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A Convenient One Pot Asymmetric Synthesis of cis-β-Lactams: Key Precursors for Optically Active 2-Oxaisocephems

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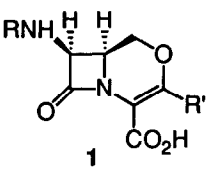
Abstract: Asymmetric annelation of the disilylated imine **3** generated in situ from D-threonine **2** with acid chlorides **4** and triethylamine followed by esterification provided cis-β-lactams **5** and **6** in excellent yields with high diastereoselectivity under mild conditions. And conversion of compounds **5** into **15**, derivatives of 2-oxaisocephems having a thio-substituted methyl group at the 3-position and a 2-aminothiazol-4-yl moiety at the 7-position, is described. Biological activities of the new compounds are presented. In particular, **15b** showed potent antibacterial activity against Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecalis* which cause a serious clinical problem in antibacterial chemotherapy.

Introduction

As part of our study towards the stereocontrolled synthesis of β-lactams, we required a practical and convenient synthesis of enantiomerically pure *N*-protected-3-amino-azetidinones. In particular, we wished to synthesize various optically active 2-oxaisocephems **1** for enhanced antibacterial activity since racemic compounds have been reported to have only partial antibacterial activity.[1] Enantiomerically pure *N*-protected-3-amino-azetidinones are considered to be key precursors for enantiomerically pure 2-oxaisocephems.



1

Among many methodologies, [2+2] cycloaddition of ketenes with imines (Staudinger reaction) is the most

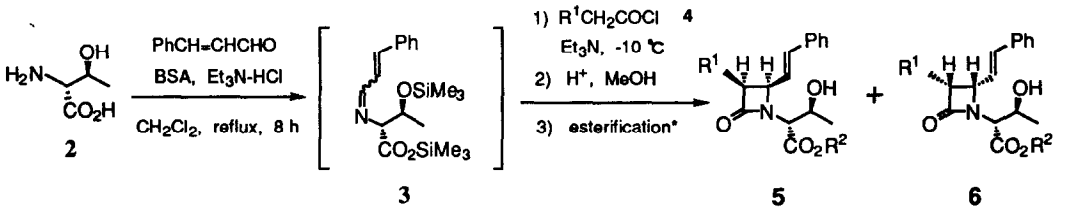
popular for the synthesis of β-lactams. Numerous investigators have reported asymmetric induction at low temperature (for example, -78 ℃) by the use of chiral elements in either the ketene[2] or the imine precursor derived from chiral aldehydes[3] or chiral amines.[4] However, this approach often was accompanied by a lengthy synthesis of the chiral auxiliary and troublesome removal of this group. We selected D-threonine **2**[5] as a readily available chiral component owing to the ease of conversion into the desired target compounds **1**. Methods using D-threonine **2** as a chiral auxiliary have been reported previously. In the publication by A. K. Bose,[5a] a mixture of diastereomers (1:1 ratio) of cis-β-lactams was obtained from the reaction of azidoacetyl chloride and the Schiff base derived from cinnamaldehyde and D-threonine esters. On the other hand, S. M. Tenneson[5b] reported that the reaction of azidoacetyl chloride and the Schiff base derived from cinnamaldehyde and *O*-tert-butyldimethylsilyl ether of D-threonine benzyl ester gave a mixture of diastereomers (9:1 ratio) of cis-β-lactams in 60% yield. Later, A. K. Bose[5c] proposed an enantiospecific synthesis of cis-β-lactams using *O*-triphenylsilyl ether of D-threonine benzyl ester. However, these enantioselective methods involve a number of steps for the synthesis of the Schiff base and silica gel column chromatography or HPLC to obtain pure products.

From this viewpoint, we attempted to find a more convenient one pot asymmetric synthetic method of cis-β-lactams that could be applicable to scale-up without column chromatography and thus readily give various esters **5** useful for the synthesis of **1**. We found that annelation of the disilylated imine **3** generated in situ with acid chlorides **4** in the presence of triethylamine at -10 ℃ followed by esterification gave cis-β-lactams **5** and **6** with high diastereoselectivity. Cinnamaldehyde was selected as the aldehyde component of the imine **3** to allow conversion of the C-4-styryl substituent into the C-4-hydroxymethyl group. We describe herein the synthesis of optically active 2-oxaisocephems by the use of compounds **5** as key precursors and their *in vitro* biological activities.

Results and Discussion

The disilylated imine **3** was prepared by stirring D-threonine **2** and an equimolar amount of cinnamaldehyde with 2 equiv. of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 0.1 equiv. of triethylamine hydrochloride for 8 h under reflux. Next, the reaction of **3** with equimolar amounts of acid chlorides **4** in the presence of 1.2 equiv. of triethylamine at -10 ℃ followed by esterification provided a diastereomeric mixture of cis-β-lactams **5** as main products together with **6**. Diastereomerically pure major diastereomer **5** was separated by recrystallization (Scheme 1). In this reaction, it was necessary to add triethylamine hydrochloride to obtain **5** in good yields. Unless triethylamine hydrochloride is added, the formation of the Schiff base **3** was not efficient and the yields of **5** were variable (20-60%). However, satisfactory results could be obtained by addition of triethylamine hydrochloride as described in Table 1. The ratio of the two diastereoisomers was determined by ^{1}H NMR

spectroscopy and HPLC.[6] The *cis*-orientation of the substituents at C-3 and C-4 was apparent from ^{1}H NMR data (for example, J = 5.4 Hz in the case of **5a**). The highest diastereoselectivity was observed in the case of a mixture of **5d** and **6d**. In this way, a high diastereoselectivity in ketene-imine cycloaddition could be achieved by the use of the disilylated imine **3** at -10 ℃ and desired optically pure main products **5** were easily obtained.



