

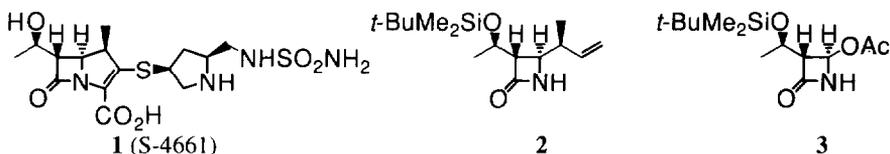
Efficient and Practical Synthesis of 1 β -Methylcarbapenems

Masaharu Kume,* Hiroaki Ooka and Hiroyuki Ishitobi

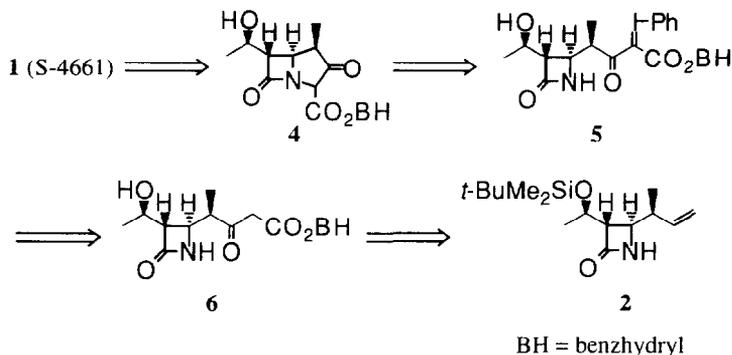
Discovery Research Laboratories I, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Abstract: An efficient and practical method of synthesizing 1 β -methylcarbapenem, S-4661, was developed. (4*R*)-4-[(1*S*)-1-Methylallyl]-2-azetidinone **2**, prepared stereoselectively from commercially available acetoxy-azetidinone **3**, was converted to the β -keto ester **6** in four steps. The iodonium ylide **5** was prepared from **6**, then cyclized to obtain the bicyclic β -keto ester **4**. Finally, **4** was processed to the target product, S-4661, by conventional procedures. © 1997, Elsevier Science Ltd. All rights reserved.

The synthesis of carbapenem antibiotics, especially 1 β -methylcarbapenems, has been an intriguing challenge, and many methods have been reported for synthesizing the key intermediates¹⁾ and for constructing the bicyclic skeleton of the 1 β -methylcarbapenems.²⁾ Several years ago, Uyeo *et al.* in our laboratories developed a simple and highly stereoselective, and therefore industrially feasible, synthesis of a novel key intermediate **2** from commercially available acetoxy-azetidinone **3**.^{1a)}

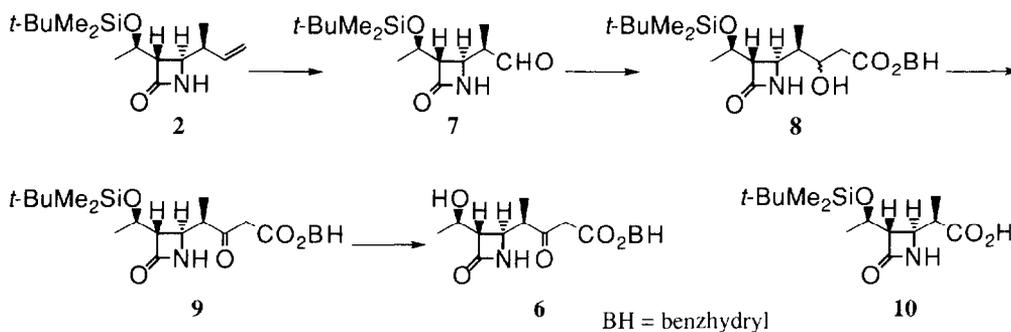


During an extensive search for new β -lactam antibiotics at our laboratories, a novel 1 β -methylcarbapenem antibiotic **1**, designated as S-4661, was discovered.³⁾ S-4661 possesses potent antibacterial activities against a wide range of gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa*, and has enhanced metabolic stability to renal dehydropeptidase-I (DHP-I). In order to develop a better industrially feasible method for the synthesis of S-4661, we decided to study a novel synthetic route starting with the allyl azetidinone **2**, described above. Our retrosynthetic analysis toward S-4661 is shown in Scheme 1. Our strategy consisted of two parts: construction of the 5-membered ring in the carbapenem skeleton utilizing cyclization of the iodonium ylide **5**, and synthesis of the requisite precursor, the β -keto ester **6**, from **2**. In the previous communication,⁴⁾ we reported the rhodium(II)-catalyzed and acid-catalyzed cyclization of the iodonium ylide **5** for construction of the carbapenem nucleus. Here we describe an efficient and practical synthesis of **6** from **2** and details of an investigation on the cyclization of the iodonium ylide **5**.



Preparation of β -keto ester **6** from allyl azetidinone **2**

The β -keto ester **6** could have been prepared from the well-established intermediate **10** according to the known procedure reported by the Merck group,⁵⁾ which involves chain extension using the Masamune condition.⁶⁾ However, the requisite carbonyldiimidazole is an expensive reagent and, also, considerable yield of the by-product cannot be avoided owing to the lability of the β -lactam in the presence of base. These problems could be circumvented by our new process from the allyl azetidinone derivative **2**. The preparation of the β -keto ester **6** from **2** is shown in Scheme 2.



Oxidation of **2** with ozone at -78°C followed by reductive treatment with dimethyl sulfide in a mixture of dichloromethane (CH_2Cl_2) and methanol gave 87% yield of the desired aldehyde **7** after crystallization from *n*-hexane. Chain extension was carried out using the Reformatsky reaction. The reaction of **7** with the organozinc reagent, prepared *in situ* from benzhydryl bromoacetate⁷⁾ and zinc powder, in tetrahydrofuran at room temperature provided the β -hydroxy ester **8** in high yield. Although zinc powder is usually pre-activated by washing with dilute hydrochloric acid, we found that it could also be activated by a catalytic amount of cupric bromide to achieve a high yield of conversion. The next step was oxidation of the hydroxy group of **8**. Several oxidation conditions were investigated. As shown in Table 1, both Swern oxidation and Pfitzner-Moffatt oxidation were effective, with the latter being more practical in that it could be performed at room

temperature. The resulting β -keto ester **9** was converted to **6** by removal of the *tert*-butyldimethylsilyl (TBDMS) group with hydrochloric acid in acetonitrile.

