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

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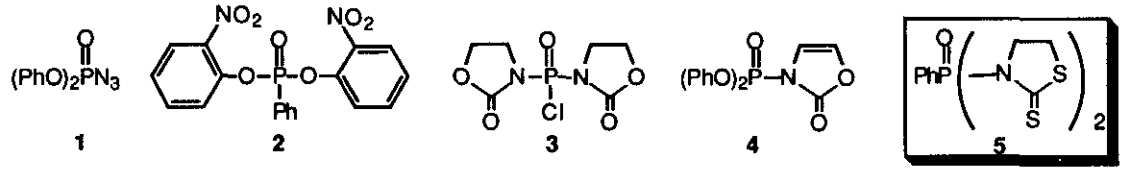
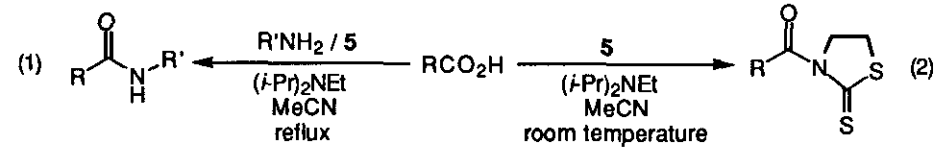
Abstract- 3,3'-(Phenylphosphoryl)-bis(1,3-thiazolidine-2-thione) (**5**), obtained from phenylphosphonic dichloride (**7**) and sodium salt of 1,3-thiazolidine-2-thione (**6**), proved to be useful for intramolecular dehydration of various β-amino acids to give the corresponding β-lactams.

In the formation of amide bond between a carboxylic acid and an amine, various organic phosphorus (V) compounds such as diphenylphosphoryl azide (**1**),[1] bis (*o*-nitrophenyl)phenyl phosphonate (**2**),[2] 3,3'-bis(2-oxo-3-oxazolidinyl)-phosphoroamidic chloride (**3**),[3] and diphenyl-2-oxo-3-oxazolidinyl phosphonate (**4**)[4] 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).[5,6] PPTT (**5**) was also efficiently exploited for the amide bond formation in the total synthesis of parabactin, a spermidine siderophore.[5d] Although the triphenylphosphine-dipyridyl disulfide reagents system proved to be available

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

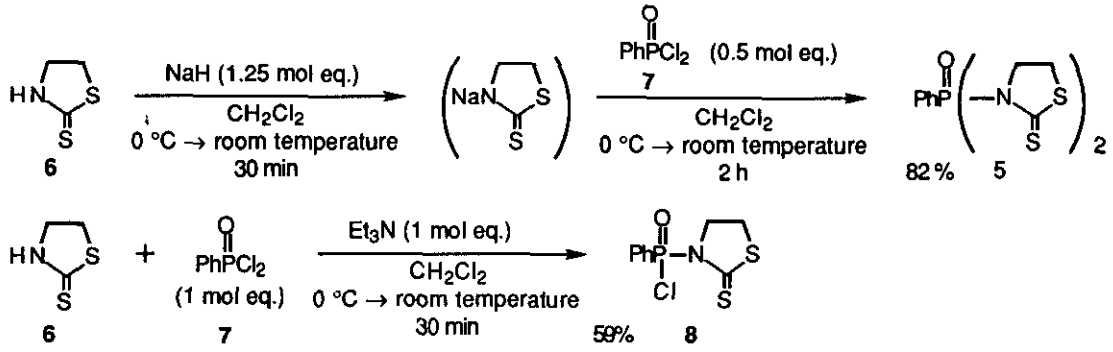
for converting β-amino acids into β-lactams,[7] we anticipated that PPTT (**5**) could be similarly employed for





the lactam ring formation of β-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 CH_2Cl_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 Et_3N in CH_2Cl_2.



