

**A FACILE SYNTHESIS OF  $\beta$ -LACTAMS BY THE CYCLIZATION OF  $\beta$ -AMINO ACIDS EXPLOITING 3,3'-(PHENYLPHOSPHORYL)-BIS(1,3-THIAZOLIDINE-2-THIONE)**

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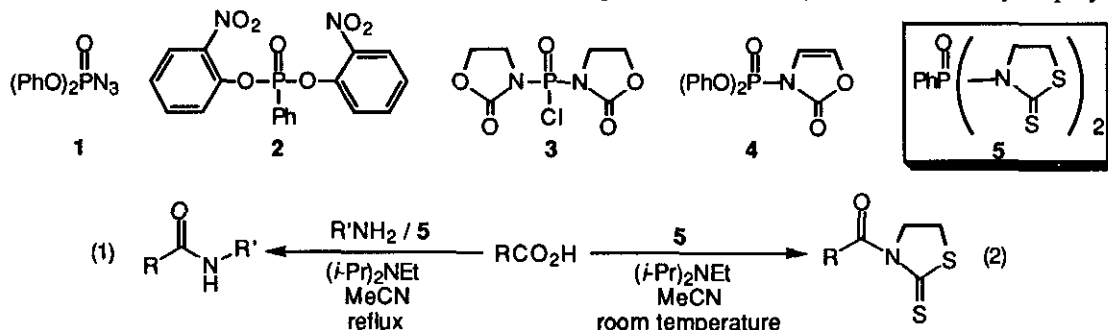
**Abstract-** 3,3'-(Phenylphosphoryl)-bis(1,3-thiazolidine-2-thione) (**5**), obtained from phenylphosphonic dichloride (**7**) and sodium salt of 1,3-thiazolidine-2-thione (**6**), proved to be useful for intramolecular dehydration of various  $\beta$ -amino acids to give the corresponding  $\beta$ -lactams.

In the formation of amide bond between a carboxylic acid and an amine, various organic phosphorus (V) compounds such as diphenylphosphoryl azide (**1**),<sup>1</sup> bis(*o*-nitrophenyl)phenyl phosphonate (**2**),<sup>2</sup> 3,3'-bis(2-oxo-3-oxazolidinyl)-phosphoroamidic chloride (**3**),<sup>3</sup> and diphenyl-2-oxo-3-oxazolidinyl phosphonate (**4**)<sup>4</sup> have been employed as the activating reagent for carboxyl group. In a series study of achiral and chiral 1,3-thiazolidine-2-thiones, we developed a dehydrating condensation reagent, 3,3'-(phenylphosphoryl)-bis(1,3-thiazolidine-2-thione) (PPTT) (**5**) which was useful not only for carboxylic amide formation (eq. 1) but also 1,3-thiazolidine-2-thione amide formation (eq. 2).<sup>5,6</sup> PPTT (**5**) was also efficiently exploited for the amide bond formation in the total synthesis of parabactin, a spermidine siderophore.<sup>5d</sup> Although the triphenylphosphine-dipyridyl disulfide reagents system proved to be available

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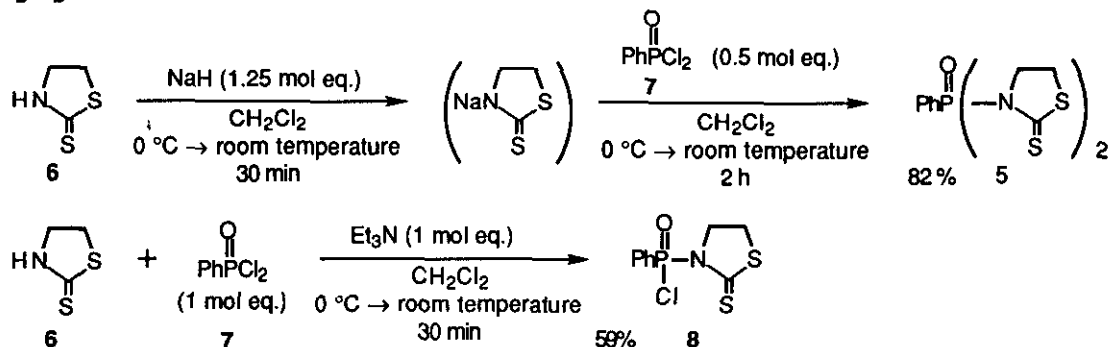
<sup>†</sup>This paper is dedicated to the memory of the late Dr. Yoshio Ban, Professor Emeritus Hokkaido University.

for converting  $\beta$ -amino acids into  $\beta$ -lactams,<sup>7</sup> we anticipated that PPTT (**5**) could be similarly employed for



the lactam ring formation of  $\beta$ -amino acids. Now, we describe our results in detail.

PPTT (pale yellow needles, mp 203-205 °C) (**5**) was readily prepared by treating phenylphosphonic dichloride (**7**) with sodium salt of 1,3-thiazolidine-2-thione (**6**) in  $\text{CH}_2\text{Cl}_2$  as shown in Scheme 1. The relating reagent (yellow oil) (**8**) was also obtained by treatment of **6** with **7** in the presence of  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$ .