Table 1. Oxidation of β -Hydroxy Ester **8** to β -Keto Ester **9**

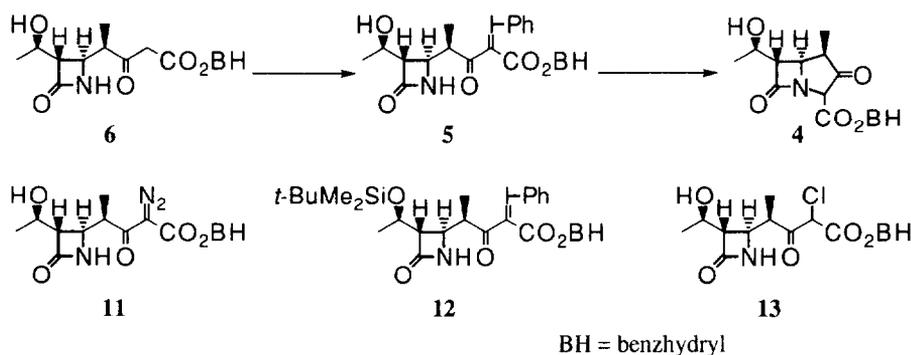
reagent	solvent	temperature	yield
DMSO (2.3 eq.), TFAA (1.5 eq.), Et ₃ N (3.2 eq.)	CH ₂ Cl ₂	-78°C	75%
DMSO (2.3 eq.), TFAA (1.5 eq.), Et ₃ N (3.7 eq.), Me ₃ SiCl (0.5 eq.)	CH ₂ Cl ₂	-78°C	61%
PCC (3 eq.)	CH ₂ Cl ₂	r.t.	55%
Na ₂ Cr ₂ O ₇ (2 eq.), H ₂ SO ₄ (4 eq.)	acetone	0°C ~ r.t.	37%
DCC (3 eq.), TFA (0.5 eq.), pyridine (1 eq.), DMSO (large excess)	toluene	r.t.	87%
DCC (1.5 eq.), TFA (0.5 eq.), pyridine (1 eq.), DMSO (2.5 eq.)	toluene	r.t.	72%*

TFAA = trifluoroacetic anhydride, PCC = pyridinium chlorochromate, DCC = dicyclohexylcarbodiimide, TFA = trifluoroacetic acid.

* Isolation yield of **6** after desilylation.

Cyclization of the iodonium ylide **5**

The iodonium ylide **5** was prepared from the corresponding β -keto ester **6** as described in the previous communication.⁴⁾ The reaction should be carried out around or under 20°C so that **5** can be precipitated from the reaction mixture. This crystalline iodonium ylide was fairly pure even without further purification and stable enough to be stored at room temperature. Using this iodonium ylide **5**, we investigated the ring closure (Scheme 3).



Scheme 3

Several transition metal catalysts were evaluated, and the results are summarized in Table 2. We were not successful with initial attempts using CuCl and copper acetylacetonate (Cu(acac)₂), which catalyze cyclopropanation of iodonium ylides.⁸⁾ Based on formal analogy between β -dicarbonyl iodonium ylides and α -

diazo β -dicarbonyl compounds, we decided to try Rh(II) acetate dimer ($\text{Rh}_2(\text{OAc})_4$) using the Merck procedure for the synthesis of carbapenems,^{2a),5)} which involves Rh(II)-catalyzed ring closure of α -diazo β -keto esters (e.g. **11**). The cyclization reaction proceeded smoothly at room temperature to give the bicyclic β -keto ester **4** in 86% yield. It is noteworthy that this ring closure occurred at room temperature, while heating was required for the reaction of **11**. Furthermore, we found that the TBDMS-protected iodonium ylide **12** prepared from the corresponding β -keto ester **9** was cyclized in the presence of $\text{Rh}_2(\text{OAc})_4$ in lower yield accompanied by several by-products. It is likely due to steric repulsion by the TBDMS group. Other transition metal catalysts such as $\text{Ni}(\text{acac})_2$, $\text{Pd}(\text{OAc})_2$ and $\text{Pd}(\text{PPh}_3)_4$, were also screened but none gave successful results.

Table 2. Transition Metal-Catalyzed Cyclization of Iodonium Ylide **5**

catalyst	reaction time	result (yield)
$\text{Rh}_2(\text{OAc})_4$ (0.01 eq.)	20 min	86%
CuCl (0.1 eq.)	2 hr	a complex mixture of products
$\text{Cu}(\text{acac})_2$ (0.1 eq.)	1 hr	a complex mixture of products
$\text{Ni}(\text{acac})_2$ (0.1 eq.)	7 hr	no reaction
$\text{Pd}(\text{OAc})_2$ (0.1 eq.)	16 hr	a complex mixture of products
$\text{Pd}(\text{PPh}_3)_4$ (0.1 eq.)	24 hr	a complex mixture of products

All reactions were carried out in dichloromethane at room temperature. acac = acetylacetonate.

Table 3. Acid-Catalyzed Cyclization of Iodonium Ylide **5**

acid	solvent	reaction time	result (yield)
$\text{TsOH}\cdot\text{H}_2\text{O}$ (0.05 eq.)	EtOH	16 min	94%
MsOH (0.05 eq.)	EtOH	15 min	81%
conc H_2SO_4 (0.05 eq.)	EtOH	11 min	91%
70% HClO_4 (0.03 eq.)	EtOH	15 min	90%
AcOH (1.2 eq.)	EtOH	4 hr	no reaction
conc HCl (1.1 eq.)	EtOH	10 min	85% of 13
$\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.1 eq.)	THF	23 min	89%
AlCl_3 (0.1 eq.)	THF	24 hr	a complex mixture of products

All reactions were carried out at room temperature.