R^1 = 4-NO_2-PhthN, PhthN, N_3 . R^2 = $CHPh_2$, p-nitrobenzyl (PNB), p-methoxybenzyl (PMB), CH_2Ph

* diphenyldiazomethane / CH_2Cl_2 at r.t.,
or p-nitrobenzyl bromide, p-methoxybenzyl chloride, or benzyl bromide / K_2CO_3 / DMF at r.t.

Scheme 1

Table 1. Cycloaddition reaction between acid chlorides **4** and the imine **3**.

Compd. (**5** and **6**)	R^1	R^2	Yield*1 (%)	Ratio (**5**:**6**)	mp*2 (℃)
a	4-NO_2-PhthN	$CHPh_2$	76	11:1	222.5-223
b	4-NO_2-PhthN	PNB	63	9:1	209-209.5
c	4-NO_2-PhthN	PMB	65	10:1	108-109
d	PhthN	$CHPh_2$	74	16:1	181-181.5
e	N_3	$CHPh_2$	52	10:1	120.5-121.5
f	N_3	CH_2Ph	54	10:1	84.5-85.5

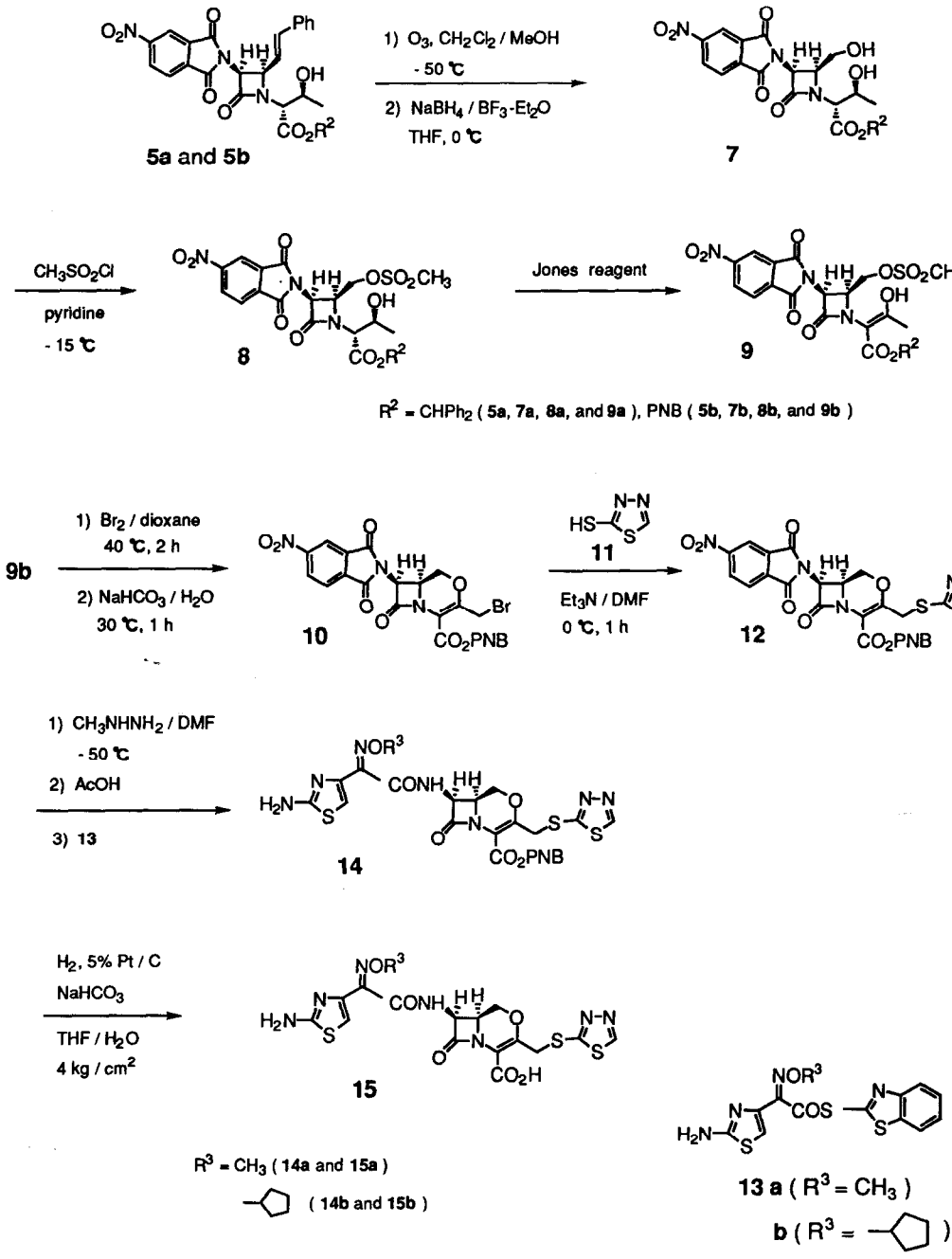
*1: Isolated yields of optically pure major diasrereomer **5**. *2: Melting points of major diastereomer **5**.