Scheme 1

The structure of both reagents (**5** and **8**) was confirmed by their  $^{13}\text{C}$  nmr (67.8 MHz,  $\text{CDCl}_3$ ) chemical shift value (**5**: 204.8 ppm, **8**: 202 ppm) due to the  $\text{C}=\text{S}$  group.<sup>5c</sup>

In order to search the optimum reaction conditions for the lactam ring formation, several reactions were investigated employing *N*-benzyl- $\beta$ -alanine (**9**) in the presence of *i*- $\text{Pr}_2\text{NEt}$  (3 mol eq.).<sup>8</sup> All experimental results are summarized in Table 1. At room temperature in MeCN and DMF or even under reflux in  $\text{CHCl}_3$  and pyridine without use of *i*- $\text{Pr}_2\text{NEt}$ , the lactam formation reaction has never occurred (Entries 1, 6, 9, and 10 in Table 1). In DMF under heating at 100 °C, the desired ring formation proceeded a little to give the known 1-benzylazetidin-2-one(**10**)<sup>9</sup> in low yields (Entries 7 and 8 in Table 1). However, in MeCN under reflux, the reaction remarkably increased the yield of azetidinone (**10**) depending on the concentration of **9** and the amount of **5** as shown in Table 1 (Entries 3-5). This reaction does not proceed

at all in the absence of an amine base such as *i*-Pr<sub>2</sub>NEt and Et<sub>3</sub>N.<sup>8</sup> Thus, we chose the reaction conditions of Entry 5 (Table 1) for the further investigation of the  $\beta$ -lactam ring formation. Subsequently, the lactam formation using PPTT (5) was compared with that using the related reagents, mono-1,3-thiazolidine-2-thione derivative (8) and phenylphosphonic dichloride (7) under the reaction conditions of Entry 5 in Table 1.

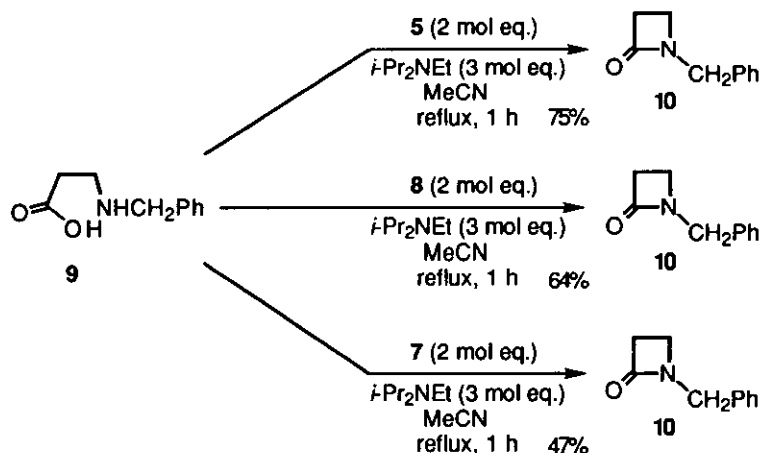
Table 1. Investigation of the reaction conditions for the  $\beta$ -lactam ring formation

Entry	Solvent	Concentration of 9 (mM)	Amount of 5 (mol eq.)	Temp.	Time	Yield <sup>a</sup> of 10 (%)
1	MeCN	26	0.66	r. t. <sup>b</sup>	60 h	0 <sup>c</sup>
2	MeCN	26	0.66	reflux	15 min	35
3	MeCN	20	1.00	reflux	1 h	66
4	MeCN	10	2.00	reflux	5.5 h	70
5	MeCN	5	2.00	reflux	1 h	75
6	DMF	26	0.66	r. t. <sup>b</sup>	13 h	0 <sup>c</sup>
7	DMF	26	0.66	100 °C	20 min	14
8	DMF	5	2.00	100 °C	1 h	16
9	CHCl <sub>3</sub>	26	0.66	reflux	13 h	0 <sup>c</sup>
10 <sup>d</sup>	pyridine	26	0.66	reflux	5 h	0 <sup>c</sup>

a) Isolated yield based on 9. b) r. t. = room temperature.

c) Compound (9) was recovered in 40-73% yields. d) Without use of *i*-Pr<sub>2</sub>NEt.

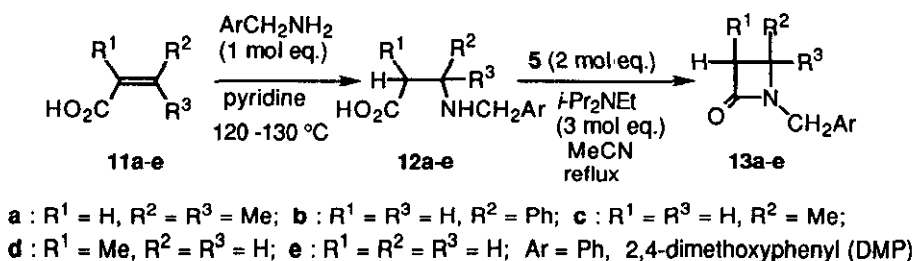
As shown in Scheme 2, PPTT (5) was confirmed to be the most efficient among the three reagents.