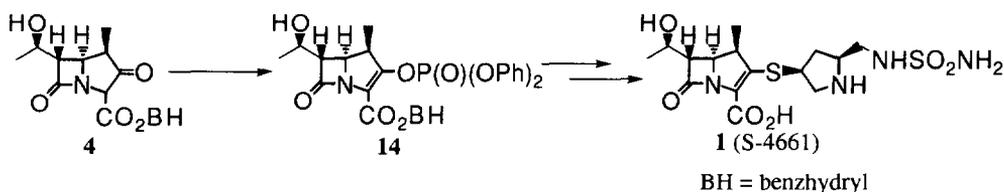
We next turned our attention to the acid-catalyzed cyclization. Neiland *et al.* reported that in the presence of strong acids, the protonation and rupture of the C–I bond of β -dicarbonyl iodonium ylides takes place with subsequent nucleophilic substitution.⁹⁾ Based on this reactivity of the iodonium ylides, we expected that the

protonation and the subsequent nucleophilic substitution by the nitrogen atom of the β -lactam would occur in the presence of a catalytic amount of acid. As shown in Table 3, exposure of the iodonium ylide **5** to a catalytic amount of *p*-toluenesulfonic acid (TsOH·H₂O) in ethanol (EtOH) at room temperature, followed by purification by chromatography on silica gel, afforded the desired bicyclic β -keto ester **4** in almost quantitative yield. Methanesulfonic acid (MsOH), sulfuric acid (conc. H₂SO₄) and perchloric acid (70% HClO₄) were also effective. No reaction occurred with acetic acid (AcOH) probably owing to its weak acidity. With hydrochloric acid (conc. HCl), use of the stoichiometric amount gave the chlorinated product **13** in 85% yield, which was consistent with Neiland's report.⁹⁾ The ring closure was effected in another solvent, such as acetonitrile, acetone or CH₂Cl₂, instead of EtOH. Lewis acid, such as trifluoroborane etherate (BF₃·Et₂O) in THF, also furnished the bicyclic product **4** in 89% yield. However, aluminum trichloride (AlCl₃) only gave a complex mixture of products difficult to identify.

For comparison, the α -diazo β -keto ester **11** was subjected to the acid-catalyzed cyclization. However, either TsOH·H₂O (in EtOH) or BF₃·Et₂O (in CH₂Cl₂) did not effect the ring closure, and **11** was recovered in almost quantitative yield.

Thermal ring closure of **5** was then tried but the desired bicyclic product **4** was not obtained. Thermolysis of the iodonium ylide **5** took place under reflux in EtOH to give the β -keto ester **6** in 78% yield.

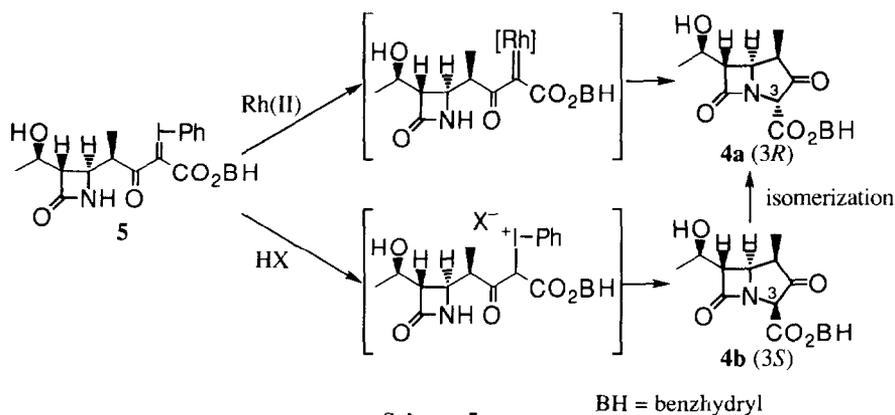
The bicyclic β -keto ester **4** obtained from the above Rh(II)- and acid-catalyzed cyclization was, without purification, converted into the enol phosphate **14** on treatment with diphenylphosphoryl chloride and diisopropylethylamine (70~75% yield from **5**). The acid-catalyzed cyclization and the following phosphorylation were also carried out by a one-pot procedure. Thus the iodonium ylide **5** was treated with a catalytic amount of H₂SO₄ in acetonitrile and, after completion of the reaction, diphenylphosphoryl chloride and diisopropylethylamine were added to the reaction mixture. Usual work-up and crystallization gave **14** in 70% yield. The obtained enol phosphate was processed to the final product, S-4661, by reaction with a corresponding thiol and subsequent deprotection (Scheme 4).³⁾



Scheme 4

Further examination of the cyclization products showed that the Rh(II)-catalyzed and the acid-catalyzed cyclization reactions had different stereoselectivities. NMR analyses of the residues, after the reaction solvent was removed, showed that the Rh₂(OAc)₄-catalyzed cyclization in CH₂Cl₂ gave (3*R*)-isomer **4a** as a single isomer, while the acid-catalyzed cyclization preferentially produced (3*S*)-isomer **4b** [**4a** : **4b** = 1 : 2 (cat. TsOH·H₂O in EtOH), 3 : 7 (cat. MsOH in EtOH)]. Further NMR studies revealed that the MsOH-catalyzed cyclization in deuterated chloroform (CDCl₃) yielded (3*S*)-isomer **4b** in a completely stereoselective manner, and it was gradually isomerized to the thermodynamically preferred (3*R*)-isomer **4a**, while the cyclization in deuterated methanol (CD₃OD) gave a mixture of **4a** and **4b** of ca. 1 : 9. Pure **4b** was obtained in 51% yield after careful evaporation of the reaction mixture (cat. MsOH in CH₂Cl₂) at -20°C, followed by crystallization

from ether. The stereochemical difference between the two reactions indicated that they proceeded *via* different reaction mechanisms (Scheme 5). As the Rh(II)-catalyzed cyclization of the α -diazo β -keto ester **11** affords (3*R*)-isomer **4a** as a single isomer, the present Rh(II)-catalyzed cyclization of **5** should have a similar mechanism to that of **11**, which would involve the formation of a Rh(II)-carbene complex. On the other hand, the acid-catalyzed cyclization would occur *via* an ionic mechanism which would require initial protonation. It is not known whether the resulting iodonium cation is directly displaced by the nitrogen atom of the β -lactam ring or *via* intervention by the formation of the N–I bond.



