Synthesis of Carbapenems with a Sulfonyl Group in the C-6 Side-Chain and Their Biological Activity\textsuperscript{1)}

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A new type of 5,6-cis-carbapenems (racemic) having a sulfonyl group in the C-6 side-chain were synthesized by employing the synthetic methodology reported in our previous papers, and an alternative stereocontrolled synthesis of these 5,6-cis-carbapenems was achieved starting from 8-oxo-7-azabicyclo[4.2.0]oct-3-ene (14) via an intramolecular aldol condensation as the key step. Chiral 5,6-cis-carbapenems were also synthesized from ($S,6R$)-8-oxo-7-azabicyclo[4.2.0]oct-3-ene (29), which was derived from cis-1,2,5,6-tetrahydrophthalic anhydride. The carbapenems thus obtained proved to be highly stable to the mouse kidney homogenate, and most of them showed good antibacterial activity as well as potent $\beta$-lactamase inhibitory activity.

\textbf{Keywords}— carbapenem; C-19393 derivative; aldol condensation; sulfonyl group; antibacterial activity; dehydropeptidase; mouse kidney homogenate; $\beta$-lactamase inhibitory activity

Since the discovery of thienamycin, many naturally occurring and synthetic carbapenem antibiotics have been reported.\textsuperscript{2)} Some of them possess highly potent, broad-spectrum \textit{in vitro} antibacterial activity. However, because of their susceptibility to renal dehydropeptidase,\textsuperscript{3)} synthesis of carbapenems which are stable to the enzyme while retaining their excellent antibacterial activity has been desired.

In previous papers\textsuperscript{4)} we described a stereoselective synthesis of 5,6-cis-carbapenems related to C-19393\textsuperscript{5)} (carpetimycine\textsuperscript{6)} via reductive desulfurization utilizing an organotin hydride, and found that the antibacterial activity of 5,6-cis-carbapenems having a bulky substituent at the C-6 position is generally more potent than that of the 5,6-trans-isomers. By applying this synthetic methodology, versatile introduction of various new substituents into the C-6 position on the carbapenem nucleus seemed possible. As a part of our research program on the modification of the C-6 substituent to obtain a carbapenem with improved biological properties, we planned to synthesize a carbapenem having a sulfonyl group in the C-6 side-chain, expecting that the bulkiness and high polarity of the sulfonyl group might affect the interaction between the carbapenem and the enzyme. Here we report the synthesis and biological properties of carbapenems with a sulfonyl group in the C-6 side-chain.

\textbf{Chemistry}

Chart 1 shows the synthetic route to the \textit{cis}-azetidinones (3a-1, 3b-1, 3c-1) from 2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (1).\textsuperscript{7)} The $\beta$-lactam 1 was converted into the aldolization products (2a, 2b, 2c) by sulfonylation with lithium diisopropylamide (LDA) and diphenyl disulfide followed by an aldol reaction with methylthioacetaldehyde,\textsuperscript{8)} 3-thiacyclopentanone\textsuperscript{9)} and 4-thiacyclohexanone, respectively (79—83\% yield). The aldolization products (2a, 2b, 2c) were subjected to desulfurization using triphenyltin hydride\textsuperscript{4)} in the presence of azobisisobutyronitrile (AIBN) (0.2 eq) to give the \textit{cis}-isomers (3a-1, 3b-1, 3c-1) predominantly
together with a small amount of the trans-isomers (3a-2, 3b-2, 3c-2) (cis : trans = 71 : 29—90 : 10). The cis and trans-isomers were separated by chromatography on silica gel. In this reaction, reductive cleavage of only the phenylthio group took place to give 3 selectively, whereas the alkylthio group in the C-7 side-chain of 2a, 2b, 2c remained intact (Table II).

The relative configuration at the C-9 position of 3a-1 was confirmed by converting the compound into the desulfurized compound 4 (Chart 2). The nuclear magnetic resonance (NMR) spectrum of 4 was identical with that of the compound with $R^*$ C-9 configuration. Therefore the relative configuration of the C-9 position of 3a-1 was determined to be $S^*$.11)

The exclusive formation of $S^*$ is likely to be consistent with Martel et al.'s prediction12) based on a six-membered transition state mechanism. The configuration of the C-9 position of 3b has not been determined yet. Chart 3 shows the preparation of carbapenem 13a from 3a-1. The hydroxy group of 3a was protected with a methoxymethoxymethyl (MEM) group.13) Oxidation of 5a with m-chloroperbenzoic acid (m-CPBA) gave the sulfone 6a (76%), which was converted into the carboxylic acid 7a by Jones oxidation.4) The unstable carboxylic acid 7a was transformed into the keto-ester 8a (53%),14) which was converted into the diazo keto-ester 9a (89%). Removal of the MEM group from 9a was effected with titanium tetrachloride to form the cyclization precursor 10a quantitatively. Construction of the carbapenem ring was achieved by the rhodium-catalyzed carbene insertion reaction.15) Reaction of 1 la with diphenyl chlorophosphate followed by treatment with N-acetylcysteamine in the presence of a base16) gave the carbapenem ester 12a (Table VII). The p-nitrobenzyl (PNB) group of 12a was
removed by hydrogenolysis using 10% palladium-charcoal to give the carboxylic acid (or sodium salt) of the carbapenem 13a. The carbapenems (13b and 13c) were also obtained from 3b-1 and 3c-1, respectively, by a process similar to that employed for the conversion of 3a-1 into 13a (Chart 4).

Our attention was then directed to establishing a new synthetic method in which the use of LDA and organotin hydride, and a tedious chromatographic separation of cis and trans isomers, could be avoided. Easily available cis-substituted 8-oxo-7-azabicyclo[4.2.0]oct-3-ene (14) seemed to be a promising starting material for this purpose. A few syntheses of 5,6-cis-
Carbapenems from 14 have already been reported, but these syntheses do not permit the introduction of a hydroxy group into the C-8 position of the side-chain. Key features of our retrosynthetic plan (Chart 5) include i) regioselective generation of the \( \alpha,\beta \)-unsaturated aldehyde D via an intramolecular aldol condensation of the dialdehyde E, ii) conversion of D into the diol C, iii) formation of the bicyclic \( \beta \)-lactam B, and iv) synthesis of the carbapenem A from B by the same procedure as described before (Chart 3).

The synthesis of 20 was carried out as shown in Chart 6. After the protection of the amide nitrogen of the \( \beta \)-lactam 14 the silylated \( \beta \)-lactam 15 was subjected to osmylation with OsO\(_4\)-N-methylmorpholine N-oxide\(^{19}\) to furnish a diol 16. The diol 16 was subsequently treated
with $\text{HIO}_4 \cdot 2\text{H}_2\text{O}$ to give a rather unstable dialdehyde 17 quantitatively. In the intramolecular aldon condensation, there is a possibility of the formation of two regioisomers (18 and 18'). Actually, by effecting the reaction with morpholine–camphoric acid, a ca. 1 : 1 mixture of 18 and 18' was obtained (the ratio was determined by NMR after reduction with $\text{NaBH}_4$ to 19 and 19'). On the other hand, treatment of 17 with piperidine–acetic acid afforded 18 highly regioselectively but in a low yield (after reduction with $\text{NaBH}_4$, 19 was isolated in 16% yield). An exclusive formation of the regiosomer 18 was achieved in a good yield by treating 17 with dibenzylammonium trifluoroacetate. Reduction of 18, without purification, with $\text{NaBH}_4$ gave 19 in 57% yield from 16 (the other regioisomer 19' was not observed by $^{13}$C-NMR or high performance liquid chromatography (HPLC)). We presumed that this high regioselectivity might be due to the bulkiness of the tert-butyldimethylsilyl group. Ozonolysis of 15 also gave 17 which contained unidentified impurities (checked by thin layer chromatography (TLC)) and the subsequent aldol reaction, without purification, effected with dibenzylammonium trifluoroacetate afforded 19 in only 19% yield.

Treatment of 19 with thionyl chloride gave a mixture of two chlorinated isomers 20a-1 and 20a-2 in a ratio of ca. 1 : 1 (determined by NMR). Compound 20a-2 was formed via allylic rearrangement. Then, 19 was treated with $N$-bromosuccinimide–dimethylsulfide to afford the bromide 20b-1 in 67% yield without concomitant formation of the allylic rearranged product 20b-2. Ozonolysis of 20b-1 and subsequent reduction with $\text{NaBH}_4$ gave the diol 21 in 97% yield (for the side-chain stereochemistry, vide post), from which the silyl group was removed with potassium fluoride to furnish the diol 22 in 92% yield. The diol 22 was treated with 2,2-dimethoxypropane to give the acetonide 23 in 63% yield. Since the bromo atom in the side-chain is susceptible to nucleophiles, 23 serves as a versatile intermediate for preparing a new type of carbapenems with a variety of functional groups in the C-6 side-chain. The acetonide 23 was converted into the selenyl compound 24 in a good yield by treatment with a thiol compound in the presence of a base (Chart 7). Preparation of the carbapenems 13 from 24 was achieved in the same manner as shown in Chart 3.

