From Penicillin to Penem and Carbapenem. IX. C_1-Unit Introduction and the Carbapenam Synthesis from the Penicillin Molecule[1)]

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(Received December 18, 1985)

An effective method for (*R*)-1-hydroxyethylation of benzyl bis(phenylseleno)penicillanate is described. The hydroxyethylated product was transformed into the 4-methylsulfonyl- and 4-phenylsulfonyl-2-azetidinone derivatives. These monocyclic compounds were reacted with potassium cyanide under two-phase conditions to give the 4-cyano-2-azetidinone derivative (C_1-unit introduction) in high yield. The cyano group was then converted into the iodomethyl group. Using the 4-iodomethyl-2-azetidinone derivative an isopenam derivative was synthesized. Furthermore, carbapenam derivative were also constructed by a novel [3+2] cyclization reaction between 4-iodomethyl-2-azetidinone and dimethyl 2-methylthio- and 2-phenylthiofumarate.

Since the discovery of thienamycin (**1**),[2)] a potent new broad spectrum antibiotic from Streptomyces cattleya, intense studies on the synthesis and structure-activity relationship of this and related compounds have revealed that the high antibiotic activity and stability against β-lactamase are linked to the combination of the *R* configuration of the 1-hydroxyethyl substituent and the trans configuration on the β-lactam ring.[3)]

There have been several reported syntheses starting from various materials; for example, 3-oxopentadioate, acetoxybutadiene, 2,2-dimethoxypropiononitrile oxide, L-aspartic acid, D-glucose, 6-bromo-3-oxobicyclo[2.2.1]heptan-7-carboxylate etc.[4)] We planned to utilize the β-lactam ring in the penicillin molecule for the synthesis of the carbapenem derivatives; in this case, however, there seemed to be three problems to be solved. The first one is how to introduce the (*R*)-1-hydroxyethyl substituent at the 6-position in the penicillin molecule, the second is concerned with introduction of a carbon substituent at the C-4 position of the 2-azetidinone ring, and the last is associated with the construction of the carbapenem skeleton. In this report we describe our approach for solving these three problems.

Concerning the first problem, we have already reported a method using methyl dibromopenicillanate[5)] as a starting material. However, our continuing interest in developing new methods prompted us to develop another route for the introduction of the (*R*)-1-hydroxyethyl substituent utilizing benzyl 6,6-bis(phenylseleno)penicillanate **3a**.

The starting materials **3a**, **4a**, and **5a** were prepared from the known diazo compound **2**[6)] by the reported method as shown in Scheme 1.

The phenylthio analogues **3b** (mp 100—103 °C), and **5b** (mp 84—86 °C) were prepared analogously, but **4b** could not be obtained by tributylstannane reduction of **3b**.

The compounds **3**—**5** were treated with methylmagnesium bromide or butyllithium in tetrahydrofuran (THF) to generate the enolates, which were reacted with acetaldehyde to yield the desired 6-hydroxyethylated products (**6**, **7**, and **8**).

As shown in Table 1, the diphenylthio derivative **3b** (Entries 1 and 2) gave no hydroxyethylated products. This is due to the well-known phenomena that

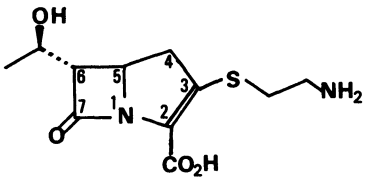

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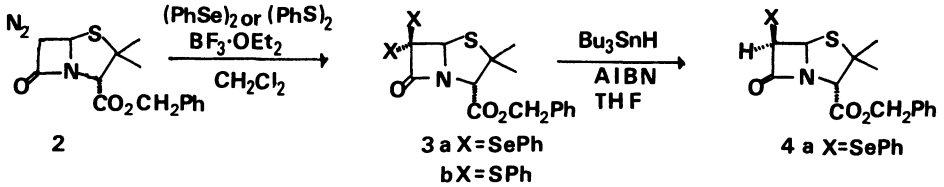
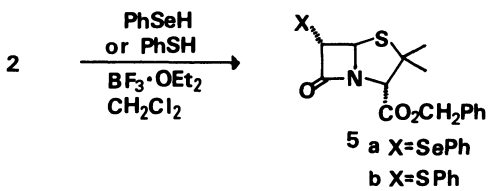
Fig. 1.



2 **3a** X=SePh, **b** X=SPh **4a** X=SePh

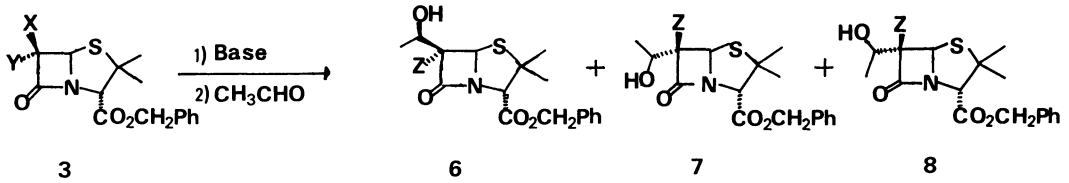


5 **a** X=SePh, **b** X=SPh

Scheme 1.

Table 1. The Results of the Introduction of the 1-Hydroxyethyl Group

Entry	X	Y	Z	Base	Yield/%	**6**:**7**:**8**	s.m./%
1	PhS	PhS	—	MeMgBr	—	—	100
2	PhS	PhS	—	BuLi	—	—	100
3	PhSe	H	—	MeMgBr	—	—	—
4	H	PhSe	PhSe	BuLi	48	1 : 2 : 1	—
5	H	PhSe	PhSe	MeMgBr	5	1 : 0 : 0	70
6	PhSe	PhSe	PhSe	BuLi	56	2 : 3 : 2	—
7	PhSe	PhSe	PhSe	MeMgBr	78	30 : 1 : 0	
8	H	PhS	PhS	BuLi	38	0 : 1 : 0	—



3 **6** **7** **8**

Scheme 2.

the selenoacetal generates a carbanion by releasing one of the seleno-parts on base treatment (i.e. pseudo halide), but this is not the case for the thioacetal. It is noteworthy that the α-phenylseleno (**5a**, Entries 4 and 5) and α-phenylthio (**5b**, Entry 8) derivatives gave the desired products, but the β-phenylseleno (**4a**, Entry 3) derivative gave only the diphenyldiselenide (about 50%). The diphenylseleno derivative (**3a**, Entries 6 and 7) gave **6**, **7**, and **8** in the ratio of 2:3:2 using butyllithium as base, and when methylmagnesium bromide was used as base **3a** gave **6** highly selectively in the ratio of **6**:**7**:**8**=30:1:0 in 78% isolated yield.

The structure of these products was determined by ^{1}H NMR and degradation study. As shown in Table 2, the two methyl groups of the compounds with β-phenylseleno group appeared at 1.70—1.78 and 1.31—1.45, and those of the compounds with an α-phenylseleno group appeared at 1.55—1.57 and 1.28—1.33. In the case of **6** and **7** these methyl group appeared at 1.55 and 1.28, and 1.78 and 1.45, respectively. These data strongly suggested that the product **6** has an α-phenylseleno group at C-6, and the product **7** has a β-phenylseleno group. Furthurmore the structures were confirmed by the chemical degradation study.

The high stereoselectivity observed in Entry 6 (Table 1) can be explained as follows: The magnesium enolate is less reactive than lithium enolate, therefore the transition state is rather product like and the bulkiness of the phenylseleno group affected the course of the approach of acetaldehyde to attack preferentially from the β-side of the molecule. In this approach the steric repulsion between the thiazolidine group and the methyl group in acetaldehyde forced the direction of aldehyde approach as shown in Fig. 2, therefore the β-(*R*)-1-hydroxyethylated product was obtained in a high selectivity.

Recently, Ishiguro and Nakatsuka calculated the energy of the enolate configuration by means of MNDO, and they announced that the most stable

Table 2. The Chemical Shifts of Methyl Groups

Compound	Me^1	Me^2
4a	1.40	1.70
5a	1.33	1.57
3a	1.31	1.70
6	1.28	1.55
7, **8**	1.45	1.78

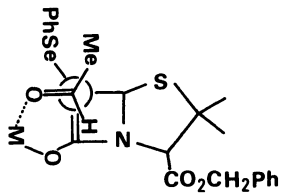
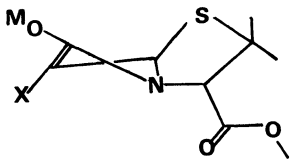


Fig. 2.

