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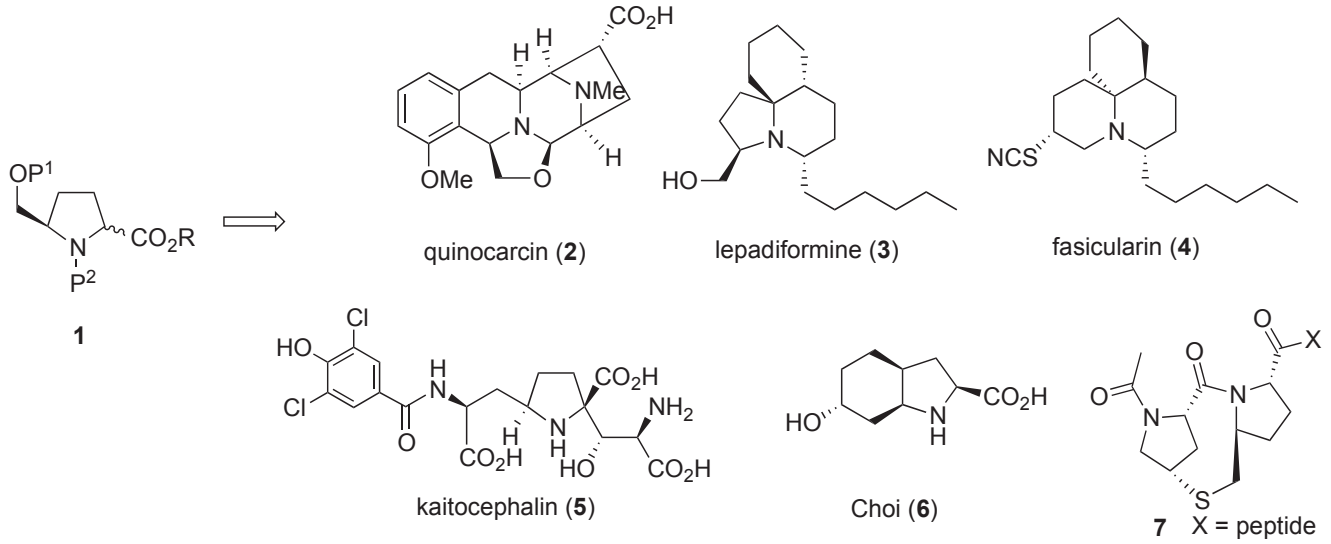
A FACILE SYNTHESIS OF (2*R/S*,5*R*)-1-*tert*-BUTYL 2-METHYL 5-(((*tert*-BUTYLDIMETHYLSILYL)OXY)METHYL)PYRROLIDINE-1,2-DICARBOXYLATE

Yoko Yasuno, Yuya Yoshida, Akito Nishimura, Yasufumi Ohfune, and Tetsuro Shinada*

Graduate School of Science, Osaka City University, 3-3-138, Sugimoto, Sumiyoshi, Osaka 558-8585 Japan (shinada@sci.osaka-cu.ac.jp)

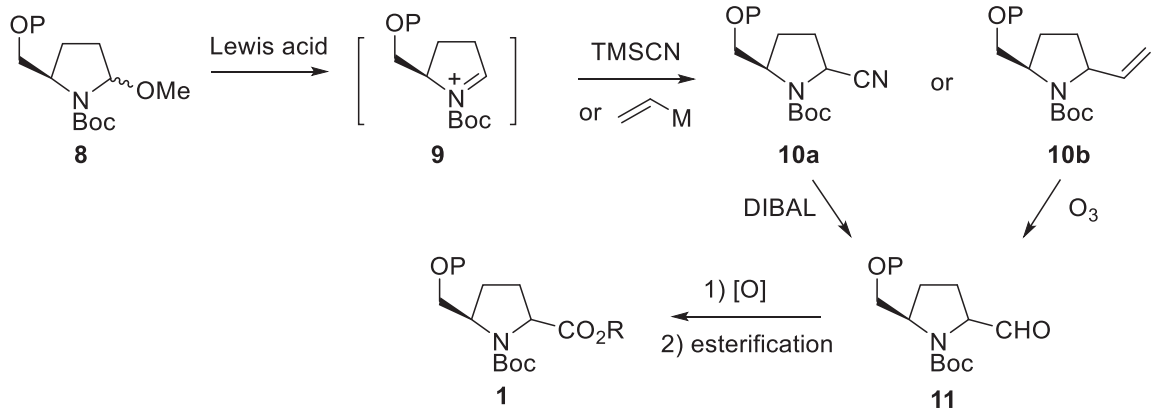
Abstract – A facile synthesis of (2*R/S*,5*R*)-1-*tert*-butyl 2-methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)pyrrolidine-1,2-dicarboxylate (**12**) was efficiently accomplished in 5 steps from aminal **17** via the mild hydrolysis of nitrile **23**.