4-NO_2-PhthN = 4-nitrophthalimido; PhthN = phthalimido; PNB = p-nitrobenzyl, PMB = p-methoxybenzyl.

Next, we wished to covert **5** into optically active 2-oxaisocephems **15** having a thio-substituted methyl group at the 3-position and a 2-aminothiazol-4-yl moiety at the 7-position with the expected enhancement of antibacterial activity (Scheme 2). Our synthetic strategy for the preparation of **15** involves the use of the important intermediate **10** with a bromomethyl substituent at the 3-position and 4-nitrophthalimido group at the 7-position readily derived from **5**.

Ozonolysis (at -50 ℃ in CH_2Cl_2 / MeOH) of **5a** and **5b** with reductive workup (addition of $NaBH_4$ with BF_3-Et_2O) was used to cleave the styryl group thus giving the alcohol **7**. Subsequently, **7** was converted into **9** easily via **8** (CH_3SO_2Cl / pyridine followed by Jones reagent).

We found that the chiral azetidinone **9b** could be easily converted into **10** and the reaction of **10** with the



Scheme 2

thiol derivative **11** in the presence of triethylamine gave the desired product **12**. The general procedures to

synthesize **12** are as follows: A mixture of **9b** and 1.15 equiv. of bromine in dioxane was stirred at 40 ℃ for 2 h. Then aqueous $NaHCO_3$ solution was added to the reaction mixture at 30 ℃. After stirring for 1h, **10** was separated out by addition of small amount of H_2O. When applied this method to **9a**, benzhydryl ester of **9a** was damaged. Then, **10** was allowed to react with an equimolar of 2-mercapto-1,3,4-thiadiazole **11** and triethylamine in DMF at 0℃ for 1h to afford **12** in good yield. In order to introduce 2-aminothiazol-4-yl moiety into the 7-position, it was necessary to deprotect the 4-nitrophthalimido group of **12**. We have reported previously that methylhydrazinolysis was effective for this deprotection.[7] When **12** was treated with 1.1 equiv. of methylhydrazine in DMF at -50℃ for 30 min, the 4-nitrophthalimido group was removed smoothly. The thus generated amine was allowed to react with an equimolar of 2-aminothiazole derivatives **13** to give **14**. Compound **14** was converted to the desired target compounds **15** by catalytic reduction with 5% Pd/C at r.t. under hydrogen pressure of 4 kg/cm^2 for 3 h. Further elaboration to optically active 2-oxaisocephems is in progress.

In summary, we have demonstrated that a high diastereoselectivity in ketene-imine cycloaddition can be achieved by the use of the disilylated imine **3** at -78 ℃ and the *cis*-β-lactam **5b** obtained by the reaction is easily converted into new optically active 2-oxaisocephems.

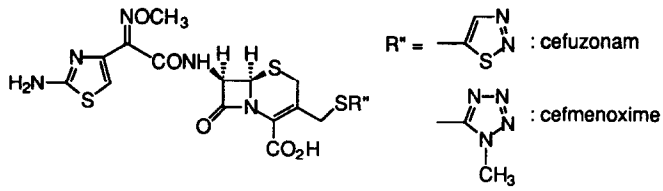
In Vitro Biological Evaluation

The minimum inhibitory concentrations (MICs: μg/ml, inoculum size: 10^6 cells/ml) against test organisms (*Staphylococcus aureus* FDA 209P, Methicillin-resistant *Staphylococcus aureus* (MRSA) 57, *Enterococcus faecalis*, *Escherichia coli* NIHJ JC-2, and *Pseudomonas aeruginosa* ATCC 10145) were determined by an agar dilution method. The *in vitro* activities of **15a** and **15b** are summarized in Table 2. The antibacterial activities of cefuzonam and cefmenoxime as reference compounds are also presented.

New 2-oxaisocephems, **15a** and **15b** have broader spectrum of antibacterial activities than the corresponding third generation cephalosporins such as cefuzonam and cefmenoxime. Among these compounds, **15b** with [2-(2-aminothiazol-4-yl)-2-(Z)-cyclopentyloxyimino]acetamido group at the 7-position showed well-

Table 2. *In Vitro* Antibacterial Activity (MICs, μg/ml)

Compd.	*S. aureus* FDA 209P	MRSA 57	*E. faecalis*	*E. coli* NIHJ JC-2	*P. aeruginosa* ATCC 10145
15a	0.39	> 100	25	0.1	12.5
15b	0.2	6.25	3.13	0.2	6.25
cefuzonam	0.39	100	100	0.1	25
cefmenoxime	1.56	> 100	> 100	0.1	25



balanced and potent activity against test organisms including MRSA and *E. faecalis* which resist most cephalosporins.

Experimental Section

All the melting points were determined on a Yanaco MP-500D apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a BRUKER AC250 instrument operating at 250 MHz. Chemical shifts are expressed in parts per million (ppm) on the δ scale from internal tetramethylsilane and coupling constants in Hz. Infrared (IR) spectra were measured for KBr pellets with a JASCO IR-810 infrared spectrophotometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. The spectroscopic data for all new compounds were consistent with the assigned structures.

