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Diastereoselective synthesis of the key intermediate of the BO-2727 side chain

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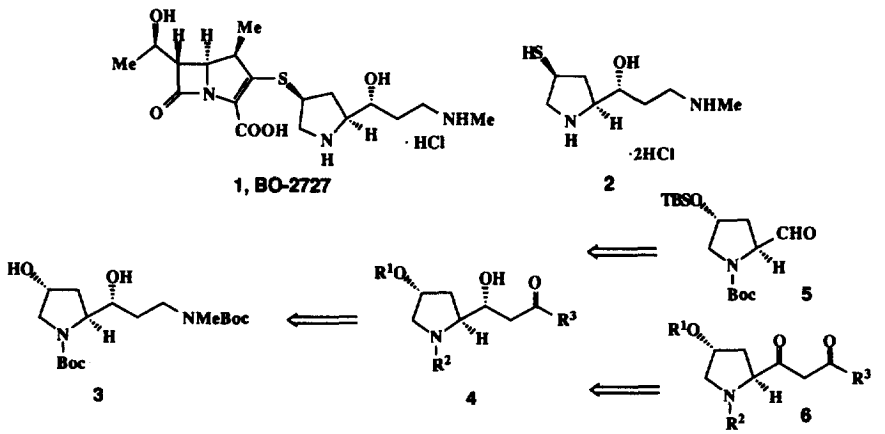
Abstract: The key intermediate of the BO-2727 side chain **3** was prepared diastereoselectively by two alternative methods: *via* the aldol reaction of (2S,4R)-N-Boc-*tert*-butyldimethylsilyloxyprolinal **5** with *in-situ*-generated ketene acetal **9** in the presence of $TiCl_4$ (95% de) and *via* the catalytic hydrogenation of β-keto amide **6i** using (S)-BINAP–Ru as a catalyst (98% de). © 1997 Elsevier Science Ltd

After the discovery of 1β-methyl carbapenems,[1] we identified BO-2727 **1**[2] as a development candidate that possesses both excellent antimicrobial activity and stability to renal dehydropeptidase-I (DHP-I).[3]



The C-2 side chain **2**, bearing the unique (R)-1-hydroxy-3-methylaminopropyl moiety on the pyrrolidine ring, is of interest from both the synthetic and biological point of view. The initial preparation[2a] of **2** was carried out *via* the key intermediate **3** from **4a** (R^1=TBS, R^2=Boc, R^3=OEt), which was obtained by aldol reaction of the lithium enolate of ethyl acetate with aldehyde **5**,[4] however, the diastereoselectivity of the aldol reaction was insufficient (anti:syn=3:1).[2a,5] Therefore, establishment of a more efficient diastereoselective synthetic method for **4** was needed for the large-scale preparation of **1**. The most straightforward methods for the diastereoselective synthesis of **4** include the aldol reaction of appropriate nucleophiles with the aldehyde **5** and reduction of β-keto esters or amides **6**. Herein we report the preliminary results of the diastereoselective synthesis of **4** using these reactions.

Few methods for the anti-stereoselective aldol reaction using N-protected prolinal derivatives have been reported so far.[6] After extensive experimentation, we found that the reaction of the ketene silyl acetal **7**[7] with **5** in the presence of Lewis acid proceeded in a stereoselective manner, affording anti-product **4a** predominantly as shown in Table 1. Of the Lewis acids tested, the use of $TiCl_4$ and Et_2AlCl

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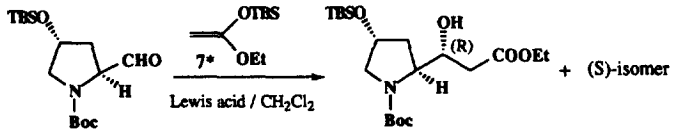
Table 1. Diastereoselectivity of the Lewis acid-mediated aldol reaction of **5** with **7**



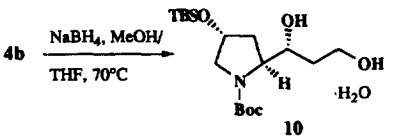
5 4a 8a

Run	Lewis acid *	Temp. (°C)	Selectivity (% de)**	Yield of 4a and 8a (%)
1	ZnI_2	-78–0	20	15
2	$TiCl_4$	-78	77	87
3	$SnCl_4$	"	69	22
4	$BF_3{\cdot}OEt_2$	"	38	94
5	Et_2AlCl	"	80	79
6	$EtAlCl_2$	"	58	62
7	$AlCl_3$	"	47	60