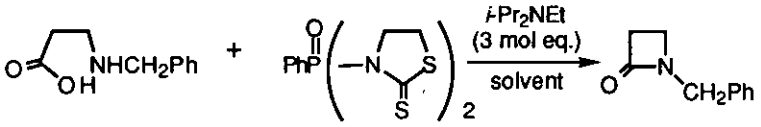
Scheme 1

The structure of both reagents (**5** and **8**) was confirmed by their ^{13}C nmr (67.8 MHz, $CDCl_3$) chemical shift value (**5**: 204.8 ppm, **8**: 202 ppm) due to the C=S group.[5c]

In order to search the optimum reaction conditions for the lactam ring formation, several reactions were investigated employing *N*-benzyl-β-alanine (**9**) in the presence of *i*-Pr_2NEt (3 mol eq.).[8] All experimental results are summarized in Table 1. At room temperature in MeCN and DMF or even under reflux in $CHCl_3$ and pyridine without use of *i*-Pr_2NEt, 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**)[9] 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_2NEt and Et_3N.[8] Thus, we chose the reaction conditions of Entry 5 (Table 1) for the further investigation of the β-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 β-lactam ring formation



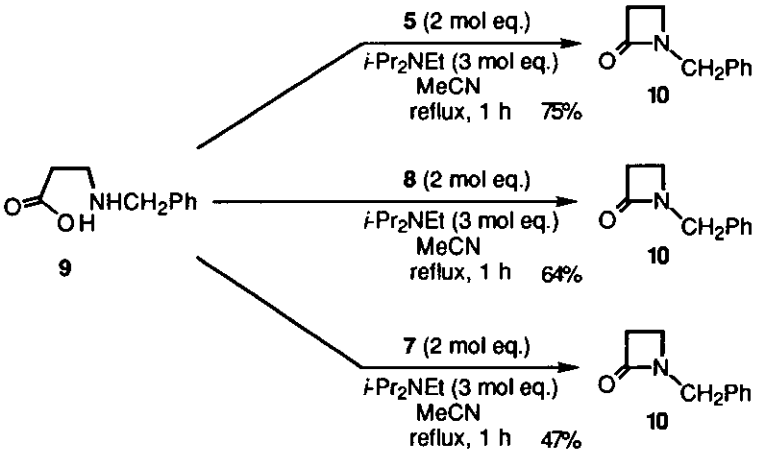
9 **5** **10**

Entry	Solvent	Concentration of **9** (mM)	Amount of **5** (mol eq.)	Temp.	Time	Yield[a] of **10** (%)
1	MeCN	26	0.66	r. t.[b]	60 h	0[c]
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.[b]	13 h	0[c]
7	DMF	26	0.66	100 °C	20 min	14
8	DMF	5	2.00	100 °C	1 h	16
9	$CHCl_3$	26	0.66	reflux	13 h	0[c]
10[d]	pyridine	26	0.66	reflux	5 h	0[c]

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_2NEt.

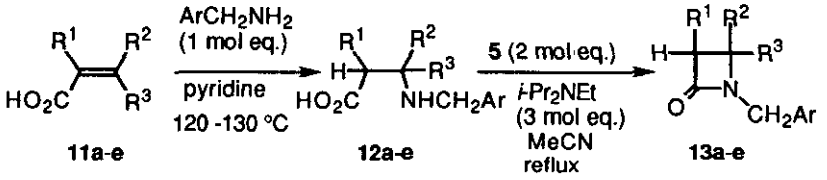
As shown in Scheme 2, PPTT (**5**) was confirmed to be the most efficient among the three reagents.



Scheme 2

Then, the β-lactam formation reactions of several β-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 α,β-unsaturated carboxylic acids (**11a-e**) in pyridine under heating at 120-130 °C. The β-amino acids (**12a-e**) were treated with 2 mol eq. of PPTT (**5**) in the presence of 3 mol eq. of *i*-Pr_2NEt in MeCN under reflux to afford the corresponding β-lactams (**13a-e**) in excellent yields as shown in Table 2.