4-Nitrophthalimidoacetic acid. A stirred mixture of 4-nitrophthalic anhydride (2 g, 10.4 mmol) and glycine (780 mg, 10.4 mmol) was heated at 190 ℃ for 30 min. The mixture was allowed to cool to room temperature and recrystallized from water to give 4-nitrophthalimidoacetic acid (2.2 g, 85%), mp 192 - 192.5 ℃. ^{1}H NMR (DMSO-d_6) δ: 4.39 (2H, s), 8.20 (1H, d, J = 8.2 Hz), 8.57 (1H, d, J = 2 Hz), 8.67 (1H, dd, J = 2, 8.2 Hz). Anal. Calcd. for $C_{10}H_6N_2O_6$: C, 48.01; H, 2.42; N, 11.20. Found: C, 47.76; H, 2.27; N, 11.13.

4-Nitrophthalimidoacetyl chloride. A stirred suspension of 4-nitrophthalimidoacetic acid (509.4 g, 2.04 mol) and phosphorus pentachloride (424 g, 2.04 mol) in toluene (1200 ml) was heated under reflux for 3 h, and then the solution was evaporated under reduced pressure. Treatment of the residue with n-hexane yielded 4-nitrophthalimidoacetyl chloride (543.5 g, 99%), which was directly used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ: 4.69 (2H, s), 8.14 (1H, d, J = 8.1 Hz), 8.68 (1H, dd, J = 1.9, 8.1 Hz), 8.75 (1H, d, J = 1.9 Hz).

(3S,4R)-1-[(R)-1-[(Benzhydryloxy)carbonyl]-(S)-2-hydroxypropyl]-3-(4-nitrophthalimido)-4-styrylazetidin-2-one (5a). A stirred suspension of D-threonine (1.19 g, 10 mmol) and cinnamaldehyde (1.39 g, 10 mmol) with BSA (4.07 g, 20 mmol) and triethylamine hydrochloride (0.14 g, 1 mmol) in methylene chloride (20 ml) was heated under reflux for 8 h. Triethylamine (1.21 g, 12 mmol) was added to this solution, which was then cooled to -10 ℃. 4-Nitrophthalimidoacetyl chloride (2.69 g, 10 mmol) in methylene chloride (20 ml) was added dropwise over a period of 30 min. The reactants were allowed to warm to room temperature, to which were added methanol (2.5 ml) and concentrated hydrochloric acid (1.25 ml). The mixture thus obtained was washed with water (3 x 20 ml) and brine (20 ml), dried over Na_2SO_4, and filtered.

To the filtrate which contains the carboxylic acid was added diphenyldiazomethane (2.14 g, 11 mmol). The reaction mixture was then stirred at room temperature for 2 h, after which time the solvent was removed. The residue was recrystallized from ethyl acetate-n-hexane to give **5a** (4.8 g, 76%) as colorless needles, mp 222.5-223 ℃. $[\alpha]_D^{28}$ -93.3 (c 0.12, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.35 (3H, d, J = 6.2 Hz), 2.97 (1H, d, J = 6 Hz), 4.41-4.52 (1H, m), 4.52 (1H, d, J = 5.1 Hz), 4.85 (1H, dd, J = 5.4, 9.4 Hz), 5.62 (1H, d, J = 5.4 Hz), 6.20 (1H, dd, J = 9.4, 15.9 Hz), 6.51 (1H, d, J = 15.9 Hz), 6.97 (1H, s), 7.15-7.37 (15H, m), 8.05 (1H, d, J = 8.1 Hz), 8.60 (1H, dd, J = 1.9, 8.1 Hz), 8.66 (1H, d, J = 1.9 Hz). IR (cm^{-1}): 3500, 3400, 1760, 1730, 1550, 1350. Anal. Calcd. for $C_{36}H_{29}N_3O_8$: C, 68.46; H, 4.63; N, 6.65. Found: C, 68.28; H, 4.49; N, 6.70.

Compounds **5d** and **5e** were obtained by the same procedure as described for **5a**.

5d: mp 181-181.5 ℃. $[\alpha]_D^{27}$ -85.9 (c 0.128, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.32 (3H, d, J = 6.3 Hz), 3.17 (1H, d, J = 5.8 Hz), 4.35-4.47 (1H, m), 4.54 (1H, d, J = 5.7 Hz), 4.82 (1H, dd, J = 5.4, 9.4 Hz), 5.60 (1H, d, J = 5.4Hz), 6.25 (1H, dd, J = 9.4, 15.9 Hz), 6.50 (1H, d, J = 15.9 Hz), 6.96 (1H, s), 7.13-7.42 (15H, m), 7.71-7.74 (2H, m), 7.76-7.86 (2H, m). IR (cm^{-1}): 3400, 3330, 1760, 1740, 1720. Anal. Calcd. for $C_{36}H_{30}N_2O_6$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.41; H, 5.11; N, 4.90.

5e: mp 120.5-121.5 ℃. $[\alpha]_D^{28}$ -94.6 (c 0.294, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.25 (3H, d, J = 6.5 Hz), 3.50 (1H, d, J = 9.4 Hz), 4.02 (1H, d, J = 4.3 Hz), 4.38-4.56 (2H, m), 4.91 (1H, d, J = 5 Hz), 6.13 (1H, dd, J = 9.6, 15.9 Hz), 6.60 (1H, d, J = 15.9 Hz), 6.88 (1H, s), 7.10-7.40 (15H, m). IR (cm^{-1}): 3400, 2100, 1760, 1721. Anal. Calcd. for $C_{28}H_{26}N_4O_4$: C, 69.70; H, 5.43; N, 11.61. Found: C, 69.51; H, 5.35; N, 11.45.