Since the synthesis of the racemic 5,6-cis-carbapenem was established, we concentrated our efforts on the synthesis of optically active 5,6-cis-carbapenems. Chart 8 shows the synthesis of the desired chiral bicyclic $\beta$-lactam 29 from the racemic compound 25, which was derived from commercially available cis-1,2,5,6-tetrahydrophthalic anhydride. Enantiomer resolution of the racemic compound 25 with cinchonidine provided the chiral half ester 26a and its enantiomer 26b. The half ester 26a was converted into 27 by Curtius rearrangement
in 79% yield, and 27 was then hydrolyzed to the β-amino acid 28 in 76% yield. The β-amino acid 28 was transformed into the optically active β-lactam 29 with Ph₃P-(PyS)₂/CH₃CN. On the other hand, 26b was also converted into 29 via esterification (92%), hydrolysis (93%), Curtius rearrangement (96%), and deprotection (73%). By the strategy we have described here, both the enantiomers (26a and 26b) resolved from 25 are wholly utilized in preparing the optically active compound 29.

The same sequence of reactions employed in the preparation of 23 from 14 was applied to the optically active compound 29 to give the desired optically active β-lactam 36. The stereochemistry of 36 was confirmed to be 6R, 7R, 9R by a single crystal X-ray analysis. The

Chart 8

Chart 9
<table>
<thead>
<tr>
<th>Biological activities</th>
<th>Compound</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
</tr>
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<tbody>
<tr>
<td>Antibacterial activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>in vitro</em> (MIC: ( \mu g/ml; 10^6 ) CFU)(^{a1} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em> FDA 209P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.13</td>
<td>1.56</td>
<td>1.56</td>
<td>1.56</td>
</tr>
<tr>
<td><em>E. coli</em> O-111</td>
<td>0.39</td>
<td>0.39</td>
<td>0.39</td>
</tr>
<tr>
<td><em>C. freundii</em> IFO 12681</td>
<td>3.13</td>
<td>1.56</td>
<td>3.13</td>
</tr>
<tr>
<td><em>K. pneumoniae</em> DT</td>
<td>3.13</td>
<td>0.78</td>
<td>1.56</td>
</tr>
<tr>
<td><em>in vivo</em> (ED(_{50}): mg/kg)(^{b})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em> O-111</td>
<td>0.329</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>( \beta )-Lactamase inhibitory activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ID(_{50}): ( \mu g/ml ))(^{c})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source and type of ( \beta )-lactamase</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><em>S. aureus</em> 1840 PCase(^d)</td>
<td>0.14</td>
<td>0.0022</td>
<td>0.21</td>
</tr>
<tr>
<td><em>E. coli</em> TN 713 PCase</td>
<td>0.014</td>
<td>0.0035</td>
<td>3.2</td>
</tr>
<tr>
<td><em>E. cloacae</em> TN 1282 CSase(^e)</td>
<td>0.19</td>
<td>0.040</td>
<td>0.025</td>
</tr>
<tr>
<td><em>P. vulgaris</em> GN 4413 CSase</td>
<td>0.25</td>
<td>0.055</td>
<td>1.7</td>
</tr>
<tr>
<td>Half-life in mouse kidney homogenate (min)</td>
<td>&gt;120</td>
<td>&gt;120</td>
<td>&gt;120</td>
</tr>
</tbody>
</table>

\(^{a1}\) The MICs were determined by a standard dilution method in Trypticase soy agar (BBL).\(^{a1}\)  \(^b\) Protective effect against experimental intraperitoneal infection in mice. \(^c\) The ID\(_{50}\) (concentrations required to cause 50% inhibition) were determined by microiodometric method.\(^{a1}\)  \(^d,e\) PCase, penicillinase; CSase, cephalosporinase.
reduction of the ozonide of 35 with NaBH₄ was proved to proceed selectively to give 9R stereochemistry. Optically active carbapenems with a sulfonyl group in the C-6 side-chain (39) were synthesized from 36 by applying the same sequence of reactions as employed for the synthesis of the racemic compound (Chart 9).

**Biological Activity**

The *in vitro* antibacterial activity of the carbapenems with a sulfonyl group in the C-6 side-chain against several bacteria is shown in Table I. Their β-lactamase inhibitory (BLI) activity and stability to the mouse kidney homogenate are also given. It should be stressed that these carbapenems are highly stable to the mouse kidney homogenate (half-life > 120 min), which should reasonably reflect the behavior towards renal dehydropeptidase. Most of the compounds showed good antibacterial activity as well as strong BLI activity. Carbapenems 13a-1 and 13b-2 showed a good *in vitro* protective effect in mouse infected with *Escherichia coli* O-111, which seems to reflect the *in vitro* antibacterial activity.

**Experimental**

Melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrophotometer. ¹H-NMR spectra were taken on a Varian EM-390 (90 MHz) and a JEOL GK-400FT (400 MHz) spectrometer, and ¹³C-NMR spectra were measured with a JEOL GK-400FT (100 MHz) spectrometer with tetramethylsilane as an internal standard. Abbreviations are follows: s = singlet; br s = broad singlet; d = doublet; dd = doublet of doublets; t = triplet; q = quartet. Ultraviolet (UV) spectra were taken with a Hitachi 557 spectrophotometer. Extracted solutions were dried over sodium sulfate. The MICs (minimum inhibitory concentrations) were determined by a standard dilution method in Trypticase soy agar (BBL) as described previously.²⁸ The BLI activity were determined as described previously and expressed in terms of ID₅₀, the concentration required to inhibit β-lactamase activity by 50%.²⁹

7-(1-Hydroxy-2-methylthioethyl)-2,2-dimethyl-3-oxa-7-phenylthio-1-azabicyclo[4.2.0]octan-8-one (2a) and 7-(1-Hydroxythiacycloalkyl)-2,2-dimethyl-3-oxa-7-phenylthio-1-azabicyclo[4.2.0]octan-8-one (2b, c)—As a typical example, the preparation of 2a from 1 is described. A solution of 2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (1) (1.00 g, 6.45 mmol) in dry tetrahydrofuran (THF) (20 ml) was added at −78 °C to a solution of LDA, prepared from n-butyl lithium (9.6 ml of 15% hexane solution, 14.7 mmol) and diisopropylamine (2.2 ml, 15.7 mmol) under a nitrogen atmosphere, and the mixture was stirred for 15 min at −78 °C. A solution of diphenyl disulfide (1.42 g, 6.50 mmol) in dry THF (6 ml) was added dropwise to this enolate over 5 min at −78 °C. The mixture was stirred for 15 min at this temperature, then methylthioacetaldehyde (1.16 g, 12.9 mmol) was added. The mixture was stirred for 30 min and poured into a mixture of 3% acetic acid (60 ml) and AcOEt (60 ml) at 0 °C with stirring. The organic phase was separated and the aqueous phase was further extracted with AcOEt. The combined extracts were washed successively with 0.5 N NaOH, water and sat. aq. NaCl, and dried. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with hexane-AcOEt (1 : 2, v/v) gave 2a (1.88 g, 83%) as colorless crystals (a mixture of two isomers at C-7). Compounds 2b and 2c were synthesized in a similar manner, by using 3-thiacyclopentanone and 4-thiacyclohexanone, respectively, in place of methylthioacetaldehyde. The stereochemistry of 2b at C-9 has not been determined.

2a: Colorless prism, mp 83—85 °C. Yield 83%. IR δ (KBr, cm⁻¹): 3020, 1730. ¹H-NMR (CDCl₃): δ: isomer A: 0.79, 1.58 (each 3H, 2 × s, 2 × Me), 1.6-2.0 (2H, m, C₅-H₂), 2.15 (3H, s, SMe), 2.89 (2H, d, J = 7.5 Hz, CH₂S), 3.3-4.0 (3H, m, C₄-H₂, C₆-H), 4.31 (1H, dd, J = 7.5, 4.8 Hz, SCH₂CH), 7.2-7.6 (5H, m, aromatic protons). Isomer B: 1.47, 1.76 (each 3H, 2 × s, 2 × Me), 1.91 (3H, s, SMe), 1.6—2.0 (2H, m, C₅-H₂), 2.96 (2H, m, CH₂S), 3.7-4.0 (3H, m, C₄-H₂, C₆-H), 4.13 (1H, dd, J = 5.1, 10.5 Hz, SCH₂CH), 7.2-7.7 (5H, m, aromatic protons). Anal. Calcd for C₁₇H₂₃NO₃S₂: C, 57.76; H, 6.56; N, 3.96; S, 18.14. Found: C, 57.69; H, 6.68; N, 4.14; S, 18.38.

