SYNTHESIS OF SEVERAL NEW CARBAPENEM ANTIBIOTICS

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A synthesis of several carbapenem antibiotics including 9-methoxythienamycin is described. The final deprotection of C-3 esters was accomplished by a novel procedure using aluminum trichloride under a very mild condition. The antibacterial activity against Gram-positive and Gram-negative bacteria is shown.

Isolation of the potent carbapenem antibiotic thienamycin (**1**) and many similar antibiotics has stimulated many chemists to try to synthesize these compounds[1]. We have also been very interested in further improvement of their antibacterial activity by modifying the C-6 side chain structure and have been investigating the synthesis of thienamycin derivatives.

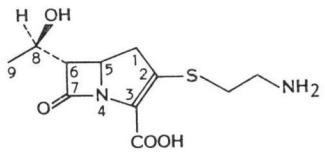
Before engaging in the synthesis of several new carbapenem antibiotics, we tried to develop a method for deprotecting the carbapenem esters[2] required in the final step of all the syntheses because these carbapenems are generally unstable under acidic conditions[3~7]. First, we examined the deprotection of *p*-methoxybenzyl (PMB) ester and benzhydryl (Bh) esters of (±)-PS-5 and its derivatives, which were prepared by application of the known straightforward sequence[8] shown in Scheme 1.

Treatment of benzhydryl esters **6a, c** or *p*-methoxybenzyl ester **6b** with aluminum trichloride in anisole gave the desired deprotected products **7a~c** in good yields.

In view of the above results, we next tried to obtain some optically active compounds, expecting to get carbapenems with significant biological activity. 6-Epicarpetimycin derivatives **13a, b** were synthesized as follows: 1) reaction of the known optically active azetidinone carboxylic acid **8**[9] with two equivalents of lithium diisopropylamide in tetrahydrofuran at −78°C followed by treatment with acetone gave hydroxycarboxylic acid **9**; 2) homologation by Arndt-Eistert reaction[10] gave **10**; 3) carboxymethylation by MASAMUNE's procedure[11], followed by desilylation and diazotization afforded **11**; 4) carbenoid cyclization with rhodium acetate[12] followed by treatment with diphenylphosphorochloridate, diisopropylethylamine and then with cysteamine derivatives **5a, b**[13] yielded PMB esters **12a, b**. Deprotection with aluminum trichloride gave 6-epicarpetimycin derivatives **13a** and **13b** in 47.6 and 56.7%, respectively. These compounds showed weak antibacterial activities as reported previously[14]. The decrease of the activity is ascribable to the bulkiness of the C-6 α-substituent which may cause difficulties when the compounds approach from the α-side to the serine hydroxyl group[15~17].

It is noteworthy that the carbapenem antibiotics bearing an α-hydroxyethyl side chain at the C-6 position show significant antibacterial activity against Gram-positive and Gram-negative bacteria including β-lactamase-producing ones. Thus, we tried to synthesize several thienamycin derivatives having a α-(2-substituted-1-hydroxy)ethyl group at the C-6 position. Stereo-controlled incorporation of the hydroxyethyl side chain *via* excellent stereo-selective C-C bond formation between the dianion derived from carboxylic acid **8** or **14** with two equivalents of lithium diisopropylamide and acetaldehyde, reported by Merck's researchers[18,19], is an important procedure in carbapenem chemistry.

Scheme 1.



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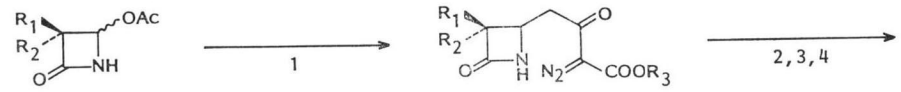
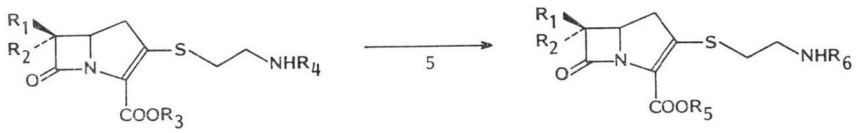


2a R_1 = H, R_2 = Et
2b R_1 = R_2 = Me

4a R_1 = H, R_2 = Et, R_3 = PMB
4b R_1 = H, R_2 = Et, R_3 = Bh
4c R_1 = R_2 = Me, R_3 = Bh



6a R_1 = H, R_2 = Et, R_3 = Bh, R_4 = Ac
6b R_1 = H, R_2 = Et, R_3 = PMB, R_4 = COOPMB
6c R_1 = R_2 = Me, R_3 = Bh, R_4 = Ac

7a R_1 = H, R_2 = Et, R_5 = Na, R_6 = Ac [(±) PS-5]
7b R_1 = H, R_2 = Et, R_5 = R_6 = H [(±) NS-5]
7c R_1 = R_2 = Me, R_5 = Na, R_6 = Ac

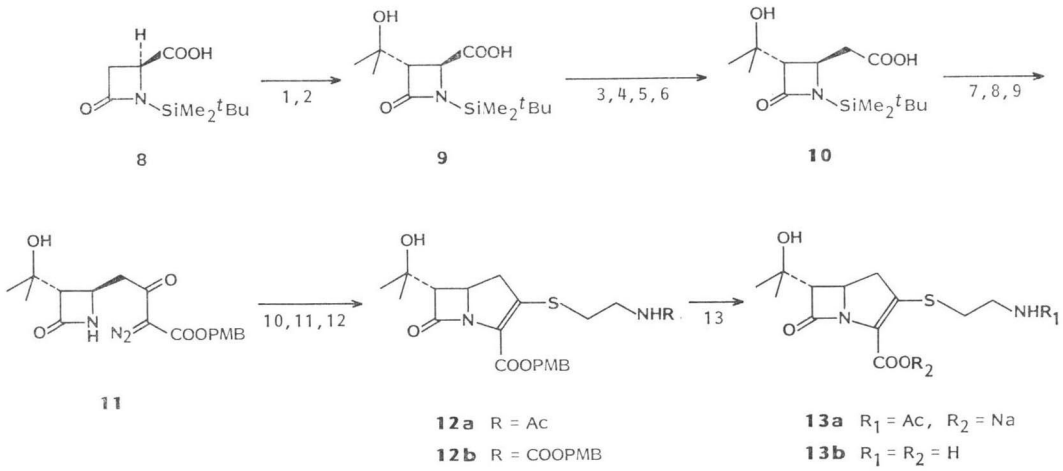
Bh = benzhydryl, PMB = *p*-methoxybenzyl
1: **3a, b** CH_2=C(OSiMe$_3$)C(N_2)COOR (**3a** R=PMB, **3b** R=Bh), 2: $Rh_2(OAc)_4$, 3: $(PhO)_2POCl$, $(^iPr)_2NEt$, 4: **5a, b** $HSCH_2CH_2NHR$ (**5a** R=Ac, **5b** R=COOPMB), $(^iPr)_2NEt$, 5: $AlCl_3$, anisole, −50°C.