Table 2. Preparation of β-amino acids and β-lactams

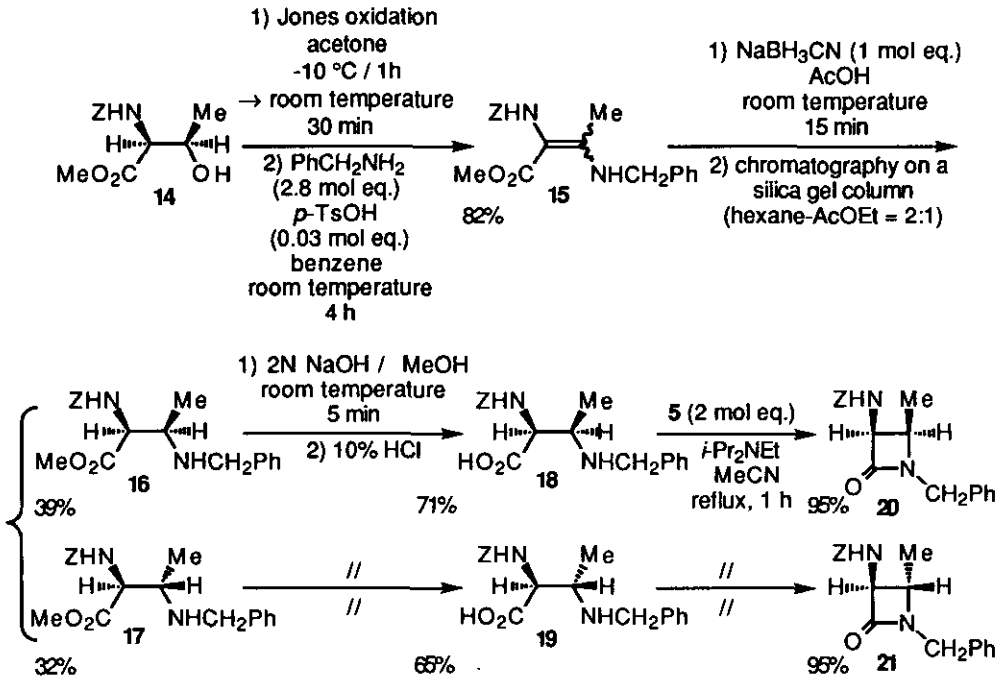


a : R^1 = H, R^2 = R^3 = Me; **b** : R^1 = R^3 = H, R^2 = Ph; **c** : R^1 = R^3 = H, R^2 = Me;
d : R^1 = Me, R^2 = R^3 = H; **e** : R^1 = R^2 = R^3 = H; Ar = Ph, 2,4-dimethoxyphenyl (DMP)

α,β-Unsaturated carboxylic acid	$ArCH_2NH_2$	Time (h)	β-Amino acid[a]	Yield (%)	Time (h)	β-Lactam[a]	Yield (%)
11a	Ar = Ph	24	**12a**	53	1	**13a**	97
11b	Ar = Ph	1	**12b**	70	1	**13b**	99
11c	Ar = Ph	1	**12c**	68	1	**13c**	95
11d	Ar = Ph	1	**12d**	65	5	**13d**	99
11e	Ar = DMP	1.5	**12e**[b]	65	1	**13e**[b]	95