Optically active 5-(hydroxymethyl)pyrrolidine-2-carboxylic acid esters **1** have been widely utilized as a versatile building block for the synthesis of biologically active heterocyclic molecules, such as quinocarcin (**2**),[1] lepadiformine (**3**),[2] fasicularin (**4**),[2] kaitocephalin (**5**),[3] and 2-carboxy-6-hydroxyoctahydroindole (Choi, **6**)[4] (Scheme 1). Moreover, **1** was successfully incorporated into the tricyclic diprolyl template **7** for inducing helicity in short *N*-terminally linked peptides.[5] According to the potential synthetic utility of **1**, the efficient synthesis of **1** has been reported by several groups.[1-6]



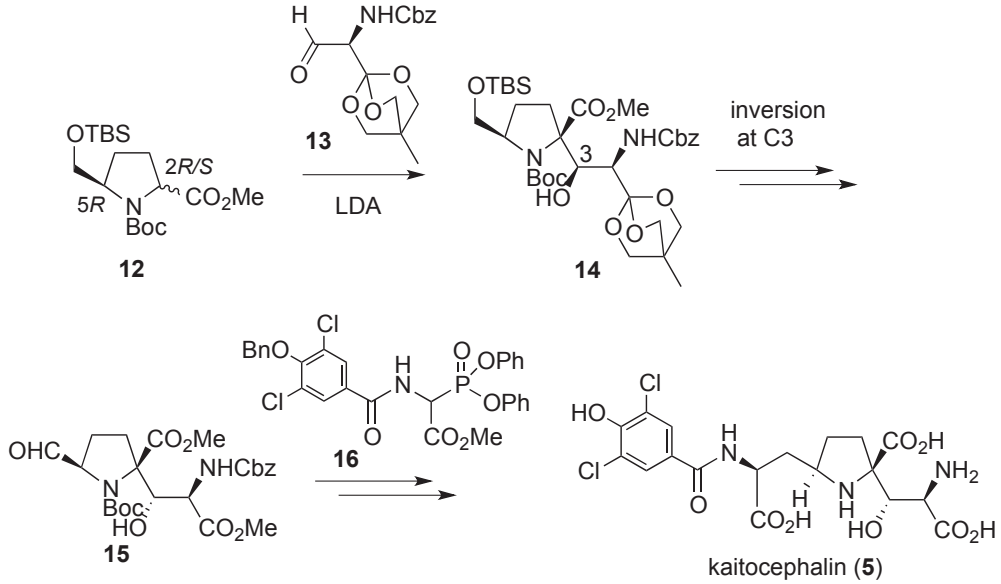
Scheme 1

Typical synthetic procedures to access **1** are depicted in Scheme 2. The synthesis was commenced with an optically active aminal **8** as a common synthetic precursor which was converted to **10a** or **10b** by the nucleophilic addition reaction of TMSCN or vinyl metals to the *N*-acyliminium intermediate **9**. Nitrile **10a** was transformed to **1** by a series of sequential transformations: i) DIBAL reduction, ii) oxidation, and iii) esterification. Pyrrolidine **10b** was converted to **1** via the oxidative cleavage reaction of the vinyl group with O_3.