* Equimolar amounts of Lewis acid and **7** (1.5 eq.) were used in each reaction.
** The diastereoselectivity was determined by HPLC [YMC A-001 (S-5, 120A SIL) hexane/isopropanol = 100/1)

resulted in good anti-selectivity (Runs 2 and 5). This anti-selectivity is in contrast to the syn-selectivity reported by Terashima *et al.*[8] under similar conditions. Better selectivity was achieved by using O-methyl-O-trimethylsilyl ketene silyl acetal **9** in the presence of $TiCl_4$ even in THF solvent (82% de). The observed anti-selectivity may be explained by a non-chelation complex model of the aldehyde **5** and $TiCl_4$ as suggested by Mikami *et al.*[9]

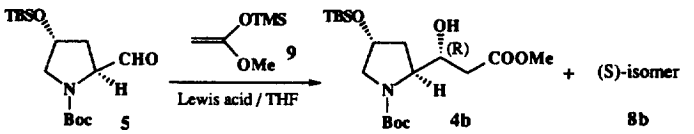
In an attempt to establish a more practical method on the basis of the above-mentioned results, preparation of the ketene silyl acetal **9** and the subsequent Lewis acid-mediated aldol reaction were carried out in the same pot. A detailed study of the reaction conditions was undertaken, which led to improvement of the anti-selectivity. Some representative results are shown in Table 2. When **9** was prepared using lithium hexamethyldisilazide as a base in THF, the ensuing aldol reaction employing $TiCl_4$ at −78 to 0°C was found to provide anti-product **4b** more selectively (Run 4). The use of Et_2AlCl in place of $TiCl_4$ resulted in a decrease in the reaction yield, probably due to the low reactivity of Et_2AlCl, and the retention of the good anti-selectivity (Run 8). In contrast, when LDA was used in this method, surprisingly the aldol products were not obtained but **5** was recovered in a 64% yield. Thus, under the best condition (Run 7), a mixture of **4b** and **8b** (95% de) was obtained in an 89% yield that was readily reduced with sodium borohydide in methanol under Soai's condition,[10] giving diol **10** exclusively in an 87% yield. The diol **10** was easily converted to the key intermediate **3**.[2a] The stereochemical structure of **10** was determined by X-ray analysis (Figure 1).



10

Next we examined the diastereoselective reduction of β-keto esters or amides **6**. Reduction[11] of the β-keto ester **6b** with various metal hydrides such as $NaBH_4$ and $Zn(BH_4)_2$ gave a mixture of β-hydroxy esters **4b** and **8b** with poor selectivity. It has recently been reported that diastereoselective synthesis of N-protected β-hydroxy-γ-amino acids was achieved *via* homogeneous asymmetric hydrogenation of the corresponding β-keto esters in the presence of BINAP–Ru catalyst.[12] Our group applied this methodology to achieve an efficient stereoselective synthesis of the C-2 side chain **2** of BO-2727 **1** *via* the catalytic diastereoselective hydrogenation (76% de) of the β-keto ester **6c** (R_1=H, R_2=Boc, R_3=OBu-*t*) using (S)-BINAP–Ru catalyst.[13] In our continuing efforts to improve selectivity,

Table 2. Diastereoselectivity of the Lewis acid-mediated aldol reaction of **5** with **9**



Run	9* (eq.)	Lewis acid (eq.)	Temp. (°C)	Selectivity (% de)	Yield of 4b and 8b (%)
1	1.5	$TiCl_4$ (2)	-78	87	74
2	2	" (3)	-78	89	80
3	3	" (4)	"	91	82
4	2	" (3)	-78 – 0	93	79
5	2	" (5)	"	92	80
6	2 **	" (5)	"	-	- ***
7	4	" (5)	"	95	89
8	3	Et_2AlCl (3)	"	94	42

* Unless otherwise noted, ketene silylacetal **9** was prepared from methyl acetate using equimolar amount of $LiN(TMS)_2$ and TMSCl in THF at -78°C.
** LDA was used as a base.
*** 4 was recovered.