In conclusion, an improved and practical synthesis of the novel 1 β -methylcarbapenem antibiotic S-4661 was established, with rhodium (II)- or acid-catalyzed cyclization of the iodonium ylide **5** as a key step. Industrially feasible synthesis of S-4661 from commercially available acetoxy-azetidinone **3** was made possible by the results of the present work and the stereoselective synthesis of allyl azetidinone **2**, which has been developed in our laboratories.

EXPERIMENTAL SECTION

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a Jasco IR-700 spectrometer. ¹H-NMR spectra were recorded at 200 MHz on a Varian VXR-200, or at 300 MHz on a Gemini-300 or Gemini 2000 spectrometer. Chemical shifts are reported in ppm (δ scale) using tetramethylsilane as an internal standard. Mass spectra (LSIMS) were measured on a Hitachi M-90 mass spectrometer. Reagents were used without any further purification and all reactions under anhydrous conditions were carried out using anhydrous solvents dried over Molecular Sieves type 4A in a nitrogen atmosphere. Column chromatography was performed with Silica gel 60 (particle size 0.063–0.200 mm or 0.040–0.063 mm E. Merck).

(3*S*,4*R*)-3-[(1*R*)-1-*t*-butyldimethylsilyloxyethyl]-4-[(1*S*)-1-methylallyl]-2-azetidinone **2**

This compound was prepared according to the published procedure^{1a)} from the corresponding 4-acetoxy azetidinone **3**. The physical data were described in the literature.^{1a),10)}

(3S,4R)-3-[(1*R*)-1-*t*-Butyldimethylsilyloxyethyl]-4-[(2*R*)-1-oxo-2-propyl]-2-azetidinone **7**

A solution of **2** (100 g, 0.353 mol) in a mixture of dichloromethane (800 ml) and methanol (200 ml) was cooled to -50°C . Ozone was bubbled through the solution which was further cooled to -78°C for an hour, after which nitrogen gas was bubbled through the mixture for 15 minutes. Dimethyl sulfide (90.7 ml) was added to the reaction mixture and the cooling bath was removed. After being warmed to room temperature, the mixture was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Crystallization of the residue from *n*-hexane gave **7** (87.3 g, 87%) as white crystals; mp $75\text{--}81^{\circ}\text{C}$. IR (CHCl_3): 3404, 1758, 1725, 1460, 1374, 1359 cm^{-1} . $^1\text{H-NMR}$ (200MHz, CDCl_3): δ 0.07 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.21 (3H, d, $J = 7.0\text{Hz}$), 1.23 (3H, d, $J = 6.2\text{Hz}$), 2.6–2.8 (1H, m), 2.98 (1H, dd, $J = 2.3\text{Hz}, 5.3\text{Hz}$), 3.94 (1H, dd, $J = 2.3\text{Hz}, 5.5\text{Hz}$), 4.20 (1H, quintet, $J = 5.3\text{Hz}$), 5.92 (1H, broad singlet), 9.76 (1H, s).

(3S,4R)-3-[(1*R*)-1-*t*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-3-diphenylmethoxycarbonyl-2-hydroxy-1-methylpropyl]-2-azetidinone **8**

A solution of **7** (5.00 g, 17.5 mmol) and benzhydryl bromoacetate⁷⁾ (16.15 g, 52.9 mmol) in tetrahydrofuran (40 ml) was dropwise added to a mixture of zinc powder (5.77 g, 88.3 mmol) and cupric bromide (0.20 g, 0.90 mmol) in tetrahydrofuran (5 ml) at $25\text{--}30^{\circ}\text{C}$. After being stirred for 1.5 hours, the mixture was filtered through Hyflo Super-Cel[®]. Hydrochloric acid (53 ml), 1 N, was added to the filtrate at ice-bath temperature, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with 5% aqueous NaHCO_3 solution and water. After being dried over anhydrous Na_2SO_4 , the solution was evaporated under reduced pressure. Purification by column chromatography on silica gel yielded **8** (a mixture of diastereomers) (7.93 g, 89%) as a colorless froth.

The mixture **8** was chromatographed again (eluent: toluene-ethyl acetate, 1 : 1) in order to prepare analytical samples of each diastereomer (less polar (major) isomer **8a** and more polar (minor) isomer **8b**). It was ascertained that oxidation of both **8a** and **8b** under the Swern condition gave the same compound **9**.

Isomer **8a**. IR (CHCl_3): 3408, 1749, 1455, 1373, 1360, 1325 cm^{-1} . $^1\text{H-NMR}$ (300MHz, CDCl_3): δ 0.07 (6H, s), 0.86 (9H, s), 0.95 (3H, d, $J = 6.9\text{Hz}$), 1.23 (3H, d, $J = 6.3\text{Hz}$), 1.55–1.7 (1H, m), 2.50 (1H, A part of ABX, $J_{AB} = 16.5\text{Hz}, J_{AX} = 2.9\text{Hz}$), 2.70 (1H, B part of ABX, $J_{AB} = 16.5\text{Hz}, J_{BX} = 10.2\text{Hz}$), 2.85 (1H, ddd, $J = 0.9\text{Hz}, 2.1\text{Hz}, 5.7\text{Hz}$), 2.88 (1H, broad doublet, $J = 3.0\text{Hz}$), 3.73 (1H, dd, $J = 2.3\text{Hz}, 5.3\text{Hz}$), 4.1–4.25 (2H, m), 5.85 (1H, broad singlet), 6.92 (1H, s), 7.25–7.4 (10H, m). Mass(HR-LSIMS) Calcd for $\text{C}_{29}\text{H}_{41}\text{NO}_5\text{SiNa}$ ($[\text{M}+\text{Na}]^+$): 534.2650; Found: m/z 534.2654 ($[\text{M}+\text{Na}]^+$).