Scheme 2

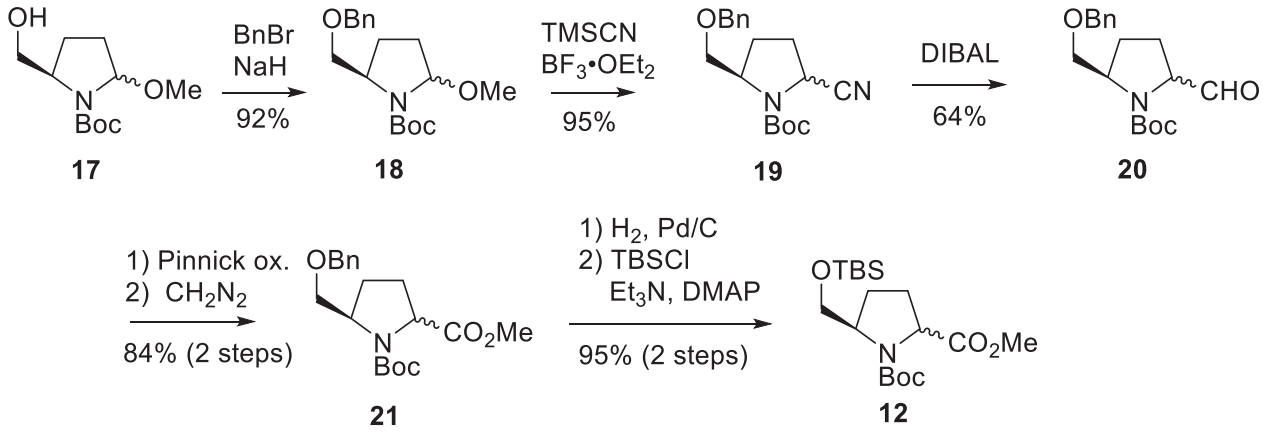
We have reported the synthesis of kaitocephalin (**5**) starting from a diastereomeric mixture of (2*R*/*S*, 5*R*)-**12** (Scheme 3). (2*R*/*S*)-Ester **12** was coupled with **13** to give **14** in a highly stereoselective manner. After the inversion at C3 of **14**, aldehyde **15** was successfully transformed to kaitocephalin (**5**) via the condensation with the left side chain synthon **16**.



Scheme 3

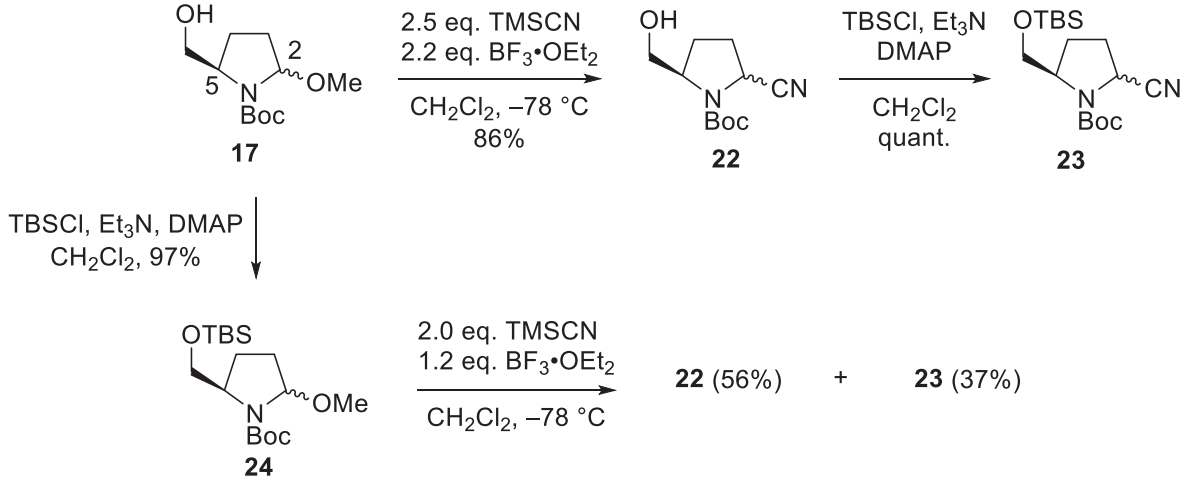
In our previous study, **12** was prepared from aminal **17** in 7 steps via nitrile **19** (Scheme 4).[3] Although the synthesis could be performed on a gram scale, the DIBAL reduction of **19** resulted in moderate yield (up

to 64%) due to the necessity of the precise temperature control to avoid the over reduction in the large scale synthesis. In order to improve this step, we started a research program focusing on the mild conversion of nitrile **19** to ester **12**.