general

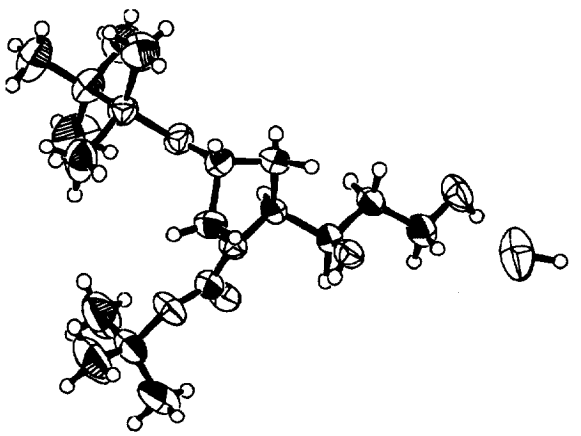
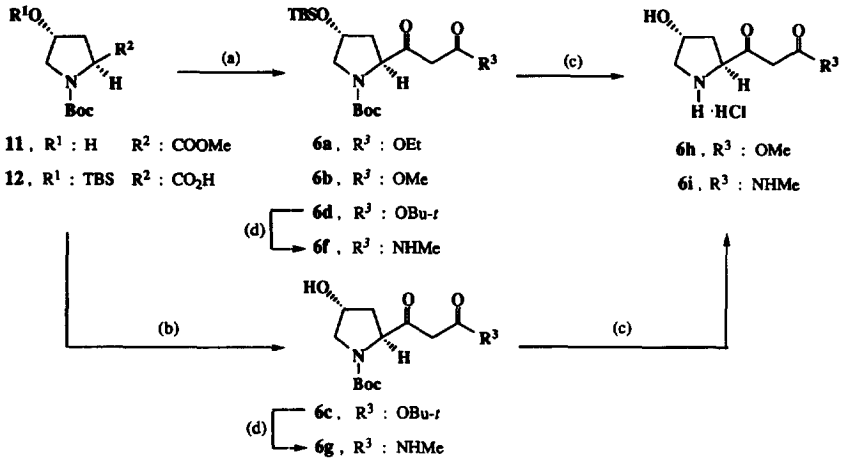


Figure 1. ORTEP drawing (50% ellipsoid) of **10**.

the catalytic diastereoselective hydrogenation of various β-keto esters or amides **6b** and **6d–i** using BINAP–Ru complexes was further investigated.

The preparation of β-keto esters **6a–d** was carried out either by Claisen condensation[14] of ester **11** with the enolate of *t*-butyl acetate or by Masamune's method[15] using carboxylic acid **12** and the magnesium salt of malonic acid monoester (Scheme 1). The β-keto amides **6f** and **6g** were prepared from **6d** and **6c**, respectively, without C-5 epimerization[16] by the modified procedure reported by Witzeman *et al.*[17]

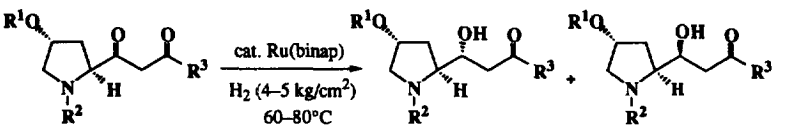
Table 3 shows the results of the diastereoselective hydrogenation of β-keto esters and amides **6b** and **6d–i** under 4–5 kg/cm^2 of hydrogen pressure at 60–80°C. When (R)-BINAP–Ru catalyst was used, substrate **6d** was converted to (S)-hydroxy ester **8d** stereoselectively, as was expected.[12,13] In contrast, the use of (S)-BINAP–Ru in the case of the β-keto esters **6b** and **6d** resulted in low (R)-diastereoselectivity. The hydrogenation of β-keto amides **6f** and **6g** also gave poor selectivity. However, we found that the β-keto amides **6h** and **6i** prepared by the deprotection of **6b** and **6g**, respectively, were



Reagents; (a) CDI, THF, then $Mg(O_2CCH_2COR^3)_2$, r.t., (b) CH_3COBu-*t*, LDA, -20°C, THF, (c) HCl-MeOH, r.t. (d) H_2NMe-dioxane, 100°C.