During independent investigations on similar procedures, we found that the reaction of **8** occurred smoothly but some difficulties were involved in that of the homologue **14**. First, incorporation of a methylthioethanol group at the C-3 position of the azetidinone **8** was attempted. Reaction of the dianion derived from **8** with methyl methylthioacetate afforded **15a** in only 20% yield after several investigations of the reaction conditions. Thus, the attempt was abandoned.

Next, methoxyethanol was chosen as a novel side chain. Reaction of the dianion with methyl methoxyacetate gave ketone **15b**, which without purification was reduced with sodium borohydride in methanol. Esterification of the resulting acid with diazomethane afforded an epimeric mixture of hydroxyesters **16a** and **16b** in 53.2% yield. Separation by silica gel chromatography gave the *S*- and *R*-epimers in a 1: 2 ratio. The stereochemistry of the side chain of the products was established later by comparing the ^1H NMR spectrum of compound **20a** with that of compound **20b**.

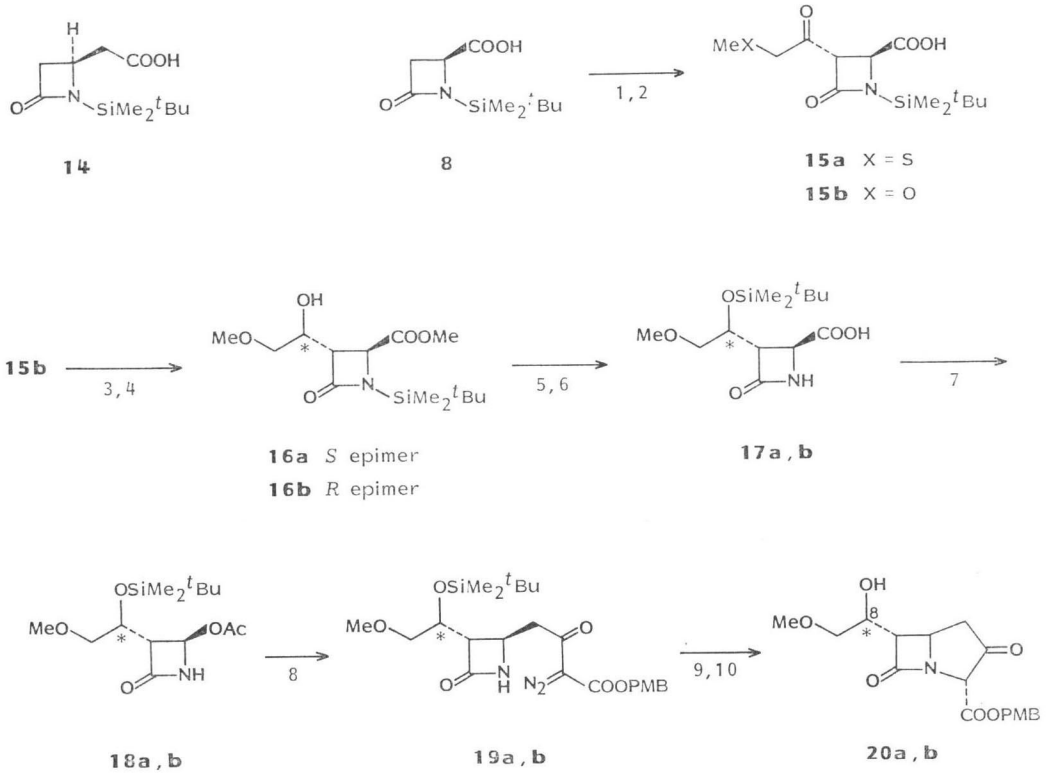
tert-Butyldimethylsilylation of the alcohol **16a** using *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide, followed by alkaline hydrolysis with one equivalent of sodium hydroxide in aqueous methanol at 0°C afforded carboxylic acid **17a** in 90% yield. Compound **17a** was converted

Scheme 2.



1: 2LDA (Lithium diisopropylamide), 2: acetone, 3: ClCOOEt, Et_3N, 4: CH_2N_2, 5: $(C_6H_5)_2$-CHOH, Et_3N, C_6H_5COOAg, 6: Pd-C, H_2, 7: carbonyldiimidazole, $CH_2\langle^{COOH}_{COOPMB}$, $Mg(OMe)_2$, 8: $Et_4NF\cdot 2H_2O$, AcOH, 9: *p*-TsN_3, Et_3N, 10: $Rh_2(OAc)_4$, 11: $(PhO)_2POCl$, $(^iPr)_2NEt$, 12: **5a, b** $HSCH_2CH_2NHR$ (**5a** R=Ac, **5b** R=COOPMB), $(^iPr)_2NEt$, 13: $AlCl_3$, anisole.

Scheme 3.



1: 2LDA, 2: $MeXCH_2COOMe$ (X=S, O), 3: $NaBH_4$, 4: CH_2N_2, 5: $^tBuMe_2SiCl$, imidazole, 6: NaOH, 7: $Pb(OAc)_4$, 8: **3a** $CH_2=C(OSiMe_3)C(N_2)COOPMB$, ZnI_2, 9: $Et_4NF\cdot 2H_2O$, AcOH, 10: $Rh_2(OAc)_4$.

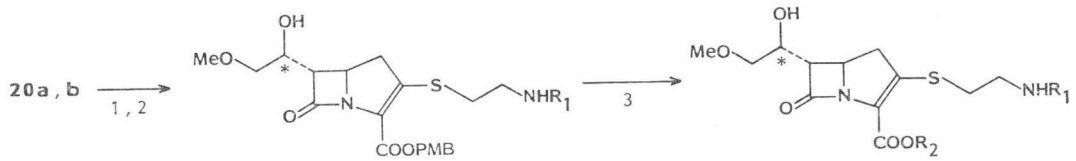
to **18a** with lead tetraacetate and then to **19a** by stereo-selective C-C bond formation using silylenolate **3a**[20] in the presence of zinc iodide. Diazoketoester **19a** was transformed into bicyclic ketone **20a** in 64.7% yield by the following established sequence: 1) removal of the *O*-silyl-protecting group with tetraethylammonium fluoride in tetrahydrofuran at room temperature and 2) cyclization with a catalytic amount of rhodium acetate in benzene. Compound **20b** was also obtained by reactions of **16b** under conditions similar to the above. The stereochemistry at the C-8 position of **20a** and **20b** was confirmed by analysis of their ^{1}H NMR spectra. Since the configuration in 8-*R* epimers of thienamycin series corresponds to that in 8-*S* epimers of its 9-methoxy derivatives, the following results previously observed in carbapenems[21~25] were applied to this case. First, the C-6 protons in 8-*R* carbapenem derivatives with the hydroxyethyl side chain are always observed in higher field than that of 8-*S* epimers, and second, coupling constants $J_{6,8}$ of the 8-*R* epimer are significantly larger. The C-6 proton in **20a** was observed at δ 3.25 with $J_{6,8}$=8 Hz, whereas δ 3.32 with $J_{6,8}$=4 Hz was observed for **20b**. Accordingly, we concluded that compound **20a** is the 8-*S* epimer and **20b** is the 8-*R* one.

