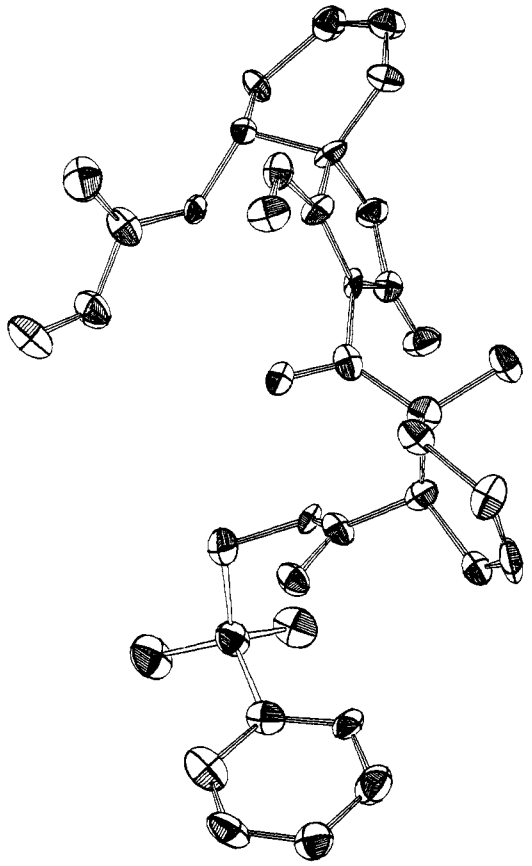

Figure 1. ORTEP drawing of compound **15a**.

as a solvent in place of benzene resulted in dramatic decrease in the yield of **16**.

Oxidation of **16** with pyridinium chlorochromate[15] in the presence of 3-Å molecular sieves[16] gave α-sulfonyl ketone (82%), which was submitted to reductive desulfonylation with Al–Hg in aqueous THF[17] to afford the ketone **17** (66%), mp 227–228 °C, whose structure was confirmed by spectral analysis.[18] Finally, reduction of **17** with sodium borohydride in MeOH proceeded stereoselectively to afford **4** in 31% yield,[19] no epimeric alcohol being detected by ^{1}H NMR (270 MHz). Resonance of the carbinyl proton in the ^{1}H NMR was observed at 4.23 ppm with $J_{w/2}$ = 9.9 Hz (coupling with the vicinal methylene protons) in accordance with axial orientation of the hydroxy group as reported for **1** and **2**.[1a,2b,c] Confirmation of the molecular structure of **4** was obtained by X-ray analysis as shown in Figure 2.

In conclusion, we could have established an efficient methodology for the construction of the macrocyclic ring of tetronolide and kijanolide. It utilizes in the key step (**15a** to **16**) an intramolecular aldol reaction between α-sulfonyl carbanion and aldehyde groups, the technique having so far been ignored or unsuccessful in large-ring synthesis.

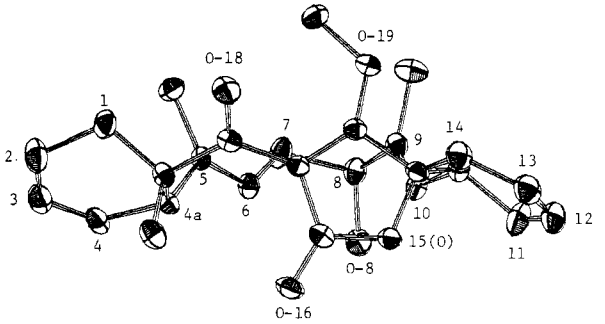

Figure 2. ORTEP drawing of compound **4**.

Acknowledgment. Support of this work by the Tamura Foundation for the Promotion of Science and Technology is gratefully acknowledged.