2b: Colorless oil. Yield 83%. IR (KBr, cm⁻¹): 1740. ¹H-NMR (CDCl₃): δ: 1.46, 1.56 (each 3H, 2 × s, 2 × Me), 1.5-1.9 (2H, m, C₄-H₂), 2.2-2.4 (2H, m, CH₂), 2.8-3.2 (4H, m, CH₂SCH₂), 3.8-4.2 (3H, m, C₅-H₂, C₆-H), 7.1-7.9 (5H, m, aromatic protons). Anal. Calcd for C₁₇H₂₃NO₃S₂: C, 57.76; H, 6.56; N, 3.96; S, 18.38. Found: C, 57.69; H, 6.68; N, 4.14; S, 18.38.

2c: Colorless prism, mp 191-192 °C. Yield 79%. IR (KBr, cm⁻¹): 1740. ¹H-NMR (CDCl₃): δ: 1.38, 1.48 (each 3H, 2 × s, 2 × Me), 1.6 (2H, m, C₅-H₂), 1.7 —3.3 (8H, m, 4 × CH₂), 3.7-4.2 (3H, m, C₅-H₂, C₆-H), 7.1-7.9 (5H, m, aromatic protons). Anal. Calcd for C₁₉H₂₅NO₃S₂: C, 60.13; H, 6.64; N, 3.79; S, 16.89. Found: C, 60.39; H, 6.49; N, 3.68; S, 17.17.

7-(1-Hydroxy-2-methylthioethyl)-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (3a) and 7-(1-Hydroxythiacycloalkyl)-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (3b, c)—As a typical example, the preparation of 3a from 2a is described. A mixture of 2a (1.32 g, 6.45 mmol), AIBN (120 mg, 0.73 mmol), triphenyltin hydride (2.62 g,
**Table II. 2,2-Dimethyl-7-(substituted-alkyl)-3-oxa-1-azabicyclo[4.2.0]octan-8-ones (3)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Stereochemistry at C(6) and C(7)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>IR cm⁻¹ (KBr)</th>
<th>NMR (CDCl₃) δ</th>
<th>Analysis (%) Found (Calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a-1</td>
<td>OH</td>
<td>cis</td>
<td>70</td>
<td>91—92.5</td>
<td>1720</td>
<td>1.38, 1.72 (each 3H, 2 x s, 2 x CH₃), 2.15 (3H, s, SCH₃), 1.5—2.2 (2H, m, CH₂), 2.68 (2H, d, J = 6 Hz, SCH₂), 3.33 (1H, dd, J = 6.8, 5.3 Hz, CH—CO), 3.6—4.0 (3H, m, OCH₂, CH—N), 4.12 (1H, m, CH—N)</td>
<td>53.85 7.81 5.82 13.06 (53.85 7.81 5.71 13.07)</td>
</tr>
<tr>
<td>3a-2</td>
<td>OH</td>
<td>trans</td>
<td>19</td>
<td>106—107</td>
<td>1740</td>
<td>1.40, 1.71 (each 3H, 2 x s, 2 x CH₃), 2.12 (3H, s, SCH₃), 1.5—2.1 (2H, m, CH₂), 2.3—3.2 (3H, m, SCH₂, CH—CO), 3.5—4.2 (4H, m, OCH₂, CH—N, CH—O)</td>
<td>54.03 7.92 5.70 12.77 (53.85 7.81 5.71 13.07)</td>
</tr>
<tr>
<td>3b-1</td>
<td>S</td>
<td>cis</td>
<td>80</td>
<td>113—115</td>
<td>1740</td>
<td>1.40, 1.74 (each 3H, 2 x s, 2 x CH₃), 1.6—2.2 (2H, m, CH₂), 2.5—3.2 (6H, m, 3 x CH₂), 3.36 (1H, d, J = 6 Hz, CHCO), 3.7—4.1 (3H, m, CHN, CH₂O)</td>
<td>56.28 7.35 5.40 12.65 (56.01 7.44 5.44 12.46)</td>
</tr>
<tr>
<td>3b-2</td>
<td>S</td>
<td>trans</td>
<td>9</td>
<td>145—147</td>
<td>1720</td>
<td>1.40, 1.69 (each 3H, 2 x s, 2 x CH₃), 1.6—2.0 (2H, m, CH₂), 2.3—3.2 (7H, m, 2 x CH₂, CH—CO), 3.5—4.0 (3H, m, CHN, CH₂O)</td>
<td>56.13 7.38 5.37 (56.01 7.44 5.44)</td>
</tr>
<tr>
<td>3c-1</td>
<td>S</td>
<td>cis</td>
<td>64</td>
<td>133—134</td>
<td>1740</td>
<td>1.38, 1.73 (each 3H, 2 x s, 2 x CH₃), 1.6—3.3 (10H, m, 5 x CH₂), 3.20 (1H, d, J = 6 Hz, CH—CO), 3.6—3.9 (3H, m, OCH₂, CH—N)</td>
<td>57.30 7.85 5.42 12.05 (57.54 7.80 5.16 11.81)</td>
</tr>
<tr>
<td>3c-2</td>
<td>S</td>
<td>trans</td>
<td>26</td>
<td>163—164</td>
<td>1720</td>
<td>1.40, 1.71 (each 3H, 2 x s, 2 x CH₃), 1.6—3.3 (10H, m, 5 x CH₂), 2.81 (1H, d, J = 2 Hz, CH—CO), 3.55 (1H, m, CH—N), 3.7—3.9 (2H, m, OCH₂)</td>
<td>57.21 7.87 5.49 (57.54 7.80 5.16)</td>
</tr>
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</table>
and acetone (45 ml) was refluxed for 5 h under a nitrogen atmosphere. After further addition of triphenyltin hydride (1.00 g, 2.84 mmol), the mixture was refluxed for an additional 14 h. The solvent was evaporated off and the residue was subjected to chromatography on silica gel. Elution with hexane–AcOEt (4:1-1:1, v/v) afforded the cis-azetidinones 3a-1 (643 mg, 70%) and the trans-azetidinone 3a-2 (172 mg, 19%), each as colorless prisms. Compounds 2b and 2c were desulfurized to give 3b and 3c, respectively, in a similar manner. The results are summarized in Table II.

Desulfurization of 3a-1—A mixture of 3a-1 (80 mg, 0.33 mmol), Raney nickel (Kawaken Fine Chemical,
NDHT-90 (1 ml) and THF (7 ml) was refluxed for 5 h. The Raney nickel was filtered off and the filtrate was concentrated. The concentrate was subjected to chromatography on silica gel. Elution with AcOEt-hexane (1 : 1—2 : 1, v/v) afforded 4 as a colorless oil (44 mg, 67%). 1H-NMR (acetone-d$_6$) $\delta$: 1.15 (3H, d, J= 6 Hz, Me), 1.36, 1.63 (each 3H, 2 ~ s, 2 ~ Me), 1.8 (2H, m, C5-H2), 2.8 (1H, br s, OH), 3.05 (1H, dd, J= 5, 7.5 Hz, C7-H), 3.6—4.3 (4H, m, C$_6$-H, C$_7$-H, CH-O).

(6R*,7R*)-7-[1-(2-Methoxyethoxymethoxy)-2-methylthioethyl]-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (5a) and (6R*,7R*)-7-[1-(2-Methoxyethoxymethoxy)thiacycloalkyl]-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (5b, c)—As a typical example, the preparation of 5a from 3a is described. A mixture of the azetidinone 3a (286 mg, 1.17 mmol) diisopropylethylamine (0.63 ml, 3.62 mmol), 2-(methoxyethoxy)methyl (MEM) chloride (0.42 ml, 3.67 mmol) and CH2Cl2 (8.5 ml) was allowed to stand at room temperature for 140 h under a nitrogen atmosphere. The mixture was then washed successively with water, 2% acetic acid, sat. aq. NaHCO3, water and sat. aq. NaCl, and dried. The solvent was evaporated off to give the azetidinone 5a (quantitatively) as a pale yellow oil, which was used in the subsequent oxidation without further purification. The results are summarized in Table III.

