the potent glutamic acid receptor antagonist, and A-315675[1] is a neuraminidase inhibitor developed by the Abott laboratories. The 3-hydroxypyrrolidine derivatives such as detoxin A_1[2] and lactacystin[3] also have promising beneficial biological activities (Figure 1). Owing to this interest, we have been intrigued with the challenge of developing an efficient and stereocontrolled synthetic method for these types of pyrrolidines. We planned the synthesis of A-315675 analogs **1** and **2** having a hydroxyl group at the C-3 position, because of our interest in their pharmacological properties.

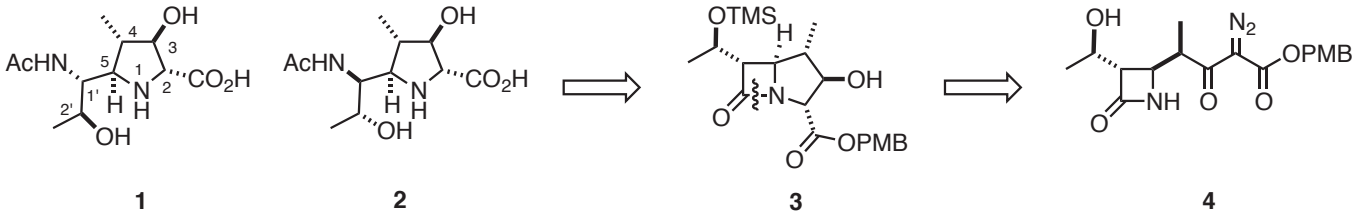


kainic acid A-315675 detoxin A_1 lactacystin

Figure 1. Structures of bioactive pyrrolidine derivatives

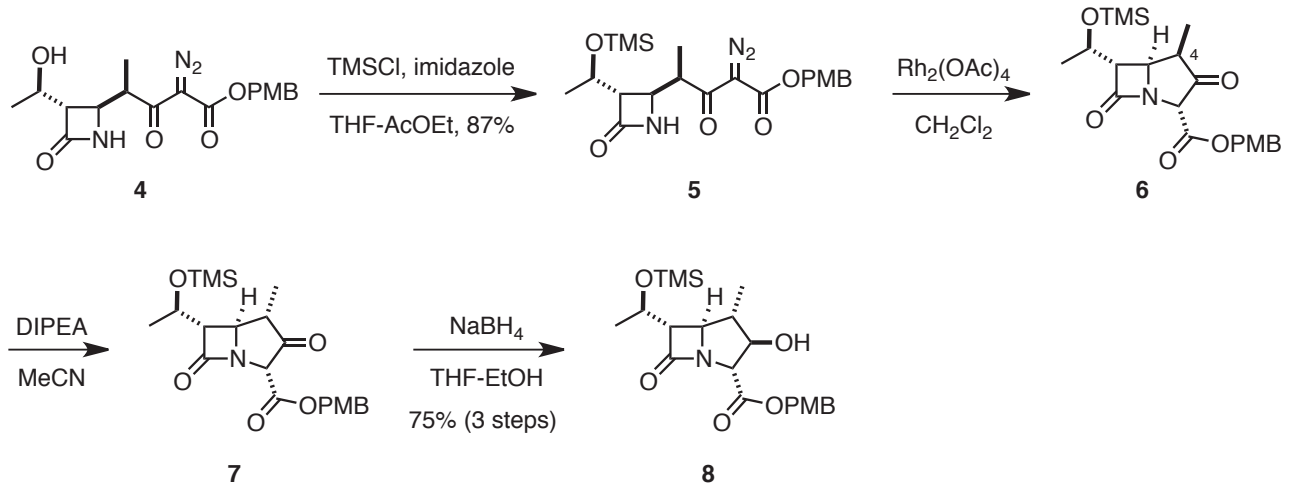
RESULTS AND DISCUSSION

The strategy toward the stereoselective synthesis of **1** and **2** is shown in Scheme 1. We planned to construct the pyrrolidine ring through cyclization of optically active β-lactam **4**[4] followed by ring cleavage of bicyclic compound **3**. The Rh-catalyzed intramolecular N-H insertion reactions of diazo keto ester **4** have been commonly used for the synthesis of carbapenem antibiotics, and the rigid conformation of the bicyclic skeleton would be advantageous for controlling the stereochemistry of the highly substituted pyrrolidine ring.



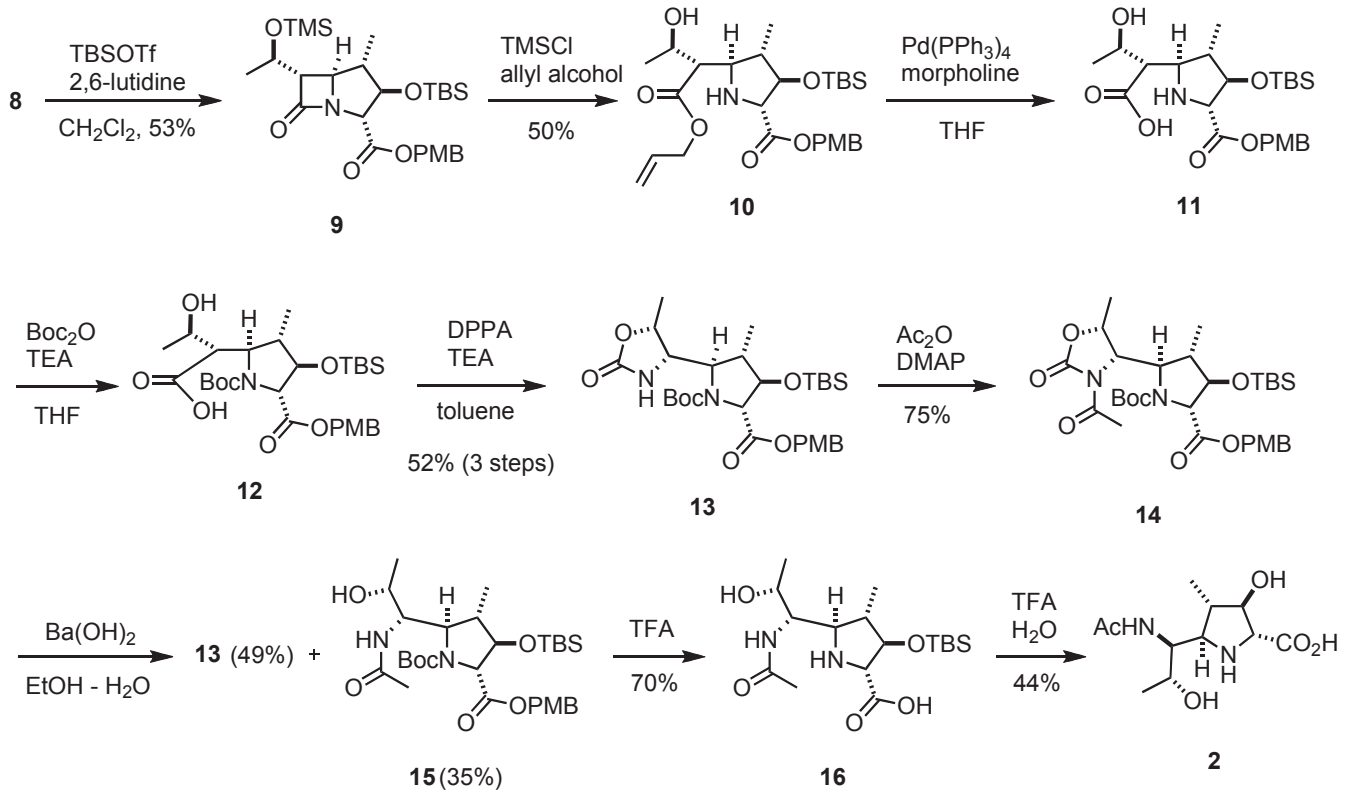
Scheme 1. Synthetic plan for **1** and **2**