Incorporation of the cysteamine derivatives **5a, b** into **20a, b** was carried out by the usual procedure[13] and afforded four compounds, **21a**, **21b**, **21c** and **21d**, in moderate yields. Final deprotection of these esters by treatment with aluminum trichloride and anisole under a mild condition[2] proceeded smoothly to afford carboxylate derivatives **22a**, **22b** (*i.e.*, 9-methoxythienamycin), **22c** and **22d** respectively in satisfactory yields.

Antimicrobial Activity

The *in vitro* antibacterial activity of compounds **22a**, **22b**, **22c** and **22d** was tested by serial agar

Scheme 4.



21a: 8*S*, R_1 = Ac
21b: 8*S*, R_1 = COOPMB
21c: 8*R*, R_1 = Ac
21d: 8*R*, R_1 = COOPMB

22a: 8*S*, R_1 = Ac, R_2 = Na
22b: 8*S*, R_1 = R_2 = H
22c: 8*R*, R_1 = Ac, R_2 = Na
22d: 8*R*, R_1 = R_2 = H

1: $(PhO)_2POCl$, $(^iPr)_2NEt$, 2: **5a, b**, $(^iPr)_2NEt$, 3: $AlCl_3$, anisole.

Table 1. Antibacterial activity of compounds **22a**, **22b**, **22c**, **22d** and thienamycin.

Organism	MIC (μg/ml)				
	22a	**22b***	**22c**	**22d**	Thienamycin
Staphylococcus aureus C-14 (*R*)	1.6	0.8	1.6	0.8	0.05
S. pyogenes C-203	1.8	0.4	0.8	0.2	N.D.
Escherichia coli EC-14	6.3	12.5	6.3	25	0.4
Klebsiella pneumoniae SRL-1	6.3	12.5	6.3	25	0.8
Proteus vulgaris CN329	12.5	25	12.5	25	0.8
Serratia marcescense 13880	25	100	12.5	50	1.6
Pseudomonas aeruginosa 25619	>100	100	>100	50	3.1

* 9-Methoxythienamycin.
N.D.: Not determined.

dilution method. The minimal inhibitory concentrations (MIC) against Gram-positive and Gram-negative bacteria including β-lactamase-producing strains are listed in Table 1 and can be compared with those of thienamycin. These compounds showed moderate antibacterial activity, which did not exceed that of thienamycin. It is very interesting that the 8-*R* epimers **22c** and **22d** show antibacterial activity comparable to that of their 8-*S* epimers **22a** and **22b**, respectively, in contrast with the case of thienamycin and its C-8 epimer[26].

Experimental

General Methods

All reactions were carried out under anhydrous conditions in a nitrogen atmosphere with anhydrous solvents dried over type 4 Å molecular sieves. Melting points were determined on a Yanagimoto apparatus and were not corrected. IR spectra were recorded on a Hitachi 215 spectrometer. ^{1}H NMR spectra were measured on a Varian T60-A or EM-390 spectrometer with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (in D_2O) as an internal reference. UV spectra were recorded on a Hitachi 323 spectrometer. For column chromatography, silica gel (Merck Silica Gel 60) or Merck's Lobar column was used.

Preparation of Trimethylsilyl Enol Ether of *p*-Methoxybenzyl α-Diazoacetoacetate (**3a**)[20]

A mixture of *p*-methoxybenzyl alcohol (12.47 ml, 0.1 mol), diketene (7.83 ml, 0.1 mol) and a catalytic amount of sodium acetate (0.6 g) was heated for 1.5 hours at 80°C, cooled to room temperature, and partitioned between ethyl acetate and water. The organic phase was washed with water, dried over sodium sulfate and concentrated *in vacuo*, giving 16.3 g of colorless oil which was treated with *p*-toluenesulfonylazide (14.4 g, 73.3 mmol) and triethylamine (10.2 ml, 73.3 mmol) in acetonitrile (80 ml) at 0°C. The mixture was stirred for 1 hour at 0°C, diluted with ethyl acetate and washed with 0.2 N HCl. The ethyl acetate solution was washed with water, dried over sodium sulfate and concentrated *in vacuo* to obtain the crude product. These crystals were washed with methylene chloride and chromatography of the filtrate on silica gel eluted with 10% ethyl acetate in *n*-hexane gave 17.1 g (68.9%) of *p*-methoxybenzyl α-diazoacetoacetate as pale yellow prisms: mp 55°C; IR ($CHCl_3$) 2140, 1715, 1658, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.77 (s, 3H), 5.17 (s, 2H), 6.73~7.30 (m, 4H). To a solution of hexamethyldisilazane (422 μl, 2 mmol) in THF (1 ml), *n*-butyllithium (1.6 M solution in *n*-hexane, 1.25 ml, 2 mmol) was added at 0°C and the mixture was stirred for 15 minutes at 0°C. The solution was added to a solution of the diazoester obtained above (496 mg, 2 mmol), tetramethylethylenediamine (302 μl, 2 mmol) and trimethylsilyl chloride (256 μl, 2 mmol) in THF (2 ml) at −78°C. The mixture was warmed to 0°C over 1 hour and *n*-hexane (20 ml) was added. The resulting pale yellow precipitate was removed by filtration and concentration of the filtrate *in vacuo* gave 642 mg (100%) of **3a**: Yellow oil; ^{1}H NMR (benzene-d_6) δ 0.21 (s, 9H), 3.40 (s, 3H), 4.50 (d, J=2 Hz, 1H), 5.14 (s, 2H), 5.66 (d, J=2 Hz, 1H), 6.70~7.35 (m, 4H). This compound was used immediately for the next reaction without purification. Enol silylate **3b** was also obtained by the above method. **3b** (60.0%): Yellow oil; ^{1}H NMR (benzene-d_6) δ 0.22 (s, 9H), 4.55 (d, J=2 Hz, 1H), 5.68 (d, J=2 Hz, 1H), 6.91 (s, 1H), 7.23~7.50 (m, 10H).