(6R*,7R*)-7-[1-(2-Methoxyethoxymethoxy)-2-methylsulfonylthethyl]-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (6a) and (6R*,7R*)-7-[1-(2-Methoxyethoxymethoxy)thiacycloalkyl,S,S-dioxide]-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-one (6b, c) As a typical example, the preparation of 6a from 5a is described. A solution of 5a prepared from 3a-1 (274 mg, 1.12 mmol) in CH2C12 (9 ml) was treated at 0 ºC with m-CPBA (ca. 70%) (597 mg). After being stirred for 2 h, the mixture was washed successively with sat. aq. NaHCO3, water and sat. aq. NaCl. The organic phase was dried and evaporated. The residue was subjected to chromatography on silica gel. Elution with AcOEt afforded 6a (310 mg, 76% from 3a-1) as a colorless oil. The azetidinones 6b and 6c were similarly prepared from 5b and 5c, respectively. The results are summarized in Table IV.

(3R*,4R*)-4-Carboxymethyl-3-[1-(2-methoxyethoxymethoxy)-2-methylsulfonylthethyl]azetidin-2-one (7a) and (3R*,4R*)-4-Carboxymethyl-3-[1-(2-methoxyethoxymethoxy)thiacycloalkyl,S,S-dioxide]azetidin-2-one (7b, c)—As a typical example, the preparation of 7a from 6a is described. An 8 N solution of Jones reagent (0.43 ml) was added dropwise to a stirred, cooled (0 ºC) solution of the azetidinone 6a (226 mg, 0.73 mmol) in acetone (4 ml). The mixture was stirred for 7 h at 0 ºC. After the addition of isopropyl alcohol (0.3 ml), the mixture was stirred for 10 min at 0 ºC.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield$^a$ (%)</th>
<th>IR cm$^{-1}$ (liquid)</th>
<th>NMR (CDCl$_3$) $\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>OMEM</td>
<td>CH$_2$SO$_2$CH$_2$CH=</td>
<td>53</td>
<td>1720, 1760</td>
</tr>
<tr>
<td>8b</td>
<td>O$_2$S</td>
<td>OMEM</td>
<td>71</td>
<td>1720—1750</td>
</tr>
<tr>
<td>8c</td>
<td>O$_2$S</td>
<td>OMEM</td>
<td>60</td>
<td>1720—1750</td>
</tr>
</tbody>
</table>

$^a$ The yields are based on 6.
and was then diluted with CH$_2$Cl$_2$ (10 ml). Insoluble materials were filtered off and the filtrate was concentrated. The concentrate was dissolved in CHCl$_3$ (10 ml) and the solution was dried and evaporated to dryness to give the acid 7a (205 mg, 82%) as a colorless oil. Similar oxidation of the azetidinones 6b and 6c gave the acids 7b and 7c, respectively. These compounds were used in the subsequent reactions without purification. IR $\nu_{\text{liquid}}$ cm$^{-1}$: 1700—1760.

(3$R^*$,4$R^*$)-3-[1-(2-Methoxyethoxymethoxy)-2-methylsulfonylethyl]-4-(p-nitrobenzoylcarbonyl-2-oxopropyl)azetidin-2-one (8a) and (3$R^*$,4$R^*$)-3-[1-(2-Methoxyethoxymethoxy)thiacycloalkyl-S,S-dioxide]-4-(p-nitrobenzoylcarbonyl-2-oxopropyl)azetidin-2-one (8b, c). As a typical example, the preparation of 8a from 7a is described. N,N-Carboxyldimidazole (132 mg, 0.814 mmol) was added to a solution of the acid 7a (230 mg, 0.68 mmol) in dry THF (9 ml). After the mixture had been stirred for 6 h at room temperature under a nitrogen atmosphere, magnesium p-nitrobenzyl malonate (407 mg, 0.81 mmol) was added. The mixture was stirred for 20 h at room temperature under a nitrogen atmosphere and was then diluted with AcOEt and washed successively with dil. HCl, water, sat. aq. NaHCO$_3$, and water. The organic phase was dried, the solvent was evaporated off, and the residue was chromatographed on silica gel. Elution with AcOEt gave the azetidinone 8a (187 mg, 53%) as a pale yellow oil. The results are summarized in Table V.

(3$R^*$,4$R^*$)-4-[3-(Diazo-3-(p-nitrobenzoylcarbonyl)-2-oxopropyl]-3-(p-nitrobenzoylcarbonyl)-2-oxopropyl]azetidin-2-ones (9). As a typical example, the preparation of 9a from 8a is described. A solution of p-toluenesulfonyl azide (84 mg, 0.43 mmol) in dry acetonitrile (1 ml) and Et$_3$N (0.19 ml, 1.36 mmol) was added to a stirred, cooled (0 °C) solution of the azetidinone 8a (187 mg, 0.36 mmol) in dry acetonitrile (6 ml). After being stirred for 1 h at room temperature, the mixture was diluted with AcOEt, washed with sat. aq. NaCl, and dried. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with AcOEt gave the diazo-azetidinone 9a (172 mg, 89%) as a pale yellow oil. The diazo-azetidinones 9b and 9c were synthesized in a similar manner. The results are summarized in Table VI.

(3$R^*$,4$R^*$)-3-(Substituted-sulfonylalkyl)-4-[3-diazo-3-(p-nitrobenzoylcarbonyl)-2-oxopropyl]azetidin-2-ones (9).

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
<th>IR cm$^{-1}$ (liquid)</th>
<th>NMR (CDCl$_3$) $\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>OMEM, CH$_3$SO$_2$CH$_2$CH$_2$-</td>
<td>89</td>
<td>2140, 1750</td>
<td>2.96 (3H, s, SO$_2$CH$_3$), 3.35 (3H, s, OCH$_3$), 3.2—4.0 (9H, m, CHCO, CH$_3$CO, OCH$_2$CH$_2$O, SO$_2$CH$_3$), 4.15 (1H, m, CHN), 4.35 (1H, m, CH-O), 4.87 (2H, ABq, $J$ = 10.5, 7.5 Hz, OCH$_2$O), 5.33 (2H, s, OCH$_2$Ar), 6.21 (1H, br, NH), 7.51 (2H, d, $J$ = 9 Hz, arom H), 8.23 (2H, d, $J$ = 9 Hz, arom H)</td>
</tr>
<tr>
<td>9b</td>
<td>OMEM</td>
<td>90</td>
<td>2140, 1760</td>
<td>2.6 (2H, m, CH$_3$), 3.31 (3H, s, OCH$_3$), 3.0—3.9 (11H, m, CH$_3$SO$_2$CH$_2$, OCH$_2$CH$_2$O, CH$_3$CO, CHCO), 4.2 (1H, m, CHN), 4.83 (2H, br, OCH$_2$O), 5.26 (2H, s, OCH$_2$Ar), 6.40 (1H, br, NH), 7.54 (2H, d, $J$ = 9 Hz, arom H), 8.24 (2H, d, $J$ = 9 Hz, arom H)</td>
</tr>
<tr>
<td>9c</td>
<td>OMEM</td>
<td>98</td>
<td>2140, 1760</td>
<td>2.1—3.0 (6H, m, 2 × CH$_2$, CHSCH), 3.36 (3H, s, OCH$_3$), 3.3—3.9 (9H, m, CH$_3$CO, CHCO, OCH$_2$CH$_2$O, CHSCH), 4.2 (1H, m, CHN), 4.93 (2H, br, OCH$_2$O), 5.38 (2H, s, OCH$_2$Ar), 6.4 (1H, br, NH), 7.54 (2H, d, $J$ = 9 Hz, arom H), 8.26 (2H, d, $J$ = 9 Hz, arom H)</td>
</tr>
</tbody>
</table>
Table VII. p-Nitrobenzyl 2-Carbapenem-3-carboxylates (12)

![Chemical Structure]