(3S,4R)-1-[(R)-1-[[(p-Nitrobenzyl)oxy]carbonyl]-(S)-2-hydroxypropyl]-3-(4-nitrophthalimido)-4-styrylazetidin-2-one (5b). The filtrate containing the carboxylic acid as described for **5a** was evaporated under reduced pressure. The residue was dissolved in DMF (20 ml), to which was added p-nitrobenzyl bromide (2.16 g, 10 mmol) and potassium carbonate (1.38 g, 10 mmol). The mixture was then stirred at room temperature for 2 h, and then diluted with ethyl acetate (100 ml). This solution was washed with water (50 ml), and the organic layer was separated. The aqueous layer was extracted with additional ethyl acetate (50 ml). The organic extracts were combined, washed with water (4 x 75 ml), dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-n-hexane to give **5b** (3.78 g, 63%) as colorless needles, mp 209-209.5 ℃. $[\alpha]_D^{28}$ -67 (c 0.194, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.41 (3H, d, J = 6.4 Hz), 3.21 (1H, d, J = 8 Hz), 4.35 (1H, d, J = 4.5 Hz), 4.40-4.55 (1H, m), 4.94 (1H, dd, J = 5.4, 9.5 Hz), 5.35 (2H, s), 5.70 (1H, d, J = 5.4 Hz), 6.26 (1H, dd, J = 9.5, 15.9 Hz), 6.66 (1H, d, J = 15.9 Hz), 7.21-7.26 (5H, m), 7.53 (2H, d, J = 8.8 Hz), 8.01 (1H, d, J = 8.1 Hz), 8.17 (2H, d, J = 8.8 Hz), 8.62 (1H, dd, J = 1.9, 8.1 Hz), 8.68 (1H, d, J = 1.9 Hz). IR (cm^{-1}): 3400, 1760, 1740, 1730,

1540, 1350. Anal. Calcd. for $C_{30}H_{24}N_4O_{10}$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.79; H, 3.91; N, 9.14.

Compounds **5c** and **5f** were obtained by the same procedure as described for **5b**.

5c: mp 108-109 ℃. $[\alpha]_D^{25}$ -92.1 (c 0.936, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.36 (3H, d, J = 6.1 Hz), 3.00 (1H, d, J = 6 Hz), 3.81 (3H, s), 4.35-4.45 (2H, m), 4.90 (1H, dd, J = 5.4, 9.4 Hz), 5.14 (1H, d, J = 11.8 Hz), 5.21 (1H, d, J = 11.8 Hz), 5.64 (1H, d, J = 5.4 Hz), 6.24 (1H, dd, J = 9.4, 15.9 Hz), 6.55 (1H, d, J = 15.9 Hz), 6.87 (2H, dd, J = 2, 6.7 Hz), 7.25-7.37 (7H, m), 8.06 (1H, d, J = 8.1 Hz), 8.61 (1H, dd, J = 2, 8.1 Hz), 8.66 (1H, d, J = 2Hz). IR (cm^{-1}): 3420, 1780, 1750, 1730, 1540, 1350. Anal. Calcd. for $C_{31}H_{27}N_3O_9$: C, 63.59; H,4.65; N, 7.18. Found: C, 63.55; H, 4.58; N, 7.14.

5f: mp 84.5-85.5 ℃. $[\alpha]_D^{25}$ -137.9 (c 1.012, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.26 (3H, d, J = 6.5 Hz), 3.49 (1H, d, J = 9.5 Hz), 3.98 (1H, d, J = 4.3 Hz), 4.32-4.48 (1H, m), 4.54 (1H, dd, J = 5, 9.6 Hz), 4.91 (1H, d, J = 5 Hz), 5.13 (1H, d, J = 12.2 Hz), 5.19 (1H, d, J = 12.2 Hz), 6.24 (1H, dd, J = 9.6, 15.9 Hz), 6.66 (1H, d, J = 15.9 Hz), 7.35-7.47 (10H, m). IR (cm^{-1}): 3400, 2100, 1740, 1730. Anal. Calcd. for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.78. Found: C, 64.90; H, 5.45; N, 13.82.