Diazo Ketoester **4a** (General Procedure for Compounds **4b, c**)

To a solution of **2a**[8] (495 mg, 3.15 mmol) and zinc chloride (1.01 g, 3.15 mmol) in methylene chloride, a solution of enol silylate **3a** (2.53 g, 7.88 mmol) in methylene chloride was added at 0°C. The reaction mixture was stirred for 2.5 hours at room temperature and partitioned between ethyl acetate and 2 N HCl. The organic solution was washed with water, dried over sodium sulfate and concentrated *in vacuo*. Chromatography of the residue on silica gel eluted with 20% ethyl acetate in benzene gave 544 mg (50.0%) of **4a**: Colorless prisms; mp 117~119°C; IR ($CHCl_3$) 3410, 2140, 1760, 1715, 1650, 1615, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J=7 Hz, 3H), 1.77 (quintet, J=7 Hz, 2H), 2.66~2.96 (m, 1H), 2.96 (dd, J=18, 9 Hz, 1H), 3.42 (dd, J=18, 4 Hz, 1H), 3.56~3.80 (m, 1H), 3.80 (s, 3H), 5.23 (s, 2H), 6.07 (br s, 1H), 6.86~7.43 (m, 4H).

Anal Calcd for $C_{17}H_{19}N_3O_5$: C 59.11, H 5.56, N 12.17.
Found: C 59.27, H 5.52, N 12.06.

Compound **4b** (51.4%): Pale yellow oil; IR ($CHCl_3$) 3410, 2140, 1760, 1718, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, J=7 Hz, 3H), 1.73 (quintet, J=7 Hz, 2H), 2.70~2.95 (m, 1H), 3.03~3.26 (m, 2H), 3.50~3.80 (m, 1H), 6.20 (br s, 1H), 6.97 (s, 1H), 7.30~7.56 (m, 10H). Compound **4c** (50.2%): Pale yellow oil; IR ($CHCl_3$) 3410, 2140, 1760, 1718, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.30 (s, 3H), 2.90 (dd, J=18, 8 Hz, 1H), 3.26 (dd, J=18, 5 Hz, 1H), 3.70 (dd, J=8, 5 Hz, 1H), 7.00 (s, 1H), 7.25~7.50 (m, 10H).

Cysteamine Derivatives **5a, b**

N-Acetylcysteamine **5a** was prepared according to the reported procedure[27]. Compound **5b** was prepared as follows. A solution of cysteamine (1.54 g, 20 mmol), *p*-methoxybenzyl *S*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate (3.04 g, 10 mmol) in ethyl acetate (30 ml) was stirred for 1.5 hours at room temperature. The reaction mixture was concentrated *in vacuo* and chromatography of the residue on silica gel eluted with 5% ethyl acetate in benzene gave 1.06 g (44.0%) of **5b**: Colorless prisms; mp 40°C; ^1H NMR ($CDCl_3$) δ 1.33 (t, J=9 Hz, 1H), 2.60 (dt, J=9, 6 Hz, 2H), 3.33 (q, J=6 Hz, 2H), 3.77 (s, 3H), 5.02 (s, 2H), 5.33 (br s, 1H), 6.77~7.43 (m, 4H).

Anal Calcd for $C_{11}H_{15}NO_3S$: C 54.74, H 6.28, N 5.81.
Found: C 54.60, H 6.25, N 5.77.

Benzhydryl Ester of (±)-PS-5, **6a** (General Procedure for Compounds **6b, c**)

A solution of **4b** (420 mg, 1.07 mmol) and a catalytic amount of rhodium acetate in benzene (50 ml) was stirred for 10 minutes at 80°C. The mixture was concentrated and chromatography of the residue on silica gel eluted with 20% ethyl acetate in benzene afforded 180 mg (46.4%) of bicyclic ketone: Colorless prisms; mp 123~125°C; IR ($CHCl_3$) 1780, 1767, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (t, J=7 Hz, 3H), 1.86 (quintet, J=7 Hz, 2H), 2.30 (dd, J=18, 8 Hz, 1H), 2.80 (dd, J=18, 6 Hz, 1H), 3.04 (td, J=7, 2 Hz, 1H), 3.80 (m, 1H), 4.77 (s, 1H), 6.85 (s, 1H), 7.23~7.60 (m, 10H).

Anal Calcd for $C_{22}H_{21}NO_4$: C 72.70, H 5.84, N 3.85.
Found: C 72.97, H 5.74, N 3.80.

The bicyclic ketone (167 mg, 0.46 mmol) was treated with diphenylphosphorochloridate (105 μl, 0.51 mmol) and diisopropylethylamine (88 μl, 0.51 mmol) in acetonitrile (2 ml) at 0°C. After the reaction mixture was stirred for 30 minutes at 0°C, *N*-acetylcysteamine (121 mg, 1.01 mmol) and diisopropylethylamine (0.51 mmol) at 0°C were added and stirring was continued for 1 hour at the same temperature followed by partitioning between ethyl acetate and 0.1 N HCl. The organic phase was washed with water, aqueous 5% sodium bicarbonate, and water, dried over sodium sulfate and concentrated *in vacuo*. Chromatography of the residue on silica gel eluted with 50% ethyl acetate in benzene gave 102 mg (47.9%) of **6a**: Colorless prisms; mp 143~144°C; IR ($CHCl_3$) 3430, 1773, 1688, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, J=7 Hz, 3H), 1.85 (quintet, J=7 Hz, 2H), 1.90 (s, 3H), 2.66~3.60 (m, 7H), 3.93 (td, J=8, 3 Hz, 1H), 6.30 (t, J=6 Hz, 1H), 6.93 (s, 1H), 7.20~7.50 (m, 10H); UV λ_{max} (CH_2Cl_2) 322 nm (ε 12,900).

Anal Calcd for $C_{26}H_{28}N_2O_4S$: C 67.20, H 6.09, N 6.03, S 6.90.
Found: C 66.79, H 5.98, N 5.95, S 7.01.

Compound **6b**: Colorless oil; IR ($CHCl_3$) 1778, 1715, 1613, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, J=7 Hz, 3H), 1.78 (quintet, J=7 Hz, 2H), 2.50~3.50 (m, 7H), 3.60~4.06 (m, 1H), 3.70 (s, 6H), 5.03 (s, 2H), 5.20 (s, 2H), 5.46 (t, J=5 Hz, 1H), 6.78~7.46 (m, 8H); UV λ_{max} (CH_2Cl_2) 317 nm (ε 9,800).

Anal Calcd for $C_{28}H_{32}N_2O_7S \cdot 0.1C_6H_5$: C 62.62, H 6.00, N 5.11, S 5.85.
Found: C 62.72, H 5.95, N 4.89, S 5.94.