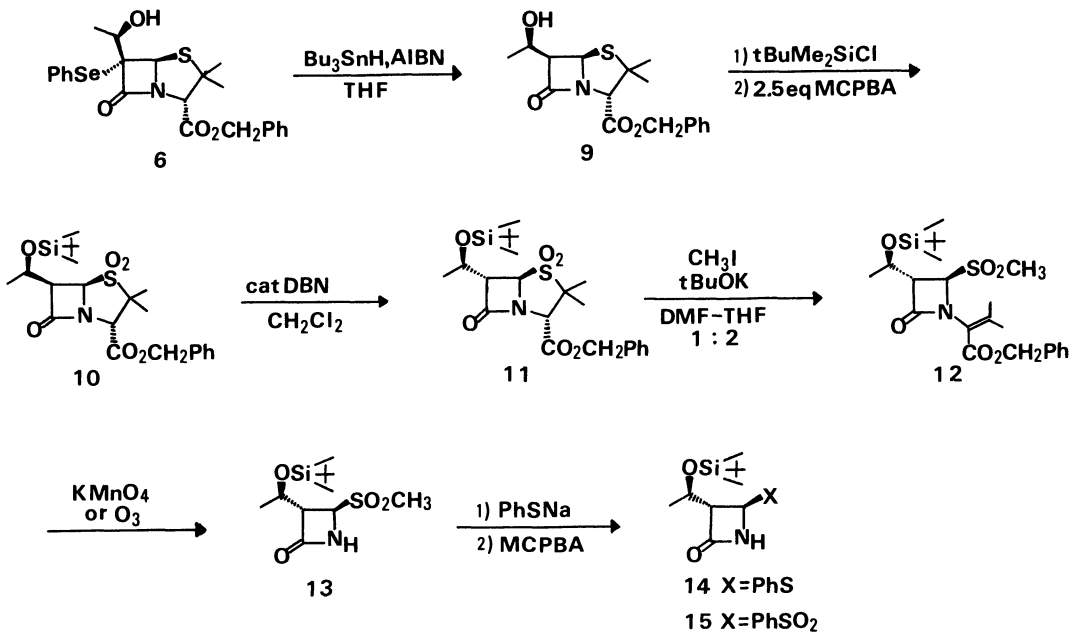


A

Fig. 3.

conformer is that as shown in Fig. 3.[7] In this conformer the upper face (β-face) is less sterically hindered than the α-face, so the metal coordination occurs on the β-face, and acetaldehyde has more chance to come from the β-face of the conformer.

With the desired product **6** in hand, we next turned our attention to conversion of **6** to 3,4-*trans*-disubstituted 2-azetidinone derivative. By tin hydride reduction, the phenylseleno group was removed to give 6β-(*R*)-1-hydroxyethylated product **9** in 95% isolated yield.[8] The coupling constant between the protons on the β-lactam ring is 4.4 Hz (cis) and the structure was confirmed as **11a** by comparison with an authentic



Scheme 3.

sample prepared from the known benzyl 6α-bromo-6β-(*R*)-1-hydroxyethylpenicillanate[9] by tin hydride reduction. After the protection of the hydroxyl group in 6, the product was oxidized with 2.5 equiv of *m*-chloroperbenzoic acid to afford the cis sulfone derivative **10** (mp 118°C).

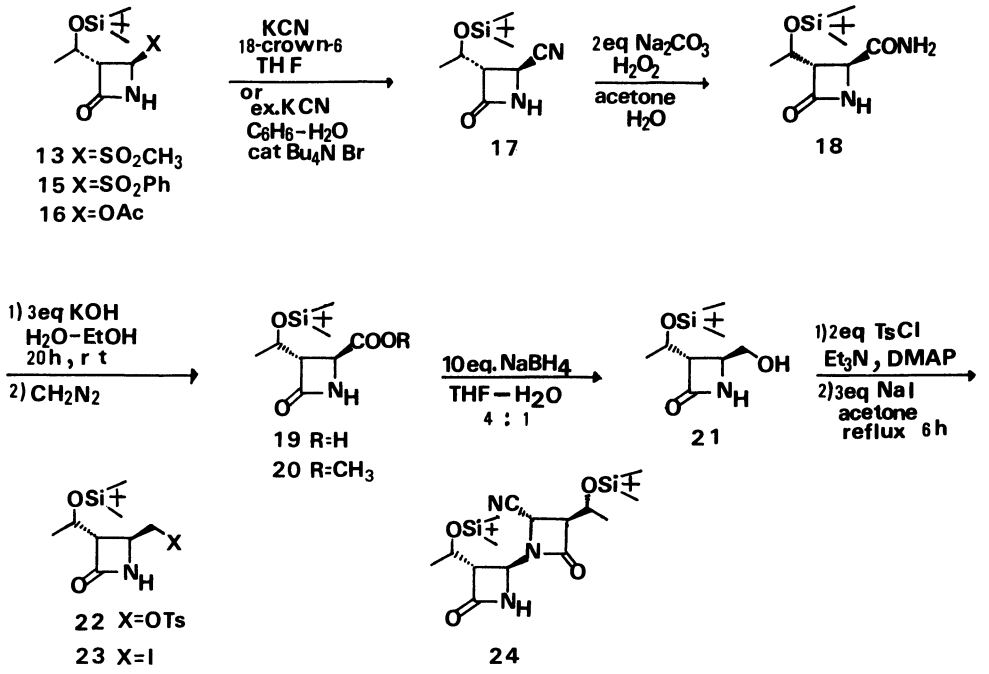
The crucial step for the isomerization of *cis*-**10** to *trans*-**11** was satisfactorily achieved by adding a catalytic amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to a solution of **10** in dichloromethane at 20—25°C. The isomerization occurred within 30 min to afford the trans product **11**.

The ring opening of the trans sulfone **11** was smoothly achieved by excess methyl iodide and potassium *t*-butoxide (2.5 equiv) in THF: DMF (1:2) to yield the monocyclic β-lactam **12**. In this ring opening reaction sodium hydride was not effective. The *N*-substituent in **12** was oxidatively removed by potassium permanganate or ozonolysis to give the desired monocyclic β-lactam **13**, mp 100°C, $[\alpha]_D^{22}$ −12.8° (*c* 1, $CHCl_3$). The sequence of the reaction in Scheme 3 was successfully applicable to benzyl 6α-bromo-6β-(1-hydroxyethyl)penicillanate to afford the same monocyclic β-lactam **13**. The methylsulfonyl group in **13** was transformed into phenylthio group in **14**, which was oxidized to the phenyl sulfone derivative **15** by the reported procedure.[10]

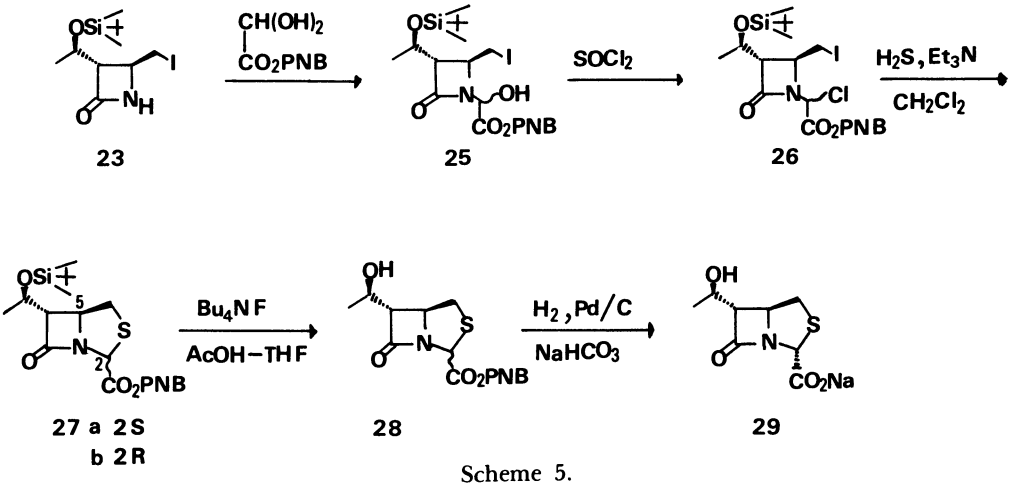
The next step to be solved was the carbon unit introduction at the C-4 position of the 2-azetidinone ring. To the best of our knowledge no method has been reported for the cyano group substitution at the C-4 position of 4-acetoxy-2-azetidinone.[11] In the case of our β-lactams **13**, **15**, and **16** which have a 1-hydroxyethyl substituent at the C-3 position we found that the cyano group was introduced in high yield at the desired position. Thus, the 2-azetidinone **15** or **16** was treated with an excess of potassium cyanide in THF in the presence of 18-crown-6 (0.1 equiv) or more conveniently with potassium cyanide under two-phase conditions (benzene–water, catalytic amount of tetrabutylammonium bromide) for 18 h to give the crystalline cyano derivative **17** in 68% isolated yield.