(3S,4S)-1-[(R)-1-[(Benzhydryloxy)carbonyl]-(S)-2-hydroxypropyl]-4-hydroxymethyl-3-(4-nitrophthalimido)azetidin-2-one (7a). A solution of **5a** (100 g, 158.3 mmol) in methylene chloride (600 ml) and methanol (75 ml) was ozonized at -50 ℃. The excess ozone was purged by passing a stream of nitrogen through the solution. Dimethyl sulfide (19.7 g, 316.6 mmol) was added to the solution, which was allowed to warm to room temperature. The mixture was evaporated to dryness under reduced pressure and the residue was dissolved in ethyl acetate (500 ml). The ethyl acetate layer was washed with 5% aqueous sodium bisulfite solusion (6 x 200 ml), 5% aqueous sodium bicarbonate solution (2 x 200 ml), and brine (200 ml). Drying ($MgSO_4$) followed by removal of the solvent gave the crude aldehyde, which was used directly in the next reaction without characterization. To a suspension of sodium borohydride (6.74 g, 178.1 mmol) and boron trifluoride etherate (56.18 g, 395.8 mmol) in dry tetrahydrofuran (360 ml) was added a solution of this aldehyde in dry tetrahydrofuran (180 ml) dropwise at 0 ℃ over a period of 1 h, and the reaction mixture was stirred for 1h. The reactants were poured into ice-water and extracted with ethyl acetate (3 x 300 ml). The extracts were combined, washed with water (2 x 300 ml) and brine (300 ml), dried over $MgSO_4$, filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give **7a** as a pale yellow powder (79.7 g). The overall yield from **5a** was 90%. ^1H NMR ($CDCl_3$) δ: 1.50 (3H, d, J = 6.5 Hz), 3.40-3.70 (3H, m), 3.75-3.90 (1H, m), 4.37-4.45 (1H, m), 4.53-4.65 (1H, m), 4.74 (1H, d, J = 3.3 Hz), 5.42 (1H, d, J = 5.6 Hz), 6.97 (s, 1H), 7.27-7.37 (10H, m), 8.07 (1H, d, J = 8.1 Hz), 8.63 (1H, dd, J = 1.9, 8.1 Hz), 8.68 (1H, d, J = 1.9 Hz). IR (cm^{-1}): 3400, 1760, 1730, 1540, 1530, 1390, 1350.

Compound **7b** was obtained by the same procedure as described for **7a**.

7b: ^1H NMR ($CDCl_3$) δ: 1.22 (3H, d, J = 6.4 Hz), 3.30-3.55 (1H, m), 3.97-4.13 (1H, m), 4.30-4.47 (2H, m), 4.68 (1H, d, J = 3 Hz), 4.88 (1H, dd, J = 4.7, 6.3 Hz), 5.37 (2H, m), 5.43 (1H, d, J = 5.5 Hz),

5.50 (1H, d, J = 4.6 Hz), 7.72 (2H, d, J = 8.8 Hz), 8.19 (1H, d, J = 8.2 Hz), 8.26 (2H, d, J = 8.8 Hz), 8.56 (1H, d, J = 2 Hz), 8.67 (1H, dd, J = 2, 8.2 Hz). IR (cm^{-1}): 3530, 3400, 1750, 1730, 1540, 1520, 1390, 1350.

(3S,4S)-1-[(R)-1-[(Benzhydryloxy)carbonyl]-(S)-2-hydroxypropyl]-4-mesyloxymethyl-3-(4-nitrophthalimido)azetidin-2-one (8a). To a solution of **7a** (60 g, 107.2 mmol) in pyridine (200 ml) was added methanesulfonyl chloride (14.7 g, 128.6 mmol) dropwise at -15℃ over a period of 30 min. The reaction mixture was stirred for 6 h, after which time the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (400 ml), and this solution was washed with 10% hydrochlotic acid (400 ml). The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate (200 ml). The organic extracts were combined, washed with water (3 x 300 ml) and brine (300 ml), dried over $MgSO_4$, filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give **8a** as a pale yellow powder (65 g, 95%). ^1H NMR ($CDCl_3$) δ: 1.41 (3H, d, J = 6.5 Hz), 2.76 (3H, s), 4.33-4.42 (1H, m), 4.48-4.78 (4H, m), 5.52 (1H, d, J = 5.2 Hz), 6.98 (1H, s), 7.20-7.45 (10H, m), 8.06 (1H, d, J = 8.1 Hz), 8.63 (1H, dd, J = 1.9, 8.1 Hz), 8.67 (1H, d, J = 1.9 Hz). IR (cm^{-1}): 3500, 1780, 1730, 1540, 1530, 1390, 1350, 1340.

Compound **8b** was obtained by the same procedure as described for **8a** without column chlomatography.

8b: colorless needles, mp 165-165.5 ℃ (from acetonitrile). $[\alpha]_D^{25}$ -37.7 (c 0.244, DMSO). ^1H NMR (DMSO-d_6) δ: 1.25 (3H, d, J = 6.4 Hz), 2.99 (3H, s), 4.20-4.47 (2H, m), 4.60-4.86 (3H, m), 5.38 (2H, s), 5.51 (1H, d, J = 4 Hz), 5.61 (1H, d, J = 5.3 Hz), 7.72 (2H, d, J = 8.8 Hz), 8.19 (1H, d, J = 8.2 Hz), 8.26 (2H, d, J = 8.8 Hz), 8.57 (1H, d, J = 2 Hz), 8.67 (1H, dd, J = 2, 8.2 Hz). IR (cm^{-1}): 3450, 1770, 1730, 1540, 1520, 1390, 1350. Anal. Calcd. for $C_{24}H_{22}N_4O_{13}S$: C, 47.53; H, 3.66; N, 9.24. Found: C, 47.33; H, 3.43; N, 9.19.