Carbapenem derivative **8** possessing the suitable protective groups was synthesized as shown in Scheme 2. First, secondary alcohol **4** was treated with TMSCl and imidazole in THF-AcOEt to afford O-protected diazo compound **5** which was subjected to the intramolecular cyclization reaction catalyzed by $Rh_2(OAc)_4$. Under the influence of *N*,*N*-diisopropylethylamine (DIPEA), ketone **6** underwent inversion of the C-4 methyl group located at the concave face, giving rise to the corresponding epimer **7**. Reduction of ketone **7** with $NaBH_4$ in THF-EtOH resulted in formation of alcohol **8** with high stereoselectivity. The configuration of the hydroxyl group in **8** was established by NOESY experiments, showing that the hydride attack occurred from the convex face of bicyclic ketone **7**.



Scheme 2. Synthesis of carbapenem derivative **8**

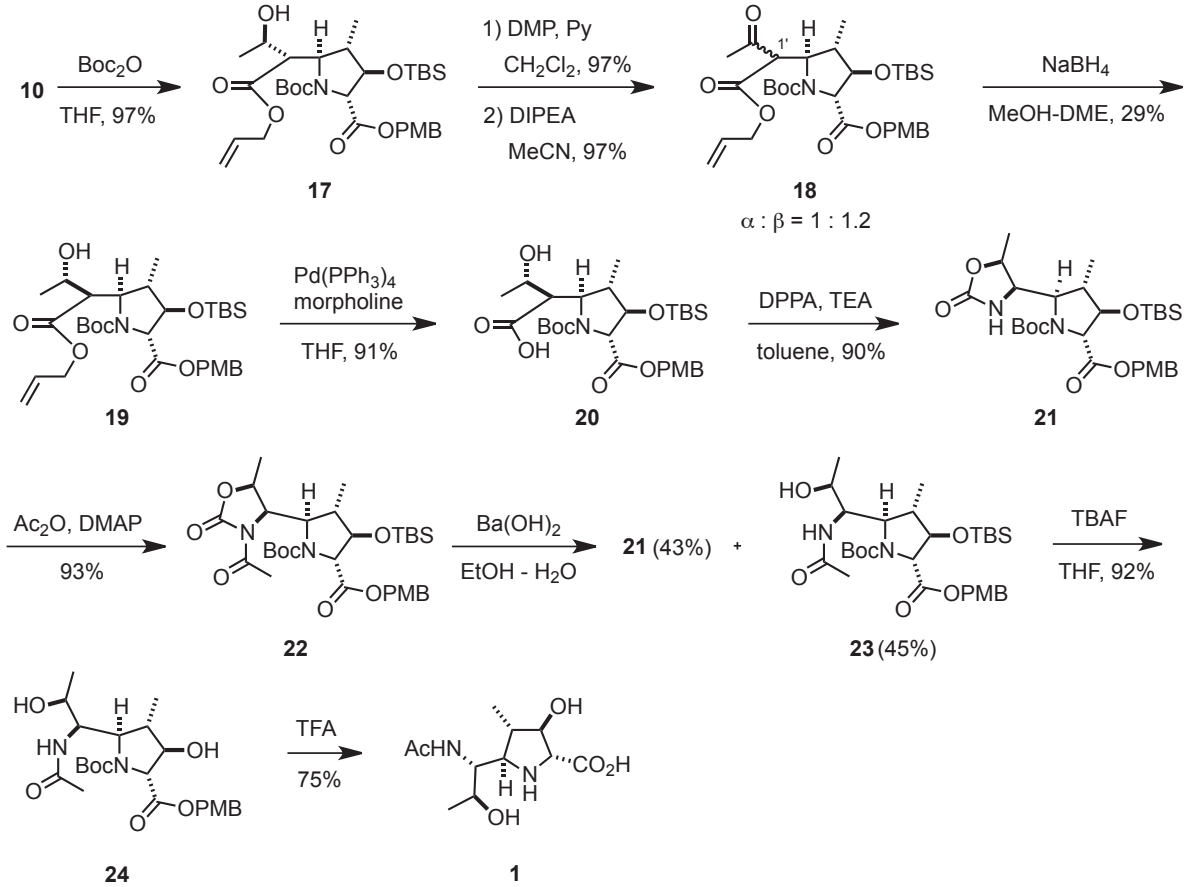
Protection of alcohol **8** by the reaction with TBSOTf and 2,6-lutidine in CH_2Cl_2 furnished **9**[5] which was further transformed into **2**, the (1'*S*, 2'*R*)-diastereomer of **1** as shown in Scheme 3. Thus, carbapenem derivative **9** was treated with TMSCl in allyl alcohol to afford allyl ester **10** through alcoholysis of the β-lactam moiety and removal of the TMS group. The Pd-catalyzed deallylation reaction of allyl ester **10** followed by protection of the secondary amine in the resulting carboxylic acid **11** with Boc_2O afforded **12**. Introduction of an amino group on the side chain was accomplished by the Curtius rearrangement of carboxylic acid **12** employing diphenylphosphoryl azide (DPPA) to yield 2-oxazolidone derivative **13**. The conformationally fixed oxazolidone ring was useful for establishing the stereochemistry of the newly formed C-N bond by the NOESY experiments. Cleavage of the oxazolidone ring was then achieved through acetylation of **13** to afford imide **14** followed by treatment with $Ba(OH)_2$, giving rise to a mixture of **13** and alcohol **15**. Finally, alcohol **15** was converted to **2** through removal of both the Boc and PMB groups mediated by TFA and desilylation in aqueous TFA.