Isomer **8b**. $^1\text{H-NMR}$ (200MHz, CDCl_3): δ 0.09 (6H, s), 0.85 (9H, s), 0.92 (3H, d, $J = 7.0\text{Hz}$), 1.29 (3H, d, $J = 6.0\text{Hz}$), 1.6–1.8 (1H, m), 2.63 (1H, d, $J = 10.7\text{Hz}$), 2.65 (1H, d, $J = 5.4\text{Hz}$), 3.13 (1H, dd, $J = 2\text{Hz}, 7\text{Hz}$), 3.53 (1H, dd, $J = 2.2\text{Hz}, 6.8\text{Hz}$), 3.7–3.9 (1H, broad singlet), 3.8–4.0 (1H, m), 4.0–4.2 (1H, m), 5.96 (1H, broad singlet), 6.92 (1H, s), 7.25–7.4 (10H, m).

(3S,4R)-3-[(1*R*)-1-*t*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-3-diphenylmethoxycarbonyl-1-methyl-2-oxopropyl]-2-azetidinone **9**

Swern oxidation. A solution of **8** (a mixture of **8a** and **8b**) (2.00 g, 3.91 mmol) in dichloromethane (20 ml) was added portionwise over 10 minutes to a cooled (-78°C) and stirred solution of dimethyl sulfoxide (0.64 ml, 9.02 mmol) and trifluoroacetic anhydride (0.83 ml, 5.88 mmol) in dichloromethane (20 ml). After being stirred for 30 minutes at the same temperature, the mixture was treated with triethylamine (1.74 ml, 12.5 mmol)

and stirred further for an hour. The reaction mixture was diluted with dichloromethane and washed successively with water, 5% aqueous NaHCO₃ solution and water. After being dried over anhydrous Na₂SO₄, the solution was evaporated under reduced pressure. Purification by column chromatography on silica gel gave **9** (1.49 g, 75%) as a colorless froth. IR (CHCl₃): 3405, 1755, 1720 (shoulder), 1647, 1620, 1455, 1374, 1359 cm⁻¹. ¹H-NMR (200MHz, CDCl₃): [3 : 2 mixture of keto and enol tautomers] δ 0.046, 0.053 and 0.059 (6H for the both, 3 singlets), 0.86 (9H for the keto, s), 0.87 (9H for the enol, s), 1.09–1.13 (3H for the enol, d), 1.13 (3H for the keto, d, J = 6.2Hz), 1.14 (3H for the keto, d, J = 6.5Hz), 1.20 (3H for the enol, d, J = 7.0Hz), 2.3–2.5 (1H for the enol, m), 2.8–3.0 (2H for the keto + 1H for the enol, m), 3.61 and 3.64 (2H for the keto, ABq, J = 15.6Hz), 3.82 (1H for the enol, dd, J = 2.4Hz, 6.4Hz), 3.90 (1H for the keto, dd, J = 2.3Hz, 4.7Hz), 4.06–4.24 (1H for the both, m), 5.20 (1H for the enol, s), 5.81 (1H for the keto, broad singlet), 5.88 (1H for the enol, broad singlet), 6.92 (1H for the both, s), 7.25–7.4 (10H for the both, m), 11.99 (1H for the enol, s).

Swern oxidation with trimethylsilyl chloride. After **8** (2.00 g) was treated with dimethyl sulfoxide (0.64 ml) and trifluoroacetic anhydride (0.83 ml) as described above, trimethylsilyl chloride (0.25 ml, 1.97 mmol) and triethylamine (2.02 ml, 14.5 mmol) were added to the reaction mixture. Compound **9** (1.22 g, 61%) was obtained after similar work-up to that described above.

Oxidation with pyridinium chlorochromate (PCC). A solution of **8** (497 mg, 0.971 mmol) in dichloromethane (3 ml) was added to a suspension of PCC (98%, 641 mg, 2.91 mmol) in dichloromethane (2 ml) and the mixture was stirred overnight at room temperature. Dried ether (5 ml) was added to the mixture, which was then filtered through Hyflo Super-Cel[®]. The filtrate was evaporated and purified by column chromatography on silica gel to give **9** (270 mg, 55%) as a colorless froth.

Oxidation with sodium dichromate (Na₂Cr₂O₇). A solution of **8** (328 mg, 0.641 mmol) in acetone (2 ml) was added to an ice-cooled solution of Na₂Cr₂O₇·2H₂O (382 mg, 1.28 mmol) and H₂SO₄ (78 μl, 1.54 mmol) in acetone (1 ml) and the mixture was stirred at room temperature for 1.75 hours. Additional H₂SO₄ (52 μl, 1.03 mmol) was added and stirring was continued for 2.5 hours. The reaction mixture was diluted with water and ethyl acetate, and then separated. The organic layer was washed with water twice, dried over anhydrous Na₂SO₄ and evaporated. Purification by column chromatography on silica gel yielded **9** (120 mg, 37%) as a colorless froth.

Pfitzner-Moffatt oxidation. A solution of **8** (737 mg, 1.44 mmol) and dicyclohexylcarbodiimide (890 mg, 4.31 mmol) in a mixture of toluene (7 ml) and dimethyl sulfoxide (7 ml), was treated with pyridine (116 μl, 1.43 mmol) and trifluoroacetic acid (55 μl, 0.714 mmol) and stirred at room temperature for 3.5 hours. The precipitate was filtered off, and the filtrate was washed successively with water, dilute hydrochloric acid, water, 5% aqueous NaHCO₃ solution and water. After being dried over anhydrous Na₂SO₄, the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel to yield **9** (640 mg, 87%) as a colorless froth.