Registry No. **1**, 76705-48-1; (±)-**4**, 104995-64-4; (±)-**5** (isomer 1), 98993-13-6; (±)-**6** (isomer 2), 99094-70-9; (±)-**7**, 104995-47-3; (±)-**7** (ethylene acetal) (isomer 1), 104995-59-7; (±)-**7** (ethylene acetal) (isomer 2), 105086-99-5; (±)-**8**, 104995-48-4; (±)-**9a**, 104995-49-5; **9a**-ol (TBDMS), 104995-60-0; (±)-**9a** (TBDMS), 104995-61-1; (±)-**9a** (tosylate), 104995-62-2; (±)-**9b**, 105086-96-2; (±)-**9b** (TBDMS), 105087-00-1; (±)-**10a**, 104995-50-8; (±)-**10b**, 105086-97-3; (±)-**11**, 105018-31-3; (±)-**12**, 104995-51-9; (±)-**13**, 104995-52-0; (±)-**13** (sulfide), 104995-63-3; **14**, 104995-53-1; (±)-**15a**, 104995-54-2; (±)-**15b**, 105086-98-4; **16**, 104995-55-3; (±)-**16**-one, 104995-56-4; (±)-**17**, 104995-57-5; (±)-**17** (desmethoxylated), 104995-65-5; (*E*,*E*)-CH_2=CHCH=CHC(CH_3)=CHCOOCH_3, 98993-08-9; 4-(1,3-dioxolan-2-yl)-3-[1-hydroxy-3-methyl-2-propen-1-yl]-4-methylcyclohexene, 104995-58-6; methacrolein, 78-85-3.

Supplementary Material Available: Experimental details of compounds prepared (11 pages). Ordering information is given on any current masthead page.

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(18) IR (KBr) 1755, 1665, 1590 cm^{-1}; MS, *m/e* (relative intensity) 422 (50, M^+), 404 (37, $M^+ - H_2O$), 315 (45, $M^+ - C_8H_{11}$, derived from a retro-Diels–Alder fragmentation of the bottom-half and α-cleavage of the (α-methylene)ketone group), 69 (100); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.32 (s, 3 H, 18a-CH_3), 1.42 (s, 3 H, 5-CH_3), 1.70 (dt, J = 14.0, 8.9 Hz, 1 H, H-1), 1.75 (d, J = 1.2 Hz, 3 H, 9-CH_3), 1.87 (ddd, J = 14.0, 4.6, 3.5 Hz, 1 H, H-1), 2.10–2.25 (m, 4 H, H-2, -11, and -14), 2.30–2.45 (m, 1 H, H-11), 2.72 (dm, J = 18.3 Hz, 1 H, H-14), 3.12 (td, J = 10.8, 6.1 Hz, 1 H, H-10a), 3.13 (ddd, J = 15.4, 5.1, 1.2 Hz, 1 H, H-7), 3.31 (dd, J = 15.4, 9.8 Hz, 1 H, H-7), 3.83 (s, 3 H, OCH_3), 3.88 (dm, J = 5.2 Hz, 1 H, H-4a), 5.28 (ddt, J = 9.8, 5.2, 2.2 Hz, 1 H, H-4), 5.68–5.81 (m, 3 H, H-3, -6, and H-12 or -13), 5.81–5.90 (m, 1 H, H-12 or -13), 6.21 (dq, J = 10.8, 1.2 Hz, 1 H, H-10).
(19) A major side reaction was hydrogenolytic elimination of the methoxy group with the ketone group unattacked.

New Methylseleno-Promoted Ketene–Imine Cycloaddition Reaction. A Simplified Stereoselective Synthesis of Penam[1]

Summary: A simplified stereoselective synthesis of penam-type β-lactams **5a–e** has been accomplished by utilizing a new methylseleno-promoted ketene–imine cycloaddition reaction and reductive elimination of the methylseleno group with *n*-Bu_3SnH.

Sir: β-Lactams can be synthesized in a practical way by the ketene–imine cycloaddition reaction,[2] but this reaction

(1) Presented at the 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, Japan, April 4, 1985; abstract paper p 630.