Scheme 3. Synthesis of **2**, the (1'*S*, 2'*R*)-diastereomer of **1**

Having established the method for conversion of the known compound **4** to tetrasubstituted pyrrolidine derivative **2**, the synthesis of its isomer **1** which possesses the stereochemistry similar to that of A-315675 was undertaken. Since it was necessary to invert the configurations at the C-1' and C-2' positions of **2**, the synthetic intermediate **10** was converted to ketone **18** through protection of the amino group and

oxidation with Dess-Martin periodinane[6] (DMP) (Scheme 4). Treatment of the product with DIPEA gave an inseparable mixture (1:1.2) of the C-1' epimers **18a** and **18b** which was subjected to $NaBH_4$ reduction in MeOH-DME. The resulting mixture involving the diastereomers of alcohol **17** was separated by silica gel column chromatography, and alcohol **19**, the configuration of which was not clear at this point, was isolated in 29% yield. Though the other diastereomers were difficult to separate from each other, the samples for NMR analysis were obtained in small amounts by HPLC. Figure 2 shows the partial ^1H NMR spectra of the alcohols; (A) alcohol **17**, (B) the mixture of diastereomers obtained by $NaBH_4$ reduction of a 1:1.2 mixture of ketones **18a** and **18b**, (C) alcohol **19** after isolation from the mixture, (D) a diastereomer of **17** and **19**, and (E) another diastereomer of **17** and **19**. Alcohol **19** was then transformed into **1** by a similar reaction sequence for the synthesis of **2**. The Pd-catalyzed deallylation of **19** followed by the Curtius rearrangement of carboxylic acid **20** afforded oxazolidone **21**, and the relative stereochemistry at the C-1' and C-2' positions was determined by NOE experiments at this stage. Acetylation of **21** using Ac_2O and DMAP gave **22**, and subsequent hydrolysis of oxazolidone with $Ba(OH)_2$ produced a separable mixture of alcohols **23** and **21**. Finally, the desired compound **1**[7] was obtained from alcohol **23** through desilylation with TBAF and removal of the Boc and DMB group with TFA.[8]



Scheme 4. Synthesis of A-315675 analog **1**

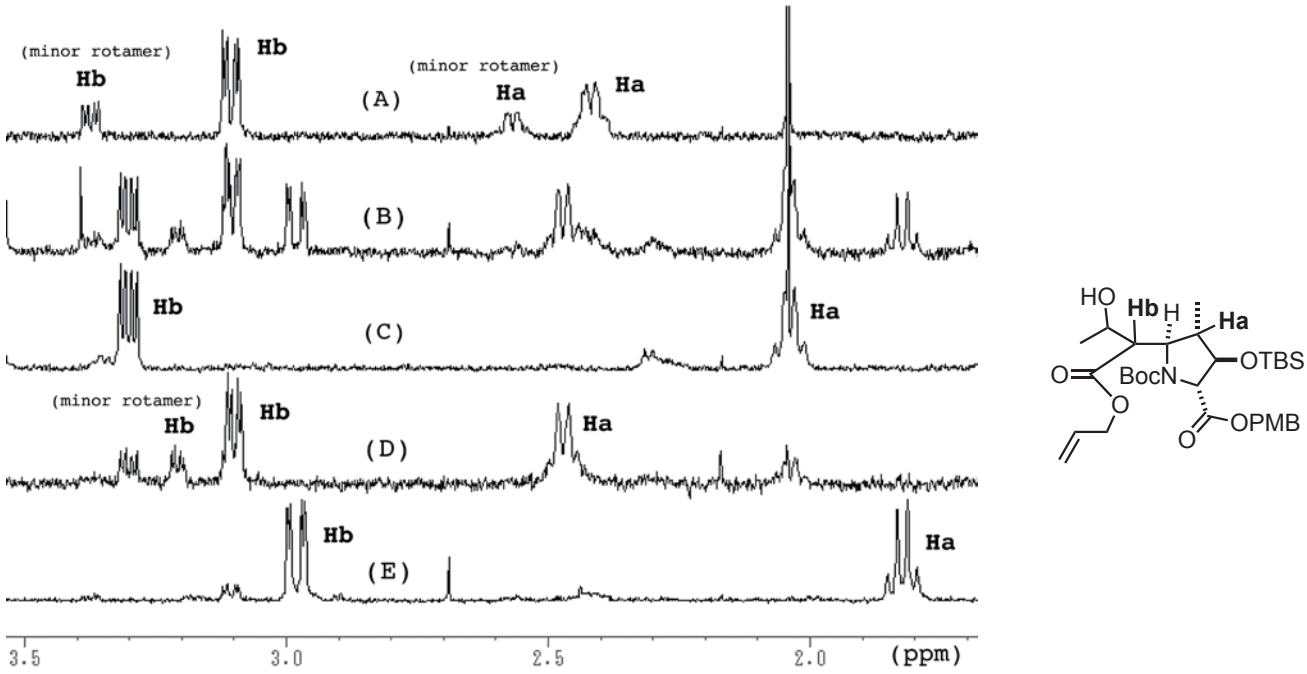


Figure 2. ^{1}H NMR Spectra (400 MHz, partial) of (A) pure alcohol **17**, (B) a mixture of diastereomers obtained by $NaBH_4$ reduction of ketones **18a** and **18b**, (C) pure alcohol **19**, (D) a diastereomer of **17** and **19** (containing a small amount of **19**), and (E) another diastereomer of **17** and **19** (containing a small amount of **17**)

In summary, we have achieved the asymmetric synthesis of A-315675 analog **1** and its side chain diastereomer **2**, on the basis of the construction of a carbapenem skeleton and the ring opening reaction of the β-lactam. This method shows promise for the stereocontrolled synthesis of various multi-substituted pyrrolidine compounds. Synthetic application to new pyrrolidine derivatives is now under investigation.

EXPERIMENTAL

IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer using 5 mm NaCl or CaF_2 plates. Wavelength of maximum absorbance ($_{\nu}$ max) is quoted in cm^{-1}. ^{1}H-NMR spectra were recorded on a Varian Unity INOVA 500 spectrometer (500 MHz) in $CDCl_3$ (δ_H 7.26) with tetramethylsilane as an internal standard. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), double triplet (dt), broad singlet (brs) and multiplet (m). ^{13}C-NMR spectra were recorded on a Varian Unity INOVA 500 spectrometer (125 MHz) in $CDCl_3$ (δ_C 77.0) with tetramethylsilane as an internal standard. Chemical shifts are reported in part per million (ppm). Electro splay ionization mass (ESI-MS) and high resolution mass (HR-MS) spectra were recorded on a Thermo Scientific Exactive at the Instrumental Analysis Division, Equipment Management Center Creative Research Institution, Hokkaido University. Reactions were monitored by

LCMS (SHIMADZU LCMS-2010EV) or TLC with Merck Kieselgel 60 F_{254}. The Silica gel used for column chromatography was ISCO gold or Yamazen pre packed columns. All experiments were carried out under positive pressure of dry nitrogen. All of the organic solvents used in this study were dried over appropriate drying agents.

***O*-Protected diazo compound** (**5**). To a solution of **4** (10.0 g, 26.6 mmol) in THF (30 mL) and AcOEt (90 mL) was added imidazole (3.26 g, 48.0 mmol) and TMSCl (4.77 mL, 37.3 mmol) at room temperature. After stirring for 1 h at the same temperature, the reaction mixture was treated with H_2O and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 1 : 1) to give **5** as a yellow oil (10.3 g, 23.1 mmol, 87%).

yellow oil. IR (neat) 3263, 2959, 2143, 1758, 1714, 1651, 1516, 1376, 1299, 1251, 991, 844 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.10 (9H, s), 1.15 (3H, d, *J* = 6.8 Hz), 1.21 (3H, d, *J* = 6.1 Hz), 2.98-2.96 (1H, m), 3.80 (1H, dd, *J* = 2.4, 4.9 Hz), 3.82 (3H, s), 3.95 (1H, ddd, *J* = 13.8, 6.8, 4.9 Hz), 5.20 (2H, dd, *J* = 18.4, 11.8 Hz), 5.95 (1H, s), 6.91 (2H, dt, *J* = 8.8, 2.2 Hz), 7.31 (2H, dt, *J* = 8.8, 2.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.37, 22.64, 43.36, 52.65, 55.44, 61.33, 65.75, 67.21, 114.27, 127.11, 130.54, 160.16, 161.25, 168.21, 194.49; HRMS (ESI) Calcd for $C_{21}H_{29}N_3O_6NaSi$ ($[M+Na]^+$): 470.1718. Found 470.1715.