<table>
<thead>
<tr>
<th>Compound</th>
<th>R^1</th>
<th>R^2</th>
<th>Yield^a (%)</th>
<th>IR cm⁻¹ (state)</th>
<th>UV (EtOH) nm</th>
<th>NMR (acetone-δ) δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>OH</td>
<td>CH₂CH₂NHAc</td>
<td>32</td>
<td>1765 (K,Br)</td>
<td>267</td>
<td>—</td>
</tr>
<tr>
<td>12b-1</td>
<td></td>
<td>CH₂CH₂NHAc</td>
<td>32</td>
<td>1770 (liquid)</td>
<td>269</td>
<td>1.90 (3H, s, COCH₃), 2.7 (2H, m, CH₂), 2.8–3.8 (10H, m, 2 SO₂CH₂, CH₂, SCH₂CH₂N), 4.08 (1H, d, J=6 Hz, CHCO), 4.4 (1H, m, CHN), 5.38 (2H, ABq, J=22, 14 Hz, OCH₂Ar), 7.4 (1H, m, NH), 7.78 (2H, d, J=9 Hz, arom H), 8.25 (2H, d, J=9 Hz, arom H)</td>
</tr>
<tr>
<td>12b-2</td>
<td></td>
<td>NHAc</td>
<td>36</td>
<td>1765 (K,Br)</td>
<td>230</td>
<td>1.97 (3H, s, COCH₃), 2.45 (2H, m, CH₂), 2.7–3.9 (6H, m, 2 SO₂CH₂, CH₂), 4.06 (1H, d, J=6 Hz, CHCO), 4.4 (1H, m, CHN), 5.38 (2H, ABq, J=22, 14 Hz, OCH₂Ar), 5.9 (1H, d, J=14 Hz, SCH=C), 7.17 (1H, dd, J=14, 13 Hz, SC=CHN), 7.73 (2H, d, J=9 Hz, arom H), 8.21 (2H, d, J=9 Hz, arom H), 9.76 (1H, d, J=13 Hz, NH)</td>
</tr>
<tr>
<td>12c</td>
<td></td>
<td>CH₂CH₂NHAc</td>
<td>25</td>
<td>1770 (K,Br)</td>
<td>268</td>
<td>1.90 (3H, s, COCH₃), 2.1–3.7 (14H, m, 5 CH₂, SCH₂CH₂N), 3.84 (1H, d, J=6 Hz, CHCO), 4.4 (1H, m, CHN), 5.40 (2H, ABq, J=24, 14 Hz, OCH₂Ar), 7.4 (1H, m, NH), 7.78 (2H, d, J=9 Hz, arom H), 8.23 (2H, d, J=9 Hz, arom H)</td>
</tr>
</tbody>
</table>

^a Overall yields from 9.  ^b Not measured. Insoluble in CDCl₃ or acetone-δ₆.
Table VIII. Sodium 2- Carbapenem-3-carboxylate (13)

<table>
<thead>
<tr>
<th>Compound&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>IR cm&lt;sup&gt;−1&lt;/sup&gt; (KBr)</th>
<th>UV (H&lt;sub&gt;2&lt;/sub&gt;O) &lt;br&gt;nm&lt;sup&gt;(E&lt;sub&gt;1%cm&lt;/sub&gt;)&lt;/sup&gt;</th>
<th>NMR (D&lt;sub&gt;2&lt;/sub&gt;O) δ &lt;br&gt;ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>OH</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;NHAc</td>
<td>36</td>
<td>1760</td>
<td>299</td>
<td>2.15 (3H, s, COCH&lt;sub&gt;3&lt;/sub&gt;), 3.31 (3H, s, SO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;), 3.0—4.1 (9H, m, SO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;, CH&lt;sub&gt;2&lt;/sub&gt;, SCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;N, CHCO), 4.4 (1H, m, CHN), 4.8 (1H, m, CH-O)</td>
</tr>
<tr>
<td>13b-1</td>
<td>O&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;OH</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;NHAc</td>
<td>26</td>
<td>1750</td>
<td>298</td>
<td>2.01 (3H, s, COCH&lt;sub&gt;3&lt;/sub&gt;), 2.5 (2H, m, CH&lt;sub&gt;2&lt;/sub&gt;), 2.8—3.9 (10H, m, 2×SO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;, CH&lt;sub&gt;2&lt;/sub&gt;, SCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;N), 4.00 (1H, d, J = 6 Hz, CHCO), 4.4 (1H, m, CHN)</td>
</tr>
<tr>
<td>13b-2</td>
<td>O&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;OH</td>
<td>NAc</td>
<td>41</td>
<td>1755</td>
<td>229</td>
<td>2.20 (3H, s, COCH&lt;sub&gt;3&lt;/sub&gt;), 2.65 (2H, m, CH&lt;sub&gt;2&lt;/sub&gt;), 3.0—4.0 (6H, m, CH&lt;sub&gt;3&lt;/sub&gt;, 2×SO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;), 4.12 (1H, d, J = 6 Hz, CHCO), 4.50 (1H, m, CHN), 6.15 (1H, d, J = 13 Hz, SCH=CHN), 7.28 (1H, d, J = 13 Hz, SCH=CHN)</td>
</tr>
<tr>
<td>13c</td>
<td>O&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;OH</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;NHAc</td>
<td>39</td>
<td>1750</td>
<td>300</td>
<td>2.13 (3H, s, COCH&lt;sub&gt;3&lt;/sub&gt;), 2.2—3.9 (14H, m, 5×CH&lt;sub&gt;2&lt;/sub&gt;, SCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;N), 3.97 (1H, d, J = 6 Hz, CHCO), 4.4 (1H, m, CHN)</td>
</tr>
</tbody>
</table>

<sup>a</sup> All the compounds were obtained as colorless powders.  <sup>b</sup> Yields were calculated on the basis of the anhydrous sodium salts obtained by hydrogenolysis of the corresponding p-nitrobenzyl esters.
mixture of 20% K₂CO₃ (50 ml) and AcOEt (20 ml). Insoluble materials were filtered off, the organic phase was separated and the aqueous phase was further extracted with AcOEt. The combined extracts were washed successively with water, 20% K₂CO₃, water, sat. aq. NaHCO₃, water and sat. aq. NaCl, and dried. Evaporation of the solvent gave the diazo-ester 10b as a pale yellow oil (IR νₗ₅₆ cm⁻¹ : 2140, 1750, 1720). The unstable compound 10b was used in the subsequent reactions without purification. A mixture of the diazo-azetidinone 10b, a catalytic amount of rhodium (II) diacetate (5 mg), dry THF (4 ml), and dry benzene (6 ml) was heated at 80°C for 7 min under a nitrogen atmosphere. After being cooled to room temperature, the mixture was evaporated to dryness to give the 2-oxocarbapenam (11b) as a foam (IR νₗ₅₆ cm⁻¹ : 1770, 1720), which was used in the subsequent reactions without purification. Disopropylethylamine (0.016 ml, 0.09 mmol) and diphenyl chlorophosphate (0.019 ml, 0.09 mmol) were added to a stirred, cooled (0°C) solution of the 2-oxocarbapenam (11b) in dry acetonitrile (6 ml) under an argon atmosphere. The mixture was stirred for 1.5 h at 0°C and then disopropylethylamine (0.016 ml, 0.09 mmol) and N-acetylcysteamine (11 mg, 0.09 mmol) were added to the residue and insoluble materials were filtered off. The organic phase was separated and the aqueous phase was further extracted with AcOEt. The mixture was diluted with AcOEt, washed with water, and dried. After evaporation of the solvent the residue was subjected to chromatography on Florisil. Elution with acetone–chloroform (1:1, v/v) afforded 12b-1 as a pale yellow foam. Other compounds (12) listed in Table VII were synthesized in the same manner. Compound 12b-2 was prepared by using the silver salt of the thiol derivative.

Deprotection of the p-Nitrobenzyl Group of the Carbapenem Esters (12) by Hydrogenolysis—As a typical example, the preparation of 13b-1 from 12b-1 is described. A mixture of 12b-1 (57 mg, 0.11 mmol) and 10% palladium–charcoal (50 mg) in THF (5 ml), pH 7.0 phosphate buffer (2.6 ml) and water (2.6 ml) was stirred under a hydrogen atmosphere at room temperature for 1.5 h. The catalyst was filtered off, and the filtrate was washed with AcOEt and concentrated under reduced pressure. The concentrate was subjected to chromatography on Diaion HP-20 using water as an eluent. The fractions (νₗ₅₆ 298 nm) were collected and lyophilized to give 13b-1 as a colorless powder. The compounds listed in Table VIII were similarly prepared from the corresponding carbapenem esters.

(1S*,6R)-3,4,8-tetrahydro-3-tert-butyl(dimethyl)silyl-7-azabicyclo[3.2.0]hept-2-ene (16)—A solution of the silylated β-lactam 15 (4.70 g, 20 mmol) in acetone (10 ml) was added to a solution of N-methylmorpholine N-oxide (160 mg, 1.65 mmol) in dry THF (10 ml) at room temperature. After being cooled to room temperature, the mixture was evaporated to dryness to give the 2-oxocarbapenam (11) as a foam (IR νₗ₅₆ cm⁻¹ : 1770, 1720), which was used in the subsequent reactions without purification. Diisopropylethylamine (0.016 ml, 0.09 mmol) and diphenyl chlorophosphate (0.019 ml, 0.09 mmol) were added to a 2-oxocarbapenam (11) in dry acetonitrile (6 ml) under an argon atmosphere. After being cooled to room temperature, the mixture was evaporated to dryness to give the 2-oxocarbapenam (11) as a foam (IR νₗ₅₆ cm⁻¹ : 1770, 1720), which was used in the subsequent reactions without purification. Disopropylethylamine (0.016 ml, 0.09 mmol) and dibenzylamine (15 mg, 0.09 mmol) were added to a 2-oxocarbapenam (11) in dry acetonitrile (6 ml) under an argon atmosphere. The mixture was stirred for 1.5 h at 0°C and then disopropylethylamine (0.016 ml, 0.09 mmol) and N-acetylcysteamine (11 mg, 0.09 mmol) were added to the residue and insoluble materials were filtered off. The organic phase was separated and the aqueous phase was further extracted with AcOEt. The mixture was diluted with AcOEt, washed with water, and dried. After evaporation of the solvent the residue was subjected to chromatography on Florisil. Elution with acetone–chloroform (1:1, v/v) afforded 12b-1 as a pale yellow foam. Other compounds (12) listed in Table VII were synthesized in the same manner. Compound 12b-2 was prepared by using the silver salt of the thiol derivative.