Scheme 2

Then, the  $\beta$ -lactam formation reactions of several  $\beta$ -amino acids (**12a-e**) were attempted as follows. These compounds (**12a-e**) were readily prepared by the Michael-type addition reaction of benzylamine and 2,4-dimethoxybenzylamine onto commercially available  $\alpha,\beta$ -unsaturated carboxylic acids (**11a-e**) in pyridine under heating at 120-130 °C. The  $\beta$ -amino acids (**12a-e**) were treated with 2 mol eq. of PPTT (**5**) in the presence of 3 mol eq. of *t*-Pr<sub>2</sub>NEt in MeCN under reflux to afford the corresponding  $\beta$ -lactams (**13a-e**) in excellent yields as shown in Table 2.

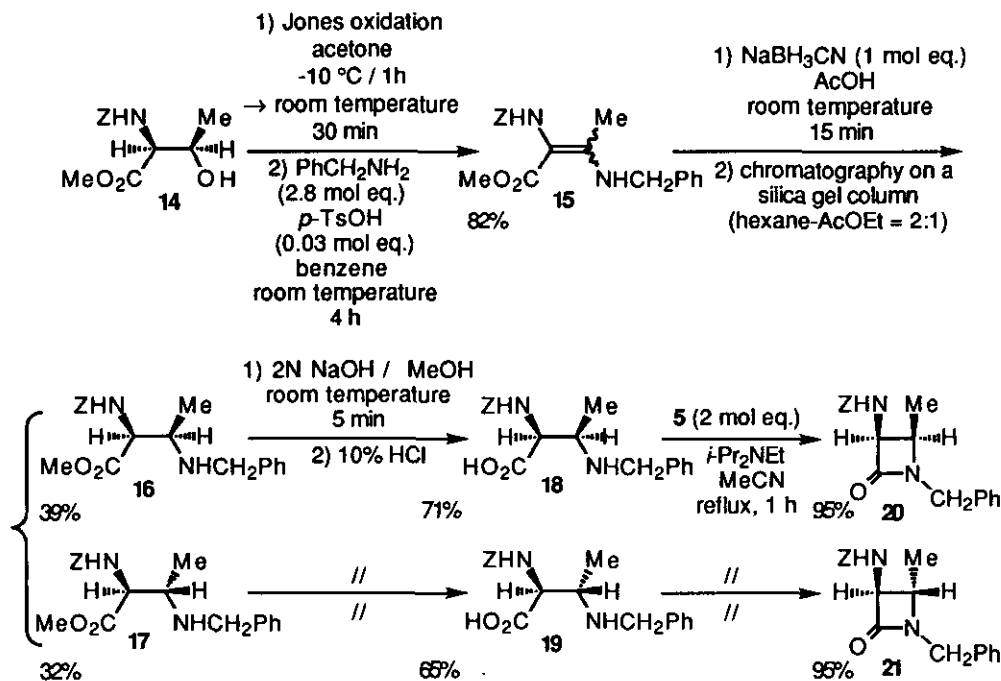
Table 2. Preparation of  $\beta$ -amino acids and  $\beta$ -lactams



$\alpha,\beta$ -Unsaturated carboxylic acid	ArCH <sub>2</sub> NH <sub>2</sub>	Time (h)	$\beta$ -Amino acid <sup>a</sup>	Yield (%)	Time (h)	$\beta$ -Lactam <sup>a</sup>	Yield (%)
<b>11a</b>	Ar = Ph	24	<b>12a</b>	53	1	<b>13a</b>	97
<b>11b</b>	Ar = Ph	1	<b>12b</b>	70	1	<b>13b</b>	99
<b>11c</b>	Ar = Ph	1	<b>12c</b>	68	1	<b>13c</b>	95
<b>11d</b>	Ar = Ph	1	<b>12d</b>	65	5	<b>13d</b>	99
<b>11e</b>	Ar = DMP	1.5	<b>12e<sup>b</sup></b>	65	1	<b>13e<sup>b</sup></b>	95

a) Unless otherwise noted, Ar is phenyl group. b) Ar = DMP group.

Finally, this PPTT reagent system was successfully utilized for the  $\beta$ -lactam ring formation of *threo*- and *erythro*- $\alpha$ -benzyloxycarbonylamino- $\beta$ -amino acids (**16** and **17**) toward monobactam<sup>10</sup> precursors (**20** and **21**). These racemic compounds (**16** and **17**), derived from *Z*-L-threonine (**14**) along the reaction pathway as shown in Scheme 3, were submitted to the same reaction with PPTT (**5**) as described above. The desired racemic  $\beta$ -lactams (**20** and **21**) were readily obtained as crystalline compounds in excellent yields, respectively. The stereochemistry of compounds (**16-21**) was assigned on the basis of the <sup>1</sup>H nmr (CDCl<sub>3</sub>) spectrum of *cis*-**20** [ $\delta$  5.00 ppm (dd, 1H, *J* = 8.6 and 5.1 Hz, C3-H)] and of *trans*-**21** [ $\delta$  4.32 ppm (dd, 1H, *J* = 6.4 and 1.5 Hz, C3-H)].