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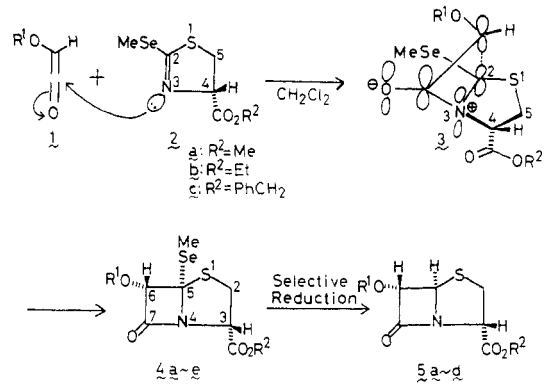
Table I. Methylseleno-Promoted Ketene–Imine Cycloaddition and Reductive Demethylselenation

entry	ketene precursor	imine 2	isolated yield of 4, %		isolated yield of 5 or 13, %	
1	$MeOCH_2COCl$	*dl*-**2a**	*dl*-**4a**	77	*dl*-**5a**	83[b]
2	$MeO(CH_2)_2OCH_2OCH_2CO_2K$[a]	*dl*-**2a**[a]	*dl*-**4b**	36[a]	*dl*-**5b**	77[c]
3	$PhCH_2OCH_2COCl$	*dl*-**2b**	*dl*-**4c**	92	*dl*-**5c**	73[d]
4	$MeOCH_2COCl$	*dl*-**2c**	*dl*-**4d**	66	*dl*-**5d**	56[b]
5	$CH_2{=}CHCH_2OCH_2COCl$	*dl*-**2c**	*dl*-**4e**	58	*dl*-**13**	62[d]
6	$MeOCH_2COCl$	(4*S*)-**2a**[e]	**4a**[e]	81	**5a**[e]	78[b]
7	$MeOCH_2COCl$	(4*S*)-**2c**[e]	**4d**[e]	52	**5d**[e]	77[b]

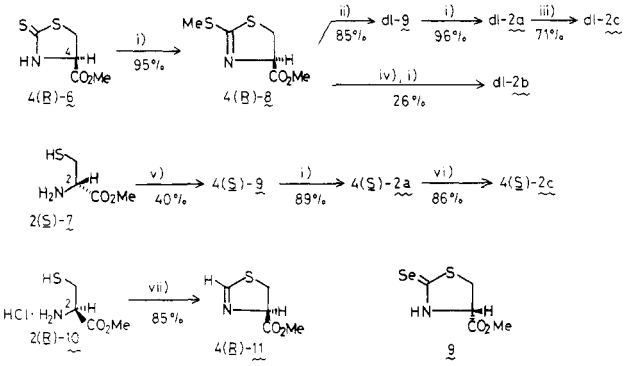
[a] Cycloaddition reaction was carried out in the presence of cyanuric chloride (4 equiv based on **2**) and Et_3N (8 equiv based on **2**) at −20 °C → room temperature. [b] Refluxed in THF for 3 h. [c] Heated at 60 °C in CH_3CN for 1 h. [d] Refluxed in CH_3CN for 1 h. [e] Enantiomeric excess (50%) was determined by ^1H NMR analysis in the presence of $Eu(hfc)_3$.

Scheme I



is very delicate. The stereochemistry (cis or trans) of substituents on the β-lactams obtained by this cycloaddition employing acyclic imine derivatives differs with the substituents of both the ketenes and the imines.[3] In some cases, the yield of the desired β-lactam product is very poor or none at all.[4] In 1977, Bose and co-workers reported a very convenient synthesis of various unusual penams with a methylthio-substituent on the ring juncture carbon atom by condensation of cyclic methylthioimidate and acetyl chlorides under basic conditions.[5] However, this simplified synthetic method is of very limited utility because selective demethylsulfurization at the ring juncture of the bicyclic penams is impossible.[6]

Scheme II[a]



[a] (i) MeI, Et_3N/MeOH; (ii) Se, $NaBH_4$/MeOH–EtOH (8:1); (iii) (a) 1.25 N KOH/MeOH, (b) $PhCH_2Br$/DMF; (iv) Se, $NaBH_4$/EtOH; (v) $CSe_2/CH_2Cl_2/0$ °C; (vi) $PhCH_2OH$, catalytic $Ti(i\text{-}PrO)_4$/100 °C; (vii) $HC(=N^+H_2Cl^-)OEt/Et_3N/CH_2Cl_2$.