The Dialdehyde 17—A solution of the dialdehyde 16 (2.08 g, 7.66 mmol) in freshly distilled THF (60 ml) was treated with periodic acid (2.16 g, 9.48 mmol) at 0°C with stirring. The mixture was stirred at room temperature for 45 min, diluted with water and extracted with CHCl₃. The extract was washed with water, dried and concentrated to give the dialdehyde 17 quantitatively as an oily substance. The unstable dialdehyde was used in the subsequent reactions without purification. IR νₗ₅₆ cm⁻¹ : 1730.

Intramolecular Aldol Condensation of the Dialdehyde 17—1) Method A: A solution of the dialdehyde 17, which was derived from the diol 16 (2.08 g, 7.66 mmol), in dry benzene (140 ml) was treated with dibenzylammonium trifluoroacetate (465 mg, 1.49 mmol). The mixture was heated at 60°C for 50 min under an argon atmosphere. Methanol (30 ml) and NaOH (540 mg, 14 mmol) were added to the mixture and the mixture was stirred for 1.5 h at room temperature. After evaporation of the solvent, AcOEt and dil. HCl were added to the residue and insoluble materials were filtered off. The organic phase was separated and the aqueous phase was further extracted with AcOEt. The combined extracts were washed successively with water and sat. aq. NaCl, dried and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel. Elution with AcOEt–CHCl₃ (1:1, v/v) afforded 19 (58 mg, 16%) as a pale yellow oil.

2) Method B: One drop each of piperidine and AcOH was added to a solution of the dialdehyde 17, which was derived from 16 (392 mg, 1.44 mmol), in dry benzene (15 ml). The mixture was heated at 60°C for 45 min under an argon atmosphere. After cooling, MeOH (5 ml) and NaBH₄ (60 mg, 1.59 mmol) were added to the reaction mixture and the mixture was stirred for 1 h at room temperature. After evaporation of the solvent, AcOEt and dil. HCl were added to the residue and insoluble materials were filtered off. The organic phase was separated and the aqueous phase was further extracted with AcOEt. The combined extracts were washed successively with water and sat. aq. NaCl, dried and concentrated. The residue was subjected to chromatography on silica gel. Elution with AcOEt–CHCl₃ (1:1, v/v) afforded 19 (58 mg, 16%) as a pale yellow oil.
3) Method C: Morpholine (0.90 ml, 10.32 mmol), camphoric acid (2410 mg, 12.04 mmol) and hexamethyldisilazane (HMPA) (0.45 ml) were added to a solution of the aldehyde 17, which was derived from 16 (480 mg, 1.77 mmol), in dry Et2O (40 ml) at 0 °C with vigorous stirring. The mixture was stirred at 0 °C under an argon atmosphere for 23 h, then the reaction mixture was diluted with water and extracted with Et2O. The extracts were washed with a large amount of water, dried and concentrated. The residue was dissolved in MeOH (20 ml) and treated with NaBH4 (75 mg, 1.98 mmol), and the mixture was stirred for 1 h at room temperature. After evaporation of the solvent, AcOEt and dil. HCl were added to the residue and insoluble materials were filtered off. The organic phase was subjected to chromatography on silica gel. Elution with AcOEt-CHCl3 (1:1, v/v) afforded a mixture of the two regioisomers 19 and 19* (130 mg, 29%) as a pale yellow oil. The two isomers could not be separated. IR νmax cm⁻¹: 1720. ¹H-NMR (CDCl3) δ: 0.23 (6H, s, 2 × SiMe), 0.94 (9H, s, 3 × Me), 2.3–2.8 (3H, m, CH2, OH), 3.7–4.4 (4H, m, CH2-C, C5-H, CH2O), 5.59 (0.5H, br s, olefinic proton). 5.87 (0.5H, br s, olefinic proton).

Chlorination of 19 —— Thionyl chloride (0.029 ml, 0.40 mmol) was added to a stirred, cooled (0 °C) solution of the azetidone 19 (100 mg, 0.39 mmol) in CHCl3 (1 ml). After being stirred for 4 h at 0 °C, the mixture was poured into ice-water and CHCl3 and extracted with CHCl3. The combined extracts were dried and evaporated. The residue was subjected to chromatography on silica gel. Elution with CHCl3 afforded an inseparable mixture of 20a-1 and 20a-2 (43 mg, 41%) as an oily substance. IR νmax cm⁻¹: 1720. ¹H-NMR (CDCl3) δ: 0.23 (6H, s, 2 × SiMe), 0.95 (9H, s, 3 × Me), 2.54 (2H, m, C4-H2), 4.0–4.3 (3.5H, m, C3-H, CH2Cl) of 20a-1, CHCl3 of 20a-2), 5.37 (0.5H, dd, J = 2, 6 Hz, olefinic proton of 20a-2), 5.73 (0.5H, br s, olefinic proton of 20a-1). The stereochemistry at C-3 of 20a-2 could not be determined.

(1S*,5R*)-2-Bromomethyl-6-tert-butyldimethylsilyl-7-oxo-6-azabicyclo[3.2.0]hept-2-ene (20-1) —— Dimethyl sulfoxide (0.27 ml, 3.68 mmol) was added dropwise to a solution containing N-bromosuccinimide (555 mg, 3.12 mmol) in dry CH2Cl2 (10 ml) at 0 °C over a period of 3 min. The mixture was cooled to –20 °C, and the azetidone 19 (526 mg, 3.68 mmol) in CH2Cl2 (5 ml) was added dropwise. Then the reaction mixture was warmed to 0 °C and stirred for 3 h, diluted with AcOEt and poured into ice-water. The organic phase was washed successively with water and sat. aq. NaCl, and dried. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with CHCl3 afforded the bromide 20b-1 (444 mg, 67 mmol) as a pale yellow oil. IR νmax cm⁻¹: 1740. ¹H-NMR (CDCl3) δ: 0.23 (6H, s, 2 × SiMe), 0.93 (9H, s, 3 × Me), 2.53 (2H, m, C4-H2), 3.9–4.4 (4H, m, C3-H, C5-H, CH2Br), 5.76 (1H, m, C2-H).

Synthesis of 19 via Ozonolysis of 15 —— A solution of 15 (473 mg, 1.57 mmol) in dry CH2Cl2 (15 ml) was ozonized at –78 °C in an acetone-dry ice bath, until the solution turned blue, at which time the ozone was replaced by a stream of dry nitrogen gas. After treatment with MeSeMe (1 ml), the solution was evaporated to dryness to give the dialdehyde 18, which was converted into 19 (75 mg, 19%) by Method A.

(3R*,4R*)-3-[(1R*)-2-Bromo-1-hydroxyethyl]-1-tert-butyldimethylsilyl-4-(2-hydroxyethyl)azetidin-2-one (21) —— A solution of 20b-1 (444 mg, 1.40 mmol) in MeOH (13 ml) was ozonized at –78 °C in an acetone-dry ice bath, until the solution turned blue, at which time the ozone was replaced by a stream of dry nitrogen gas. The reaction mixture was warmed to –40 °C, NaBH4 (50 mg, 1.32 mmol) was added, and the mixture was stirred for 1 h at room temperature. After evaporation of the solvent, AcOEt and dil. HCl were added to the residue and the organic phase was separated. The aqueous phase was further extracted with AcOEt. The combined extracts were washed successively with water and sat. aq. NaCl, and dried. The solvent was evaporated off and the diol 21 (478 mg, 97%) as a pale yellow oil. IR νmax cm⁻¹: 1740. ¹H-NMR (CDCl3) δ: 0.23 (6H, s, 2 × SiMe), 0.97 (9H, s, 3 × Me), 2.0 (2H, m, CH2), 3.3–4.4 (7H, m, OCH2, C3-H, C4-H, C5-H, CH2Br, H–C–O).