Scheme 1. Preparation of β-keto esters and amides **6**.

Table 3. Diastereoselectivity of the BINAP–Ru-catalyzed hydrogenation of **6**



6 **4** **8**

Run	Substrates 6	R¹	R²	R³	Config. of catalyst	Time (h)	Products Yield (%)	4 : 8*	de (%)
1	b	TBS	Boc	OMe	S	48	34	2.5 : 1	43
2	d	TBS	"	OBu-*t*	S	48	<10	ca. 1 : 1	0
3	d	TBS	"	OBu-*t*	R	48	97	1 : 25	92
4	e	Ms	"	OMe	S	24	15	4.6 : 1	64
5	f	TBS	"	NHMe	S	24	79	1.9 : 1	31
6	g	H	"	NHMe	S	144	80	3.3 : 1 **	53
7	h	H	H·HCl	OMe	S	24	45	14.9 : 1 **	87
8	i	H	"	NHMe	S	26	92	99 : 1 **	98

The reaction was carried out in THF-MeOH. Substrate/catalyst = 100/1–1000/1.
* The diastereoselectivity of **4b**/and **8b**, and **4d–f**/and **8d–f** were determined by HPLC (YMC AQ- 302, 120A, ODS, CH_3CN/H_2O = 50/50–70/30, Detection; 210nm).
** Diastereoselectivity was determined after converting the mixtures of **4h**/and **8h** to **4b**/and **8b**; **4g**, **i**/and **8g**, **i** were converted to **4f**/and **8f**.

hydrogenated using (S)-BINAP–Ru catalyst to afford **4h** and **4i** with high (R)-diastereoselectivity. In particular, the combination of **6i** with (S)-BINAP–Ru complex resulted in the best diastereoselectivity, giving **4i** and **8i** in a ratio of 99:1 in a 92% yield. These findings indicated that the unprotected γ-amino moiety in **6h** and **6i** plays an important role in the (S)-BINAP–Ru catalyzed asymmetric hydrogenation.

The β-hydroxy amide **4i** was reprotected with di-*tert*-butyl dicarbonate to give **4g** in a good yield. Reduction of the amide group of **4g** with $BH_3 \cdot Me_2$ followed by protection with di-*tert*-butyl dicarbonate afforded the key intermediate **3**.

In summary, we developed efficient methods to diastereoselectively synthesize the β-hydroxy ester **4b** by the aldol reaction (95% de) of **5** with *in-situ*-prepared ketene silyl acetal **9** in the presence of

$TiCl_4$ and the β-hydroxy amide **4i** by catalytic hydrogenation (98% de) of the β-keto amide **6i** using (S)-BINAP–Ru catalyst. These methods will contribute to the efficient synthesis of BO-2727 **1**.

Experimental section

General methods

Melting points were measured on a Yanaco MP micromelting point apparatus and were not corrected. The ^1H NMR spectra were recorded on a Varian GX-300 spectrometer (300 MHz) with tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. IR absorption spectra were recorded with a Horiba FT-200 spectrometer. Optical rotations were measured with a Jasco DIP 370 polarimeter. Mass spectra (MS) were measured on a JEOL JMS-SX102A spectrometer. TLC was done with Merck Kieselgel F_{254} precoated plates. The silica gel used for column chromatography was WAKO gel C-300.

*(2S,4R)-N-*tert*-Butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-formylpyrrolidine 5*

(2S,4R)-N-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-hydroxymethylpyrrolidine was prepared from commercially available (2S,4R)-L-hydroxyproline according to the published method.[4] Conversion of this compound to **5** was carried out by Swern oxidation.[18]

5: mp 53–54°C (from heptane). $[\alpha]_D^{20}$ −65.8 (c 1.04, $CHCl_3$). IR (KBr): 2927, 1738, 1676, 1417, 1140, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 1.44, 1.49 (9H, each s), 1.88–2.11 (2H, m), 3.33–3.42 (0.4H, m), 3.48–3.60 (1.6H, m), 4.19–4.28 (0.6H, m), 4.32–4.44 (1.4H, m), 9.45 (0.6H, d, *J*=3.6 Hz), 9.57 (0.4H, d, *J*=2.6 Hz). FAB-HRMS *m/z* Calcd for $C_{16}H_{32}NO_4Si$ $(M+H)^+$: 330.2101. Found: 330.2098; Anal. Calcd for $C_{16}H_{31}NO_4Si$: C, 58.32; H, 9.48; N, 4.25. Found: C, 58.26; N, 9.47; N, 4.14.