In our continuing studies on C4-chiral thiazolidine chemistry,[7] we designed a new methylseleno-promoted ketene–imine cycloaddition reaction between **1** and **2** which gives the bicyclic product **4** via the presumable transition state **3** (Scheme I). The desired compound **5** was expected to be obtained by selective reduction[8] of the methylseleno group in **4**.

Several alkoxyacetyl chlorides as precursors of ketene **1** were readily prepared by conventional methods. New cyclic methylseleno imino compounds such as 4(*S*)-(methoxycarbonyl)- and 4(*S*)-(benzyloxycarbonyl)-2-(methylseleno)-Δ^2-thiazoline (**2a,c**), *dl*-**2a,c**, and the *dl*-4-ethoxycarbonyl derivative (**2b**) were synthesized by the reactions shown in Scheme II starting from D-cysteine methyl ester (**7**) or 4(*R*)-(methoxycarbonyl)thiazolidine-2-thione (**6**).[9] Compound (4*S*)-**9** was shown to be optically pure by HPLC analysis of its (α*R*)-α-methoxy-α-(trifluoro-

(2) (a) *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Elks, J., Ed.; The Royal Society of Chemistry: London, 1977. (b) *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Gregory, G. I., Ed.; The Royal Society of Chemistry: London, 1981. (c) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 2. (d) A review in Japanese entitled "Recent Advances in the Field of the β-Lactam Ring Formation Reaction from the Aspect of the Synthetic Chemistry": Hirai, K. *J. Synth. Org. Chem. Jpn.* **1980**, *38*, 97 and references cited therein. (e) For recent communications, see: Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783, 3787.

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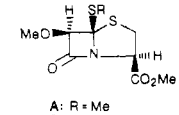
(6) 5-Methylthio penams A and B, which were prepared by our own method, were allowed to react with *n*-Bu_3SnH in the presence of catalytic AIBN giving inseparable complicated products respectively.



A: R = Me
B: R = CH_2Ph

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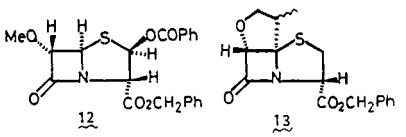
methyl)phenylacetyl (MTPA) derivative [99% ee of (4*S*)-**9a**].[10] In the course of the methylation reaction from (4*S*)-**9** to (4*S*)-**2a**, however, the C4 atom was considerably epimerized [50% ee of (4*S*)-**2a** (400-MHz ^{1}H NMR analysis in the presence of Eu(hfc)$_3$)]. The optical purity of (4*S*)-**2c** was determined to be the same as that of (4*S*)-**2a** by the similar ^{1}H NMR analysis. We employed these optically active and inactive cyclic imino compounds for the following cycloaddition reactions.

In a typical example of methylseleno-promoted ketene–imine cycloaddition reactions, a solution of methoxyacetyl chloride (4.8 mmol) in CH_2Cl_2 (2 mL) was added to a solution of *dl*-**2a** (4 mmol) and Et_3N (8 mmol) in CH_2Cl_2 (2 mL) over a period of 15 min with stirring at 0 °C under N_2. After being stirred at room temperature for 22 h, Et_3N (2 mmol) and a solution of methoxyacetyl chloride (2 mmol) in CH_2Cl_2 (1 mL) were added.[11] The mixture was stirred at room temperature for 14 h and treated as usual[12] to give exclusively *dl*-methyl (3*S**,5*S**,6*S**)-6-methoxy-5-(methylseleno)penam-3-carboxylate (**4a**) (77% yield) as a yellow oil. In the reaction between optically active imine (4*S*)-**2a** (50% ee) or (4*S*)-**2c** (50% ee) and methoxyacetyl chloride, the corresponding chiral penam **4a** [81% yield, $[\alpha]^{27}_D$ +110.1° (*c* 1.0, $CHCl_3$)] or **4d** [52% yield, $[\alpha]^{27}_D$ + 119.3° (*c* 1.0, $CHCl_3$)] having the same optical purity (50% ee) as the starting imines was also obtained exclusively. Similar cycloaddition reactions gave the desired bicyclic products **4** in fairly good yields (see Table I).