Scheme 3

In conclusion, we demonstrated that PPTT (5) reagent could be efficiently exploited for the  $\beta$ -lactam ring formation of various  $\beta$ -amino acids.

## EXPERIMENTAL

Melting points were determined on a Yamato MP-21 and Yanagimoto micro melting point apparatus, and are uncorrected. The ir spectra were run on a Hitachi 260-50 spectrophotometer. <sup>1</sup>H Nmr spectra were recorded on JEOL JNM-FX 100, Hitachi R-900, and Varian EM-360 instruments and chemical shifts are reported in  $\delta$  (ppm) relative to Me<sub>4</sub>Si or TSP as an internal standard. <sup>13</sup>C Nmr spectra were determined on a JEOL JNM-FX 100 and chemical shifts are reported in  $\delta$  (ppm) relative to Me<sub>4</sub>Si as an internal standard. Mass spectra were taken on a JEOL JMS-DX 300 mass spectrometer. Column chromatography was performed on a silica gel (Wakogel C-100 and C-200). All reactions were monitored by silica gel F254 plates (Merck). All organic extracts were dried over anhydrous sodium sulfate.

**3,3'-(Phenylphosphoryl)-bis(1,3-thiazolidine-2-thione) (5).** To a stirred suspension of 50% mineral oil dispersion of NaH (3.0 g, 62.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml) was added dropwise 1, 3-thiazolidine-2-thione (6.0 g, 50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) under N<sub>2</sub> at 0 °C. After being stirred for 30 min at room temperature, to this mixture was added phenylphosphonic dichloride (7) (4.9 g, 25 mmol) in

CH<sub>2</sub>Cl<sub>2</sub> (25 ml) under N<sub>2</sub> at 0 °C. The whole mixture was stirred at room temperature for 2 h and then poured into H<sub>2</sub>O (500 ml). Organic layer was separated, washed with brine, dried, and then evaporated *in vacuo* to give an oily product. Crystallization of the crude product from CH<sub>2</sub>Cl<sub>2</sub>-AcOEt gave compound (5) (7.0 g, 82% yield) as pale yellow needles. mp 203-205 °C. Ir  $\nu_{\max}$  (KBr) cm<sup>-1</sup>: 1355, 1245, 1200, 1080. <sup>1</sup>H Nmr (60 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.33 (t, 4H, *J* = 7 Hz), 4.00-4.60 (m, 4H), 7.30-7.50 (m, 3H), 7.70-8.10 (m, 2H). <sup>13</sup>C Nmr (67.8 Hz, CDCl<sub>3</sub>)  $\delta$ : 32.4, 58.7, 128.8, 129.0, 132.0, 132.2, 133.9, 204.8. Ms *m/e* 360 (M<sup>+</sup>). Anal. Calcd for C<sub>12</sub>H<sub>13</sub>N<sub>2</sub>OPS<sub>4</sub>: C, 39.98; H, 3.63; N, 7.77. Found: C, 39.80; H, 3.60; N, 7.71.

***N*-(2-Thioxo-1,3-thiazolidinylphenyl)phosphoroamidic chloride (8).** To a solution of 6 (119 mg, 1 mmol) and 7 (195 mg, 1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added Et<sub>3</sub>N (101 mg, 1 mmol) under N<sub>2</sub> at 0 °C. The mixture was stirred at room temperature for 24 h and then evaporated *in vacuo* to give an oily residue. The residue was chromatographed on a silica gel column with CHCl<sub>3</sub> as eluent to afford compound (8) (163.4 mg, 59% yield) as a yellow oil. Ir  $\nu_{\max}$  (neat) cm<sup>-1</sup>: 1490, 1220, 1110. <sup>1</sup>H Nmr (60 MHz, CDCl<sub>3</sub>)  $\delta$ : 3.50 (t, 2H, *J* = 7 Hz), 4.50-4.85 (m, 2H), 7.40-7.80 (m, 3H), 7.90-8.20 (m, 2H). <sup>13</sup>C Nmr (67.8 Hz, CDCl<sub>3</sub>)  $\delta$ : 31.9, 56.6, 128.4, 128.5, 131.1, 131.2, 133.6, 202.0. Ms *m/z* 277 (M<sup>+</sup>). Anal. Calcd for C<sub>9</sub>H<sub>9</sub>NOCIPS<sub>2</sub>: C, 38.92; H, 3.27; N, 5.04. Found: C, 38.70; H, 3.12; N, 5.18.

#### Investigation of the reaction conditions for the $\beta$ -lactam ring formation.

**Typical example (Entry 5 in Table 1):** A suspension of *N*-benzyl- $\beta$ -alanine (9) (18 mg, 0.1 mmol), PPTT (5) (72 mg, 0.2 mmol), and *i*-Pr<sub>2</sub>NEt (38.7 mg, 0.3 mmol) in MeCN (20 ml) was refluxed for 1 h. After removal of the solvent *in vacuo*, the oily residue was purified on a silica gel column impregnated with 5% AgNO<sub>3</sub> by employing AcOEt to give known 1-benzylazetidinone (10) (12.1 mg, 75% yield) as a colorless oil. Ir and <sup>1</sup>H nmr data of the synthesized compound (10) was consistent with those of the authentic compound.<sup>9</sup> Other experiments (Entries 1-4 and 6-10) were similarly carried out. Their results are shown in Table 1.