The dimeric product **24** was obtained in 10% yield as a by-product, but when the methylsulfonyl derivative **13** was used instead of **15** or **16** the formation of the dimeric product **24** was supressed to less than 10% of the monomer **17**. Manipulation of the cyano group in **17** was carried out as follows. Alkaline hydrolysis of **17** in the presence of hydrogen peroxide gave the amide derivative **18** in 85% isolated yield, which was further hydrolyzed to the acid **19**. Esterification with diazomethane gave the ester derivative **20**; $[\alpha]_D^{20}$ −12.8 (*c* 1.01, $CHCl_3$), which was then converted to the alcohol **21**. This was tosylated to the tosyl derivative **22**. The Finkelstein substitution reaction (NaI in acetone) of **22** was successfully performed to afford the 4-(iodomethyl)-2-azetidinone derivative **23** in 95% yield.

Compound **23** has been previously converted to thienamycin (**1**),[12] and was thought to be a useful precursor for the synthesis of isopenam derivative **29**. The aminal **25**, prepared via reaction of **23** with *p*-nitrobenzyl glyoxylate refluxing benzene, was chlorinated (thionyl chloride, 2,6-lutidine/THF) to give **26**, which was then transformed into isopenam derivative **27a** and **27b** (5:3) with hydrogen sulfide and triethylamine in dichloromethane. These structures were deduced from ^1H NMR spectra. The NMR spectra of 4,5-fused β-lactam system (i.e. penicillin) normally show the C-2 proton in the "natural" series



Scheme 4.

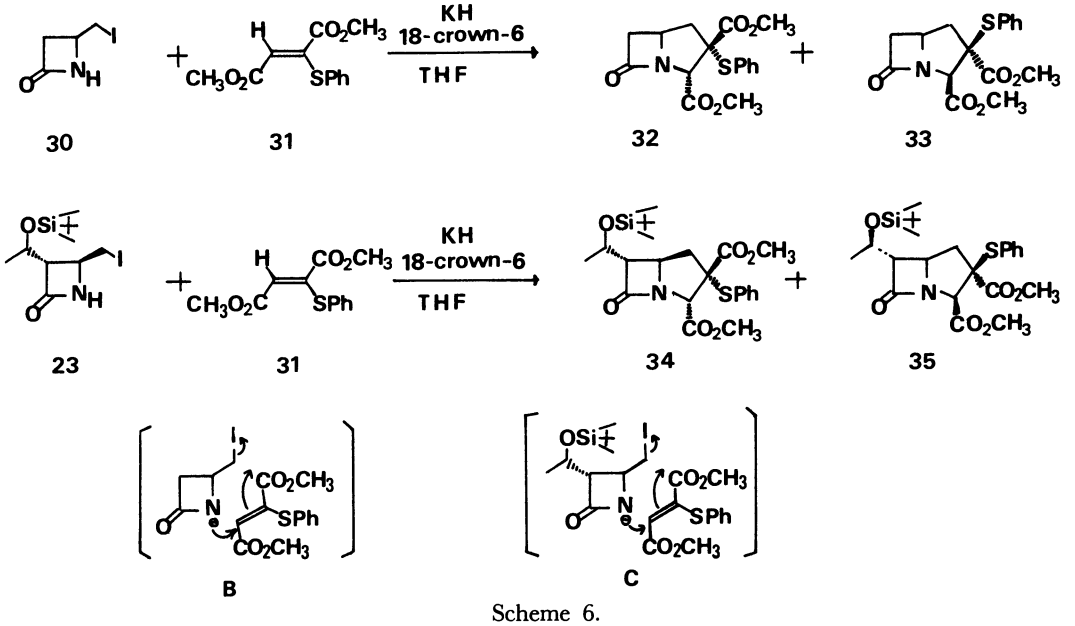


Scheme 5.

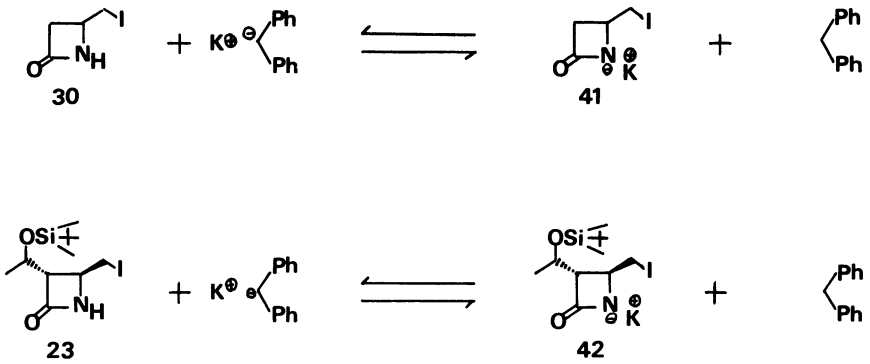
(2,5-trans) at a 0.5—1 ppm lower field than that of the corresponding "unnatural" series (2,5-cis).[13] In our case **27a** and **27b** showed the C-2 protons at δ 4.82 and 5.49 respectively. Therefore **27b** was the "natural" form (2,5-trans). Under the deprotection conditions (tetrabutylammonium fluoride, acetic acid–THF) both **27a** and **27b** gave the same alcoholic derivative **28**. In the presence of one equivalent of aqueous sodium hydrogencarbonate **28** was subjected to hydrogenolysis to give the sodium salt **29**, which has no remarkable antibacterial activity, MIC: Staphylococcus aureus 56, 200 $\mu g\,ml^{-1}$.

The following two methods are representative for constructing the carbapenem (or carbapenam): The first one is the internal Wittig type of reaction between C-2 and C-3 originally developed by Woodward in the field of penem synthesis, and the second one is the Merck method of the carbene insertion reaction between C-2 and N1-H to build up the 3-oxocarbapenam molecule. Beside these, several other methods have been reported, one of which is the aldol type reaction between C-2 and C-3, or C-3 and C-4 under basic conditions. We have already succeeded in the synthesis of Δ^3-carbapenem by aldol condensation between C-3 and C-4 using a dialdehyde intermediate.[14] Our continuing interest in constructing the carbapenam molecule by ring closure between C-3 and C-4 prompted us to develop another method for the synthesis of this unique carbapenam molecule.

Our 4-iodomethyl-2-azetidinone (**23**) has the nucleophilic center and at the same time the electrophilic center in itself. The nitrogen anion of **23** is sufficiently active to attack the α,β-unsaturated carbonyl compound (the Michael reaction) and the resulting



Scheme 6.



Scheme 7.

enolate has a chance to capture the electrophilic center (e.g. iodomethyl part) to give the cyclic compound.

On the basis of these hypotheses we investigated the reaction of 4-iodomethyl-2-azetidinone (**30**) with dimethyl 2-(phenylthio)fumarate (**31**) under basic conditions. The nitrogen anion **41** was generated by treatment of **30** with potassium hydride and 18-crown-6 in THF and reacted with **31** for 3 h at −78—0°C. After the usual work-up the products were purified by careful TLC method to give **32** and **33** (1:1) in 27% isolated yield.

Likewise, the compound **23** gave the corresponding cyclized products (**34** and **35**) under the same conditions in 15% isolated yield.