Bicyclic products **4** were assigned the stereostructures shown in Scheme I by chemical correlation[13] of *dl*-**4d** to *dl*-**12** whose stereochemistry had been clarified by X-ray analysis.[14] Hence, this cycloaddition reaction may proceed in an extremely high stereoselective fashion via transition state **3**, which is preferred to the other one which would be destabilized by steric repulsion between the C4-alkoxycarbonyl group and the N3-enolate group approaching from the α-side.

The reaction between methoxyacetyl chloride and (4*R*)-**8** or (4*R*)-**11** gave the corresponding bicyclic product in only a moderate yield (58% in (4*R*)-**8**) or in a very poor yield (5% in (4*R*)-**11**). Therefore, a methylseleno group substituent on the imine moiety efficiently promotes this ketene–imine cycloaddition reaction.

Reductive demethylselenation of **4** was carried out by treatment with *n*-Bu_3SnH (ca. 1.2–1.5 equiv) in refluxing THF and CH_3CN or in CH_3CN at 60 °C in the presence of catalytic AIBN to give compound **5** with high stereoselectivity[13,14] and in good yield (Table I). Interestingly, similar demethylselenation of *dl*-**4e** gave tricyclic products *dl*-**13** with a high strain in 62% yield. ^{1}H NMR analysis showed compound **13** to be a 7:3 mixture of diastereoisomers due to a secondary methyl group. This radical cyclization[8,15] offers a unique synthesis of a new type of β-lactams.



We succeeded in synthesizing penam in just a few steps by utilizing a methylseleno-promoted ketene–imine cycloaddition reaction. This new procedure should be useful for large-scale syntheses of various penam-type β-lactams.

Supplementary Material Available: Crystal data of *dl*-**12**, atomic parameters for non-hydrogen atoms, fractional coordinates and isotropic thermal parameters for hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, bond lengths, valence angles, and torsion angles, and the perspective view for *dl*-**12** and ^{1}H NMR spectral data of new compounds (9 pages). Ordering information is given on any current masthead page.

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A Novel [3,3]-Rearrangement of 1,2-Dihydro(*N*-arylamino)pyridines: Formation of Unusual Fused Indolines

Summary: Treatment of *N*-(*N*-aryl-*N*-mesylamino)-pyridiniums with base leads to the 1,2-dihydropyridines which undergo a [3,3]-rearrangement and ring closure to give the bridged tetrahydro-α-carbolines **3**, whose structures were established by NMR spectroscopy and single-crystal X-ray crystallography and by reduction to the interesting nine-membered ring compound **8**.

Sir: The addition of suitable bifunctional reagents to pyridine 1-oxides gives the unstable 1,2-dihydropyridine 1-oxides, which rearrange in a number of ways: 1,3-, 1,5-, and 3,5-shifts.[1] *N*-Iminopyridinium ylides give 1,2-dihydropyridine derivatives, which tend to aromatize[2] rather

(10) *cf.* Nagao, Y.; Kumagai, T.; Yamada, S.; Fujita, E.; Inoue, Y.; Nagase, Y.; Aoyagi, S.; Abe, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2361.
(11) Because the presence of the starting cyclic imino compound **2** was still recognized by TLC analysis even after the reaction for 22 h, more reagents were added. This operation gave a higher yield of **4** than when a large amount of the reagents were added once.
(12) The reaction mixture was successively washed with 5% HCl, saturated aqueous $NaHCO_3$, and brine and evaporated under reduced pressure to give an oily residue. Chromatography on a silica gel column with CH_2Cl_2–AcOEt (25:1) gave the desired penam **4**.
(13) Compound *dl*-**5d** derived from *dl*-**4d** was treated with benzoyl peroxide (4 equiv) in refluxing CCl_4 to give stereoselectively *dl*-**12** as colorless needles (mp 127–128 °C, AcOEt–hexane).
(14) Crystallographic structure of compound *dl*-**12** and its data are available as supplementary material.
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