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

Finally, this PPTT reagent system was successfully utilized for the β-lactam ring formation of *threo*- and *erythro*-α-benzyloxycarbonylamino-β-amino acids (**16** and **17**) toward monobactam[10] 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 β-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 ^1H nmr ($CDCl_3$) spectrum of *cis*-**20** [δ 5.00 ppm (dd, 1H, J = 8.6 and 5.1 Hz, C3-H)] and of *trans*-**21** [δ 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 β-lactam ring formation of various β-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. ^{1}H Nmr spectra were recorded on JEOL JNM-FX 100, Hitachi R-900, and Varian EM-360 instruments and chemical shifts are reported in δ (ppm) relative to Me_4Si or TSP as an internal standard. ^{13}C Nmr spectra were determined on a JEOL JNM-FX 100 and chemical shifts are reported in δ (ppm) relative to Me_4Si 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 F_{254} 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_2Cl_2 (50 ml) was added dropwise 1, 3-thiazolidine-2-thione (6.0 g, 50 mmol) in CH_2Cl_2 (100 ml) under N_2 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_2Cl_2 (25 ml) under N_2 at 0 °C. The whole mixture was stirred at room temperature for 2 h and then poured into H_2O (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_2Cl_2-AcOEt gave compound (**5**) (7.0 g, 82% yield) as pale yellow needles. mp 203-205 °C. Ir ν_{max} (KBr) cm^{-1}: 1355, 1245, 1200, 1080. ^1H Nmr (60 MHz, $CDCl_3$) δ : 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). ^{13}C Nmr (67.8 Hz, $CDCl_3$) δ: 32.4, 58.7, 128.8, 129.0, 132.0, 132.2, 133.9, 204.8. Ms *m/e* 360 (M^+). *Anal.* Calcd for $C_{12}H_{13}N_2OPS_4$: 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_2Cl_2 (5 ml) was added Et_3N (101 mg, 1 mmol) under N_2 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 $CHCl_3$ as eluent to afford compound (**8**) (163.4 mg, 59% yield) as a yellow oil. Ir ν_{max} (neat) cm^{-1}: 1490, 1220, 1110. ^1H Nmr (60 MHz, $CDCl_3$) δ: 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). ^{13}C Nmr (67.8 Hz, $CDCl_3$) δ: 31.9, 56.6, 128.4, 128.5, 131.1, 131.2, 133.6, 202.0. Ms *m/z* 277 (M^+). *Anal.* Calcd for $C_9H_9NOClPS_2$: 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 β-lactam ring formation.

Typical example (Entry 5 in Table 1): A suspension of *N*-benzyl-β-alanine (**9**) (18 mg, 0.1 mmol), PPTT (**5**) (72 mg, 0.2 mmol), and *i*-Pr_2NEt (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% $AgNO_3$ by employing AcOEt to give known 1-benzylazetidinone (**10**) (12.1 mg, 75% yield) as a colorless oil. Ir and ^1H nmr data of the synthesized compound (**10**) was consistent with those of the authentic compound.[9] Other experiments (Entries 1-4 and 6-10) were similarly carried out. Their results are shown in Table 1.

Treatment of *N*-benzyl-β-alanine (9) with compound (8). A mixture of **9** (18 mg, 0.1 mmol), **8** (56 mg, 0.2 mmol), and *i*-Pr_2NEt (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-β-alanine (9) with compound (7). A mixture of **9** (36 mg, 0.2 mmol), **7** (78 mg, 0.4 mmol), and *i*-Pr_2NEt (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 β-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_2 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 ν_{max} (KBr) cm^{-1}: 1550. ^1H Nmr (90 MHz, D_2O) δ: 1.30 (s, 6H), 2.33 (s, 2H), 3.93 (s, 2H), 7.20-7.50 (m, 5H). Ms *m/z* 207 (M^+). *Anal.* Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.48; H, 8.18; N, 6.79. Other β-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_2O). Ir ν_{max} (KBr) cm^{-1}: 1550. ^1H Nmr (100 MHz, CD_3OD) δ: 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^+). *Anal.* Calcd for $C_{16}H_{17}NO_2$: 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 ν_{max} (KBr) cm^{-1}: 1560. ^1H Nmr (90 MHz, D_2O) δ: 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^+). *Anal.* Calcd for $C_{11}H_{15}NO_2$: 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 ν_{max} (KBr) cm^{-1}: 1550. ^1H Nmr (90 MHz, D_2O) δ: 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^+). *Anal.* Calcd for $C_{11}H_{15}NO_2$: 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 ($CHCl_3$). Ir ν_{max} (KBr) cm^{-1}: 1600. ^1H Nmr (90 MHz, D_2O) δ: 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^+). *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.92; H, 7.07; N, 5.68.