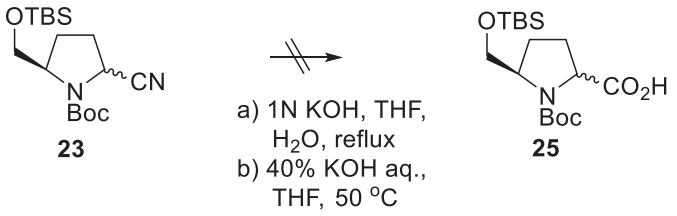
Scheme 4

The starting material **23** was prepared from (2*R/S*,5*R*)-**17**[1] in two steps (Scheme 5). Two different synthetic routes were tested. Treatment of **17** with TMSCN in the presence of BF_3•OEt_2 provided **22** in 86% yield. The resulting nitrile **22** was smoothly converted to TBS ether **23** in high yield. According to this synthetic process, 8 g of **23** was prepared. On the other hand, the initial TBS protection of **17** followed by the introduction of TMSCN to the resulting **24**[7] suffered from the partial removal of the TBS group to give a mixture of **22** and **23** in 56% and 37%, respectively.



Scheme 5

The conversion of nitrile **23** to ester **12** is a challenging synthetic task due to the inert and robust propensity of the nitrile moiety in the hydrolysis or transesterification reaction. In fact, the direct conversion of nitrile **23** to the corresponding carboxylic acid **25** was failed to give rise to a mixture of the undesired highly polar byproducts under the basic conditions (1N KOH or 40% KOH aq. solution).



Scheme 6

These results led us to explore more mild reaction conditions in which the Boc and TBS groups are compatible during the conversion (Scheme 7, Table 1). After several experiments, we established a stepwise reaction sequence involving i) platinum-catalyzed hydration of nitrile **23**,[8] ii) activation of the resulting amide as a Boc carbamate, and iii) mild transesterification of the activated amide.[9] Nitrile **23** was quantitatively converted to amide **27** by the transition metal catalyst-promoted hydration in the presence of platinum catalyst **26**[8] in EtOH/H_2O at the elevated temperature. Treatment of **27** with an excess amount of Boc_2O in the presence of DMAP in CH_2Cl_2 gave di-Boc amide **28** in high yield, which underwent transesterification to provide **12** using NaOMe in MeOH in 70% yield (Table 1). The mild synthetic method was successfully applied to the gram scale synthesis of **12** (5.4 g) from **28** (11 g).