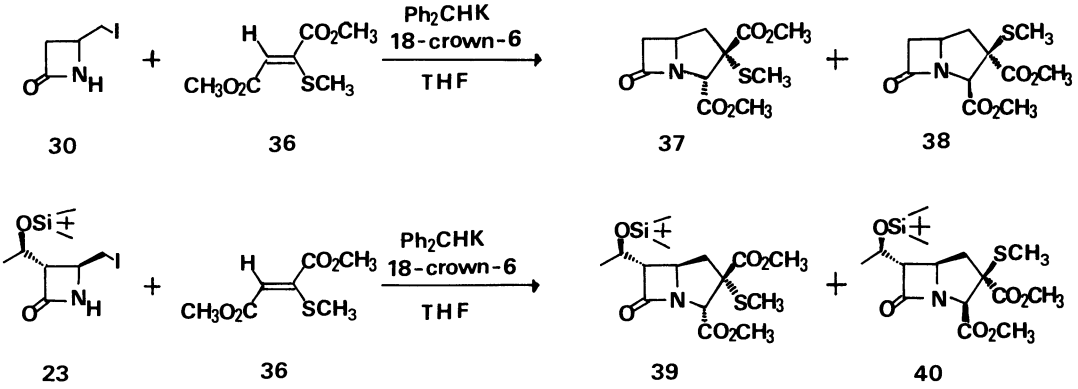
As compounds **32**, **33**, **34**, and **35** have both phenylthio substituent and methoxycarbonyl group at C-3 position, we attempted an oxidative decarboxylation, but the desired 3-oxopenam derivative was not obtained on *N*-chlorosaccinimide (NCS) treatment of the corresponding sodium salt. Therefore we changed the phenylthio group to methylthio group.

The reaction of 2-(methylthio)fumarate (**36**) with **30** and **23** did not give the expected cyclized products. Therefore, we checked the base effect on our cyclization and found that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), potassium fluoride, triphenylmethylpotassium, and lithium diisopropylamide faild to give the desired compound, but gave the polymeric or intractable products. We thought that these undesirable side reactions occured because of the high concentration of the nitrogen anions. In other to suppress these side reactions the nitrogen anion **41** and **42** should be kept in low concentration. Therefore we took advantage of the generation of these anions under the equilibrium conditions using diphenylmethanide (pK_a=33).

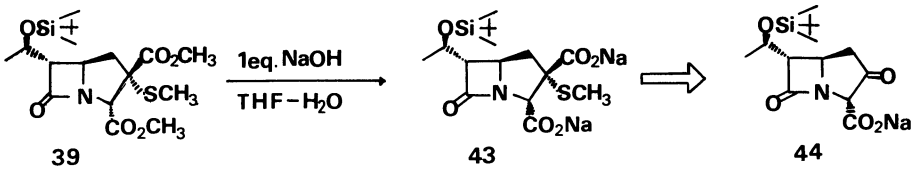
Diphenylmethylpotassium was prepared by the reaction of diphenylmethane with potassium hydride and 18-crown-6 in THF at room temperature. The 2-azetidinone **23** was added to the above solution and the mixture was stirred for 2 h at −40°C to generate the nitrogen anion **42**. Dimethyl 2-(methylthio)fumarate was added to react with **42** for 2 h at −40—−20°C to give **39** and **40** (2:1) in 18% yield.

Under the same conditions compound **30** gave the carbapenams **37** and **38** in 9% yield.

The purified compound **39** was carefully hydrolyzed



Scheme 8.



Scheme 9.

with aqueous sodium hydroxide to give the disodium salt **43**.

The structure of **32**, **33**, **34**, **35**, **37**, **38**, **39**, and **40** were determined by the same considerations as described for isopenam derivatives.

We are now investigating conversion of **43** to the 3-oxocarbapenam derivative (**44**) via Trost's oxidative decarboxylation method.[15] Compound **44** is an important intermediate for the synthesis of thienamycin and related carbapenem antibiotics.

Experimental

General. All melting points are uncorrected. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on JASCO A102 and JEOL A320 Infrared spectrometers. NMR spectra were taken using a Varian EM 360L spectrometer (60 MHz) and the chemical shifts are expressed in ppm units using TMS as internal standard: s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; t, triplet; q, quartet; dq, doublet of quartet; m, multiplet; br, broad. Mass spectra (MS) were measured on JEOL JMS 01SG and JMS D300 mass spectrometers. (Preparative) TLC was carried out on Merck TLC-plates silica-gel F_{254} Pre-coated, layer thickness: (2 mm) 0.25 mm and spots were made visible by ultraviolet irradiation.

Benzyl (2*S*,5*R*,6*S*)-3,3-Dimethyl-7-oxo-6-phenylseleno-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate [(2*S*,5*R*,6*S*)-6-(Phenylseleno)penicillanate] (5a), Benzyl (2*S*,5*R*,6*S*)-6-(Phenylthio)penicillanate (5b), and Benzyl (2*S*,5*R*)-6,6-Bis(phenylseleno)penicillanate (3a): These materials were synthesized according to the method of Giddrings et al.[16]

5a: ^{1}H NMR ($CDCl_3$) δ=1.32 (3H, s), 1.57 (3H, s), 4.45 (1H, s), 4.46 (1H, d, J=2 Hz), 5.08 (2H, s), 5.17 (1H, d, J=2 Hz), 7.0—7.8 (10H, m).

5b: ^{1}H NMR ($CDCl_3$) δ=1.36 (3H, s), 1.59 (3H, s), 4.43 (1H, d, J=2 Hz), 4.50 (1H, s), 5.10 (2H, s), 5.19 (1H, d, J=2 Hz), 7.0—8.2 (10H, m).

3a: Mp 104—105 °C (recrystallized from ethanol); ^{1}H NMR ($CDCl_3$) δ=1.30 (3H, s), 1.70 (3H, s), 4.36 (1H, s), 4.90 (1H, AB type, J=12.6 Hz), 5.00 (1H, AB type, J=12.6 Hz), 5.33 (1H, s), 7.0—8.1 (15H, m).

Benzyl (2*S*,5*R*)-6,6-Bis(phenylthio)penicillanate (3b): To a mixture of benzyl 6-diazopenicillanate and diphenyldiselenide in dichloromethane was added a catalytic amount of boron trifluoride etherate. The solvent was removed under reduced pressure to give **3b**: Mp 99—103 °C (recrystallized from acetone-hexane); ^{1}H NMR ($CDCl_3$) δ=1.35 (3H, s), 1.70 (3H, s), 4.41 (1H, s), 5.04 (2H, s), 5.46 (1H, s), 7.15—7.80 (15H, m).

Found: C, 63.97; H, 4.93; N, 2.55%. Calcd for $C_{27}H_{25}NO_3S_3$: C, 63.82; H, 4.96; N, 2.76%.

Benzyl (2*S*,5*R*,6*R*)-6-(Phenylseleno)penicillanate (4a): To a solution of 317 mg (0.527 mmol) of benzyl 6,6-bis-(phenylseleno)penicillanate (**3a**) in 10 ml of THF was added 367 mg of tributylstannane and a catalytic amount of AIBN. The solution was refluxed for 2 h and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (benzene-ethyl acetate, 10:1 v/v) to give 153 mg (65%) of **4a**: ^{1}H NMR ($CDCl_3$) δ=1.40 (3H, s), 1.70 (3H, s), 4.52 (1H, s), 4.76 (1H, d, J=4 Hz), 5.15 (2H, s), 5.54 (1H, d, J=4 Hz), 6.9—7.9 (10H, m).

Benzyl (2*S* 5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-6-(phenylselenopenicillanate (6): To a solution of 6.0 g of methyl 6,6-bis-(phenylseleno)penicillanate (**5a**) in 60 ml of THF was added 15 ml of methylmagnesium bromide in THF (1 mol dm^{-3}, Tokyo Kasei), keeping the reaction temperature below −50 °C. After stirring for 80 min at −78 °C, 4 ml of acetaldehyde was added and the whole mixture was stirred for 40 min. The reaction was quenched at −78 °C with 60 ml of a saturated aqueous ammonium chloride. The Dry-Ice acetone bath was removed, and the mixture was stirred to become two phase at ambient temperature. The organic phase was separated and the aqueous phase was extracted with ethyl acetate three times. The combined extracts were washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. After removal of the solvent

under reduced pressure the crude product was purified by dry column chromatography (benzene–ethyl acetate, 5:1 v/v) to give 3.68 g of **6** (74%): R:S=30:1.