*(3R,5S)-N-*tert*-Butoxycarbonyl-3-*tert*-butyldimethylsilyloxy-5-[(R)-1-hydroxy-2-(methoxycarbonyl) -ethyl]pyrrolidine 4b*

The experimental procedure for Table 2, run 7, is used as a representative example.

A 1.6 M solution of n-BuLi in hexane (75.6 ml, 121 mmol) was slowly added to a solution of hexamethyldisilazane (25.6 ml, 121 mmol) in THF (100 ml) at −78°C under a nitrogen atmosphere, and the mixture was stirred for 15 min. Methyl acetate (9.66 ml, 121 mmol) was added to the mixture and the mixture was further stirred for 30 min at the same temperature, then chlorotrimethylsilane (13.1 g, 121 mmol) in THF (30 ml) was added. After being stirred for 3 h at −78°C, **5** (10.0 g, 30.3 mmol) in THF (50 ml) and $TiCl_4$ (16.7 ml, 157 mmol) were added to the mixture. After being stirred for 3 h at −78 to 0°C, the mixture was quenched with aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a crude mixture of **4b** and **8b**, which was purified by silica gel column chromatography to afford a mixture of **4b** and **8b** (10.9 g, 89% combined yield). The ratio of the mixture was determined as 40:1 by HPLC [HPLC analysis: column, YMC A-001 (S-5, 120A SIL); eluent, 100:1 hexane–isopropanol mixture; flow rate, 2 ml/min; t_R of **4b**, 8.3 min; t_R of **8b**, 6.2 min]. **4b**: oil. $[\alpha]_D^{20}$ −23.0 (c 1.17, $CHCl_3$); IR (KBr): 3447, 2954, 1744, 1697, 1406, 1367, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.46 (9H, s), 1.76–2.12 (2H, m), 2.34–2.43 (1.7H, m), 2.57–2.69 (0.3H, m), 3.27 (1H, dd, *J*=4.2, 11.4 Hz), 3.42–3.67 (1H, m), 3.71 (3H, s), 3.80–3.96 (0.3H, m), 4.06–4.16 (0.7H, m), 4.22–4.41 (2H, m); FAB-HRMS *m/z* Calcd for $C_{19}H_{38}NO_6Si$ $(M+H)^+$: 404.2468. Found: 404.2445; Anal. Calcd for $C_{20}H_{37}NO_6Si$: C, 56.54; H, 9.24; N, 3.47. Found: C, 56.71; N, 9.54; N, 3.37. **8b**: oil. $[\alpha]_D^{20}$ −48.1 (c 0.95, $CHCl_3$); IR (KBr): 3341, 2956, 1734, 1653, 1410, 1365, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.46 (9H, s), 1.63–1.75 (1H, m),1.90–2.02 (1H, m), 2.38–2.53 (2H, m), 3.27 (1H, dd, *J*=3.9, 11.8 Hz), 3.48–3.59 (1H, m), 3.71 (3H, s), 3.94–4.05 (1H, br), 4.08 (1H, dd, *J*=7.3, 14.4 Hz), 4.27–4.41 (1H, br), 5.20 (1H, brs); FAB-HRMS *m/z* Calcd for $C_{19}H_{38}NO_6Si$ $(M+H)^+$: 404.2468. Found 404.2478.