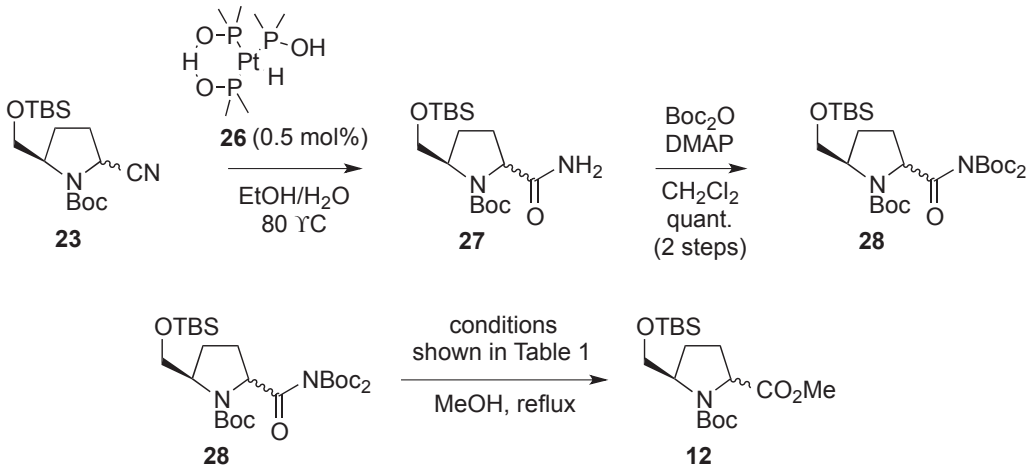


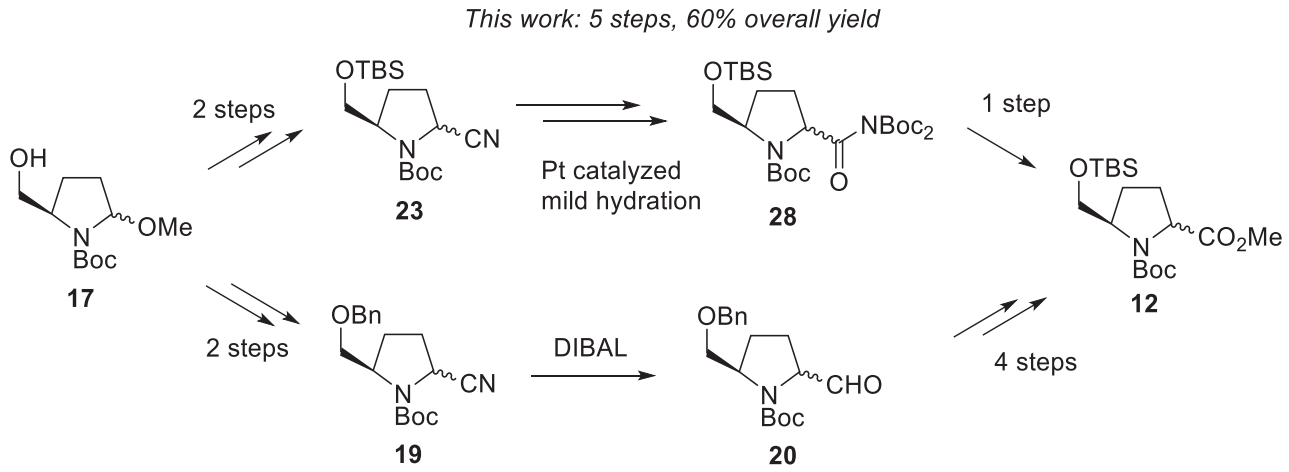
Table 1. Transesterification of **28** to **12**

Base (eq.)	Yield
K_2HPO_4 (0.1)	SM[a]
K_2CO_3 (1.0)	12%
NaOMe (1.0)	70%[b]

[a] Trace amout of mono-Boc compound was observed by TLC analysis.
[b] 11g scale

Scheme 7

We also tested the feasibility of less basic inorganic catalysts, K_2HPO_4[10] and K_2CO_3, for the mild conversion. However, transesterifications resulted in poor yields.



Scheme 8

In conclusion, we have established a short and efficient synthetic protocol to access **12** from **17** in 5 steps (Scheme 8). This was successfully applied to the gram scale preparation of **12**. It is noteworthy that this conversion was achieved without the significant loss of the TBS and Boc groups of **23** and **28**. The present synthetic procedure could aid for the synthesis of nitrogen-containing natural products and biologically active molecules possessing the 2,5-disubsituted pyrrolidine core.

EXPERIMENTAL

All reagents and solvents were purchased from either Aldrich Chemical Company, Inc., Kanto Kagaku Co., Inc., Merck KGaA, Inc., Nacalai Tesque Company, Ltd., Peptide Institute, Tokyo Kasei Kogyo Co., Ltd., or Wako Pure Chemical Industries, Ltd., and used without further purification unless otherwise indicated. Dichloromethane (CH_2Cl_2) was distilled from phosphoric pentaoxide (P_2O_5). Melting point was determined with a Yanaco MP-21 melting point apparatus and was uncorrected. FTIR spectra were measured on a JASCO FT/IR-6200 infrared spectrophotometer. ^{1}H NMR spectra were recorded on an either Bruker AVANCE 300 (300 MHz) or JEOL JNM-LA 400 (400 MHz) spectrometer. Chemical shifts of ^{1}H NMR were reported in perts per million (ppm, δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$. ^{13}C NMR spectra were recorded on Bruker AVANCE 300 (75 MHz) spectrometer. Chemical shifts of ^{13}C NMR were reported in ppm (δ) relative to $CHCl_3$ (δ = 77.0) in $CDCl_3$. Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were obtained on a JEOL JMS-AX500 for fast atom bombardment ionization (FAB). All reactions were monitored by thin layer chromatography (TLC), which was performed with precoated plates (silica gel 60 F-254, 0.25 mm thickness, manufactured by Merck). TLC visualization was accompanied using UV lamp (254 nm) or a charring solution (ethanoic