**Treatment of *N*-benzyl- $\beta$ -alanine (9) with compound (8).** A mixture of 9 (18 mg, 0.1 mmol), 8 (56 mg, 0.2 mmol), and *i*-Pr<sub>2</sub>NEt (38.7 mg, 0.3 mmol) in MeCN (20 ml) was refluxed for 1 h. The reaction mixture was treated in the same manner as described above to give 10 (10.3 mg, 64% yield) as a colorless oil.

**Treatment of *N*-benzyl- $\beta$ -alanine (9) with compound (7).** A mixture of 9 (36 mg, 0.2 mmol), 7 (78 mg, 0.4 mmol), and *i*-Pr<sub>2</sub>NEt (77.4 mg, 0.6 mmol) in MeCN (40 ml) was refluxed for 1 h. The usual

treatment of the reaction mixture was carried out as described above to give **10** (15.1 mg, 47% yield) as a colorless oil.

#### Preparation of $\beta$ -amino acids (**12a-e**).

Typical example: 3, 3-Dimethylacrylic acid (**11a**) (2 g, 20 mmol) and benzylamine (2.1 g, 20 mmol) were added to pyridine (10 ml). After the mixture was stirred at 120-130 °C under N<sub>2</sub> for 24 h, the solvent was evaporated *in vacuo* to afford a crude crystalline product. Recrystallization of the crude product from MeOH-acetone gave 3-benzylamino-3, 3-dimethylpropionic acid (**12a**) (2.1 g, 53% yield) as colorless needles. mp 198-199 °C. Ir  $\nu_{\max}$  (KBr)  $\text{cm}^{-1}$ : 1550. <sup>1</sup>H Nmr (90 MHz, D<sub>2</sub>O)  $\delta$ : 1.30 (s, 6H), 2.33 (s, 2H), 3.93 (s, 2H), 7.20-7.50 (m, 5H). Ms  $m/z$  207 (M<sup>+</sup>). Anal. Calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub>: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.48; H, 8.18; N, 6.79. Other  $\beta$ -amino acids (**11b-e**) were similarly prepared. Their physical data are as follows.

**3-Benzylamino-3-phenylpropionic acid (12b)** 70% yield. Colorless needles. mp 192-193 °C (MeOH-Et<sub>2</sub>O). Ir  $\nu_{\max}$  (KBr)  $\text{cm}^{-1}$ : 1550. <sup>1</sup>H Nmr (100 MHz, CD<sub>3</sub>OD)  $\delta$ : 2.60 (dd, 1H,  $J = 17.0$  Hz, 5.4 Hz), 2.86 (dd, 1H,  $J = 17.0$  Hz, 9.3 Hz), 7.41 (s, 5H), 7.48 (s, 5H). Ms  $m/z$  255 (M<sup>+</sup>). Anal. Calcd for C<sub>16</sub>H<sub>17</sub>NO<sub>2</sub>: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.32; H, 6.77; N, 5.32.

**3-Benzylaminobutyric acid (12c)**. 68% yield. Colorless needles. mp 190.5-191.5 °C (MeOH-acetone). Ir  $\nu_{\max}$  (KBr)  $\text{cm}^{-1}$ : 1560. <sup>1</sup>H Nmr (90 MHz, D<sub>2</sub>O)  $\delta$ : 1.40 (d, 3H,  $J = 6.5$  Hz), 2.53 (d, 2H,  $J = 6.5$  Hz), 3.35-3.65 (m, 1H), 4.10 (d, 1H,  $J = 13.5$  Hz), 4.33 (d, 1H,  $J = 13.5$  Hz), 7.50 (s, 5H). Ms  $m/z$  193 (M<sup>+</sup>). Anal. Calcd for C<sub>11</sub>H<sub>15</sub>NO<sub>2</sub>: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.56; H, 7.81; N, 7.26.

**3-Benzylamino-2-methylpropionic acid (12d)**. 65% yield. Colorless needles. mp 153-154 °C (MeOH-acetone). Ir  $\nu_{\max}$  (KBr)  $\text{cm}^{-1}$ : 1550. <sup>1</sup>H Nmr (90 MHz, D<sub>2</sub>O)  $\delta$ : 1.15 (d, 3H,  $J = 7.0$  Hz), 2.43-2.83 (m, 1H), 2.90-3.20 (m, 2H), 4.26 (s, 2H), 7.55 (s, 5H). Ms  $m/z$  193 (M<sup>+</sup>). Anal. Calcd for C<sub>11</sub>H<sub>15</sub>NO<sub>2</sub>: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.39; H, 7.75; N, 7.13.