Benzyl (2*S*,5*R*,6*R*)-6-[(*S*)-1-Hydroxyethyl]-6-(phenylseleno)-penicillanate (7): R_f=0.5 (benzene–ethyl acetate, 10:1 v/v); mp 195 °C; ^{1}H NMR ($CDCl_3$) δ=1.28 (3H, d, J=6.4 Hz), 1.45 (3H, s), 1.78 (3H, s), 1.8—2.5 (1H, m), 3.5—4.1 (1H, m), 4.53 (1H, s), 5.17 (2H, s), 5.47 (1H, s), 7.0—8.0 (10H, s).

Found: C, 56.25; H, 5.15; N, 2.77; S, 6.53%. Calcd for $C_{23}H_{25}NO_4SSe$: C, 56.32; H, 5.14; N, 2.86; S, 6.53%.

Benzyl (2*S*,5*R*,6*S*)-[(*R*)-1-Hydroxyethyl]-6-(phenylseleno)-penicillanate (6): R_f=0.41 (benzene–ethyl acetate, 10:1 v/v); ^{1}H NMR ($CDCl_3$) δ=1.28 (3H, s), 1.33 (3H, d, J=6.0 Hz), 1.55 (3H, s), 2.89 (1H, br s), 4.30 (1H, s), 4.46 (1H, q, J=6.0 Hz), 4.7—5.3 (2H, m), 5.12 (1H, s), 6.9—7.8 (10H, m).

All other aldol type reactions were performed by the same procedure.

Benzyl (2*S*,5*R*,6*R*)-6-[(*S*)-1-Hydroxyethyl]-6-(phenylthio)-penicillanate (7): Mp 179 °C; IR (nujol) 3475, 1780, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.23 (3H, d, J=6.5 Hz), 1.38 (3H, s), 1.70 (3H, s), 3.7—3.9 (1H, m), 4.49 (1H, s), 5.19 (2H, s), 5.58 (1H, s), 7.2—7.85 (10H, m).

Found: C, 62.14; H, 5.63; N, 3.16; S, 14.57%. Calcd for $C_{23}H_{25}NO_4S_2$: C, 62.28; H, 5.68; N, 3.16; S, 14.46%.

Benzyl (2*R*,5*R*,6*R*)-6-[(*R*)-1-Hydroxyethyl]penicillanate (9): A solution of 3.5 g of **6**, 4.0 g of tributylstannan, and catalytic amount of AIBN in 35 ml of THF was stirred for 2 h at 60 °C. The solvent was removed under reduced pressure and the residue was purified by TLC (benzene–ethyl acetate, 5:1 v/v) to give 2.65 g of **9** (quantitative): R_f=0.2 (benzene–ethyl acetate, 10:1 v/v); ^{1}H NMR ($CDCl_3$) δ=1.22 (3H, d, J=6 Hz), 1.41 (3H, s), 1.66 (3H, s), 2.88 (1H, OH), 3.49 (1H, dd, J=4.4 and 9 Hz), 3.8—4.5 (1H, m), 4.48 (1H, s), 5.20 (2H, s), 5.40 (1H, d, J=4.4 Hz), 7.43 (5H, m).

Benzyl (2*S*,5*R*,6*R*)-6-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-penicillanate 1,1-Dioxide (10): To a stirred solution of 2.65 g of **9** in 20 ml of DMF was added 680 mg of imidazole and 1.5 g of *t*-butylchlorodimethylsilane at room temperature. After 20 h ethyl acetate was added to the mixture, and the solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (benzene–ethyl acetate, 20:1 v/v) to give 1.9 g of the silyl ether.

To a stirred solution of 1.9 g of the silyl ether thus obtained in 25 ml of dichloromethane was added 2.2 g of *m*-chloroperbenzoic acid at room temperature. After 2 h the mixture was diluted with dichloromethane and washed with 5% aqueous potassium hydroxide. The solvent was removed under reduced pressure and the residue crystallized from ether to give **10**: Mp 118 °C (recrystallized from ether); R_f=0.36 (benzene–ethyl acetate, 20:1 v/v); IR (nujol) 1810, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.10 (3H, s), 0.15 (3H, s), 0.91 (9H, s), 1.26 (3H, s), 1.28 (3H, d, J=7 Hz), 1.52 (3H, s), 3.80 (1H, dd, J=5.5 and 10 Hz), 4.46 (1H, s), 4.59 (1H, d, J=5.5 Hz), 4.85 (1H, m), 5.20 (2H, br s), 7.40 (5H, s).

Found: C, 57.29; H, 7.31; N, 2.87; S, 6.60%. Calcd for $C_{23}H_{35}NO_5SSi$: C, 57.35; H, 7.32; N, 2.91; S, 6.60%.

Benzyl (2*S*,5*R*,6*R*)-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-penicillanate 1,1-Dioxide (11): To a stirred solution of 1 g of the cis sulfone derivative **10** in 5 ml of chloroform was added 0.05 ml of DBN. After 1 h the completion of the reaction was checked by ^{1}H NMR. The mixture was washed successively with 1% hydrochloric acid and water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 980 mg of **11**: ^{1}H NMR ($CDCl_3$) δ=0.10 (6H, s), 0.91 (9H, s), 1.26 (3H, d, J=7 Hz), 1.31 (3H, s), 1.55 (3H, s), 3.66 (1H, dd, J=2.0 and 3.8 Hz), 4.2—4.55 (1H, m), 4.39 (1H, s), 4.61 (1H, d, J=2 Hz), 5.22 (2H, s), 7.42 (5H, s).

Benzyl 2-[(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-methylsulfonyl-2-oxo-1-azetidinyl]-3-methyl-2-butenoate (12): To a stirred solution of 100 mg (0.208 mmol) of the trans sulfone **11** in 2 ml of THF–DMF (2:1) was added 0.5 ml of methyl iodide and 70 mg of potasium *t*-butoxide successively. After about 30 min the completion of the reaction was checked by TLC and ethyl acetate was added. The mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by TLC (benzene–ethyl acetate,10:1 v/v) to give 78 mg of **12**: IR (neat): 1780, 1722, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.07 (3H, s), 0.13 (3H, s), 0.92 (9H, s), 1.30 (3H, d, J=7 Hz), 2.06 (3H, s), 2.22 (3H, s), 2.56 (3H, s), 3.55 (1H, dd, J=2.5 and 4 Hz), 4.1—4.6 (1H, m), 5.17 (1H, d, J=2.5 Hz), 4.9—5.5 (2H, m), 7.35 (5H, s).

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-(methylsulfonyl)-2-azetidinone (13): To a stirred solution of 68 mg of the seco derivative **12** and 0.05 ml of acetic acid in 8 ml of acetone was added slowly a solution of 50 mg of potassium permanganate in 5 ml of water. After 16 h the reaction mixture was filtered through Celite, and the solvent was evaporated. The residual solution was extracted with ethyl acetate and the combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by TLC (benzene–ethyl acetate, 1:1 v/v) to give 40 mg (94%) of **13**: Mp 100 °C; $[\alpha]_D^{20}$ −12.8° (*c* 1 $CHCl_3$); IR (nujol): 3350, 1795, 1780, 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.09 (6H, s), 0.88 (9H, s), 1.28 (3H, d, J=6 Hz), 2.94 (3H, s), 3.54 (1H, t, J=2 Hz), 4.1—4.5 (1H, m), 4.70 (1H, d, J=2 Hz), 6.95 (1H, br s).

Found: C, 46.66; H, 8.18; N, 4.33; S, 10.57%. Calcd for $C_{12}H_{25}NO_4SSi$: C, 46.87; H, 8.20; N, 4.56; S, 10.43%.

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-(phenylthio)-2-azetidinone (14): To a stirred solution of 3.38 g (10.99 mmol) of 4-(methylsulfonyl)-2-azetidinone **13** in 40 ml of absolute ethanole was added sodium phenyl sufide in absolute ethanol (prepared from 12.86 mmol of sodium ethoxide in ethanol and 12.05 mmol of thiophenol) at 5 °C. After 2 h, 600 ml of ethyl acetate was added, washed successively with neutral phosphate buffer (pH 6.86) three times and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (benzene–ethyl acetate, 95:5 v/v) to give 3.42 g (95%) of **14**: ^{1}H NMR ($CDCl_3$) δ=0.07 (6H, s), 0.83 (9H, s), 1.22 (3H, d, J=6.0 Hz), 3.08 (1H, dd, J=2.0 and 4.0 Hz), 3.90—4.5 (1H, m), 4.85 (1H, d, J=2.0 Hz), 6.70 (1H, br s), 7.20—7.60 (5H, m).