phosphomolybdic acid, aqueous potassium permanganate and butanoic ninhydrin). Daisogel IR-60 1002W (40/63 μm) was used for flash column chromatography on silica gel.

(2*R/S*,5*R*)-*tert*-Butyl 2-cyano-5-(hydroxymethyl)pyrrolidine-1-carboxylate (22)

Alcohol **17**[1] (6.60 g, 28.5 mmol) was dissolved in CH_2Cl_2 (140 mL), and the solution was stirred for 20 min at –78 °C under argon. To the solution were added TMSCN (8.9 mL, 71.4 mmol) and BF_3•OEt_2 (7.8 mL, 62.8 mmol), and the mixture was stirred for 1 h and quenched with sat. aq. $NaHCO_3$ (150 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (150 mL × 2). The combined organic layers were washed with brine (450 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10 : 1 to 1 : 1) to give **22** (5.57 g, 86%); Colorless oil; FTIR (neat) 3447, 2978, 2883, 1698, 1477, 1457, 1384, 1367, 1256, 1220, 1164, 1125, 1089, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (m, 1 H), 4.09 (m, 1 H), 3.94 and 3.41 (each brs, 1 H), 3.70–3.61 (m, 2 H), 2.32–2.16 (m, 3 H), 1.89 (m, 1 H), 1.50 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 118.8, 82.3, 81.5, 65.6, 64.7, 63.3, 61.0, 59.2, 58.5, 48.4, 48.1, 29.5, 28.7, 28.1, 27.6, 27.3, 26.8; HRMS (FAB) calcd for $C_{11}H_{19}N_2O_3$ *m*/*z* 227.1396 $[M+H]^+$, found 227.1393.

(2*R*,5*R/S*)-*tert*-Butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-cyanopyrrolidine-1-carboxylate (23)

To a solution of **22** (5.55 g, 24.5 mmol) in CH_2Cl_2 (120 mL) were added Et_3N (5.1 mL, 36.8 mmol), DMAP (299 mg, 2.45 mmol), and TBSCl (5.55 g, 36.8 mmol) at 0 °C under argon. The mixture was stirred for 17 h at room temperature and quenched with sat. aq. NH_4Cl (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL × 2). The combined organic layers were washed with brine (300 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 40 : 1 to 8 : 1) to give **23** (8.35 g, quant.); Colorless oil; FTIR (neat) 3517, 2955, 2930, 2884, 2858, 1702, 1472, 1462, 1367, 1254, 1167, 1110, 1045, 1009 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 and 4.42 (each d, J = 7.8 Hz, 1 H), 3.96 and 3.70 (each m, 1 H), 3.81 (dd, J = 10.4, 4.7 Hz, 1 H), 3.61 (m, 1 H), 2.50–2.03 (m, 4 H), 1.51 and 1.49 (each s, 9 H), 0.90 and 0.86 (each s, 9 H), 0.08, 0.07, 0.02, and 0.01 (each s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 152.6, 119.3, 119.0, 81.3, 81.1, 63.5, 63.1, 59.4, 58.5, 58.4, 48.3, 48.1, 48.0, 29.9, 28.7, 28.3, 28.1, 27.7, 27.0, 25.9, 25.7, 25.6, 18.2, 18.0, 17.9, –3.7, –5.4, –5.65, –5.67; HRMS (FAB) calcd for $C_{17}H_{33}N_2O_3Si$ *m*/*z* 341.2260 $[M+H]^+$, found 341.2238.