Preparation of β-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_2NEt (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% $AgNO_3$ 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 ν_{max} (neat) cm^{-1}: 1720. ^1H Nmr (60 MHz, $CDCl_3$) δ: 1.30 (s, 6H), 2.87 (s, 2H), 4.37 (s, 2H), 7.50 (s 5H). High-resolution ms *m/z* Calcd for $C_{12}H_{15}NO$ (M^+): 189.1153. Found: 189.1126. Other β-lactams (**13b-e**) were similarly prepared. Their physical data are as follows.

1-Benzyl-4-phenyl-2-azetidinone (13b). 99% yield. Colorless oil. Ir ν_{max} (neat) cm^{-1}: 1725. ^1H Nmr (100 MHz, $CDCl_3$) δ: 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 $C_{16}H_{15}NO$ (M^+): 237.1154. Found: 237.1169.

1-Benzyl-4-methyl-2-azetidinone (13c). 95% yield. Colorless oil. Ir ν_{max} (neat) cm^{-1}: 1730. ^1H Nmr (60 MHz, $CDCl_3$) δ: 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 $C_{11}H_{13}NO$ (M^+): 175.0997. Found: 175.1014.

1-Benzyl-3-methyl-2-azetidinone (13d). 99% yield. Colorless oil. Ir ν_{max} (neat) cm^{-1}: 1730. ^1H Nmr (100 MHz, $CDCl_3$) δ: 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 $C_{11}H_{13}NO$ (M^+): 175.0997. Found: 175.0995.

1-(2,4-Dimethoxybenzyl)-2-azetidinone (13e). 95% yield. Colorless oil. Ir ν_{max} (neat) cm^{-1}: 1720. ^1H Nmr (90 MHz, $CDCl_3$) δ: 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 $C_{11}H_{13}NO$ (M^+): 221.1052. Found: 221.1068.

Methyl 3-Benzylamino-2-benzyloxycarbonylaminocrotonate (15). Jones reagent[11] (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_2O 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 ν_{max} ($CHCl_3$) cm^{-1}: 1720. ^1H Nmr (60 MHz, $CDCl_3$) δ: 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 $C_{20}H_{22}N_2O_4$ (M^+): 354.1579. Found: 354.1603.

***threo*-Methyl 3-Benzylamino-2-benzyloxycarbonylaminobutyrate (16)** and ***erythro*-Methyl 3-Benzylamino-2-benzyloxycarbonylaminobutyrate (17)**. $NaBH_3CN$ (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 $NaHCO_3$ 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 ν_{max} ($CHCl_3$) cm^{-1}: 1720. ^1H Nmr (60 MHz, $CDCl_3$) δ: 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 $C_{20}H_{24}N_2O_4$ (M^+): 356.1736. Found: 356.1742. The second eluate gave compound (**17**) (0.9g, 32%) as a colorless oil. Ir ν_{max} ($CHCl_3$) cm^{-1}:1720. ^1H Nmr (60 MHz, $CDCl_3$) δ: 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 $C_{20}H_{24}N_2O_4$ (M^+): 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_2O and then washed with Et_2O. 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_2O 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 ν_{max} (KBr) cm^{-1}:

1700 and 1610. ^{1}H Nmr (100 MHz, CD_3OD) δ: 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 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_4$: 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 ν_{max} (KBr) cm^{-1}: 1700 and 1610. ^{1}H Nmr (100 MHz, CD_3OD) δ: 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 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O_4$: 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_2NEt (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 ν_{max} ($CHCl_3$) cm^{-1}: 1740 and 1720. ^{1}H Nmr (100 MHz, $CDCl_3$) δ: 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 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_3$: 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 ν_{max} ($CHCl_3$) cm^{-1}: 1740 and 1720. ^{1}H Nmr (100 MHz, $CDCl_3$) δ: 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 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.52; H, 6.33; N, 8.55.

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