Ketone (**6**). To a solution of **5** (10.3 g, 23.1 mmol) in CH_2Cl_2 (40 mL) was added $Rh_2(OAc)_4$ (68.0 mg, 0.155 mmol) at room temperature. After stirring for 6 h at 43 °C, the reaction mixture was concentrated under vacuum to give **6** that was used for the next step without purification.

purple oil. IR (neat) 3446, 2959, 1770, 1614, 1517, 1303, 1252, 1175, 1035, 845 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.13 (9H, s), 1.17 (3H, d, *J* = 7.8 Hz), 1.28 (3H, d, *J* = 6.1 Hz), 2.72-2.79 (1H, m), 3.19 (1H, dd, *J* = 6.1, 2.4 Hz), 3.80 (3H, s), 4.15 (1H, dd, *J* = 7.8, 2.4 Hz), 4.23-4.29 (1H, m), 4.64 (1H, s), 5.13 (2H, s), 6.88 (2H, d, *J* = 8.8 Hz), 7.29 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.34, 12.53, 22.79, 41.76, 55.37, 55.71, 62.26, 62.58, 66.25, 67.88, 114.12, 127.05, 130.22, 159.96, 165.26, 172.82, 209.27

Ketone (**7**). To a solution of **6** (9.68 g, 23.1 mmol) in MeCN (40 mL) was added DIPEA (2.02 mL, 11.5 mmol) at 0 °C. After stirring for 20 h at the same temperature, the reaction mixture was treated with aqueous citric acid and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum to give **7** that was used for the next step without purification.

orange oil. IR (neat) 3447, 2961, 2839, 1767, 1517, 1251, 1175, 1035, 845 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.13 (9H, s), 1.24 (3H, d, *J* = 7.1 Hz), 1.31 (3H, d, *J* = 6.1 Hz), 2.23-2.32 (1H, m), 3.13 (1H, d,

J = 7.1 Hz), 3.60 (1H, d, *J* = 7.6 Hz), 3.81 (3H, s), 4.22-4.29 (1H, m), 4.72 (2H, s), 5.13 (3H, s), 6.89 (2H, d, *J* = 8.6 Hz), 7.29 (2H, d, *J* = 8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.25, 11.84, 22.79, 47.54, 55.29, 59.02, 63.77, 66.30, 67.78, 68.54, 114.03, 126.98, 130.15, 159.87, 165.37, 171.97, 208.96

Alcohol (**8**). To a solution of **7** (9.68 g, 23.1 mmol) in THF (100 mL), EtOH (100 mL) was added $NaBH_4$ (436 mg, 11.5 mmol) at -78 °C After stirring for 1 h at the same temperature, to the mixture was added AcOH (0.658 mL, 11.5 mmol) and stirred for 10 min at the room temperature. The reaction mixture was treated with H_2O and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 1 : 3) to give **8** as a yellow oil (7.30 g, 17.3 mmol, 75% for 3 steps).

yellow oil. IR (neat) 3460, 2959, 1746, 1614, 1516, 1251, 1174, 1111, 1034, 844 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.11 (9H, s), 1.12 (3H, d, *J* = 6.6 Hz), 1.25 (3H, d, *J* = 6.4 Hz), 1.83-1.92 (1H, m), 2.92 (1H, br s), 3.00 (1H, d, *J* = 7.1 Hz), 3.29 (1H, d, *J* = 8.3 Hz), 3.80 (3H, s), 4.09-4.24 (3H, m), 5.13 (2H, s), 6.88 (2H, d, *J* = 8.1 Hz), 7.29 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ:0.28, 13.65, 22.79, 46.20, 55.31, 60.27, 65.48, 65.80, 66.35, 67.13, 86.01, 114.05, 127.40, 130.20, 159.81, 170.56, 175.29; HRMS (ESI) Calcd for $C_{21}H_{31}NO_6NaSi$ ($[M+Na]^+$): 444.1813. Found 444.1805.

Silyl ether (**9**). To a solution of **8** (1.00 g, 2.37 mmol) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.553 mL, 4.74 mmol) and TBSOTf (0.818 mL, 3.56 mmol) at 0 °C. After stirring for 30 min at the same temperature, the reaction mixture was treated with aqueous citric acid and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 5 : 1) to give **9** as a white solid (0.670 g, 1.25 mmol, 53%).

white solid. mp 71-73 °C; IR (neat) 2956, 2937, 2855, 1758, 1744, 1516, 1250, 1176, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.11 (6H, s), 0.83 (9H, s), 1.02 (3H, d, *J* = 7.1 Hz), 1.25 (3H, d, *J* = 6.1 Hz), 1.55 (9H, s), 1.87-1.94 (1H, m), 3.01 (1H, d, *J* = 7.1 Hz), 3.32 (1H, d, *J* = 6.8 Hz), 3.81 (3H, s), 4.09-4.16 (1H, m), 4.20 (1H, d, *J* = 5.4 Hz), 4.33 (1H, t, *J* = 5.4 Hz), 5.07-5.14 (2H, m), 6.87 (2H, d, *J* = 8.5 Hz), 7.30 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ:-4.89, -4.82, 0.29, 14.60, 17.77, 22.81, 25.59, 47.11, 55.29, 61.02, 66.21, 66.63, 66.97, 67.02, 87.27, 113.93, 127.39, 130.32, 159.78, 170.30, 175.21; Calcd for $C_{27}H_{45}NO_6NaSi_2$ ($[M+Na]^+$): 558.2678. Found 558.2670.

Allyl ester (**10**). To a solution of **9** (510 mg, 0.952 mmol) in allyl alcohol (5.2 mL) was added TMSCl (1.22 mL, 9.52 mmol) at 0 °C. After stirring for 1.5 h at the same temperature, the reaction mixture was treated with aqueous K_2CO_3 and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 1 : 1) to give

10 as a yellow oil (246 mg, 0.472 mmol, 50%).

yellow oil. IR (neat) 3345, 2956, 2931, 2857, 1733, 1517, 1251, 1173, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: -0.01 (3H, s), 0.02 (3H, s), 0.86 (9H, s), 0.92 (3H, d, *J* = 6.4 Hz), 1.20 (3H, d, *J* = 6.4 Hz), 2.05-2.12 (1H, m), 2.59-2.62 (1H, m), 3.30-3.34 (1H, m), 3.62 (1H, d, *J* = 4.2 Hz), 3.81 (3H, s), 3.94 (1H, t, *J* = 4.2 Hz), 4.24-4.31 (1H, m), 4.55-4.64 (2H, m), 5.06 (1H, d, *J* = 12.0 Hz), 5.14 (1H, d, *J* = 12.0 Hz), 5.24 (1H, d, *J* = 10.3 Hz), 5.34 (1H, d, *J* = 17.1 Hz), 5.86-5.95 (1H, m), 6.88 (2H, d, *J* = 7.3 Hz), 7.29 (2H, d, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.74, -4.71, 15.80, 17.90, 21.43, 25.70, 45.00, 53.30, 55.30, 62.68, 65.19, 66.55, 66.69, 66.82, 83.06, 113.95, 118.78, 127.49, 130.42, 131.86, 159.82, 172.40, 173.72; HRMS (ESI) Calcd for $C_{27}H_{44}NO_7Si$ ($[M+H]^+$): 522.2882. Found 522.2872.