Compound **6c**: Colorless prisms; mp 193~195°C; IR ($CHCl_3$) 3440, 1775, 1690, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.47 (s, 3H), 1.90 (s, 3H), 2.67~3.57 (m, 6H), 4.00 (dd, J=10, 9 Hz, 1H), 6.33 (t, J=5 Hz, 1H), 7.00 (s, 1H); UV λ_{max} (CH_2Cl_2) 321 nm (ε 12,300).

Anal Calcd for $C_{26}H_{28}N_2O_4S$: C 67.21, H 6.09, N 6.03, S 6.90.
Found: C 66.78, H 6.00, N 5.85, S 6.87.

Sodium Salt of (±)-PS-5, **7a** (General Procedure for Compounds **7b, c**, Compounds **13a, b** and Compounds **22a~d**)

A stirred solution of **6a** (46.4 mg, 0.1 mmol) in a mixture of anisole (0.8 ml) and methylene chloride (0.2 ml) was cooled to −50°C and treated with aluminum trichloride (33.3 mg, 0.25 mmol). The reaction mixture was stirred for 30 minutes at −50°C, quenched with aqueous 5% sodium bicarbonate solution (3 ml) at the same temperature and partitioned between ethyl acetate and water. The resulting precipitates were removed by filtration and the filtrate was separated. The aqueous phase was passed through Diaion HP-20 (30 ml) column, with elution with deionized water followed by freeze-drying and gave 18.0 mg (56.3%) of **7a** as a pale yellow powder: mp 135~142°C (dec); identical in all respects (UV, IR, ^{1}H NMR, HPLC) except for biological activity (half of (+)-PS-5) with natural PS-5.

Compound **7b** (53.6%): mp 140°C (dec); IR (KBr) 1766, 1570 cm^{-1}; UV λ_{max} (H_2O) 297 nm (ε 6,800).

Anal Calcd for $C_{11}H_{16}N_2O_3S \cdot 0.7H_2O$: C 49.12, H 6.53, N 10.42.
Found: C 49.01, H 6.43, N 10.18.

Compound **7c** (56.3%): Pale yellow powder; mp 150°C (dec); IR (KBr) 1753, 1655, 1596, 1553 cm^{-1}; UV λ_{max} (H_2O) 300 nm (ε 8,600).

Anal Calcd for $C_{13}H_{17}N_2O_4SNa \cdot H_2O$: C 46.14, H 5.67, N 8.28.
Found: C 46.31, H 6.00, N 8.07.

6-Epicarpetimycin derivative **13a** (47.6%): Colorless powder; IR (KBr) 3400, 1750, 1640, 1586, 1552, 1394 cm^{-1}; UV λ_{max} (H_2O) 302 nm (ε 8,800); ^{1}H NMR (D_2O-TMS as an external reference) δ 1.76 (s, 3H), 1.81 (s, 3H), 2.44 (s, 3H), 3.30~3.90 (m, 6H), 3.87 (d, J=2.7 Hz, 1H), 4.64 (td, J=9, 2.7 Hz, 1H).

Anal Calcd for $C_{14}H_{19}N_2O_5SNa \cdot 1.4H_2O$: C 44.77, H 5.85, N 7.46.
Found: C 44.81, H 5.64, N 7.79.

Compound **13b** (56.7%): Pale yellow powder; IR (KBr) 3385, 1755, 1580, 1387 cm^{-1}; UV λ_{max} (H_2O) 298 nm (ε 6,800); ^{1}H NMR (D_2O-TMS (ext)) δ 1.76 (s, 3H), 1.81 (s, 3H), 3.20~3.80 (m, 6H), 3.91 (d, J=2.8 Hz, 1H), 4.67 (td, J=9, 2.8 Hz, 1H).

Anal Calcd for $C_{12}H_{18}N_2O_4S \cdot 1.5H_2O$: C 45.99, H 6.75, N 8.94.
Found: C 46.13, H 6.51, N 8.85.

9-Methoxythienamycin derivative **22a** (60%): Pale yellow powder; IR (KBr) 1750, 1655, 1590 cm^{-1}; UV λ_{max} (H_2O) 301 nm (ε 4,800); ^{1}H NMR (D_2O) δ 1.98 (s, 3H), 2.88, 2.98 (AB qd, J=14, 7 Hz, 2H), 3.10, 3.24 (AB qd, J=17, 10, 8 Hz, 2H), 3.39 (s, 3H), 3.30~3.64 (m, 5H), 4.10~4.32 (m, 2H). Compound **22b** (36%): Pale yellow powder; IR (Nujol) 1753, 1575 cm^{-1}; UV λ_{max} (H_2O) 299 nm (ε 6,100); ^{1}H NMR (D_2O) δ 2.90~3.32 (m, 6H), 3.40 (s, 3H), 3.52, 3.60 (AB qd, J=10, 6, 4 Hz, 2H), 3.54 (m, 1H), 4.16~4.34 (m, 2H). Compound **22c** (29%): Pale yellow powder; mp 130°C (dec); IR (KBr) 1755, 1660, 1610 cm^{-1}; UV λ_{max} (H_2O) 301 nm (ε 3,900); ^{1}H NMR (D_2O) δ 1.98 (s, 3H), 2.88, 2.97, (AB qd, J=14, 8, 6 Hz, 2H), 3.11, 3.25 (AB qd, J=17, 9 Hz, 2H), 3.30~3.70 (m, 5H), 3.40 (s, 3H), 4.10~4.32 (m, 2H). Compound **22d** (24%): Pale yellow powder; IR (KBr) 1755, 1583 cm^{-1}; UV λ_{max} (H_2O) 299 nm (ε 4,600); ^{1}H NMR (D_2O) δ 2.86~3.65 (m, 9H), 3.40 (s, 3H), 4.10~4.30 (m, 2H).

Hydroxycarboxylic Acid **9**

To a solution of diisopropylamine (6.53 ml, 46.6 mmol) in THF (50 ml), *n*-butyllithium (1.6 M solution in *n*-hexane, 29.1 ml, 46.6 mmol) was added at −10°C. After stirring for 10 minutes at −10°C, the mixture was added to a solution of compound **8** (5.34 g, 23.3 mmol) in THF (40 ml) at −78°C. Next, acetone (6 ml) was added, and the mixture was gradually warmed to −20°C and then partitioned between ethyl acetate and 0.1 N HCl. The organic phase was washed with water, dried over magnesium sulfate and concentrated *in vacuo*, giving 3.80 g (56.8%) of **9** as colorless prisms: mp 141°C; IR ($CHCl_3$) 3450, 3075, 1738, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 3H), 0.30 (s, 3H), 0.98 (s, 9H), 1.33 (s, 3H), 1.42 (s, 3H), 3.28 (d, J=3 Hz, 1H), 4.13 (d, J=3 Hz, 1H), 6.43 (br, s 2H); $[\alpha]_D^{24}$ −45.3±0.4° (*c* 1.0, MeOH).