**3-(2,4-Dimethoxybenzylamino)propionic acid (12e)**. 65% yield. Colorless plates. mp 184-185 °C (CHCl<sub>3</sub>). Ir  $\nu_{\max}$  (KBr)  $\text{cm}^{-1}$ : 1600. <sup>1</sup>H Nmr (90 MHz, D<sub>2</sub>O)  $\delta$ : 2.50 (t, 2H,  $J = 7.0$  Hz), 3.20 (t, 2H,  $J = 7.0$  Hz), 3.85 (s, 3H), 3.90 (s, 3H), 4.15 (s, 2H), 6.60-6.73 (m, 2H), 7.27-7.43 (m, 1H). Ms  $m/z$  239 (M<sup>+</sup>). Anal. Calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>4</sub>: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.92; H, 7.07; N, 5.68.

#### Preparation of $\beta$ -lactams (**13a-e**).

**Typical example:** A suspension of 3-benzylamino-3,3-dimethylpropionic acid (**12a**) (207 mg, 1 mmol), PPTT (**5**) (720 mg, 2 mmol), and *i*-Pr<sub>2</sub>NEt (387 mg, 3 mmol) in MeCN (200 ml) was refluxed for 1 h. After removal of the solvent of the reaction mixture *in vacuo*, the residue was purified on a silica gel column impregnated with 5% AgNO<sub>3</sub> with hexane-AcOEt (7:3) to give 1-benzyl-4,4-dimethyl-2-azetidinone (**13a**) as a colorless oil (183.3 mg, 97% yield). Ir  $\nu_{\max}$  (neat) cm<sup>-1</sup>: 1720. <sup>1</sup>H Nmr (60 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.30 (s, 6H), 2.87 (s, 2H), 4.37 (s, 2H), 7.50 (s, 5H). High-resolution ms  $m/z$  Calcd for C<sub>12</sub>H<sub>15</sub>NO (M<sup>+</sup>): 189.1153. Found: 189.1126. Other  $\beta$ -lactams (**13b-e**) were similarly prepared. Their physical data are as follows.

**1-Benzyl-4-phenyl-2-azetidinone (13b).** 99% yield. Colorless oil. Ir  $\nu_{\max}$  (neat) cm<sup>-1</sup>: 1725. <sup>1</sup>H Nmr (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.86 (ddd, 1H,  $J$  = 14.7, 2.4, and 1.0 Hz (long range coupling)), 3.36 (dd, 1H,  $J$  = 14.7 and 4.9 Hz), 3.76 (d, 1H,  $J$  = 14.7 Hz), 4.20 (dd, 1H,  $J$  = 4.9 and 2.4 Hz), 4.80 (d, 1H,  $J$  = 14.7 Hz), 7.04-7.40 (m, 10H). High-resolution ms  $m/z$  Calcd for C<sub>16</sub>H<sub>15</sub>NO (M<sup>+</sup>): 237.1154. Found: 237.1169.

**1-Benzyl-4-methyl-2-azetidinone (13c).** 95% yield. Colorless oil. Ir  $\nu_{\max}$  (neat) cm<sup>-1</sup>: 1730. <sup>1</sup>H Nmr (60 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.15 (d, 3H,  $J$  = 7.0 Hz), 2.40 (dd, 1H,  $J$  = 15.0 and 3.0 Hz), 3.00 (dd, 1H,  $J$  = 15.0 and 5.0 Hz), 3.30-3.76 (m, 1H), 4.03 (d, 1H,  $J$  = 16.0 Hz), 4.53 (d, 1H,  $J$  = 16.0 Hz), 7.30 (s, 5H). High-resolution ms  $m/z$  Calcd for C<sub>11</sub>H<sub>13</sub>NO (M<sup>+</sup>): 175.0997. Found: 175.1014.

**1-Benzyl-3-methyl-2-azetidinone (13d).** 99% yield. Colorless oil. Ir  $\nu_{\max}$  (neat) cm<sup>-1</sup>: 1730. <sup>1</sup>H Nmr (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.30 (d, 3H,  $J$  = 7.3 Hz), 2.67-2.83 (m, 1H), 3.06-3.96 (m, 2H), 4.37 (s, 2H), 7.18-7.44 (m, 5H). High-resolution ms  $m/z$  Calcd for C<sub>11</sub>H<sub>13</sub>NO (M<sup>+</sup>): 175.0997. Found: 175.0995.

**1-(2,4-Dimethoxybenzyl)-2-azetidinone (13e).** 95% yield. Colorless oil. Ir  $\nu_{\max}$  (neat) cm<sup>-1</sup>: 1720. <sup>1</sup>H Nmr (90 MHz, CDCl<sub>3</sub>)  $\delta$ : 2.93 (t, 2H,  $J$  = 4.0 Hz), 3.20 (t, 2H,  $J$  = 4.3 Hz), 3.82 (s, 6H), 4.35 (s, 2H), 6.36-6.56 (m, 2H), 7.10-7.23 (m, 1H). High-resolution ms  $m/z$  Calcd for C<sub>11</sub>H<sub>13</sub>NO (M<sup>+</sup>): 221.1052. Found: 221.1068.