(3S,4S)-1-[1-[(Benzhydryloxy)carbonyl]-2-hydroxypropenyl]-4-mesyloxymethyl-3-(4-nitrophthalimido)azetidin-2-one (9a). To a stirred solution of **8a** (50 g, 78.4 mmol) in acetonitrile (1500 ml) was added Jones reagent (23.7 ml), prepared by dissolving CrO_3 (26.72 g) in concentrated sulfuric acid (23 ml) and diluting the solution to a volume of 100 ml with water, at room temperature. Vigorous stirring was maintained for 40 min, after which time the mixture was filtrated to remove the chromous salts. The filtrate was evaporated under reduced pressure and the residue was taken up in methylene chloride (788 ml). This solution was washed with water (300 ml) and the organic layer was separated. The aqueous layer was extracted with additional methylene chloride (300 ml). The organic extracts were combined, washed with water (5 x 300 ml), dried over $MgSO_4$, filtrated, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give **9a** (47.3 g, 95%) as a pale yellow powder. ^1H NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.83 (3H, s) 4.30-4.55 (3H, m), 5.56 (1H, d, J = 5.2 Hz), 6.98 (1H, s), 7.25-7.50 (10H, m), 8.10 (1H, d, J = 8.1 Hz), 8.64 (1H, dd, J = 2, 8.1 Hz), 8.69 (1H, d, J = 2 Hz). IR (cm^{-1}): 3400,

1760, 1730, 1540, 1520, 1350, 1330.

Compound **9b** was obtained by the same procedure as described for **9a** without column chromatography.

9b: colorless needles, mp 186-188 ℃ (from acetonitrile). $[\alpha]_D^{25}$ -37 (c 0.292, DMSO). ^{1}H NMR (DMSO-d_6) δ: 2.26 (3H, s), 3.01 (3H, s), 4.33-4.65 (3H, m), 5.22-5.60 (2H, m), 5.65-5.83 (1H, m), 7.73 (2H, d J = 8.2 Hz), 8.14-8.33 (3H, m), 8.56 (1H, d, J = 2 Hz), 8.68 (1H, dd, J = 2, 8.1 Hz). IR (cm^{-1}): 3500, 1770, 1730, 1520, 1360, 1340. Anal. Calcd. for $C_{24}H_{20}N_4O_{13}S$: C, 47.69; H, 3.33; N, 9.27. Found: C, 47.89; H, 3.16; N, 9.10.

p-Nitrobenzyl (6S,7S)-3-bromomethyl-7-(4-nitrophthalimido)-8-oxo-1-aza-4-oxabicyclo [4.2.0]oct-2-ene-2-carboxylate (10). A suspension of **9b** (20 g, 33.1 mmol) and bromine (6.08 g, 38.0 mmol) in dioxane (200 ml) was stirred at 40 ℃ for 2 h. Then, to this solution was added 5% aqueous sodium bicarbonate solution (195 ml) at 30 ℃. After being allowed to stir for 1 h, precipitates were separated out by addition of water (200 ml). The precipitates were collected by filtration, washed with water, and recrystallized from acetonitrile to give **10** (13 g, 67%) as pale yellow needles, mp 186-186.5 ℃. $[\alpha]_D^{25}$ -26.8 (c 0.276, DMSO). ^{1}H NMR (DMSO-d_6) δ: 4.00-4.15 (2H, m), 4.52 (1H, d, J = 10.6 Hz), 4.63 (1H, d, J = 10.6 Hz), 4.70-4.82 (1H, m), 5.40 (1H, d, J = 13.8 Hz), 5.51 (1H, d, J = 13.8 Hz), 6.13 (1H, d, J = 4.3 Hz), 7.78 (2H, d, J = 8.8 Hz), 8.18 (1H, d, J = 8.2 Hz), 8.23 (2H, d, J = 8.8 Hz), 8.56 (1H, d, J = 2 Hz), 8.67 (1H, dd, J = 2, 8.2 Hz). IR (cm^{-1}): 1780, 1730, 1540, 1520, 1350. Anal. Calcd. for $C_{23}H_{15}BrN_4O_{10}$: C, 47.04; H, 2.57; N, 9.54. Found: C, 46.99; H, 2.62; N, 9.44.

p-Nitrobenzyl (6S,7S)-7-(4-nitrophthalimido)-8-oxo-3-[(1,3,4-thiadiazol-2-yl)thiomethyl]-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (12). To a solution of **10** (5 g, 8.5 mmol) and 2-mercapto-1,3,4-thiadiazole **11** (1 g, 8.5 mmol) in DMF (25 ml) was added triethylamine (860 mg, 8.5 mmol) dropwise at 0 ℃. After 1 h's stirring, the mixture was poured into water (250 ml). The resulting precipitates were collected by filtration, washed with water, and recrystallized from acetonitrile to give **12** (5.2 g, 98%), as pale yellow needles, mp 213-214 ℃. $[\alpha]_D^{25}$ -113.6 (c 0.22, DMSO). ^{1}H NMR (DMSO-d_6) δ: 3.95-4.15 (2H, m), 4.46-4.76 (3H, m), 5.35 (1H, d, J = 12.5 Hz), 5.50 (1H, d, J = 12.5 Hz), 6.09 (1H, d, J = 5.3 Hz), 7.77 (2H, d, J = 8.6 Hz), 8.18 (1H, d, J = 8.2 Hz), 8.22 (2H, d, J = 8.6 Hz), 8.55 (1H, d, J = 2 Hz), 8.66 (1H, dd, J = 2, 8.2 Hz), 9.57 (1H, s). IR (cm^{-1}): 1780, 1730, 1540, 1520, 1350. Anal. Calcd. for $C_{25}H_{16}N_6O_{10}S_2$: C, 48.08; H, 2.58; N, 13.46. Found: C, 47.78; H, 2.55; N, 13.29.