Anal Calcd for $C_{13}H_{25}NO_4Si$: C 54.31, H 8.78, N 4.87.
Found: C 54.56, H 8.81, N 4.76.

Homologated Carboxylic Acid **10**

To a solution of **9** (3.23 g, 11.23 mmol) in THF (30 ml) were added triethylamine (1.71 ml, 12.35 mmol) and ethylchloroformate (1.18 ml, 12.35 mmol) at 0°C. The mixture was stirred for 45 minutes at 0°C, treated with excess of diazomethane in ether and stirred for 3 hours at 0°C. The reaction mixture was partitioned between ethyl acetate and 0.01 N HCl. Concentration of the organic phase *in vacuo* gave a pale yellow oil (diazoketone). To a solution of this diazoketone in THF (50 ml), diphenylmethanol (18.37 g, 112.3 mmol), triethylamine (1.56 ml, 11.2 mmol) and a catalytic amount of silver benzoate were added at room temperature. The mixture was stirred for 30 minutes at 40°C, poured into 0.1 N HCl and extracted with ethyl acetate. The ethyl acetate phase was washed with water, dried over sodium sulfate and concentrated *in vacuo*. The resulting crystals (diphenylmethanol) were removed by filtration and concentration of the filtrate gave a colorless oil, which when hydrogenated in ethanol (40 ml) with 10% palladium carbon afforded 2.00 g (59.2%) of **10** as colorless prisms: mp 90°C; IR ($CHCl_3$) 3380, 1730, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.23 (s, 3H), 0.27 (s, 3H), 0.97 (s, 9H), 1.32 (s, 6H), 2.50 (dd, J=17, 9 Hz, 1H), 2.94 (dd, J=17, 4 Hz, 1H), 3.10 (d, J=2.5 Hz, 1H), 3.85 (ddd, J=9, 4, 2.5 Hz, 1H), 6.93 (br s, 2H); $[\alpha]_D^{21}$ $-50.0\pm0.9°$ (c 1.0, MeOH).

Anal Calcd for $C_{14}H_{27}NO_4Si$: C 55.77, H 9.04, N 4.65.
Found: C 55.79, H 9.03, N 4.67.

Diazoketoester **11**

Magnesium methoxide (0.94 M solution in methanol, 5.76 ml, 5.43 mmol) was added to a solution of mono-*p*-methoxybenzyl malonate (2.44 g, 10.87 mmol) in THF (8 ml) at 0°C. The mixture was stirred for 10 minutes at 20°C and concentrated *in vacuo*. A solution of the residue in THF (6 ml) was added to a solution of **10** (745 mg, 2.47 mmol) and carbonyldiimidazole (440 mg, 2.72 mmol) in THF (4 ml). The reaction mixture was stirred for 1.5 hours at room temperature, poured into 0.1 N HCl and extracted with ethyl acetate. The organic layer was concentrated and the residue was chromatographed on silica gel eluted with benzene - ethyl acetate (2: 1), giving 953 mg of ketoester as a colorless oil. The oil was dissolved in a mixture of THF (36 ml) and acetic acid (0.5 ml) and treated with tetrabutylammonium fluoride dihydrate (306 mg, 2.05 mmol) for 1 hour at 0°C. The reaction mixture was poured into cold 0.2 N HCl and extracted with ethyl acetate. The organic layer was washed with 5% aqueous sodium bicarbonate solution, dried over magnesium sulfate and concentrated *in vacuo*, giving 710 mg of *N*-desilylated product as a colorless oil. The oil was treated with *p*-toluenesulfonylazide (800 mg, 4.06 mmol) and triethylamine (564 μl, 4.06 mmol) in acetonitrile (10 ml) for 30 minutes at 0°C. Usual workup gave a crude oil, which was chromatographed on silica gel eluted with 50% benzene in ethyl acetate and afforded 691 mg (75.0%) of **11** as a colorless foam: IR ($CHCl_3$) 3410, 2150, 1762, 1718, 1652, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.37 (s, 3H), 2.51 (br s, 1H), 2.70~3.50 (m, 3H), 3.77 (s, 3H), 3.92 (m, 1H), 5.15 (s, 2H), 6.27 (br s, 1H), 6.81~7.19 (m, 4H).

p-Methoxybenzyl Esters of 6-Epicarpetimycin Derivative **12a**

A solution of **11** (1.28 g, 3.41 mmol) and rhodium acetate (64 mg) in benzene (300 ml) was stirred for 20 minutes at 80°C. The catalyst was removed by decantation and the pale green solution was concentrated *in vacuo*, giving crude crystals, which were recrystallized from ether and afforded 886 mg (74.8%) of bicyclic ketone. To a solution of the above ketone (200 mg, 0.58 mmol) in acetonitrile (4 ml), diphenylphosphorochloridate (131 μl, 0.64 mmol) and diisopropylethylamine (111 μl, 0.64 mmol) were added at 0°C. After stirring for 20 minutes at 0°C, *N*-acetylcysteamine (152 mg, 1.28 mmol) and diisopropylethylamine (111 μl, 0.64 mmol) were added to the mixture, which was stirred for 1 hour at 0°C, poured into 0.1 N HCl, and extracted with ethyl acetate. Usual workup gave the crude product which was chromatographed on silica gel eluted with ethyl acetate - methanol (30: 1) and afforded 125 mg (48.1%) of **12a**: Colorless prisms; mp 97~99°C; IR (Nujol) 3550, 3395, 1780, 1688, 1662, 1603 cm^{-1}; UV λ_{max} (MeOH) 226 nm (ε 13,800), 275 (3,900), 282 (4,400), 319 (12,100); $[\alpha]_D^{20}$ $+35.8\pm1.4°$ (c 0.5, MeOH); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.38 (s, 3H), 1.95 (s, 3H), 2.33 (m, 1H), 2.73~3.60 (m, 7H), 3.77 (s, 3H), 4.18 (td, J=9, 2.5 Hz, 1H), 5.20 (s, 2H), 6.17 (m, 1H), 6.84~7.33 (m, 4H).

Anal Calcd for $C_{22}H_{28}N_2O_6S \cdot 0.8H_2O$: C 57.07, H 6.45, N 6.05, S 6.93.
Found: C 56.87, H 6.12, N 5.96, S 6.81.