**Methyl 3-Benzylamino-2-benzyloxycarbonylaminocrotonate (15).** Jones reagent<sup>11</sup> (7.6 ml) was added dropwise to a solution of Z-L-threonine methyl ester (4 g, 16 mmol) in acetone (40 ml) with stirring at -10 °C. After being stirred at -10 °C for 1 h and further at room temperature for 30 min, isopropanol (50 ml) was added. The resulting precipitate was filtered off and then the filtrate was evaporated *in vacuo*. To the residue was added AcOEt (30 ml) and then the organic layer was washed with



H<sub>2</sub>O and brine, dried, and evaporated *in vacuo*. To the residue was added benzene (38 ml), *p*-toluenesulfonic acid (100 mg), and benzylamine (4.81 g, 44.9 mmol), followed by stirring at room temperature for 4 h. The reaction mixture concentrated *in vacuo* to afford an oily residue. The residue was chromatographed on a silica gel column with hexane-AcOEt (4:1) to give compound (**15**) (4.4 g, 81.9% yield) as a yellow oil. Ir  $\nu_{\max}$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 1720. <sup>1</sup>H Nmr (60 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.98 (s, 3H), 3.60 (s, 3H), 4.45 (d, 2H, *J* = 6 Hz), 5.20 (s 2H), 5.90 (br s, 1H), 7.40 (s, 10H), 9.50 (t, 1H, *J* = 6.0 Hz). High-resolution ms *m/z* Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> (M<sup>+</sup>): 354.1579. Found: 354.1603.

**threo**-Methyl 3-Benzylamino-2-benzyloxycarbonylaminobutyrate (**16**) and **erythro**-Methyl 3-Benzylamino-2-benzyloxycarbonylaminobutyrate (**17**). NaBH<sub>3</sub>CN (493 mg, 7.8 mmol) was added to a solution of **15** (2.8 g, 7.8 mmol) in AcOH (30 ml). The mixture was stirred at room temperature for 15 min followed by concentration *in vacuo*. The residue was dissolved in AcOEt and then the solution was successively washed with saturated aqueous NaHCO<sub>3</sub> and brine, dried, and evaporated *in vacuo* to give an oily residue. The residue was chromatographed on a silica gel column with hexane-AcOEt (2:1). The first eluate gave compound (**16**) (1.1 g, 39% yield) as a colorless oil. Ir  $\nu_{\max}$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 1720. <sup>1</sup>H Nmr (60 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.13 (d, 3H, *J* = 6.5 Hz), 1.40 (s, 1H), 3.10-3.40 (m, 1H), 3.63 (s, 3H), 3.65 (s, 2H), 4.30 (dd, 1H, *J* = 3 and 9 Hz), 5.10 (s 2H), 5.95 (d, 1H, *J* = 9 Hz), 7.30 (s, 5H), 7.35 (s, 5H). High-resolution ms *m/z* Calcd for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub> (M<sup>+</sup>): 356.1736. Found: 356.1742. The second eluate gave compound (**17**) (0.9g, 32%) as a colorless oil. Ir  $\nu_{\max}$  (CHCl<sub>3</sub>) cm<sup>-1</sup>:1720. <sup>1</sup>H Nmr (60 MHz, CDCl<sub>3</sub>)  $\delta$ : 1.03 (d, 3H, *J* = 6.5 Hz), 1.40 (s, 1H), 2.90-3.30 (m, 1H), 3.70 (s, 3H), 3.73 (s, 2H), 4.57 (dd, 1H, *J* = 4 and 9 Hz), 5.15 (d 2H, *J* = 3 Hz), 5.70 (d, 1H, *J* = 8 Hz), 7.32 (s, 5H), 7.35 (s, 5H). High-resolution ms *m/z* Calcd for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub> (M<sup>+</sup>): 356.1736. Found: 356.1759.

**threo**-3-Benzylamino-2-benzyloxycarbonylaminobutyric Acid (**18**) and **erythro**-3-Benzylamino-2-benzyloxycarbonylaminobutyric Acid (**19**). 2N NaOH (2 ml) was added to a solution of **16** (712 mg, 2 mmol) in MeOH (2 ml). The mixture was stirred at room temperature for 1 h. After the solvent of the reaction mixture was evaporated *in vacuo*, the residue was dissolved in a small amount of H<sub>2</sub>O and then washed with Et<sub>2</sub>O. To the aqueous layer was added 10% HCl solution to adjust to pH 3 and the resulting solution was evaporated *in vacuo*. To the residue was added pyridine and then the resulting suspension was filtered. The filtrate was evaporated *in vacuo* to give an oily residue, which was treated with Et<sub>2</sub>O to give a crude solid product. Recrystallization of the crude product from MeOH gave compound (**18**) (486.3 mg, 71% yield) as colorless needles. mp 175-176 °C. Ir  $\nu_{\max}$  (KBr) cm<sup>-1</sup>:

1700 and 1610.  $^1\text{H}$  Nmr (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$ : 1.27 (d, 3H,  $J = 6.4$  Hz), 3.40-3.70 (m, 1H), 4.20-4.50 (m, 3H), 5.11 (s, 2H), 7.32 (s, 5H), 7.40-7.60 (m, 5H). Ms  $m/z$  342 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4$ : C, 66.65; H, 6.48; N, 8.18. Found: C, 66.58; H, 6.43; N, 8.11. The similar treatment of **17** as described above afforded compound (**19**) in 65% yield as colorless needles from MeOH. mp 198-199 °C. Ir  $\nu_{\text{max}}$  (KBr)  $\text{cm}^{-1}$ : 1700 and 1610.  $^1\text{H}$  Nmr (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$ : 1.32 (d, 3H,  $J = 6.4$  Hz), 3.70-4.06 (m, 1H), 4.27 (d, 1H,  $J = 13.4$  Hz), 4.45 (d, 1H,  $J = 13.4$  Hz), 5.18 (s, 2H), 7.20-7.40 (m, 5H), 7.47 (s, 5H). Ms  $m/z$  342 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4$ : C, 66.65; H, 6.48; N, 8.18. Found: C, 66.50; H, 6.41; N, 8.11.

**3,4-cis-1-Benzyl-3-benzyloxycarbonylamino-4-methyl-2-azetidinone (20)**. A suspension of compound (**18**) (342 mg, 1 mmol), PPTT (**5**) (720 mg, 2 mmol), and *i*-Pr<sub>2</sub>N<sub>2</sub>Et (387 mg, 3 mmol) in MeCN (200 ml) was refluxed for 1 h. Then the reaction mixture was submitted to the usual workup to give azetidinone (**20**) (307.8 mg, 95% yield) as colorless needles from hexane-AcOEt. mp 145-146 °C. Ir  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 1740 and 1720.  $^1\text{H}$  Nmr (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.06 (d, 3H,  $J = 6.3$  Hz), 3.67-3.90 (m, 1H), 4.13 (d, 1H,  $J = 15.1$  Hz), 4.56 (d, 1H,  $J = 15.1$  Hz), 5.00 (dd, 1H,  $J = 8.6$  and 5.1 Hz), 5.11 (s, 2H), 5.45 (d, 1H,  $J = 8.6$  Hz), 7.30 (s, 10H). Ms  $m/z$  324 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$ : C, 70.35; H, 6.21; N, 8.64. Found: C, 70.09; H, 6.21; N, 8.57.

**3,4-trans-1-Benzyl-3-benzyloxycarbonylamino-4-methyl-2-azetidinone (21)**.

95% yield. Colorless needles. mp 90-91 °C (hexane-AcOEt). Ir  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )  $\text{cm}^{-1}$ : 1740 and 1720.  $^1\text{H}$  Nmr (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.27 (d, 3H,  $J = 5.9$  Hz), 3.67-3.90 (m, 1H), 4.11 (d, 1H,  $J = 15.1$  Hz), 4.32 (dd, 1H,  $J = 6.4$  and 1.5 Hz), 4.62 (d, 1H,  $J = 15.1$  Hz), 5.09 (s, 2H), 5.45 (d, 1H,  $J = 6.4$  Hz), 7.30 (s, 10H). Ms  $m/z$  324 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$ : C, 70.35; H, 6.21; N, 8.64. Found: C, 70.52; H, 6.33; N, 8.55.

## REFERENCE AND NOTES

1. T. Shioiri and S. Yamada, *J. Synth. Org. Chem. Jpn.*, 1973, **31**, 666.
2. T. Mukaiyama, N. Morito, and Y. Watanabe, *Chem. Lett.*, 1979, 1305.
3. J. Diago-Meseguer and A. L. Palomo-Coll, *Synthesis*, 1980, 547.
4. T. Kunieda, Y. Abe, T. Higuchi, and M. Hirobe, *Tetrahedron Lett.*, 1981, **22**, 1257.
5. (a) Y. Nagao, T. Kumagai, S. Yamada, and E. Fujita, unpublished result. (b) Y. Nagao, S. Yamada, Y. Hagiwara, and E. Fujita, The 46th National Meeting of the Chemical Society of Japan, Niigata,

- October, 1982, Abstr., p. 773. (c) Y. Nagao, *Yakugaku Zasshi*, 1982, **102**, 401. (d) Y. Nagao, T. Miyasaka, Y. Hagiwara, and E. Fujita, *J. Chem. Soc., Perkin Trans. I*, 1984, 183.
6. Y. Ueno, N. Yumino, and M. Okawara, The 45th National Meeting of the Chemical Society of Japan, Tokyo, April, 1982, Abstr., p. 944.
7. M. Ohno, S. Kobayashi, T. Iimori, Y. F. Wang, and T. Izawa, *J. Am. Chem. Soc.*, 1981, **103**, 2405.
8. Using 3 mol eq. of *i*-Pr<sub>2</sub>NEt as a base resulted in the most satisfactory yield for  $\beta$ -lactam formation.
9. H. Takahata, Y. Ohnishi, H. Takehara, K. Tsuritani, and T. Yamazaki, *Chem. Pharm. Bull.*, 1981, **29**, 1063.
10. D. M. Floyd, A. W. Fritz, and C. M. Cimarusti, *J. Org. Chem.*, 1982, **47**, 176.
11. A. Bowers, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1953, 2548.

Received, 23rd August, 1995