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-(phenylsulfonyl)-2-azetidinone (15): A solution of 4.12 g (12.2 mmol) of phenylthioazetidinone **14** in 150 ml of ethyl acetate was cooled in an ice bath. Sodium acetate (1.66 g, 12.2 mmol), 0.26 g of manganese(II) acetylacetonate, and 12.4 ml (73.2 mmol) of 40 % peracetic acid was added and the mixture was stirred for 2 h. Ethyl acetate was added and the reaction mixture was washed successively with aqueous sodium hydro-

gensulfite two times, saturated sodium hydrogencarbonate and brine two times and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (benzene–ethyl acetate,95:5 v/v) to give 3.3 g (73%) of **15**: ^{1}H NMR ($CDCl_3$) δ=0.05 (6H, s), 0.83 (9H, s), 1.25 (3H, d, J=6.0 Hz), 3.45 (1H, dd, J=2.0 and 3.5 Hz), 3.90—4.40 (1H, m), 4.56 (1H, d, J=2.0 Hz), 6.85 (1H, br s), 7.6—8.1 (5H, m).

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-cyano-2-azetidinone (17): i) To a solution of 57 mg of methyl sulfone **13** in 2 ml of benzene was added a solution of 57 mg of potassium cyanide in 2 ml of water and a catalytic amount of tetrabutylammonium bromide. The mixture was stirred for 24 h and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate and evaporated. The residue was purified by TLC (benzene–ethyl acetate, 5:1 v/v) to give 42 mg (89%) of **17**.

ii) To a solution of 150 mg of **16** in 4 ml of anhydrous THF was added 100 mg of finely powdered potassium cyanide and 14 mg of 18-crown-6. The mixture was stirred vigorously for 2—8 h. The completion of the reaction was checked by TLC (benzene–ethyl acetate, 5:1 v/v). Ethyl acetate was added and the solution was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by TLC (benzene–ethyl acetate, 5:1 v/v, R_f=0.38) to give 70 mg of **17**: Mp 136—138 °C (recrystallized from dichloromethane–hexane); IR (nujol): 3220, 2240, 1780, 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.08 (6H, s), 0.88 (9H, s), 1.25 (3H, d, J=6 Hz), 3.65 (1H, t, J=2.5 Hz), 4.35 (1H, d, J=2.5 Hz), 4.30 (1H, dq, J=2.5 and 6 Hz), 6.65 (1H, br s).

Found: C, 56.57; H, 8.66; N, 11.00%. Calcd for $C_{12}H_{22}N_2O_2Si$: C, 56.65; H, 8.72; N, 11.01%.

(3*S*,4*R*)-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(3*S*,4*S*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-cyano-2-oxo-1-azetidinyl]-2-azetidinone (24): Mp 158 °C (recrystallized from chloroform–hexane); IR (nujol): 3225, 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.10 (12H, s), 0.90 (18H, s), 1.25 (6H, d, J=5.6 Hz), 3.5—3.9 (2H, m), 4.0—5.3 (2H, m), 4.48 (1H, d, J=2 Hz), 5.45 (1H, d, J=2 Hz), 6.23 (1H, br s).

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-carbamoyl-2-azetidinone (18): To a stirred solution of 163 mg of **17** in 3 ml of acetone was added 0.1 ml of 30% aqueous hydrogen peroxide and 1.4 ml of 0.5 mol dm^{-3} aqueous sodium carbonate at room temperature. After 30 min ethyl acetate was added and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by TLC (benzene–ethyl acetate, 1:2 v/v, R_f=0.2) to give 130 mg of **18** as crystals: Mp 87 °C (recrystallized from acetone–hexane); IR (nujol): 3100—3600, 1750, 1730, 1685, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.09 (6H, s), 0.90 (9H, s), 1.26 (3H, d, J=6.5 Hz), 3.21 (1H, dd, J=2.5 and 4.0 Hz), 4.15 (1H, d, J=6.5 Hz), 4.20 (1H, dq, J=4.0 and 6.5 Hz), 6.76 (2H), 7.36 (1H).

Found: C, 52.48; H, 8.98; N, 10.15%. Calcd for $C_{12}H_{24}N_2O_3Si$: C, 52.91; H, 8.88; N, 10.28%.

Methyl (3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-2-oxoazetidine-4-carboxylate (20): i) To a stirred solution of 210 mg of **17** in 6 ml of ethanol was added a solution of 100 mg of sodium hydroxide in 2.6 ml of water and 0.15 ml of 30% aqueous hydrogen peroxide. After 15 min the mixture was warmed up to 50 °C and stirred for 1.5 h at that temperature. After cooling, water and ethyl acetate was added and the organic layer was separated. From the organic layer 60 mg of **17** was obtained. The aqueous layer was acidified (about pH 2) with hydrochloric acid and the mixture was extracted with ethyl acetate. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. After filtration, a solution of diazomethane in ether was added to the filtrate. The solvent was removed under reduced pressure to give 95 mg of **20** as crystals.

ii) To a solution of 180 mg of **18** in 4 ml of ethanol was added a solution of 40 mg of sodium hydroxide in 1 ml water. The reaction mixture was warmed up to 50 °C and stirred for 1 h at 50 °C. After cooling the solution was washed with ethyl acetate and acidified with hydrochloric acid. The organic layer was extracted with ethyl acetate and dried over anhydrous magnesium sulfate. After filtration a solution of diazomethane in ether was added and the solvent was removed under reduced pressure to give 90 mg of **20**: R_f= 0.4 (cyclohexane–ethyl acetate, 2:1 v/v); mp 78 °C; $[\alpha]_D^{25}$ −12.8° (c 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.09 (6H, s), 0.89 (9H, s), 1.24 (3H, d, J=6 Hz), 3.25 (1H, m), 4.28 (1H, d, J=2.5 Hz), 4.2 (1H, m), 6.4 (1H, br s).

Found: C, 54.22; H, 8.86; N, 4.82%. Calcd for $C_{13}H_{25}NO_4Si$: C, 54.43; H, 8.77; N, 4.87%.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-(hydroxymethyl)-2-azetidinone (21): A solution of 100 mg of **20** in 3 ml of water–THF (9:1) was cooled to 0 °C and 25 mg of sodium tetrahydroborate was added. The mixture was stirred for 15 min and ethyl acetate was added. The solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 70 mg (78%) of **21**: Mp 90 °C (recrystallized from ether–hexane).

Found: C, 55.51; H, 9.84; N, 5.13%. Calcd for $C_{12}H_{25}NO_3Si$: C, 55.55; H, 9.71; N, 5.40%.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-(*p*-tolylsulfonyloxymethyl)-2-azetidinone (22): To a solution of 100 mg of **21** in 2 ml of anhydrous THF–dichloromethane (1:1) was added 0.1 ml of pyridine and 100 mg of *p*-toluenesulfonyl chloride. The mixture was stirred overnight and dichloromethane was added. The solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by TLC (benzene–ethyl acetate, 5:1 v/v) to give 110 mg (68%) of **22**: Mp 89 °C (recrystallized from ether–hexane); IR (neat): 3300, 1778, 1375, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.08 (6H, s), 0.88 (9H, s), 1.18 (3H, d, J=6 Hz), 2.47 (3H, s), 2.7—3.0 (1H, m), 3.7—4.3 (4H, m), 6.00 (1H, br s), 7.2—7.85 (4H, m).

Found: C, 55.06; H, 7.47; N, 3.23; S, 7.75%. Calcd for $C_{19}H_{31}NO_5SSi$: C, 55.18; H, 7.55; N, 3.39; S, 7.75%.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-iodomethyl-2-azetidinone (23): Sodium iodide (200 mg) was added to a solution of 100 mg of **22** in 3 ml of acetone. The mixture was warmed up to 60 °C and stirred for 7 h at the same temperature. After cooling the reaction mixture was filtered and the filtrate was evaporated. The residue was purified by TLC (benzene–ethyl acetate, 5:1 v/v) to give 85 mg of **23**: Mp 129 °C; IR (nujol): 3200, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.08 (6H, s), 0.88 (9H, s), 1.26 (3H, d, J=6 Hz), 2.85 (1H, dd, J=2 and 5 Hz), 3.2—3.5 (2H, m), 3.7—4.5 (2H, m), 6.24

(1H, br s).