Amino acid (**11**). To a solution of **10** (340 mg, 0.652 mmol) in THF (4 mL) was added morpholine (0.114 mL, 1.30 mmol) and $Pd(PPh_3)_4$ (37.7 mg, 0.0330 mmol) at room temperature. After stirring for 30 min at the same temperature, to the mixture was further added morpholine (0.114 mL, 1.30 mmol) and $Pd(PPh_3)_4$ (37.7 mg, 0.0330 mmol). After stirring for additional 30 min, the reaction mixture was treated with aqueous citric acid and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum to give **11** that was used for the next step without purification.

colorless oil. IR (neat) 3250, 2927, 2856, 1741, 1614, 1558, 1515, 1397, 1248, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: -0.11 (3H, s), -0.01 (3H, s), 0.79 (9H, s), 1.04 (3H, d, *J* = 6.1 Hz), 1.28 (3H, d, *J* = 6.4 Hz), 1.99-2.08 (1H, m), 2.40 (1H, d, *J* = 6.8 Hz), 3.68 (1H, d, *J* = 11.7 Hz), 3.78 (3H, s), 3.92 (1H, d, *J* = 5.9 Hz), 4.01 (1H, t, *J* = 7.8 Hz), 4.06-4.13 (1H, m), 5.06 (1H, d, *J* = 11.7 Hz), 5.11 (1H, d, *J* = 11.7 Hz), 6.82 (2H, d, *J* = 8.5 Hz), 7.24 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.81, -4.47, 13.97, 17.82, 22.06, 25.63, 44.57, 53.34, 55.25, 59.92, 63.43, 66.15, 68.04, 80.54, 113.99, 126.53, 130.79, 160.01, 169.64, 177.11; HRMS (ESI) Calcd for $C_{24}H_{39}NO_7NaSi$ ($[M+Na]^+$): 504.2388. Found 504.2384.

Boc carbamate (**12**). To a solution of **11** (314 mg, 0.652 mmol) in THF (3 mL) was added Boc_2O (0.499 mL, 2.15 mmol) and Et_3N (0.271 mL, 1.96 mmol) at room temperature. After stirring for 4 h at the same temperature, the reaction mixture was treated with aqueous citric acid and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum to give **12** that was used for the next step without purification.

colorless oil. IR (neat) 3447, 2957, 2933, 2859, 1746, 1700, 1517, 1369, 1253, 1172, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 1.04 (3H, d, *J* = 7.3 Hz), 1.24 (3H, d, *J* = 6.1 Hz), 1.34 (9H, s), 2.38-2.45 (1H, m), 3.09-3.12 (1H, m), 3.80 (3H, s), 3.91-3.97 (2H, m), 4.09-4.26 (2H, m), 5.09 (1H, d, *J* = 11.7 Hz), 5.13 (1H, d, *J* = 11.7 Hz), 6.88 (2H, d, *J* = 8.3 Hz), 7.30 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.10, -4.96, 18.13, 19.11, 21.41, 25.71, 28.08, 45.02, 55.17,

55.31, 64.44, 65.85, 66.96, 70.21, 81.07, 82.39, 113.98, 127.31, 130.62, 154.32, 159.92, 170.87, 177.34; HRMS (ESI) Calcd for $C_{29}H_{47}NO_9NaSi$ ($[M+Na]^+$): 604.2912. Found 604.2907.

Carbamate (**13**). To a solution of **12** (379 mg, 0.652 mmol) in toluene (4 mL) was added Et_3N (0.298 mL, 2.15 mmol) and DPPA (0.420 mL, 1.95 mmol) at room temperature. After stirring for 1 h at 80 °C, the reaction mixture was treated with aqueous citric acid and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 1 : 1) to give **13** as a white amorphous (197 mg, 0.340 mmol, 52% for 3 steps).

white amorphous. IR (neat) 3384, 2955, 2858, 1748, 1697, 1683, 1518, 1457, 1395, 1257, 1186, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.05 (3H, s), 0.09 (3H, s), 0.88 (9H, s), 1.01 (3H, d, *J* = 7.6 Hz), 1.32 (3H, d, *J* = 6.4 Hz), 1.35 (9H, s), 1.79 (1H, q, *J* = 7.6 Hz), 3.81 (3H, s), 3.88 (1H, s), 3.95 (1H, d, *J* = 9.5 Hz), 4.15 (1H, s), 4.29-4.33 (1H, m), 4.50-4.56 (1H, m), 5.05 (1H, d, *J* = 11.7 Hz), 5.17 (1H, d, *J* = 11.7 Hz), 6.46 (1H, s), 6.88 (2H, d, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.15, -4.90, 14.96, 17.12, 17.84, 25.67, 28.03, 45.48, 55.30, 60.82, 65.18, 67.00, 69.93, 75.40, 81.07, 81.78, 113.98, 127.27, 130.59, 155.49, 157.93, 159.98, 169.93; HRMS (ESI) Calcd for $C_{29}H_{46}N_2O_8NaSi$ ($[M+Na]^+$): 601.2916. Found 601.2906.

Acetylated carbamate (**14**). To a solution of **13** (176 mg, 0.305 mmol) in Ac_2O (4.32 mL, 45.7 mmol) was added DMAP (37.2 mg, 0.305 mmol) at room temperature. After stirring for 5 h at 80 °C, the reaction mixture was treated with aqueous K_2CO_3 and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 1 : 1) to give **14** as a white amorphous (143 mg, 0.230 mmol, 75%).

white amorphous. IR (neat) 2955, 2933, 2857, 1792, 1748, 1715, 1517, 1374, 1252, 1204, 1173, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.00 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 1.10 (3H, d, *J* = 7.3 Hz), 1.33 (9H, s), 1.47 (3H, d, *J* = 6.6 Hz), 1.89-1.97 (1H, m), 2.44 (3H, s), 3.81 (3H, s), 3.87 (1H, s), 4.17-4.23 (2H, m), 4.60-4.69 (1H, m), 5.01-5.10 (1H, m), 5.04 (1H, d, *J* = 11.7 Hz), 5.14 (1H, d, *J* = 11.7 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 7.28 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.36, -4.86, 14.10, 14.38, 17.76, 23.96, 25.63, 28.04, 55.27, 55.30, 61.71, 62.12, 66.67, 69.06, 74.30, 80.64, 82.66, 113.93, 127.43, 130.46, 153.26, 153.82, 159.84, 169.83, 170.85; HRMS (ESI) Calcd for $C_{31}H_{48}N_2O_9NaSi$ ($[M+Na]^+$): 643.3021. Found 643.3012.