(2*R*,5*R/S*)-*tert*-Butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methoxypyrrolidine-1-carboxylate (24)

To a solution of **17** (5.13g, 22.2 mmol) in CH_2Cl_2 (74 mL) were added Et_3N (4.6 mL, 33.3 mmol), DMAP (271 mg, 2.22 mmol), and TBSCl (5.02 g, 33.3 mmol) at 0 °C under argon. The mixture was stirred for 15 h at room temperature and quenched with sat. aq. NH_4Cl (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL × 2). The combined organic layers were washed with brine (300 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 30 : 1 to 20 : 1) to give **24** (7.44 g, 97%). The spectroscopic data of **24** was identical with those of the reported data;[7] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (m, 1 H), 3.96-3.38 (m, 3 H), 3.29 (s, 3 H), 2.03 (m, 2 H), 1.87 (m, 1 H), 1.76 (m, 1 H), 1.47 (s, 9 H), 0.88 (s, 9 H), 0.050 and 0.047 (each s, 6 H).

Reaction of 24 with TMSCN/BF_3•OEt_2

In a similar manner to the synthesis of **23**, **24** (7.44 g, 21.5 mmol) was treated with TMSCN (5.4 mL, 43.1 mmol) and BF_3•OEt_2 (3.2 mL, 25.8 mmol) at −78 °C for 1 h. After the work up, the crude mixture of **22** and **23** was separated by flash column chromatography on silica gel (hexane/EtOAc = 30 : 1 to 0 : 1) to give **22** (2.71 g, 56%) and **23** (2.68 g, 37%). These analytical data were identical with those of the data reported above.

Di-Boc amide 28

A mixture of **23** (6.90 g, 20.3 mmol) and Pt catalyst **26** (43.8 mg, 102 μmol) was dissolved in EtOH/H_2O (2 : 1, 25 mL). The mixture was stirred at 80 °C for 1 h, and the volatiles were removed under reduced pressure. The residue was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure to give amide **27**, which was subjected to the next reaction without further purification. Boc_2O (14 mL, 60.8 mmol) and DMAP (2.48 g, 20.3 mmol) were subsequently added to a solution of the crude **27** in CH_2Cl_2 (100 mL) at 0 °C under argon. The mixture was stirred for 2 h at room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 30 : 1 to 5 : 1) to give **28** (11.5 g, quant.); White solid; mp 94–105 °C ; FTIR (neat) 2980, 2955, 2932, 2859, 1781, 1751, 1700, 1473, 1460, 1370, 1302, 1251, 1155, 1117 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 and 5.09 (each d, J = 9.0 Hz, 1 H), 4.06 and 3.93 (each m, 1 H), 3.72–3.45 (m, 2 H), 2.36 (m, 1 H), 2.11–1.86 (m, 3 H), 1.51, 1.49. 1.44, and 1.39 (each s, 27 H), 0.87 (s, 9 H), 0.024 and 0.017 (each s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 173.3, 154.0, 153.4, 149.2, 149.1, 84.7, 84.4,

79.7, 79.6, 63.7, 63.4, 61.1, 60.6, 59.4, 59.2, 28.6, 28.3, 27.9, 27.4, 25.8, 25.6, 25.4, 18.1, –3.7, –5.5, –5.6; HRMS (FAB) calcd for $C_{27}H_{51}N_2O_8Si$ *m*/*z* 559.3415 $[M+H]^+$, found 559.3423.

(2*R*/*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)pyrrolidine-1,2-dicarboxylate (12)

To a solution of **28** (11.5 g, 20.6 mmol) in MeOH (210 mL) was added NaOMe (1.17 g, 20.6 mmol, 95% purity). The mixture was refluxed for 22 h with stirring and concentrated under reduced pressure. The residue was diluted with Et_2O and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 30 : 1 to 15 : 1) to give **12** (5.38 g, 70%). The spectroscopic data of **12** was identical with those of the reported data;[3] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32–3.86 (m, 2 H), 3.80–3.44 (m, 5 H), 2.46–2.14 (m, 1 H), 2.11–1.81 (m, 3 H), 1.47 and 1.40 (each s, 9 H), 0.884 and 0.876 (each s, 9 H), 0.07, 0.06, 0.05, 0.04, and 0.02 (each s, 6 H).

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