(3R*,4R*)-3-[(1R*)-2-Bromo-1-hydroxyethyl]-4-(2-hydroxyethyl)azetidin-2-one (22) —— Potassium fluoride (346 mg, 5.96 mmol) was added to a solution of 21 (1050 mg, 2.98 mmol) in dry MeOH (20 ml) and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated off, and the residue was purified by chromatography on silica gel. Elution with AcOEt-MeOH (20:1, v/v) afforded 22 (656 mg, 93%) as a colorless oil. IR νmax cm⁻¹: 1740. ¹H-NMR (acetone-d6) δ: 1.7–2.1 (2H, m, CH2), 3.1–4.2 (7H, m, CH2O, CH–O, C3-H, C4-H, C5-H, CH2Br), 7.2 (1H, br s, NH).

(6R*,7R*)-7-[(1R*)-2-Bromo-1-hydroxyethyl]-2,2-dimethyl-3-oxo-8-oxa-1-azabicyclo[4.2.0]octane (23) —— Dimethoxypropane (0.44 ml, 3.58 mmol) and one drop of BF3·OEt2 were added to a solution of 22 (656 mg, 2.76 mmol) in dry CH2Cl2 (10 ml) and the reaction mixture was stirred for 1.5 h at room temperature. The mixture was poured into pH 6.86 buffer and extracted with CH2Cl2. The organic phase was washed with sat. aq. NaCl, dried and concentrated. The concentrate was subjected to chromatography on silica gel. Elution with hexane–AcOEt (1:1, v/v) afforded the acetone 23 (482 mg, 63%) as colorless prisms, mp 133–135 °C. Anal. Calcd for C10H17BrNO3: C, 43.18; H, 5.80; N, 5.04. Found: C, 43.34; H, 5.59; N, 5.11. IR νmax cm⁻¹: 1740. ¹H-NMR (CDCl3) δ: 1.40, 1.69 (each 3H, 2 × s, 2 × Me), 1.7–2.0 (2H, m, CH2), 2.50 (1H, br s, OH), 3.29 (1H, dd, J = 11, 6 Hz, C3-H), 3.5–4.3 (6H, m, C4-H, C5-H, CH–O, C6-H, CH2Br).

(6R*,7R*)-7-[(1R*)-1-Hydroxy-2-{methylthio}ethyl]-2,2-dimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (24a) —— An aqueous solution of sodium methythiolate (15%) (0.60 ml) was added to a solution of 23 (239 mg,
0.859 mmol) in dimethylformamide (DMF) (10 ml) and the reaction mixture was stirred for 1 h at room temperature under an argon atmosphere. AcOEt and water were added to the mixture and the aqueous phase was extracted with AcOEt. The organic phase was washed successively with water and sat. aq. NaCl, and dried. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with hexane-AcOEt (1:10) afforded 24a (190 mg, 90\%) as colorless prisms. **Found:** C, 53.7; H, 7.1; N, 5.6. **IR \nu_{\mathrm{KBr}} \mathrm{cm}^{-1}: 1740.** **H-NMR (CDCl3) \delta: 2.10 (3H, s, COMe), 3.05 (3H, s, SO2Me), 5.70 (2H, s, olefinic protons), 7.30 (1H, br s, NH), 7.70 (2H, d, J=9 Hz, aromatic protons). **3.39 (1H, dd, J=10.3, 5.2 Hz, C7-H), 3.6-4.3 (6H, m, C4-H2, C6-H, CH-O, CH2-C).**

**6(R*,7R*)-2-Dimethyl-7-[1(R*)-2-methylthio-1-(p-nitrobenzoyloxy)ethyl]-1-oxo-3-oxa-1-azabicyclo[4.2.0]octane (5a-2) —** Dimethylaminopyridine (495 mg, 4.05 mmol) and p-nitrobenzyl chloroformate (436 mg, 2.02 mmol) were added to a solution of 24a (333 mg, 1.36 mmol) in CH2Cl2 (20 ml) at 0°C under an argon atmosphere. The reaction mixture was stirred for 18 h at room temperature. After evaporation of the solvent, AcOEt and dil. HCl were added to the residue. The organic phase was separated, washed successively with water and sat. aq. NaCl, and dried. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with hexane-AcOEt (2:1 to 1:1, v/v) afforded 5a-2 (240 mg, 73\%) as a colorless oil. **\([\alpha]_{25}^D +3.36 \ (c=1.24, \mathrm{CHC}13).** 1H-NMR (D2O) \delta: 1.41, 1.64 (each 3H, s, 2Me), 3.08 (3H, s, SO2Me), 2.9-3.3 (8H, m, 2CH2, 2CH2-N). **3.97 (1H, dd, J=10, 5 Hz, C6-H), 4.3-4.9 (2H, m, C5-H, CH-O).**

**5a-2**

**6(R*,7R*)-7-[[1(R*)-2-Methylsulfonyl-1-(p-nitrobenzoyloxy)ethyl]-2,2-dimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (6a-2) —** Starting from 5a-2, 6a-2 was obtained as a colorless oil. Yield 97\%. **IR \nu_{\mathrm{KBr}} \mathrm{cm}^{-1}: 1755, 1720.** **H-NMR (acetone-d6) \delta: 2.10 (3H, s, COMe), 3.05 (3H, s, SO2Me), 5.70 (2H, s, olefinic protons), 7.30 (1H, br s, NH), 7.63 (2H, d, J=9 Hz, aromatic protons). 8.18 (2H, d, J=9 Hz, aromatic protons).**

**3.4-4.0 (3H, s, SO2Me), 2.8-3.2 (2H, m, C,-H, C2-H), 3.70 (3H, s, OMe), 5.67 (2H, s, CH2-C, C2-H, C-H).**

**8a-2**

**6(R*,8R*)-3-[(1R*)-3-Diazo-3-(p-nitrobenzoyloxy)carbonyl]-2-oxopropyl]azetidin-2-one (9a-2) —** Starting from 8a-2, 9a-2 was obtained quantitatively as crystals. **IR \nu_{\mathrm{KBr}} \mathrm{cm}^{-1}: 2140, 1770, 1730.**

**1-Methyl Hydrogen (1R,2S)-1,2-Cyclohex-4-ene Dicarboxylate (26b) —** Racemic 1-methyl hydrogen 1,2-cis-1,2-dicarboxylic acid (82.3 g, 0.464 mol) and cinchonidine (136.3 g, 0.463 mol) were dissolved in MeOH (400 ml) and insoluble materials were filtered off. The filtrate was concentrated and dissolved in acetone (150 ml), and the solution was allowed to stand for 4 d at 5°C. The resulting precipitate was collected by filtration and washed with acetone. The precipitate was dissolved in a mixture of MeOH (75 ml) and acetone (150 ml). The solution was allowed to stand at 5°C for 1 d. The resulting precipitate was collected by filtration, washed with acetone to afford the cinchonidine salt of the half ester was dissolved in AcOEt (100 ml) and the solution was washed with 1 N HCl and sat. aq. NaCl, and dried. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with hexane-AcOEt (1:2) afforded 26b (22 g, 27\%) as a pale yellow oil. **\([\alpha]_{25}^D -3.34 \ (c=1.685, \mathrm{CHC}1).** 1H-NMR (CDCl3) \delta: 2.1-2.9 (4H, m, 2 x CH2), 2.9-3.2 (2H, C1-H, C2-H), 3.70 (3H, s, OMe), 5.67 (2H, s, olefinic protons), 11.68 (1H, s, COOH).**

**1-Methyl Hydrogen (1S,2R)-1,2-Cyclohex-4-ene Dicarboxylate (26a) —** The mother liquor of the cinchonidine salt of the half ester was dissolved in AcOEt (100 ml) and the solution was washed with 1 N HCl and sat. aq. NaCl, dried and concentrated. After filtration of insoluble materials, the chiral half ester 26a (23 g, 28\%) was obtained as a pale yellow oil. **\([\alpha]_{25}^D +3.36 \ (c=1.24, \mathrm{CHC}1).** Methyl (1S,2R)-2-[[2-Methylsulfonyl]ethoxycarbonylmino]-1-cyclohex-4-ene Carboxylate (27) — Triethylamine (11 g, 0.108 mol) and ethyl chloroformate (11.8 g, 0.108 mol) were added to a solution of the chiral half ester 26a (23 g, 28\%) in dry CH2Cl2 (100 ml). The reaction mixture was stirred for 18 h at room temperature. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with hexane-AcOEt (2:1 to 1:1, v/v) afforded 27 (19 g, 84\%) as colorless prisms, **\([\alpha]_{25}^D -3.36 \ (c=1.685, \mathrm{CHC}1).** 1H-NMR (acetone-d6) \delta: 1.41, 1.64 (each 3H, s, 2Me), 3.05 (3H, s, SO2Me), 2.8-3.3 (8H, m, 2CH2, 2CH2-N). **3.97 (1H, dd, J=10, 5 Hz, C6-H), 4.3-4.9 (2H, m, C5-H, CH-O).**

**3.6-4.3 (6H, m, C4-H2, C6-H, CH-O, CH2-C).**
and dried. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with ice-water. The aqueous phase was extracted with AcOEt. The combined extracts were washed with sat. aq. NaCl, and the mixture was subjected to chromatography on silica gel. Elution with hexane-AcOEt (1:2, v/v) afforded 27 (24.6 g, 79%) as crystals, mp 90-92 °C. Anal. Calcd for C17H16NO2: C, 68.04; H, 7.29; N, 11.23. Found: C, 68.04; H, 7.24; N, 11.23. IR ν cm⁻¹: 1730, 1700. H-NMR (CDCl3): δ: 7.0-7.3 (5H, m, C6-H), 6.5-6.8 (1H, s, SO2Me), 3.9-4.2 (2H, t, J= 5 Hz, SO2CH2), 3.68 (3H, s, OMe).  