Alcohol (**15**). To a solution of **14** (142 mg, 0.229 mmol) in EtOH (1 mL) and H_2O (0.5 mL) was added $Ba(OH)_2\,8H_2O$ (216 mg, 0.686 mmol) at room temperature. After stirring for 1 h at the same temperature, the reaction mixture was treated with aqueous citric acid and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate

was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 100 : 0 ~ 0: 100) to give **15** as a colorless oil (47.1 mg, 0.0790 mmol, 35%) and **13** as a colorless oil (65.3 mg, 0.113 mmol, 49%).

colorless oil. IR (neat) 3362, 2956, 2932, 2858, 1684, 1518, 1374, 1252, 1172, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.00 (3H, d, *J* = 7.8 Hz), 1.11 (3H, d, *J* = 6.1 Hz), 1.37 (9H, s), 2.17 (1H, q, *J* = 7.8 Hz), 3.81 (3H, s), 3.89 (2H, brs), 4.15 (1H, s), 4.41 (1H, d, *J* = 4.9 Hz), 4.50-4.55 (1H, m), 5.05 (1H, d, *J* = 11.7 Hz), 5.17 (1H, d, *J* = 11.7 Hz), 6.88 (2H, d, *J* = 8.8 Hz), 7.30 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.09, -4.94, 17.23, 17.68, 17.88, 23.12, 25.66, 27.98, 45.37, 55.33, 61.24, 64.84, 66.93, 69.05, 69.97, 81.68, 81.95, 113.97, 127.35, 130.55, 156.90, 159.93, 170.29, 172.84; HRMS (ESI) Calcd for $C_{30}H_{50}N_2O_8NaSi$ ($[M+Na]^+$): 617.3229. Found 617.3218.

β-Siloxy amino acid (**16**). A mixture of **15** (37.5 mg, 0.0630 mmol) and TFA (0.704 mL, 9.14 mmol) was stirred for 15 min at room temperature. The reaction mixture was treated with aqueous K_2CO_3 (pH = 5) and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography ($CHCl_3$: MeOH : H_2O = 32 : 9 : 1) to give **16** as a white amorphous (16.4 mg, 0.0440 mmol, 70%).

white amorphous. IR (neat) 3309, 2956, 2932, 2859, 1683, 1653, 1557, 1541, 1255, 1203, 1145, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.11 (3H, s), 0.12 (3H, s), 0.89 (9H, s), 1.12 (3H, d, *J* = 6.4 Hz), 1.27 (3H, d, *J* = 5.9 Hz), 1.94-2.02 (1H, m), 2.06 (3H, s), 3.67 (1H, d, *J* = 11.5 Hz), 3.91-4.01 (2H, m), 4.05-4.19 (2H, m), 7.83 (1H, d, *J* = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.72, -4.70, 13.84, 17.91, 20.77, 22.81, 25.67, 43.64, 52.03, 63.24, 65.10, 68.20, 79.74, 171.42, 172.15; HRMS (ESI) Calcd for $C_{17}H_{35}N_2O_5Si$ ($[M+H]^+$): 375.2310. Found 375.2304.

β-Hydroxy amino acid (**2**). A mixture of **16** (10.0 mg, 0.0270 mmol), TFA (0.206 mL, 2.67 mmol), and H_2O (0.0216 mL, 1.20 mmol) was stirred for 15 h at room temperature. The reaction mixture was concentrated in *vacuo*, the residue was washed with Et_2O to give **2** as a white powder (4.40 mg, 0.0120 mmol, 44%).

white powder. $[\alpha]_D^{27.4}$ +21.87 (*c* 0.49, MeOH). IR (neat) 3274, 2974, 2927, 1669, 1653, 1558, 1541, 1198, 1136 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 1.00 (3H, d, *J* = 6.8 Hz), 1.13 (3H, d, *J* = 5.6 Hz), 1.73-1.82 (1H, m), 1.91 (3H, s), 3.54 (1H, d, *J* = 11.0 Hz), 3.72-3.85 (4H, m), 7.66 (1H, d, *J* = 9.0 Hz);. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.67, 20.88, 22.60, 42.05, 51.95, 61.95, 63.89, 66.22, 77.54, 169.72, 169.82; HRMS (ESI) Calcd for $C_{11}H_{21}N_2O_5$ ($[M+H]^+$): 261.1445. Found 261.1444.

Boc carbamate (**17**). To a solution of **10** (1.83 g, 3.51 mmol) in THF (20 mL) was added Boc_2O (2.69 mL, 11.6 mmol) at room temperature. After stirring for 13 h at 50 °C, the reaction mixture was

concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 2 : 1) to give **17** as a colorless oil (2.11 g, 3.39 mmol, 97%).

colorless oil. IR (neat) 3460, 2957, 2933, 2858, 1736, 1699, 1517, 1385, 1253, 1172, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 1.03 (3H, d, *J* = 7.3 Hz), 1.18 (3H, d, *J* = 6.1 Hz), 1.35 (9H, s), 2.42 (1H, d, *J* = 6.4 Hz), 3.12 (1H, d, *J* = 8.5 Hz), 3.80 (3H, s), 3.91 (1H, s), 4.08-4.26 (3H, m), 4.51-4.61 (2H, m), 5.10 (2H, s), 5.21 (1H, d, *J* = 10.0 Hz), 5.32 (1H, d, *J* = 17.1 Hz), 5.85-5.94 (1H, m), 6.87 (2H, d, *J* = 7.3 Hz), 7.29 (2H, d, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.90, -4.83, 18.29, 19.36, 21.62, 25.85, 28.23, 44.91, 55.46, 55.77, 64.74, 65.37, 65.96, 67.04, 70.45, 81.01, 82.54, 114.09, 118.61, 127.45, 130.75, 132.16, 154.37, 160.03, 171.12, 172.42; HRMS (ESI) Calcd for $C_{32}H_{51}NO_9NaSi$ ($[M+Na]^+$): 644.3225. Found 644.3213.

Ketone (**18a**). To a solution of **17** (1.53 g, 2.46 mmol) in CH_2Cl_2 (20 mL) was added pyridine (0.597 mL, 7.38 mmol) and DMP (2.09 g, 4.92 mmol) at room temperature. After stirring for 2 h at the same temperature, the reaction mixture was treated with aqueous $Na_2S_2O_3$ and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 2 : 1) to give **18a** as a colorless oil (1.48 g, 2.39 mmol, 97%).

colorless oil. IR (neat) 2955, 2933, 2858, 1748, 1715, 1517, 1375, 1252, 1173, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.01 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.06 (3H, d, *J* = 7.6 Hz), 1.33 (9H, s), 2.01-2.10 (1H, m), 2.18 (3H, s), 3.81 (3H, s), 3.87 (1H, s), 4.19 (1H, s), 4.29-4.40 (2H, m), 4.52-4.62 (2H, m), 5.05-5.33 (4H, m), 5.85-5.98 (1H, m), 6.87 (2H, d, *J* = 8.8 Hz), 7.29 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.12, -4.99, 17.81, 17.99, 25.73, 28.05, 30.67, 46.17, 55.31, 61.44, 64.17, 66.05, 66.79, 69.79, 80.64, 81.94, 113.94, 118.30, 127.43, 130.50, 131.92, 153.82, 159.86, 168.06, 170.61, 202.46; HRMS (ESI) Calcd for $C_{32}H_{49}NO_9NaSi$ ($[M+Na]^+$): 642.3069. Found 642.3062.