*(3R,5S)-N-*tert*-Butoxycarbonyl-3-*tert*-butyldimethylsilyloxy-5-[(R)-1,3-dihydroxypropyl]pyrrolidine* ***10***

MeOH (10 ml) was slowly added to a suspension of the above mixture (10.9 g) and $NaBH_4$ (1.72 g, 45.5 mmol) in THF (50 ml) over 15 min at 60°C. The reaction mixture was quenched with 10% aqueous citric acid solution and extracted with EtOAc. The combined organic layer was washed with H_2O and brine, and was concentrated *in vacuo*. The residue was crystallized from wet heptane to give **10** (9.38 g, 79% from **5**) [HPLC analysis: column, YMC A-001 (S-5, 120A SIL); eluent, 100:1 hexane–isopropanol mixture; flow rate, 2 ml/min; t_R of **10**, 9.3 min]; mp 89–90°C (from heptane); $[\alpha]_D^{20}$ −28.9 (c 1.05, $CHCl_3$); IR (KBr): 3234, 2941, 1653, 1417, 1365, 1169, 1122 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.47 (9H, s), 1.40–1.69 (2H, m), 1.70–2.10 (2H, m), 3.27 (1H, dd, *J*=3.7, 11.6 Hz), 3.45–3.56 (1H, m), 3.79–3.92 (2H, m), 3.93–4.40 (3H, m), 4.70–4.90 (1H, br); FAB-HRMS *m/z* Calcd for $C_{19}H_{38}NO_5Si$ $(M+H)^+$: 376.2519. Found: 376.2538; Anal. Calcd for $C_{19}H_{37}NO_5Si \cdot H_2O$: C, 54.92; H, 9.99; N, 3.56. Found: C, 55.20; N, 10.16; N, 3.48.

X-Ray crystallographic analysis of ***10***

White clear plane crystals of **10** were obtained from heptane. Diffraction measurements were performed on Enrraf-Nonius CAD4 diffractometer using CuKα radiation (1.54184 Å). Crystal data: $C_{19}H_{37}NO_5Si \cdot H_2O$, *Mr*=393.60, monoclinic, size 0.2×0.35×0.35 mm, $P2_1$, a=6.629 (2) Å, b=10.098 (2) Å, c=17.861 (6) Å, α=90.02 (2) Å, ##β=93.61 (3)°, γ=90.00 (2)°, V=1193.25 (0) $Å^3$, Z=2, D_{calcd}=1.095 g/cm^3, μ=10.9 cm^{-1}, F(000)=432, T=298±1.0 K. A total of 1715 reflections (1599 unique reflections) were collected using w-2q scan technique within a 2q range of 110.0°. The structure was solved by a direct method using MULTAN82 and refined by a full-matrix least squares method using 1522 reflections (Io>3.0 σ(I)). The final refinement converged to R=0.055.

*(3R,5S)-N-*tert*-Butoxycarbonyl-5-(2-*tert*-butoxycarbonyl-1-oxoethyl)-3-hydroxypyrrolidine* ***6c***

(2S,4R)-N-*tert*-Butoxycarbonyl-2-methoxycarbonyl-4-hydroxypyrrolidine[4] (49.0 g, 0.21 mol) in THF (100 ml) was added dropwise to a stirred solution of lithium enolate of *tert*-butyl acetate, generated from *tert*-butyl acetate (108 ml, 0.80 mol) and lithium diisopropylamide (0.80 mol) in THF (1.0 L) at −70°C. After the mixture was stirred for 1 h at −20°C, the reaction was quenched by adding a saturated ammonium chloride aqueous solution, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from heptane to give **6c** (54.6 g, 83%): HPLC [YMC AQ-302 (S-5 120A ODS); 50:50 CH_3CN–H_2O, flow rate; 0.5 ml/min, t_R; 9.1 min, detection; 210 nm, column temp.; 40°C]; mp 94–95°C. $[\alpha]_D^{20}$ −79.2 (c 1.0, $CHCl_3$). IR (KBr): 3427, 1728, 1716, 1417, 1398, 1333 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (6H, s), 1.47 (12H, s), 1.90–2.30 (2H, m), 3.33–3.69 (4H, m), 4.45–4.60 (2H, m); FAB-HRMS *m/z* calcd for $C_{16}H_{28}NO_6$ $(M+H)^+$: 330.1917. Found: 330.1917; Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.3; H, 8.26; N, 4.25. Found: C, 58.3; H, 8.21; N, 4.33.