**tert-Butyl (1S,2R)-2-(2-Methylsulfonyl)ethoxycarbonylaminomethyl-1-cyclohex-4-ene Carboxylate (31)** — Isobutene was bubbled into a mixture of 26b (25.7 g, 0.139 mol), CH2Cl2 (280 ml) and sulfuric acid (1.5 ml) for 30 min at 0 °C with stirring. The mixture was allowed to stand for 3 d. After further bubbling of isobutene for 30 min, the mixture was allowed to stand for 1 d. After evaporation of the solvent, the residue was dissolved in Et2O (300 ml) and the organic phase was washed successively with aq. NaHCO3 and sat. aq. NaCl, then dried. After evaporation of the solvent, the diester 30a (30.6 g, 92%) was obtained as a colorless oil. The diester 30a (30.6 g, 0.127 mol) was dissolved in MeOH (250 ml) and a solution of NaOH (8.34 g, 0.209 mol) in water (100 ml) was added. The mixture was allowed to stand for 20 h at room temperature. After evaporation of the solvent, the residue was dissolved in water, and washed with Et2O. Conc. HCl (21.5 ml, 0.212 mol) was added to the aqueous phase, which was extracted with Et2O. The organic phase was washed with sat. aq. NaCl and dried. After evaporation of the solvent, the half ester 30b (26.9 g, 93%) was obtained as colorless crystals. The half ester 30b was transformed into 31 (39.3 g, 96%) as a colorless oil in a manner similar to that described for the preparation of 27 from 26. IR ν cm⁻¹: 1725, 1520. 1H-NMR (CDCl3): δ: 1.44 (9H, s, CMe3), 2.0-2.6 (4H, m, 2 x CH2), 2.6-2.9 (1H, m, C1-H), 2.98 (3H, s, SO2Me), 3.32 (2H, t, J=5 Hz, SO2CH2), 4.0-4.4 (1H, m, C1-H), 4.48 (2H, t, J=5 Hz, CO2CH3), 5.5-5.8 (2H, m, olefinic protons).  

(1S,2R)-2-Amino-1-cyclohex-4-ene Carboxylic Acid (28) — A 1 N NaOH solution (10 ml, 10 mmol) was added to a solution of 27 (1.53 g, 5 mmol) in MeOH (25 ml) and the mixture was stirred for 12 h. After further addition of 1 N NaOH (3 ml, 30 mmol) the mixture was stirred for 4 h. The precipitate was dissolved in water and IRA-401 ion exchange resin (OH⁻ type, wet 49 ml) was added to the solution. The mixture was stirred and the resin was collected by filtration and washed with water. The desired fraction, obtained by eluting the column containing the resin with 5% AcOH (200 ml), was concentrated. The concentrate was dissolved in water and the solution was stirred with Dowex 50W (H⁺, 15 ml). The desired fraction, obtained by eluting the column containing the resin with 5% aq. ammonia, was evaporated. Acetone was added to the residue and the resulting precipitate was collected by filtration and washed with acetone to give 28 (532 mg, 76%) as colorless crystals. [α]D25 + 36.4 ° (c=0.45, H2O).

b) Aqueous 5 N NaOH (15 ml) was added to a mixture of 31 (8.69 g, 25 mmol), dioxane (210 ml) and MeOH (75 ml). The reaction mixture was stirred for 15 min at room temperature. AcOH (4.6 ml, 75 mmol) was added, and the mixture was concentrated. Aqueous NaHCO3 was added to the residue and the aqueous phase was extracted with CHCl3. The organic phase was washed with water and dried. After evaporation of the solvent, trifluoroacetic acid (15 ml) was added to the residue and allowed to stand for 24 h at room temperature. Dowex 50W (H⁺, 75 ml) and water (50 ml) were added to the mixture at 0 °C. After being stirred at 0 °C for 1 h, the resin was collected by filtration. The desired fraction, collected by eluting the column containing the resin with 5% aq. ammonia, was evaporated. Acetone was added to the residue and the resulting precipitate was collected by filtration and washed with acetone to give 28 (532 mg, 76%) as colorless crystals. [α]D25 + 36.4 ° (c=0.45, H2O).

(1S,6R)-8-Oxo-7-azabicyclo[4.2.0]oct-3-ene (29) — A mixture of 28 (424 mg, 3 mmol), triphenylphosphine (997 mg, 3.8 mmol), 2,2'-dipyridyl disulfide (838 mg, 3.8 mmol) and manganese oxide (652 mg, 7.5 mmol) and acetonitrile (60 ml) were refluxed for 3.5 h with vigorous stirring. After cooling, insoluble materials were filtered off and the filtrate was added to a solution of sodium azide (14 g, 0.216 mol) in water (75 ml) and tetrabutylammonium hydrogen sulfate (7.3 g, 0.0216 mol) were added to the mixture and the mixture was stirred for 1 h at 0 °C. The organic phase was subjected to chromatography on silica gel. Elution with hexane–AcOEt (1:2, v/v) afforded 29 (251 mg, 68%) as a colorless prism, mp 163-164 °C. [α]D25 + 28.6 ° (c=0.585, CHCl3). Anal. Calcd for C17H16NO2: C, 68.04; H, 7.29; N, 11.23. Found: C, 68.04; H, 7.24; N, 11.23. IR ν cm⁻¹: 1725, 1700. 1H-NMR (CDCl₃): δ: 2.0-2.8 (4H, m, 2 x CH2), 3.35 (1H, m, C1-H), 3.98 (1H, m, C1-H), 5.5-6.1 (3H, m, olefinic protons).  

(1S,6R)-7-tert-Butyldimethylsilyl-8-oxo-7-azabicyclo[4.2.0]oct-3-ene (32) — The β-lactam 29 (251 mg, 2.04 mmol) was dissolved in DMF (9 ml). tert-Butyldimethylsilyl chloride (498 mg, 3.3 mmol) and Et3N (0.46 ml, 3.3 mmol) were added to the solution at 0 °C and the mixture was stirred for 1.5 h at room temperature, then poured into ice-water. The aqueous phase was extracted with AcOEt. The combined extracts were washed with sat. aq. NaCl, and dried. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with hexane–AcOEt (6:1, v/v) afforded 32 (676 mg, quantitatively) as a colorless oil. [α]D25 -45.9 ° (c=1.43, EtOH). IR
\[ \text{Compound 34} \] was prepared from optically active 16 in the same manner as that described for the preparation of the racemic compound 19. Yield 40%.

\[ \text{Compound 35} \] was prepared from 34 in the same manner as that described for the preparation of the racemic compound 20b-1. Yield 66%.

\[ \text{Compound 36} \] was prepared from optically active 22 in the same manner as that described for the preparation of the racemic 23. Yield 71%, mp 141-142 °C. Anal. Calcd for C_{10}H_{16}BrNO_3: C, 43.18; H, 5.80; N, 5.04. Found: C, 43.12; H, 5.79; N, 5.04. \[ \text{Compound 37} \] was prepared from 36 quantitatively as a pale yellow oil. IR \( \text{v}_{\text{max}} \) cm\(^{-1}\): 1740. \[ \text{Compound 38} \] was prepared from the optically active 10 in a manner similar to that described for the preparation of the racemic compound 12. Yield 56%. IR \( \text{v}_{\text{max}} \) cm\(^{-1}\): 1770, 1700, 1620. UV \( \lambda_{\text{max}} \) (EtOH) nm: 263, 325. \[ \text{Compound 39} \] was prepared from 36 quantitatively as a pale yellow oil. IR \( \text{v}_{\text{max}} \) cm\(^{-1}\): 1755, 1670. UV \( \lambda_{\text{max}} \) (EtOH) nm: 218 (\( \varepsilon = 17650 \)), 305 (\( \varepsilon = 8780 \)), 372 (\( \varepsilon = 185 \)).

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References and Notes


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27) We thank Dr. K. Komiya and Mr. Y. Wada of this Division for this analysis.