Ketone (**18**) (α:β=1:1.2). To a solution of **18a** (1.48 g, 2.39 mmol) in MeCN (15 mL) was added DIPEA (0.417 mL, 2.39 mmol) at room temperature. After stirring for 1 h at 60 °C, the reaction mixture was treated with H_2O and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum to give **18** as a colorless oil (1.44 g, 2.32 mmol, 97%) that was used for the next step without purification.

colorless oil. IR (neat) 2955, 2933, 2858, 1748, 1708, 1517, 1379, 1252, 1169, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.01 (3H, s), 0.04 (3H, s), 0.85 (9H, s), 1.07 (3H, d, *J* = 7.6 Hz), 1.31 (9H, s), 1.95-2.02 (1H, m), 2.24 (3H, s), 3.81 (3H, s), 3.86 (1H, s), 4.14-4.44 (3H, m), 4.58-4.62 (2H, m), 5.03-5.34 (4H, m), 5.81-5.96 (1H, m), 6.87 (2H, d, *J* = 8.3 Hz), 7.29 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, major peaks) δ: -4.98, -4.93, 17.72, 17.82, 25.69, 28.00, 30.68, 47.01, 55.31, 63.87, 64.20, 65.77, 66.75, 69.59, 80.64, 82.13, 113.95, 119.04, 127.48, 130.51, 131.50, 153.71, 159.87, 168.95, 170.58, 201.46.

Alcohol (**19**). To a solution of **18** (1.40 g, 2.26 mmol) in DME (14 mL), MeOH (14 mL) was added $NaBH_4$ (85.0 mg, 2.26 mmol) at -78 °C. After stirring for 1 h at 0 °C, to the mixture was further added $NaBH_4$ (85.0 mg, 2.26 mmol). After stirring for additional 15 min, the reaction mixture was added AcOH (0.258 mL, 4.52 mmol) and stirred for 10 min at the room temperature .The reaction mixture was treated with H_2O and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 100 : 0 ~ 50 : 50) to give **19** as a colorless oil (411 mg, 0.661 mmol, 29%).

colorless oil. IR (neat) 3446, 2956, 2932, 2858, 1733, 1698, 1684, 1518, 1395, 1253, 1173, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: -0.01 (3H, s), 0.01 (3H, s), 0.85 (9H, s), 1.07 (3H, d, *J* = 7.6 Hz), 1.25 (3H, d, *J* = 7.1 Hz), 1.36 (9H, s), 2.00-2.06 (1H, m), 3.30 (1H, dd, *J* = 4.2, 9.0 Hz), 3.58 (1H, d, *J* = 9.0 Hz), 3.81 (3H, s), 3.83 (1H, s), 4.08 (1H, d, *J* = 1.2 Hz), 4.11-4.17 (1H, m), 4.29 (1H, dd, *J* = 1.2, 9.0 Hz), 4.56-4.60 (1H, m), 5.07 (1H, d, *J* = 11.7 Hz), 5.15 (1H, d, *J* = 11.7 Hz), 5.22 (1H, dd, *J* = 1.2, 10.3 Hz), 5.32 (1H, dd, *J* = 1.2, 17.1 Hz), 5.85-5.93 (1H, m), 6.88 (2H, d, *J* = 8.3 Hz), 7.29 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.06, -4.96, 17.87, 17.95, 21.75, 25.70, 28.11, 46.97, 55.12, 55.30, 63.39, 65.19, 66.80, 67.53, 70.02, 81.18, 82.24, 113.95, 118.59, 127.41, 130.54, 132.00, 154.74, 159.88, 170.69, 172.93; HRMS (ESI) Calcd for $C_{32}H_{51}NO_9NaSi$ ($[M+Na]^+$): 644.3225. Found 644.3219.

Carboxylic acid (**20**). To a solution of **19** (622 mg, 1.00 mmol) in THF (7 mL) was added morpholine (0.174 mL, 2.00 mmol) and $Pd(PPh_3)_4$ (57.8 mg, 0.0500 mmol) at room temperature. After stirring for 45 min at the same temperature, the reaction mixture was treated with aqueous citric acid and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 100 : 0 ~ 0 : 100) to give **20** as a white amorphous (529 mg, 0.909 mmol, 91%).

white amorphous. IR (neat) 3279, 2956, 2932, 2858, 1748, 1699, 1684, 1517, 1395, 1252, 1172, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.87 (9H, s), 1.03 (3H, d, *J* = 7.6 Hz), 1.27 (3H, d, *J* = 6.6 Hz), 1.37 (9H, s), 2.26-2.35 (1H, m), 3.16-3.22 (1H, m), 3.81 (3H, s), 3.89 (1H, s), 4.10-4.16 (3H, m), 5.07 (1H, d, *J* = 11.7 Hz), 5.17 (1H, d, *J* = 11.7 Hz), 6.88 (2H, d, *J* = 8.6 Hz), 7.29 (2H, d, *J* = 8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.14, -5.03, 17.52, 17.86, 21.43, 25.65, 28.05, 47.84, 55.32, 55.99, 62.98, 66.91, 67.44, 70.09, 81.87, 82.07, 113.97, 127.32, 130.54, 155.42, 159.90, 170.32, 176.80; HRMS (ESI) Calcd for $C_{29}H_{47}NO_9NaSi$ ($[M+Na]^+$): 604.2912. Found 604.2907.

Carbamate (**21**). To a solution of **20** (529 mg, 0.909 mmol) in toluene (10 mL) was added Et_3N (0.416 mL, 3.00 mmol) and DPPA (0.586 mL, 2.73 mmol) at room temperature. After stirring for 1 h at 80 °C, the reaction mixture was treated with aqueous citric acid and the aqueous layer was extracted with AcOEt.

The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 100 : 0 ~ 50 : 50) to give **21** as a yellow amorphous (472 mg, 0.816 mmol, 90%).

yellow amorphous. IR (neat) 3383, 2956, 2933, 2858, 1771, 1749, 1698, 1517, 1374, 1254, 1174, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.15 (3H, s), 0.19 (3H, s), 0.93 (9H, s), 1.00 (3H, d, *J* = 7.6 Hz), 1.34 (9H, s), 1.39 (3H, d, *J* = 6.6 Hz), 2.17 (1H, q, *J* = 7.6 Hz), 3.81 (3H, s), 3.96 (1H, s), 4.02 (1H, s), 4.15 (1H, s), 4.39 (1H, d, *J* = 8.3 Hz), 4.80-4.87 (1H, m), 5.08 (1H, d, *J* = 11.7 Hz), 5.18 (1H, d, *J* = 11.7 Hz), 5.62 (1H, s), 6.88 (2H, d, *J* = 7.1 Hz), 7.30 (2H, d, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.01, -4.85, 16.15, 17.87, 18.44, 26.11, 28.07, 41.86, 55.32, 57.13, 65.75, 67.11, 69.71, 75.01, 81.11, 82.31, 113.97, 127.24, 130.70, 154.41, 159.02, 159.98, 170.44; HRMS (ESI) Calcd for $C_{29}H_{46}N_2O_8NaSi$ ($[M+Na]^+$): 601.2916. Found 601.2910.