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-4-[(1*R*)-3-diphenylmethoxycarbonyl-1-methyl-2-oxopropyl]-2-azetidinone
6

Pfitzner-Moffatt oxidation and desilylation. An ice-cooled solution of **8** (5.08 g, 9.93 mmol) in toluene (25 ml) was treated with dimethyl sulfoxide (1.76 ml, 24.8 mmol), dicyclohexylcarbodiimide (3.07 g, 14.9 mmol), pyridine (0.80 ml, 9.89 mmol) and trifluoroacetic acid (0.38 ml, 4.93 mmol) and stirred at the same temperature for 40 minutes. The ice bath was removed and stirring was continued for an hour. The reaction mixture was again cooled to ice-bath temperature and stirred for 20 minutes. After the precipitate was removed by filtration, the filtrate was washed successively with dilute hydrochloric acid, water, 5% aqueous NaHCO₃ solution and water, then dried over anhydrous Na₂SO₄ and evaporated. The residue was dissolved in acetonitrile (25 ml) and treated with 12 N hydrochloric acid (1.66 ml, 19.9 mmol) at ice-bath temperature. After an hour, the reaction mixture was neutralized with a solution of NaHCO₃ (1.84 g, 21.9 mmol) in water (37%). The mixture was diluted with toluene, washed with brine and dried over anhydrous Na₂SO₄. Concentration and crystallization from dichloromethane with *n*-hexane afforded **6** (2.82 g, 72%) as white crystals; mp 119–122°C. IR (CHCl₃): 3402, 1755, 1720 (shoulder), 1646, 1494, 1452, 1404, 1370 cm⁻¹. ¹H-NMR (200MHz, CDCl₃): [3 : 1 mixture of keto and enol tautomers] δ 1.17 (3H for the both, d, J = 7.2Hz), 1.25 (3H for the both, d, J = 6.2Hz), 2.32 (1H for the enol, broad doublet, J = 4 Hz), 2.42 (1H for the enol, quintet, J = 7Hz), 2.73 (1H for the keto, broad doublet, J = 3.2Hz), 2.81 (1H for the keto, dd, J = 2.0Hz, 7Hz), 2.86 (1H for the keto, quintet, J = 7.0Hz), 3.00 (1H for the enol, dd, J = 2.7Hz, 5.3Hz), 3.60 and 3.68 (2H for the keto, ABq, J = 15.8Hz), 3.76 (1H for the keto, dd, J = 2.0Hz, 6.8Hz), 3.79 (1H for the enol, dd, J = 2.7Hz, 5–6Hz), 4.0–4.2 (1H for the both, m), 5.22 (1H for the enol, s), 6.23 (1H for the keto, broad singlet), 6.26 (1H for the enol, broad singlet), 6.92 (1H for the both, s), 7.3–7.4 (10H for the both, m), 12.03 (1H for the enol, broad singlet). *Anal.* Calcd for C₂₃H₂₅NO₅: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.60; H, 6.27; N, 3.58. Mass(HR-LSIMS) Calcd for C₂₃H₂₅NO₅Na ([M+Na]⁺): 418.1629; Found: *m/z* 418.1630 ([M+Na]⁺).

(3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-4-[(1*R*)-3-diphenylmethoxycarbonyl-1-methyl-2-oxo-3-phenyliodonio-propyl]-2-azetidinone **5**

Preparation of **5** was described in the previous communication.⁴⁾ A solution of iodosobenzene diacetate (8.40 g, 26.1mmol) in methanol (100 ml) was treated with sodium methoxide in methanol (22.3%, 12.63 g) and **6** (10.0 g, 25.3 mmol) was added to the mixture. The reaction mixture was stirred at ca. 20°C for an hour. Then water (200ml) was added dropwise to the mixture and the precipitate was collected by filtration. After being dried in vacuo, **5** (13.0 g, 86%) was obtained as white crystals; mp 139–141°C (decomp).¹¹⁾ IR (CHCl₃): 3400, 1752, 1655, 1560, 1545, 1538, 1380, 1370, 1340 cm⁻¹. ¹H-NMR (200MHz, CDCl₃): δ 1.20 (3H, d, J = 6.8Hz), 1.26 (3H, d, J = 6.4Hz), 2.69 (1H, broad doublet, J = 8.8Hz), 3.77 (1H, dd, J = 1.8Hz, 8.3Hz), 3.65–3.85 (1H, broad singlet), 3.88–4.14 (2H, m), 6.05 (1H, broad singlet), 6.86 (1H, s), 7.2–7.4 (12H, m), 7.53 (1H, t, J = 8.2Hz), 7.66 (2H, d, J = 8.2Hz). *Anal.* Calcd for C₂₉H₂₈INO₅: C, 58.30; H, 4.72; N, 2.34. Found: C, 58.36; H, 4.80; N, 2.52. Mass(HR-LSIMS) Calcd for C₂₉H₂₉INO₅ ([M+H]⁺): 598.1090, Found: *m/z* 598.1095 ([M+H]⁺).

Diphenylmethyl (2*R*,4*R*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]heptan-2-carboxylate **4**(= **4a**)

Rh(II)-catalyzed cyclization. Rhodium(II) acetate dimer (1.5 mg, 0.0034 mmol) was added to a suspension of **5** (200 mg, 0.335 mmol) in dichloromethane (6 ml), which was stirred at room temperature for 20 minutes. Concentration and column chromatography on silica gel (eluent: toluene-ethyl acetate-acetic acid, 250 : 250 : 1) yielded **4** (113 mg, 86%) as a colorless froth. IR (CHCl₃): 3600, 3500 (broad), 1765, 1750 (shoulder), 1495, 1455, 1380, 1360 cm⁻¹. ¹H-NMR (200MHz, CDCl₃): δ 1.21 (3H, d, J = 7.8Hz), 1.38 (3H, d, J = 6.2Hz), 2.78 (1H, quintet, J = 7.6Hz), 3.25 (1H, dd, J = 1.9Hz, 7.1Hz), 4.22 (1H, dd, J = 2.3Hz, 7.9Hz), 4.30 (1H, quintet, J = 6.6Hz), 4.77 (1H, s), 6.87 (1H, s), 7.3–7.4 (10H, m). *Anal.* Calcd for C₂₃H₂₃NO₅·0.3H₂O: C, 69.26; H, 5.96; N, 3.51. Found: C, 69.28; H, 5.88; N, 3.54.