Diester **12b** was obtained by the above procedure by using *N*-*p*-methoxybenzyloxycarbonyl cysteamine in place of *N*-acetylcysteamine. (61.6%); Colorless foam; IR ($CHCl_3$) 3450, 1779, 1715, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.35 (s, 3H), 2.02 (m, 1H), 2.37 (m, 1H), 2.67~3.47 (m, 7H), 3.73 (s, 6H), 4.10 (td, J=9, 2.5 Hz, 1H), 4.98 (s, 2H), 5.17 (s, 2H), 6.80~7.28 (m, 8H).

Methylthiomethyl Ketone **15a**

To a solution of diisopropylamine (2.05 ml, 14.04 mmol) in THF, *n*-butyllithium (1.6 M solution in *n*-hexane, 8.79 ml, 14.04 mmol) was added at −20°C. After stirring for 10 minutes at −10°C, the mixture was added to a solution of compound **8** (1.61 g, 7.02 mmol) in THF (28 ml) at −78°C. The reaction mixture was stirred for 5 minutes at −78°C, methyl methylthioacetate (1.69 g, 14.04 mmol) was added, and the mixture was gradually warmed to 0°C over 2 hours. The reaction mixture was partitioned between ethyl acetate and 0.2 N HCl. The organic phase was washed with water and extracted with aqueous 5% sodium bicarbonate solution. The aqueous solution was washed with ethyl acetate, acidified with 2 N HCl, and extracted with ethyl acetate. Drying the organic solution over sodium sulfate and concentrating it *in vacuo* gave the acylated carboxylic acid **15a**, which was characterized by transforming it into the methyl ester with diazomethane. The crude product was chromatographed on silica gel eluted with 10% ethyl acetate in *n*-hexane and afforded 434 mg (20%) of the methyl ester of **15a** (colorless oil): IR ($CHCl_3$) 1753, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 3H), 0.30 (s, 3H), 0.95 (s, 9H), 2.13 (s, 3H), 3.31, 3.43 (AB q, J=15 Hz, 2H), 3.77 (s, 3H), 4.43 (d, J=2.5 Hz, 1H), 4.75 (d, J=2.5 Hz, 1H).

Hydroxy Ester **16a, b**

Carboxylic acid **15b** was obtained in the same manner as the thio-analogue **15a**. The methoxy analogue **15b** (11.1 g, 36.8 mmol) prepared from **8** and methyl methoxyacetate was dissolved in methanol (100 ml) and treated with sodium borohydride (1.4 g, 36.8 mmol) at 0°C. The mixture was stirred for 1 hour at 0°C and partitioned between ethyl acetate and 1 N HCl. The organic phase was washed with water, dried over sodium sulfate and concentrated *in vacuo*, giving 8.8 g (66% from **8**) of the alcohol. Esterification of this alcohol with diazomethane followed by separation using silica gel chromatography eluted with benzene - ethyl acetate (2: 1) afforded 4.1 g (53.8%) of **16b** and 2.1 g (26.9%) of **16a**. **16a**: Colorless gum; IR ($CHCl_3$) 3450, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.29 (s, 3H), 0.96 (s, 9H), 3.13~3.70 (m, 3H), 3.37 (s, 3H), 3.77 (s, 3H), 4.17 (m, 1H), 4.20 (d, J= 3 Hz, 1H). **16b**: Colorless gum; IR ($CHCl_3$) 3500, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.25 (s, 3H), 0.95 (s, 9H), 2.95 (br s, 1H), 3.30~3.67 (m, 3H), 3.37 (s, 3H), 3.73 (s, 3H), 3.95~4.30 (m, 1H), 4.13 (d, J=3 Hz, 1H).

O-Silylated Carboxylic Acid **17a**

To a solution of **16a** (1.00 g, 3.15 mmol) in dimethylformamide (7 ml), *tert*-butyldimethylsilyl chloride (1.42 g, 9.45 mmol) and imidazole (0.64 g, 9.45 mmol) were added at 0°C. The mixture was stirred for 1 hour at room temperature, allowed to stand overnight and partitioned between ethyl acetate and 0.1 N HCl. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel eluted with 2% ethyl acetate in *n*-hexane and gave 1.35 g of *O*-silylated ester as a colorless oil. A solution of the oil in methanol (85 ml) was treated with 0.1 N NaOH (31.5 ml) at 0°C. The mixture was stirred for 1 hour at 0°C, diluted with ethyl acetate and washed with 0.1 N HCl. The organic phase was extracted with aqueous 5% sodium bicarbonate solution. The aqueous solution was washed with ethyl acetate, acidified with 2 N HCl and extracted with ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and concentrated *in vacuo*, giving 860 mg (90.0%) of **17a**: Colorless prisms; mp 105~106°C; IR ($CHCl_3$) 3400, 3400~ 2400, 1780, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 6H), 0.89 (s, 9H), 3.40 (s, 3H), 3.20~3.73 (m, 3H), 4.05~4.45 (m, 1H), 4.42 (d, J=2.5 Hz, 1H), 6.96 (br s, 1H), 9.38 (br s, 1H).

Anal Calcd for $C_{13}H_{25}NO_5Si$: C 51.14, H 8.32, N 4.62.
Found: C 51.17, H 8.35, N 4.66.

Compound **17b** was obtained by the same procedure (68.1%): Colorless needles; mp 98~100°C; IR ($CHCl_3$) 3425, 3500~2400, 1779, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.89 (s, 9H), 3.37 (s, 3H), 3.40~3.65 (m, 1H), 3.55 (d, J=6 Hz, 2H), 4.12 (d, J=2.5 Hz, 1H), 3.93~4.30 (m, 1H), 6.95 (br s, 1H), 9.33 (br s, 1H).

Anal Calcd for $C_{13}H_{25}NO_5Si \cdot 0.5H_2O$ (hygroscopic): C 49.96, H 8.40, N 4.48.
Found: C 50.02, H 8.45, N 4.40.

4-Acetoxy Azetidinone **18a**

A solution of **17a** (1.00 g, 3.29 mmol), acetic acid (3 ml) and lead tetraacetate (1.75 g, 6.58 mmol) in dimethylformamide (6 ml) was stirred for 15 minutes at 65°C and then diluted with ethyl acetate. The solution was washed with water, dried over sodium sulfate and concentrated *in vacuo*. Chromatography of the residue on silica gel eluted with 10% ethyl acetate in benzene afforded 934 mg (89.5%) of **18a**: Colorless prisms; mp 86~88°C; IR ($CHCl_3$) 3410, 1785, 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.86 (s, 9H), 2.08 (s, 3H), 3.35 (s, 3H), 3.35~3.55 (m, 1H), 3.39 (d, J=6 Hz, 2H), 4.20 (td, J=6, 3 Hz, 1H), 5.91 (d, J=1.5 Hz, 1H), 6.91 (br s, 1H).

Anal Calcd for $C_{14}H_{27}NO_5Si$: C 52.96, H 8.59, N 4.41.
Found: C 52.96, H 8.63, N 4.39.