Acetylated carbamate (**22**). To a solution of **21** (472 mg, 0.816 mmol) in Ac_2O (4.63 mL, 48.9 mmol) was added DMAP (100 mg, 0.816 mmol) at room temperature. After stirring for 1.5 h at 80 °C, the reaction mixture was treated with aqueous K_2CO_3 and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 100 : 0 ~ 50 : 50) to give **22** as a white amorphous (470 mg, 0.757 mmol, 93%).

white amorphous. IR (neat) 2974, 2931, 2360, 1715, 1698, 1684, 1558, 1541, 1519 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.05 (3H, s), 0.05 (3H, s), 0.84 (9H, s), 1.18 (3H, d, *J* = 7.6 Hz), 1.39 (9H, s), 1.49 (3H, d, *J* = 6.8 Hz), 2.02-2.08 (1H, m), 2.47 (3H, s), 3.81 (3H, s), 3.88-3.91 (2H, m), 3.99-4.01 (1H, m), 4.66-4.75 (1H, m), 5.05 (1H, d, *J* = 11.7 Hz), 5.12 (1H, d, *J* = 11.7 Hz), 5.35 (1H, dd, *J* = 1.5, 7.6 Hz), 6.87 (2H, d, *J* = 8.8 Hz), 7.29 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.76, -4.37, 14.87, 18.67, 18.97, 23.84, 26.18, 28.14, 43.34, 55.31, 55.69, 65.85, 66.87, 69.67, 74.72, 80.81, 83.34, 113.94, 127.29, 130.75, 153.42, 154.06, 159.89, 170.16, 171.67; HRMS (ESI) Calcd for $C_{31}H_{48}N_2O_9NaSi$ ($[M+Na]^+$): 643.3021. Found 643.3011.

Alcohol (**23**). To a solution of **22** (386 mg, 0.622 mmol) in EtOH (4 mL) and H_2O (2 mL) was added $Ba(OH)_2$ $8H_2O$ (588 mg, 1.87 mmol) at room temperature. After stirring for 30 min at the same temperature, the reaction mixture was treated with aqueous citric acid and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography (hexane-AcOEt = 100 : 0 ~ 0: 100) to give **23** as a white amorphous (166 mg, 0.279 mmol, 45%) and **21** as a white amorphous (155 mg, 0.268 mmol, 43%).

white amorphous. IR (neat) 3355, 2933, 2859, 1698, 1684, 1557, 1541, 1520, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.09 (3H, s), 0.10 (3H, s), 0.90 (9H, s), 1.04 (3H, d, *J* = 7.6 Hz), 1.17 (3H, d, *J* = 6.4 Hz),

1.33 (9H, s), 1.82 (1H, brs), 1.99 (3H, s), 2.35-2.41 (1H, m), 3.29 (1H, brs), 3.79-3.99 (7H, m), 4.14 (1H, s), 4.37-4.41 (1H, m), 5.09 (1H, d, J = 11.7 Hz), 5.13 (1H, d, J = 11.7 Hz), 6.88 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -4.93, -4.80, 18.20, 18.82, 20.13, 23.49, 25.76, 28.06, 45.61, 55.33, 56.58, 67.03, 67.65, 68.45, 70.83, 81.23, 81.74, 113.98, 127.27, 130.67, 154.87, 159.96, 170.62, 170.82; HRMS (ESI) Calcd for $C_{30}H_{50}N_2O_8NaSi$ ($[M+Na]^+$): 617.3229. Found 617.3220.

Diol (**24**). To a solution of **23** (148 mg, 0.249 mmol) in THF (3 mL) was added 1.0M TBAF (0.498 mL, 0.498 mmol) at room temperature. After stirring for 30 min at the same temperature, the reaction mixture was treated with brine and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo*, the residue was purified by flash silica gel column chromatography ($CHCl_3$: MeOH : H_2O = 32 : 9 : 1) to give **24** as a white amorphous (110 mg, 0.229 mmol, 92%).

colorless oil. IR (neat) 3308, 2973, 2931, 1698, 1684, 1653, 1558, 1541, 1518, 1396, 1374, 1250, 1173 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.99 (3H, d, J = 7.6 Hz), 1.21 (3H, d, J = 6.1 Hz), 1.32 (9H, s), 1.99 (3H, s), 2.41-2.49 (1H, m), 3.67 (1H, s), 3.80 (3H, s), 3.85-3.93 (2H, m), 4.22-4.28 (1H, m), 4.37 (1H, s), 5.08 (1H, d, J = 12.0 Hz), 5.14 (1H, d, J = 12.0 Hz), 6.87 (2H, d, J = 6.8 Hz), 7.30 (2H, d, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.20, 20.62, 23.56, 28.00, 46.93, 55.32, 56.63, 67.00, 68.70, 69.22, 71.04, 79.96, 81.26, 113.97, 127.41, 130.62, 155.97, 159.89, 170.30, 171.07; HRMS (ESI) Calcd for $C_{24}H_{36}N_2O_8Na$ ($[M+Na]^+$): 503.2364. Found 503.2360.

β-Hydroxy amino acid (**1**). A mixture of **24** (110 mg, 0.229 mmol) and TFA (1.06 mL, 13.7 mmol) was stirred for 30 min at room temperature. The reaction mixture was concentrated in *vacuo*, the residue was washed with Et_2O to give **1** as a white powder (44.4 mg, 0.171 mmol, 75%).

white powder. $[\alpha]_D^{28.6}$ -14.64 (*c* 0.54, MeOH). IR (neat) 3275, 2925, 1698, 1684, 1653, 1558, 1541, 1203, 1140 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03 (3H, d, J = 6.6 Hz), 1.10 (3H, d, J = 6.1 Hz), 1.89 (3H, s), 1.92-1.99 (1H, m), 3.55-3.67 (2H, m), 3.74 (1H, d, J = 5.6 Hz), 3.84 (1H, t, J = 6.1 Hz), 3.92-3.98 (1H, m), 8.03(1H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.06, 21.21, 22.39, 41.69, 55.23, 63.93, 64.14, 66.51, 78.41, 169.11, 171.30; HRMS (ESI) Calcd for $C_{11}H_{21}N_2O_5$ ($[M+H]^+$): 261.1445. Found 261.1443.

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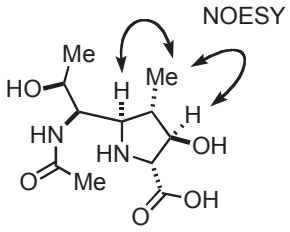
7. The following NOESY was observed.



1

8. In the synthesis of **2** (Scheme 3), purification of amino acid **16** was found to be difficult because of its high polarity. The result led us to design a new sequence for the synthesis of **1** (Scheme 4), employing ester **24** with a Boc-protected amino group as the precursor of the desired amino acid.