Acid-catalyzed cyclization. *p*-Toluenesulfonic acid monohydrate (3 mg, 0.016 mmol) was added to a suspension of **5** (200 mg, 0.335 mmol) in ethanol (2 ml), which was stirred at room temperature for 16 minutes. Concentration and column chromatography on silica gel (eluent: toluene-ethyl acetate-acetic acid, 250 : 250 : 1) yielded **4** (124 mg, 94%) as a colorless froth. Other acid-catalyzed cyclizations (MsOH, H₂SO₄, HClO₄, and BF₃·Et₂O) were similarly carried out under the reaction conditions shown in Table 3.

Diphenylmethyl (2S,4R,5R,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]heptan-2-carboxylate 4b

Methanesulfonic acid (5 μl, 0.077 mmol) was added to a cooled (–20°C) suspension of **5** (500 mg, 0.838 mmol) in dichloromethane (5 ml), which was stirred at –20––15°C for an hour. Removal of the solvent *in vacuo* at –20°C and crystallization from ether yielded **4b** (168 mg, 51%) as white crystals; mp 110–120°C (decomp). IR (CHCl₃): 1764, 1740 (shoulder), 1453, 1353, 1325 cm⁻¹. ¹H-NMR (300MHz, CDCl₃): δ 1.19 (3H, d, J = 7.8Hz), 1.32 (3H, d, J = 6.3Hz), 2.73 (1H, quintet, J = 7.7Hz), 3.35 (1H, dd, J = 2.4Hz, 5.4Hz), 4.07 (1H, dd, J = 2.4Hz, 7.5Hz), 4.21 (1H, s), 4.28 (1H, quintet, J = 6.1Hz), 6.87 (1H, s), 7.3–7.4 (10H, m). *Anal.* Calcd for C₂₃H₂₃NO₅·0.3H₂O: C, 69.26; H, 5.96; N, 3.51. Found: C, 69.21; H, 6.04; N, 3.59. Mass(HR-LSIMS) Calcd for C₂₃H₂₃NO₅Na ([M+Na]⁺): 416.1473, Found: *m/z* 416.1474 ([M+Na]⁺).

(3S,4R)-3-[(1R)-1-Hydroxyethyl]-4-[(1R)-3-chloro-3-diphenylmethoxycarbonyl-1-methyl-2-oxopropyl]-2-azetidinone 13

A suspension of **5** (200 mg, 0.335 mmol) in ethanol (2 ml) was treated with 12 N hydrochloric acid (31 μg, 0.372 mmol) at room temperature and stirred for 10 minutes. The mixture was diluted with ethyl acetate and washed with dilute NaHCO₃ solution and brine. Drying over anhydrous Na₂SO₄ and concentration, followed by column chromatography on silica gel (eluent: toluene-ethyl acetate-acetic acid, 250 : 250 : 1) yielded **13** (123 mg, 85%) as a colorless froth. IR (CHCl₃): 3402, 1757, 1636, 1598, 1453, 1368 cm⁻¹. ¹H-NMR (300MHz, CDCl₃): [2 : 1 mixture of keto (1 : 1 mixture of diastereomers) and enol tautomers] δ 1.09 (3H x 1/3, d, J = 6.9Hz), 1.19–1.24 (3H x 3/3 + 3H x 2/3, multiplet which consists of 5 doublets), 2.84 (1H x 1/3, dd, J = 2.2Hz, 6.6Hz), 2.91 (1H x 1/3, dd, J = 2.2Hz, 6.6Hz), 3.04 (1H x 1/3, dd, J = 2.2Hz, 5.1Hz), 3.18 (1H x 1/3, quintet, J = 6.6Hz), 3.25 (1H x 1/3, quintet, J = 6.6Hz), 3.36 (1H x 1/3, quintet, J = 6.3Hz), 3.78 (1H x 2/3, dd, J = 2.1Hz, 6.3Hz), 3.85 (1H x 1/3, dd, J = 2.1Hz, 6.6Hz), 4.07 (1H x 1/3, quintet, J = 6.3Hz), 4.08 (1H x 1/3, quintet, J = 6.3Hz), 4.17 (1H x 1/3, quintet, J = 5.7Hz), 5.01 (1H x 1/3, s), 5.06 (1H x 1/3, s), 5.96 (1H x 1/3, broad singlet), 5.98 (1H x 1/3, broad singlet), 6.06 (1H x 1/3, broad singlet),

6.94 (1H x 1/3, s), 6.95 (1H x 2/3, s), 7.25–7.45 (10H x 3/3, m), 12.43 (1H x 1/3, s). Mass(HR-LSIMS) Calcd for C₂₃H₂₄NO₅ClNa ([M+Na]⁺): 452.1240, Found: *m/z* 452.1241 ([M+Na]⁺).

Thermolysis of the idonium ylide 5

A suspension of **5** (200 mg, 0.335 mmol) in ethanol (2 ml) was heated under reflux for 20 minutes. The mixture was cooled to room temperature and evaporated. Purification by column chromatography on silica gel (eluent: toluene-ethyl acetate-acetic acid, 250 : 250 : 1) gave **6** (103 mg, 78%).