Found: C, 38.94; H, 6.49; N, 3.60%. Calcd for $C_{12}H_{24}NO_2SiI$: C, 39.02; H, 6.50; N, 3.79%.

***p*-Nitrobenzyl 2-[(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)-ethyl]-4-iodomethyl-2-oxo-1-azetidinyl]-2-hydroxyacetate (25):** A solution of 301.8 mg of **23** and 371.3 mg of *p*-nitrobenzyl glyoxylate hydrate in 100 ml of benzene was refluxed with stirring for 10 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (cyclohexane–ethyl acetate, 2:1 v/v) to give 318 mg (67%) of **25** as a mixture of the two diastereomers: R_f= 0.3 and 0.4 (cyclohexane–ethyl acetate, 2:1 v/v); ^{1}H NMR ($CDCl_3$) δ=0.07 (6H, s), 0.75 (9H, s), 1.28 (3H, d, J=6.4 Hz), 2.91 (1H, dd, J=2 and 4 Hz), 3.25—3.60 (2H, m), 3.75—4.45 (3H, m), 5.35 (2H, s), 5.25—5.65 (1H, m), 7.35—8.45 (4H, m).

***p*-Nitrobenzyl 2-[(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)-ethyl]-4-iodomethyl-2-oxo-1-azetidinyl]-2-chloroacetate (26):** To a solution of 321 mg of **25** in 18 ml of THF was added 0.18 ml of 2,6-lutidine and 0.12 ml of thionyl chloride at −40 °C. After stirring for 20 min the reaction mixture was filtered through Celite and evaporated to give the crude chloro derivative **26**.

***p*-Nitrobenzyl (2*S*,5*S*,6*S*)-6-[(*R*)-1-(*t*-Butyldimethylsilyloxy)-ethyl]-7-oxo-3-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (27a) and *p*-Nitrobenzyl (2*R*,5*S*,6*S*)-6-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-7-oxo-3-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate (27b):** To a solution of **26** in 9 ml of dichloromethane was added 0.23 ml of triethylamine at 0 °C. Hydrogene sulfide was bubbled through this solution for 2 h at that temperature. The mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by TLC (hexane–acetone–ethyl acetate, 25:3:6) to give 92.5 mg (36%) of **27b** and 157.5 mg (60%) of **27a**.

27a: R_f=0.8 (hexane–acetone–ethyl acetate, 25:3:6 v/v); mp 95 °C (recrystallized from hexane–ether); IR ($CHCl_3$): 1770, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.10 (6H, s), 0.90 (9H, s), 1.25 (3H, d, J=6 Hz), 2.7—3.3 (3H, m), 3.9—4.6 (2H, m), 4.82 (1H, s), 5.33 (2H, s), 7.4—8.5 (4H, m).

Found: C, 53.99; H, 6.41; N, 5.99; S, 6.83%. Calcd for $C_{21}H_{30}N_2O_6SSi$: C, 54.05; H, 6.48; N, 6.00; S, 6.87%.

27b: R_f=0.9 (hexane–acetone–ethyl acetate, 25:3:6 v/v); IR ($CHCl_3$): 1770, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.09 (6H, s), 0.88 (9H, s), 1.24 (3H, d, J=6 Hz), 2.7—3.7 (3H, m), 3.8—4.7 (2H, m), 5.26 (2H, s), 5.49 (1H, s), 7.3—8.4 (4H, m).

***p*-Nitrobenzyl (2*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-7-oxo-3-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (28):** To a solution of 180 mg of **27** in 4 ml of THF was added 0.21 ml of acetic acid and 0.552 mg of tetrabutylammonium fluoride trihydrate at 0 °C. After stirring overnight the reaction mixture was poured into a large quantity of ethyl acetate, washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by TLC (cyclohexane–ethyl acetate–acetone, 8:6:3 v/v) to give 37 mg (27%) of the diastereomer I and 35 mg (26%) of the diastereomer II. When the reaction time was overnight, diastereomer II changed to diastereomer I. Diastereomer I **28**: R_f=0.5 (cyclohexane–ethyl acetate–acetone, 8:6:3 v/v); ^{1}H NMR ($CDCl_3$) δ=1.37 (3H, d, J= 6 Hz), 2.0—2.5 (1H, br s), 2.8—3.8 (3H, m), 3.9—4.9 (2H, m), 5.28 (2H, s), 5.62 (1H, s), 7.3—8.5 (4H, m). Diastereomer II: R_f=0.4 (cyclohexane–ethyl acetate–acetone, 8:6:3 v/v); ^{1}H NMR ($CDCl_3$) δ=1.30 (3H, d, J=6 Hz), 1.7—2.5 (1H, br s), 2.7—3.6 (3H, m), 3.8—4.6 (2H, m), 4.76 (1H, s), 5.16 (2H, s), 7.3—8.5 (4H, m).

Sodium (2*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-7-oxo-3-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (29): To a solution of 46 mg of **28** in 5 ml of THF was added a solution of 11 mg of sodium hydrogencarbonate in 1.0 ml of water and 144.5 mg of 10% palladium on carbon. The mixture was shaken under a hydrogen atmosphere at 1 atm for 2 h, filtered through Celite, washed with ethyl acetate, and decolorized by activated carbon powder. The solution was lyophilized to give 11.4 mg (37%) of **29**: ^{1}H NMR (D_2O, DSS) δ=1.27 (3H, d, J=6 Hz), 2.7—3.4 (3H, m).

Methyl *dl*-[(2*R,3*S**,5*R**)-7-Oxo-3-phenylthio-1-azabicyclo[3.2.0]heptane]-2,3-dicarboxylate (32) and Methyl *dl*-[(2*R**,3*S**,5*S**)-7-Oxo-3-phenylthio-1-azabicyclo[3.2.0]heptane]-2,3-dicarboxylate (33):** Potassium hydride (35% in mineral oil, 8.015 mmol) was placed in the reaction flask and washed three times with dry hexane. The solid reagent was then slurried in 10 ml of dry THF and cooled to −40 °C. A solution of iodomethyl derivative **30** (1.127 g, 5.343 mmol) in 5 ml of THF and 2.12 g (8.015 mmol) of **31** in 5 ml of THF was added and the mixture was stirred at −25—−40 °C for 3 h. The reaction was quenched with sat. ammonium chloride and the organic layer was extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (cyclohexane–ethyl acetate, 2:1 v/v) to give 478.9 mg (27%) of a mixture of **32** and **33**. These diastereomers were separated by TLC (cyclohexane–ether, 1:2 v/v).

32: R_f=0.35 (cyclohexane–ether, 1:2 v/v); ^{1}H NMR ($CDCl_3$) δ=2.2—3.3 (4H, m), 3.48 (3H, s), 3.86 (3H, s), 3.8—4.3 (1H, m), 5.28 (1H, s), 7.3—7.8 (5H, m).

33: R_f=0.30 (cyclohexane–ether, 1:2 v/v); mp 137—139 °C (recrystallized from hexane–ether); IR (KBr pellet): 1765, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.22 (1H, dd, J=10 and 14 Hz), 2.74 (1H, dd, J=5 and 14 Hz), 2.8—3.3 (2H, m), 3.46 (3H, s), 3.5—3.9 (1H, m), 3.88 (3H, s), 4.69 (1H, s), 7.0—7.7 (5H, m).

Found: C, 57.36; H, 4.93; N, 4.20; S, 9.63%. Calcd for $C_{16}H_{17}NO_5S$: C, 57.47; H, 4.82; N, 4.19; S, 9.59%.

Dimethyl (2*R*,3*S*,5*R*,6*S*)-6-[(*R*)-1-(*t*-Butyldimethylsilyloxy)-ethyl]-7-oxo-3-phenylthio-1-azabicyclo[3.2.0]heptane-2,3-dicarboxylate (34) and Dimethyl (2*S*,3*R*,5*R*,6*S*)-6-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-7-oxo-3-phenylthio-1-azabicyclo-[3.2.0]-heptane-2,3-dicarboxylate (35): Starting with **23** and **31**, the above procedure gave a mixture of **34** and **35**. Reaction time 2.5 h. Reaction temperature −70—−10 °C. Yield 15%. ^{1}H NMR ($CDCl_3$) δ=0.05 (6H, s), 0.81 (9H, s), 1.20 (3/2H, d, J=6 Hz), 1.23 (3/2H, d, J=6 Hz), 1.5—2.0 (1H, m), 2.7—3.6 (2H, m), 3.66 (3/2H, s), 3.69 (3/2H, s), 3.71 (3/2H, s), 3.84 (3/2H, s), 3.8—4.5 (1H, m), 5.48 (1/2H, s), 5.61 (1/2H, s), 6.9—7.7 (5H, m).