Compound **18b** was prepared by the above reaction (85.2%): Colorless needles; mp 69~70°C; IR ($CHCl_3$) 3410, 1783, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 6H), 0.87 (s, 9H), 2.07 (s, 3H), 3.33 (s, 3H), 3.35~3.57 (m, 1H), 3.50 (d, J=6 Hz, 2H), 4.20 (td, J=6, 3 Hz, 1H), 5.72 (d, J=1.5 Hz, 1H), 6.70 (br s, 1H).

Anal Calcd for $C_{14}H_{27}NO_5Si$: C 52.96, H 8.59, N 4.41.
Found: C 52.95, H 8.65, N 4.39.

Diazo Ketoester **19a**

To a solution of **18a** (1.00 g, 3.15 mmol) and zinc iodide (1.01 g, 3.15 mmol) in methylene chloride, a solution of enol silylate **3a** (2.53 g, 7.88 mmol) in methylene chloride was added at 0°C. The reaction mixture was stirred for 2.5 hours at room temperature and partitioned between ethyl acetate and 2 N HCl. The organic solution was washed with water, dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel eluted with 20% ethyl acetate in benzene and gave 830 mg (52.1%) of **19a**: Pale yellow gum; IR ($CHCl_3$) 3410, 2140, 1758, 1710, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.88 (s, 9H), 2.97, 3.40 (AB qd, J=18, 9, 4 Hz, 2H), 3.06 (t, J=3 Hz, 1H), 3.32 (s, 3H), 3.36 (d, J=3 Hz, 2H), 3.81 (s, 3H), 4.15 (m, 2H), 5.19 (s, 2H), 6.10 (br s, 1H), 6.83~7.43 (m, 4H). Compound **19b** was obtained by the same procedure (41.0%): Colorless gum; IR ($CHCl_3$) 3410, 2140, 1760, 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 3.00~3.37 (m, 3H), 3.33 (s, 3H), 3.50 (d, J=6 Hz, 2H), 3.80 (s, 3H), 4.10 (m, 2H), 5.18 (s, 2H), 5.96 (br s, 1H), 6.77~7.43 (m, 4H).

Bicyclic Ketone **20a**

A mixture of **19a** (830 mg, 1.64 mmol), acetic acid (3.76 ml) and tetraethylammonium fluoride dihydrate (2.45 g, 16.4 mmol) in THF was allowed to stand for 10 days at room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel eluted with 50% ethyl acetate in benzene and gave the *O*-desilylated product. To a solution of the above alcohol in benzene (60 ml), rhodium acetate (20 mg) was added and the mixture was stirred for 15 minutes at 80°C, then cooled to 20°C. After decantation to remove the catalyst, the solution was concentrated *in vacuo* and the resulting crystals were washed with ether, giving 385 mg (64.7%) of **20a**: Colorless prisms; mp 103~104°C; IR ($CHCl_3$) 3530, 1770, 1748, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (br s, 1H), 2.40, 2.84 (AB qd, J=18, 7 Hz, 2H), 3.25 (dd, J=8, 2 Hz, 1H), 3.38 (s, 3H), 3.44, 3.58 (AB qd, J=9, 6, 3 Hz, 2H), 3.78 (s, 3H), 4.00~4.30 (m, 2H), 4.64 (s, 1H), 5.10 (s, 2H), 6.76~7.36 (m, 4H).

Anal Calcd for $C_{18}H_{21}NO_7$: C 59.49, H 5.84, N 3.86.
Found: C 59.19, H 5.82, N 3.93.

Compound **20b** was prepared by the same procedure (68.6%): Colorless prisms; mp 108°C; IR

($CHCl_3$) 3500, 1768, 1745, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41, 2.83 (AB qd, J=19, 8 Hz, 2H), 2.50 (br s, 1H), 3.32 (dd, J=4, 1.5 Hz, 1H), 3.38 (s, 3H), 3.46, 3.53 (AB qd, J=16, 6, 4 Hz, 2H), 3.78 (s, 3H), 3.95~4.31 (m, 2H), 4.66 (s, 1H), 5.10 (s, 2H), 6.78~7.35 (m, 4H).

Anal Calcd for $C_{18}H_{21}NO_7$: C 59.49, H 5.84, N 3.86.
Found: C 59.31, H 5.76, N 3.91.

PMB Ester of 9-Methoxythienamycin Derivative **21a** (General Procedure for Compounds **21b~d**)

To a solution of **20a** (190 mg, 0.52 mmol) in acetonitrile (4 ml), diisopropylethylamine (100 μl, 0.57 mmol) and diphenylphosphorochloridate (119 μl, 0.57 mmol) were added at 0°C. The reaction mixture was stirred for 1 hour at 0°C, treated with *N*-acetylcysteamine (72 μl, 0.68 mmol) and diisopropylethylamine (118 μl, 0.68 mmol) at −15°C, stirred for 5 hours at 0°C, diluted with ethyl acetate, and washed successively with 0.1 N HCl, water, aqueous 1% sodium bicarbonate solution and water. The organic solution was dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel eluted with 10% methanol in ethyl acetate and afforded 49 mg (20.2%) of **21a**: Pale yellow foam; IR ($CHCl_3$) 3440, 1775, 1672, 1608, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (s, 3H), 2.50~3.65 (m, 9H), 3.35 (s, 3H), 3.74 (s, 3H), 3.95~4.40 (m, 2H), 5.18 (s, 2H), 6.36 (t, J= 6 Hz, 1H), 6.75~7.46 (m, 4H).

Compound **21b** (59.5%): Pale yellow foam; IR ($CHCl_3$) 3425, 1772, 1715, 1702, 1608, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30~3.63 (m, 9H), 3.36 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 3.93~4.40 (m, 2H), 5.00 (s, 2H), 5.18 (s, 2H), 5.26 (t, J=6 Hz, 1H), 6.73~7.45 (m, 8H).

Compound **21c** (36.7%): Colorless foam; IR ($CHCl_3$) 3445, 3350, 1778, 1673, 1612, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (s, 3H), 2.60~3.63 (m, 9H), 3.35 (s, 3H), 3.74 (s, 3H), 3.96~4.36 (m, 2H), 5.16 (s, 2H), 6.39 (t, J=6 Hz, 1H), 6.75~7.45 (m, 4H).

Compound **21d** (34.2%): Colorless foam; IR ($CHCl_3$) 3430, 1778, 1715, 1612, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60~3.67 (m, 9H), 3.39 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.95~4.33 (m, 2H), 5.00 (s, 2H), 5.16 (s, 2H), 5.28 (t, J=6 Hz, 1H), 6.70~7.43 (m, 8H).

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