*(3R,5S)-N-*tert*-Butyoxycarbonyl-5-(2-*tert*-butoxycarbonyl-1-oxoethyl)-3-*tert*-butyl-dimethylsilyl-oxypyrrolidine* ***6d***

12 (5.1 g, 14.8 mmol) in THF (20 ml) was added to a solution of carbonyldiimidazole (3.1 g, 16.7 mmol) in DMF (16 ml), and the mixture was stirred for 40 min at room temperature. Triethylamine (6.1 ml, 43.9 mmol) was added to an ice-cooled suspension of malonic acid mono*tert*-butylester (6.4 g, 39.9 mmol) and magnesium chloride (2.3 g, 24.1 mmol) in THF (90 ml). After being stirred for 80 min at the same temperature, the above prepared imidazolide was added to this mixture. The resulting mixture was stirred for 4 days at room temperature and the insoluble material was removed by filtration. The filtrate was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography gave **6d** (15.6 g, 79%): $[\alpha]_D^{20}$ −7.7 (c 1.0, $CHCl_3$); IR (KBr) 1747, 1712, 1473, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 1.43–1.58 (18H, m),

2.02–2.19 (2H, m), 3.33–3.54 (4H, m), 4.36–4.58 (2H, m); FAB-HRMS *m/z* calcd for $C_{22}H_{42}NO_6Si$ $(M+H)^+$: 444.2781. Found: 444.2796.

*(3R,5S)-N-*tert-*Butoxycarbonyl-3-hydroxy-5-[3-(N-methylamino)-1,3-dioxopropyl]pyrrolidine* ***6g***

A 2.94 M solution of N-methylamine in dioxane (34.2 ml) was added to a solution of **6c** (28.9 g, 87.6 mmol) in dioxane (500 ml) and the mixture was stirred for 2 h at 100°C in a sealed tube. The mixture was allowed to cool to room temperature and was then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **6g** (24.6 g, 98%): HPLC [YMC AQ-302 (S-5 120A ODS); 50:50 CH_3CN–H_2O, flow rate; 0.5 ml/min, t_R; 3.9 min, detection; 210 nm, column temp.; 40°C]; IR (KBr) 3372, 1675, 1550 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.37–1.53 (9H, m), 1.82–2.03 (1H, m), 2.15–2.36 (1H, m), 2.85 (3H, m), 3.43–3.52 (2H, m), 3.52–3.70 (2H, m), 4.45–4.60 (2H, m); FAB-HRMS *m/z* calcd for $C_{13}H_{23}N_2O_5$ $(M+H)^+$: 287.1607. Found: 287.1599.

(3R,5S)-3-Hydroxy-5-[3-(N-methylamino)-1,3-dioxopropyl]pyrrolidine·hydrochloride ***6i***

A 5.4 M solution of hydrogen chloride in MeOH (100 ml) was added to a solution of **6g** (24.6 g, 86.0 mmol) in MeOH (200 ml) and the mixture was stirred for 6 h at room temperature. The mixture was concentrated under reduced pressure and the residue was recrystallized from ethanol–acetone to give **6i** (16.1 g, 84%): $[\alpha]_D^{20}$ −3.2 (c 1.0, H_2O); ^1H NMR (300 MHz, D_2O) δ 2.20 (1H, ddd, *J*=4.1, 10.8, 13.7 Hz), 2.61 (1H, dd, *J*=8.8, 13.7 Hz), 2.78 (3H, s), 3.38–3.48 (2H, m), 4.71 (1H, m), 4.92 (1H, dd, *J*=8.8, 10.8 Hz); FAB-MS *m/z* 187 $(M+H)^+$; Anal. Calcd for $C_8H_{14}N_2O_3 \cdot HCl$: C, 43.1; H, 6.79; N, 12.6. Found: C, 42.9; H, 6.42; N, 12.7.

(3R,5S)-3-Hydroxy-5-[(R)-1-hydroxy-3-(N-methylamino)-3-oxopropyl]pyrrolidine·hydrochloride ***4i***

The experimental procedure for Table 1, Run 8 was described as a representative procedure.