Diphenylmethyl (4R,5R,6S)-3-Diphenylphosphoryloxy-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylate 14

Reaction of **5** (12.0 g, 20.1 mmol) with rhodium(II) octanoate dimer (16 mg, 0.021 mmol)¹² was carried out in dichloromethane (120 ml) as described above. The crude oily product was dissolved in acetonitrile (60 ml) and cooled to ice-bath temperature. Diphenylphosphoryl chloride (5.62 g, 20.9 mmol) and diisopropylethylamine (2.70 g, 20.9 mmol) were dropwise added to the solution, which was stirred at the same temperature for an hour. The mixture was diluted with ethyl acetate and washed successively with dilute hydrochloric acid, 5% NaHCO₃ solution and brine. Drying over anhydrous Na₂SO₄ and concentration, followed by crystallization from toluene (30 ml) with *n*-hexane (18 ml) afforded **14** (9.45 g, 75%) as white crystals; mp 99–100°C. IR (CHCl₃): 1776, 1719, 1635, 1590, 1489 cm⁻¹. ¹H-NMR (200MHz, CDCl₃): δ 1.20 (3H, d, J = 7.2Hz), 1.33 (3H, d, J = 6.2Hz), 3.29 (1H, dd, J = 2.8Hz, 6.7Hz), 3.52 (1H, m), 4.17 (1H, dd, J = 2.8Hz, 10 Hz), 4.23 (1H, m), 7.00 (1H, s), 7.1–7.5 (20H, m). Anal. Calcd for C₃₅H₃₂NO₈P: C, 67.20; H, 5.16; N, 2.24. Found: C, 67.18; H, 5.28; N, 2.34. Mass(HR-LSIMS) Calcd for C₃₅H₃₂NO₈PNa ([M+Na]⁺): 648.1762, Found: *m/z* 648.1765 ([M+Na]⁺).

One-pot procedure. A suspension of **5** (1.00 g, 1.68 mmol) in acetonitrile (10 ml) was treated with 18 M sulfuric acid (4 μ l, 0.072 mmol) and stirred at room temperature for 16 min. To the ice-cooled reaction mixture were dropwise added diphenylphosphoryl chloride (0.36 ml, 1.74 mmol) and diisopropylethylamine (0.33 ml, 1.89 mmol). After being stirred at ice-bath temperature for an hour, the mixture was diluted with ethyl acetate and washed successively with water, dilute hydrochloric acid, 5% NaHCO₃ solution and brine. Drying over anhydrous Na₂SO₄ and concentration, followed by crystallization from toluene (2.5 ml) with *n*-hexane (1.5 ml) afforded **14** (729 mg, 70%) as white crystals.

REFERENCES AND NOTES

- (a) Uyeo, S.; Itani, H. *Tetrahedron Lett.* **1991**, *32*, 2143–2144; (b) Haruta, J.; Nishi, K.; Kikuchi, K.; Matsuda, S.; Tamura, Y.; Kita, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2338–2343; (c) Prasad, J.S.; Liebeskind, L.S. *Tetrahedron Lett.* **1987**, *28*, 1857–1860; (d) Choi, W.-B.; Churchill, H.R.O.; Lynch, J.E.; Thompson, A.S.; Humphrey, G.R.; Volante, R.P.; Reider, P.J.; Shinkai, I. *ibid.* **1994**, *35*, 2275–2278; (e) Kang, S.H.; Lee, H.S. *ibid.* **1995**, *36*, 6713–6716.
- (a) Ratcliffe, R.W.; Salzmann, T.N.; Christensen, B.G. *Tetrahedron Lett.* **1980**, *21*, 31–34; (b) Yoshida, A.; Tajima, Y.; Takeda, N.; Oida, S. *ibid.* **1984**, *25*, 2793–2796; (c) Feigelson, G.B. *ibid.* **1993**, *34*, 4747–4750; (d) Sakurai, O.; Ogiku, T.; Takahashi, M.; Horikawa, H.; Iwasaki, T.

- ibid.* **1994**, *35*, 2187–2190; (e) Sakurai, O.; Takahashi, M.; Ogiku, T.; Hayashi, M.; Horikawa, H.; Iwasaki, T. *ibid.* **1994**, *35*, 6317–6320; (f) Sunagawa, M.; Sasaki, A.; Matsumura, H.; Goda, K.; Tamoto, K. *Chem. Pharm. Bull.* **1994**, *42*, 1381–1387.
3. (a) Iso, Y.; Irie, T.; Nishino, Y.; Motokawa, K.; Nishitani, Y. *J. Antibiotics* **1996**, *49*, 199–209; (b) Iso, Y.; Irie, T.; Iwaki, T.; Kii, M.; Sendo, Y.; Motokawa, K.; Nishitani, Y. *ibid.* **1996**, *49*, 478–484
 4. Kume, M.; Kubota, T.; Iso, Y. *Tetrahedron Lett.*, **1995**, *36*, 8043–8046.
 5. Shih, D.H.; Baker, F.; Cama, L.; Christensen, B.G. *Heterocycles* **1984**, *21*, 29–40.
 6. Brooks, D.W.; Lu, L.D.; Masamune, S. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 72–74
 7. Benzhydryl bromoacetate was prepared from bromoacetyl bromide and diphenylmethanol in the presence of pyridine in dichloromethane and was used without any purification.
 8. (a) Moriarty, R. M.; Prakash, O.; Vaid, R. K.; Zhao, L. *J. Am. Chem. Soc.* **1989**, *111*, 6443–6444; (b) Gallos, J. K.; Koftis, T. V.; Koumbis, A. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 611–612.
 9. (a) Neiland, O. *Zh. Organ. Khim.* **1965**, *1*, 1858–1862; (b) Neiland, O.; Karele, B. *ibid.* **1966**, *2*, 488–492; (c) Neiman, D.É.; Neiland, O. *ibid.* **1970**, *6*, 633–634.
 10. Fliri, H.; Mak, C-P. *J. Org. Chem.* **1985**, *50*, 3438–3442.
 11. The melting point of **5** was corrected from the value (109~111°C) reported in the previous communication⁴) to the present value (139~141°C).
 12. Rhodium(II) octanoate dimer is more efficient than rhodium(II) acetate dimer due to the solubility in dichloromethane.

(Received in Japan 28 October 1996; accepted 21 November 1996)