p-Nitrobenzyl (6S,7S)-7-[2-(2-aminothiazol-4-yl)-2-[(Z)-methoxyimino]acetamido]-8-oxo-3-[(1,3,4-thiadiazol-2-yl)thiomethyl]-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylate (14a). To a solution of **12** (10g, 16 mmol) in DMF (60 ml) was added methylhydrazine (811 mg, 17.6 mmol) dropwise at -50℃, and then the mixture was stirred for 30 min. Acetic acid (4 ml) was added to the solution, which was allowed to warm to room temperature. The resulting precipitates were filtered off, and the filtrate was taken up in methylene chloride (300 ml). The solution was washed with 5% aqueous sodium bicarbonate

solution (4 x 100 ml) and brine (100 ml), dried over Na_2SO_4. After filtration, to the filtrate was added **13a** (5.6 g, 16 mmol), and the mixture was stirred at room temperature overnight. The solvent was removed and the residue was purified by silica gel column chlomatography to give **14a** (6.38 g, 63%) as a pale yellow powder. ^1H NMR ($CDCl_3$) δ: 3.80-4.20 (5H, m), 4.43 (1H, d, J = 13.8 Hz), 4.65 (1H, dd, J = 3.7, 11 Hz), 4.79 (1H, d, J = 13.8 Hz), 5.28 (1H, d, J = 13.5 Hz), 5.45 (1H, d, J = 13.5 Hz), 5.70-5.85 (3H,m), 6.68 (1H, s), 7.62 (2H, d, J = 8.8 Hz), 8.21 (2H, d, J = 8.8 Hz), 8.61 (1H, d, J = 7.3 Hz), 9.03 (1H, s). IR (cm^{-1}): 3320, 1770, 1710, 1670, 1610, 1520, 1350.

Compound **14b** was obtained from **12** in 67% yield by the same procedure as described for **14a** without column chromatography.

14b: colorless needles, mp 190-190.5 ℃ (from acetonitrile). $[\alpha]_D^{25}$ -21.9 (c 0.356, DMSO). ^1H NMR (DMSO-d_6) δ: 1.33-1.85 (8H, m), 3.90-4.15 (2H, m), 4.47-4.74 (4H, m), 5.35 (1H, d, J = 13.9 Hz), 5.44 (1H, d, J = 13.9 Hz), 5.72 (1H, dd, J = 4.7, 8.5 Hz), 6.75 (1H, s), 7.74 (2H, d, J = 8.8 Hz), 8.23 (2H, d, J = 8.8 Hz), 9.18 (1H, d, J = 8.5 Hz), 9.57 (1H, s). IR (cm^{-1}): 3320, 1760, 1710, 1670, 1520, 1350. Anal. Calcd. for $C_{27}H_{26}N_8O_8S_2$: C, 47.22; H, 3.82; N, 16.32. Found: C, 46.99; H, 3.65; N, 16.47.

(6S,7S)-7-[2-(2-Aminothiazol-4-yl)-2-[(Z)-methoxyimino]acetamido]-8-oxo-3-[(1,3,4-thiadiazol-2-yl)thiomethyl]-1-aza-4-oxabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (15a).

To a solution of **14a** (10 g, 15.8 mmol) and sodium bicarbonate (1.46 g, 17.4 mmol) in tetrahydrofuran (150ml) and water (100 ml) was added 10% Pt/C (4 g). The suspension was stirred at room temperature under the hydrogen pressure of 4 kg/cm^2 for 3 h. The catalyst was removed by filtration through Celite, and the filter-cake washed with tetrahydrofuran and water. The filtrate and washing were combined, and the solution was washed with ethyl acetate (2 x 100 ml). The aqueous layer was separated. The pH of this solution was adjusted to 4 with 10% hydrochloric acid, and the resulting aqueous solution was subjected to chromatography on Diaion HP-20 using acetonitrile-water mixtures as solvent. After combining the appropriate fractions and evaporation under reduced pressure to remove acetonitrile, freeze-drying gave **15a** (4.95 g, 63%) as a powder. ^1H NMR ($CDCl_3$) d: 3.78-4.07 (5H, m), 4.46-4.65 (3H, m), 5.72 (1H, dd, J = 4.7, 9.1 Hz), 6.83 (1H, s), 7.32 (2H, s), 9.27 (1H, d, J = 9.1 Hz), 9.58 (1H, s). IR (cm^{-1}): 3400, 1760, 1750, 1700, 1670.

Compound **15b** was obtained from **14b** in 65% yield by the same procedure as described for **15a**.

15b: ^1H NMR (DMSO-d_6) δ: 1.40-1.88 (8H, m), 3.84-4.07 (2H, m), 4.45-4.73 (4H, m), 5.65 (1H, dd, J = 4.8, 8.5 Hz), 6.74 (1H, s), 9.16 (1H, d, J = 8.5 Hz), 9.57 (1H, s). IR (cm^{-1}): 3400, 1760, 1750, 1700, 1670.

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Footnote

"This paper is dedicated to Professor Yasumitsu Tamura on the ocassion of his 70th birthday."

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