6i (22.3 g, 100 mmol) and $RuCl_2$[(S)-binap]·1/2NEt_3 (75 mg, 0.09 mmol) in MeOH (300 ml) were added to a stainless steel autoclave under an argon atmosphere, and the mixture was stirred at 62°C with a hydrogen pressure of 5 kg/cm^2 for 26 h. The mixture was allowed to cool to room temperature and was then concentrated under reduced pressure.[19] The residue was recrystallized from ethanol–acetone to give **4i** (22.9 g, 88%): $[\alpha]_D^{20}$ −1.4 (c 1.0, H_2O). IR (KBr) 3442, 1643, 1562, 1411 cm^{-1}. ^1H NMR (300 MHz, D_2O) δ 2.10 (1H, brd, *J*=8.2 Hz), 2.42 (1H, dd, *J*=8.5, 14.4 Hz), 2.50 (1H, dd, *J*=4.5, 14.4 Hz), 2.74 (3H, s), 3.32 (1H, d, *J*=12.5 Hz), 3.43 (1H, dd, *J*=3.6, 12.5 Hz), 4.01 (1H, dt, *J*=4.5, 8.2 Hz), 4.46 (1H, dt, *J*=4.5, 8.5 Hz), 4.68 (1H, m); FAB-MS *m/z* 189 $(M+H)^+$. Anal. Calcd for $C_8H_{16}N_2O_3 \cdot HCl \cdot 2H_2O$: C, 36.8; H, 8.12; N, 10.7. Found: C, 36.9; H, 8.11; N, 10.7.

*(3R,5S)-N-*tert-*Butoxycarbonyl-3-hydroxy-5-[(R)-1-hydroxy-3-(N-methylamino)-3-oxopropyl]-pyrrolidine* ***4g***

Triethylamine (16.7 ml, 120 mmol) and di-*tert*-butyl dicarbonate (23.0 g, 105 mmol) were added to a stirred solution of **4i** (26.1 g, 100 mmol) in MeOH (100 ml). After being stirred for 16 h at room temperature, the mixture was concentrated under reduced pressure. THF (300 ml) was added to the residue and the mixture was stirred for 15 min. The resulting precipitate were removed by filtration and washed with THF. The combined filtrate and washings were concentrated under reduced pressure, and the residue was purified by column chromatography to give **4g** (28.8 g, 100%): $[\alpha]_D^{20}$ −19.8 (c 1.0, $CHCl_3$); IR (KBr) 3365, 1664, 1562, 1415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (9H, s), 1.92 (1H, m), 2.03 (1H, m), 2.22 (2H, m), 2.80 (3H, d, *J*=3.3 Hz), 3.37 (1H, dd, *J*=4.0, 12.0 Hz), 3.57 (1H, brd, *J*=12.0 Hz), 3.99 (1H, m), 4.16 (1H, m), 4.41 (1H, m), 7.25 (1H, m); FAB-HRMS *m/z* Calcd for $C_{13}H_{25}N_2O_5$ $(M+H)^+$: 289.1764. Found: 289.1779.

*(3R,5S)-N-*tert-*Butoxycarbonyl-3-hydroxy-5-[(R)-1-hydroxy-3-(N-*tert-*butoxycarbonyl-N-methyl-amino)propyl]pyrrolidine* ***3***

Borane·dimethylsufide complex (50 ml, 500 mmol) was added to a stirred solution of **4g** (28.8 g, 100 mmol) in THF (500 ml) at 0°C. After being stirred for 2 h at reflux temperature, the mixture was

allowed to cool to 0°C. The reaction was quenched by adding MeOH (200 ml), and the mixture was concentrated under reduced pressure. Triethylamine (17.4 ml, 125 mmol) and di-*tert*-butyl dicarbonate (21.8 g, 100 mmol) were added to a solution of the residue in EtOH (300 ml), and the mixture was stirred for 2.5 h at room temperature. The mixture was concentrated under reduced pressure, and the residue was poured into H_2O and extracted with EtOAc. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting solid was recrystallized from diisopropyl ether to give **3** as a white crystal (27.7 g, 74%): mp 104–105°C; $[\alpha]_D^{20}$ −54.8 (c 1.0, $CHCl_3$). IR (KBr) 3404, 2977, 2941, 1662, 1425, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (18H, s), 1.79–2.31 (2H, m), 2.83 (3H, s), 2.98 (1H, m), 4.44 (1H, m). FAB-HRMS *m/z* calcd for $C_{18}H_{35}N_2O_6$ $(M+H)^+$: 375.2495. Found: 375.2509; Anal. Calcd for $C_{18}H_{34}N_2O_6$: C, 57.7; H, 9.15; N, 7.48. Found: C, 57.9; H, 9.25; N, 7.54.

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