Dimethyl *dl*-(2*R,3*S**,5*S**)-3-Methylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2,3-dicarboxylate (37) and Dimethyl *dl*-(2*R**,3*S**,5*R**)-3-methylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2,3-dicarboxylate (38):** Potassium hydride (35% in mineral oil, 2.59 mmol) was placed in the reaction flask and washed twice with dry hexane. The solid reagent was then slurried in 5 ml of THF and cooled to −78 °C. Catalytic amount of 18-crown-6 and 435.1 mg (2.59 mmol) of diphenylmethane was added and stirred for 2 h at −78—20 °C.

The mixture was cooled to −40 °C and a solution of 273.2 mg (1.30 mmol) of **30** in 5 ml of THF and 509.4 mg (2.68 mmol) of **36**. The reaction mixture was stirred for 3 h at −40—−20 °C. The reaction was quenched with sat. ammonium chloride and the organic layer was extracted with ethyl acetate. The combined extracts was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (cyclohexane–ethyl acetate, 2:1 v/v)to give 15 mg (4%) of a mixture of **37** and **38**.

The diastereomer **38**: ^{1}H NMR ($CDCl_3$) δ=2.14 (3H, s), 2.43 (1H, dd, J=6 and 15 Hz), 2.87 (1H, dd, J=1 and 6 Hz), 2.9—3.6 (2H, m), 3.76 (3H, s), 3.80 (3H, s), 3.8—4.4 (1H, m), 5.31 (1H, s).

Dimethyl (2*R*,3*S*,5*R*,6*S*)-6-[(*R*)-1-(*t*-Butyldimethylsilyloxy)-ethyl]-3-methylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2,3-dicarboxylate (39) and Dimethyl (2*S*,3*R*,5*R*,6*S*)-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-3-methylthio-7-oxo-1-azabicyclo[3.2.0]-heptane-2,3-dicarboxylate (40): Potassium hydride (35% in mineral oil, 2.26 mmol) was placed in the reaction flask and washed with dry hexane. The solid reagent was then slurried in 2 ml of THF and cooled to −78 °C. Diphenylmethane (384.6 mg, 2.289 mmol) and 18-crown-6 (599.9 mg, 2.272 mmol) was added and stirred for 2.5 h at −78—20 °C. The reaction mixture was cooled to −40 °C and a solution of 804 mg (2.179 mmol) of **23** in 6 ml of THF was added to the mixture. After stirringfor 5 min a solution of 858.8 mg (4.520 mmol) of **36** in 4 ml of THF was added slowly. The reaction mixture was stirred for 2.75 h at −40—−20 °C. The reaction was quenched with sat. aqueous ammonium chloride and the organic layer was extracted with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (cyclohexane–dichloromethane, 10:1 v/v) to give 165.9 mg (18%) of the products as a mixture of two diastereomers which were separated by TLC (cyclohexane–ethyl acetate, 1:1 v/v).

39: R_f=0.65 (cyclohexane–ether, 1:1 v/v); IR ($CHCl_3$): 1772, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.05 (6H, s), 0.88 (9H, s), 1.19, (3H, d, J=6.6 Hz), 2.16 (3H, s), 2.1—2.5 (1H, m), 2.7—3.2 (2H, m), 3.79 (3H, s), 3.80 (3H, s), 3.8—4.4 (2H, m), 5.34 (1H, s).

Found: C, 52.83; H, 7.89; N, 3.33%. Calcd for $C_{19}H_{33}NO_6SSi$: C, 52.88; H, 7.70; N, 3.25%.

40: R_f=0.60 (cyclohexane–ether, 1:1 v/v); IR (neat) 1770, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.04(6H, s), 0.84 (9H, s), 1.15 (3H, d, J=6 Hz), 2.10 (3H, s), 2.18 (1H, d, J=12.6 Hz), 2.71 (1H, dd, J=6 and 12.6 Hz), 3.08 (1H, dd, J=3 and 6 Hz), 3.3—3.8 (1H, m), 3.77 (3H, s), 3.87 (3H, s), 3.8—4.4 (1H, m), 4.69 (1H, s).

Disodium (2*R*,3*S*,5*R*,6*S*)-6-[(*R*)-1-(*t*-Butyldimethylsilyloxy)-ethyl]-3-methylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2,3-dicarboxylate (43): To a solution of 92.4 mg (0.214 mmol) of **39** in 10 ml of THF–water (1:1) was added 1 equiv of 0.1 mol dm^{-3} aqueous sodium hydroxide for 8 h. The mixture was stirred for 3 d and evaporated. The solution was lyophilized to give 88.4 mg (92%) of **43**: ^{1}H NMR ($CDCl_3$) δ=0.17 (6H, s), 0.93 (9H, s), 1.28 (3H, d, J=5.4 Hz), 2.10 (3H, s), 2.0—2.5 (3H, m), 5.36 (1H, s).

References

1) Part VIII, K. Fujimoto, Y. Iwano, and K. Hirai, submitted for publication in this journal. Preliminary communications: a) K. Hirai, Y. Iwano, and K. Fujimoto, *Tetrahedron Lett.*, **23**, 4021 (1982); *ibid.*, **23**, 4025 (1982); K. Fujimoto, Y. Iwano, and K. Hirai, *ibid.*, **25**, 1151 (1984).

2) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, *J. Antibiot.*, **32**, 1 (1979); G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).

3) W. J. Leanza, K. J. Wildonger, J. Hannah, D. H. Shih, R. W. Ratcliffe, L. Barash, E. Walton, R. A. Firestone, G. F. Patel, F. M. Kahan, J. S. Kahan, and B. G. Christensen, "Recent Advances in the Chemistry of β-Lactam Antibiotics," ed by G. I. Gregory second international symposium, Cambridge, England, The Royal Society of Chemistry p. 240 (1980); W. Drückheimer, J. Blumbach, R. Lattrell, and K. H. Scheunemann, *Angew. Chem. Int. Ed. Eng.*, **24**, 189 (1985).

4) P. A. Grieco, D. L. Flynn, and R. E. Zelle, *J. Am. Chem. Soc.*, **106**, 6414 (1984) and the references cited therein.

5) K. Hirai, Y. Iwano, and K. Fujimoto, *Heterocycles*, **17**, 201 (1982).

6) J. C. Sheehan, Y. S. Lo, J. Loliger, and C. C. Podewell, *J. Org. Chem.*, **39**, 1444 (1974).

7) M. Ishiguro and T. Nakatsuka, the 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, April. 1985, Abstr. No. 4P 9—3, p. 623.

8) J. A. Aimetti, E. S. Hamanaka, D. A. Johnson, and M. S. Kellog, *Tetrahedron Lett.*, **1979**, 4631.

9) F. A. Bouffard and B. G. Christensen, *J. Org. Chem.*, **46**, 2208 (1981).

10) K. Clauss, D. Grimm, and G. Prossel, *Liebig's Ann. Chem.*, **1974**, 539.

11) Recent Review: T. Kametani, K. Fukumoto, and M. Ihara, *Heterocycles*, **17**, 463 (1982).

12) K. Hirai, Y. Iwano, and K. Fujimoto, *Tetrahedron Lett.*, **24**, 3251 (1983).

13) T. C. Smale, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 187; E. G. Brain, A. J. Eglington, J. H. C. Nayler, N. F. Osbone, R. Southgate, and P. Tolliday, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2479; A. G. Brown, D. F. Corbett, and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, **1977**, 359.

14) K. Hirai, K. Fujimoto, Y. Iwano, T. Hiraoka, T. Hata, and C. Tamura, *Tetrahedron Lett.*, **22**, 1021 (1981).

15) B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, **99**, 3101 (1977).

16) P. J. Giddings, D. I. John, and E. J. Thomas, *Tetrahedron Lett.*, **1978**, 995; *ibid.*, **21**, 399 (1980).