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. 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 required in the final step of all the syntheses because these carbapenems are generally unstable under acidic conditions. 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 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 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 gave 10; 3) carboxymethylation by MASAMUNE's procedure, followed by desilylation and diazotization afforded 11; 4) carbenoid cyclization with rhodium acetate followed by treatment with diphenylphosphorochloridate, diisopropylethylamine and then with cysteamine derivatives 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. 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.

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, is an important procedure in carbapenem chemistry.
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.

![Chemical structures](image)

1: 2LDA (Lithium diisopropylamide), 2: acetone, 3: CICOEt, EtL,N, 4: CH3NH2, 5: (C6H5)2CHOH, EtL,N, C6H5COOAg, 6: Pd-C, H2, 7: carbonyldimidazole, CH2<COOH COOPMB, Mg(OMe)2, 8: Et4NBF4-2H2O, AcOH, 9: p-TsN3, EtL,N, 10: Rh2(OAc)4, 11: (PhO)2POCl, (iPr)NEt, 12: 5a, b HSCH2CH2NHR (5a R=Ac, 5b R=COOPMB), (iPr)2NEt, 13: AlCl3, anisole.

Scheme 3.

![Chemical structures](image)

1: 2LDA, 2: MeXCH2COOMe (X=S, O), 3: NaBH4, 4: CH3NH2, 5: 'BuMe2SiCl, imidazole, 6: NaOH, 7: Pb(OAc)4, 8: 3a CH3—C(OSiMe3)C(NH)COOPMB, ZnL2, 9: Et4NBF4-2H2O, AcOH, 10: Rh2(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 hydroxylethyl 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 \(\delta\ 3.25\) with \(J_{6,8}=8\) Hz, whereas \(\delta\ 3.32\) 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.**

<table>
<thead>
<tr>
<th>Organism</th>
<th>22a</th>
<th>22b*</th>
<th>22c</th>
<th>22d</th>
<th>Thienamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> C-14 (R)</td>
<td>1.6</td>
<td>0.8</td>
<td>1.6</td>
<td>0.8</td>
<td>0.05</td>
</tr>
<tr>
<td><em>S. pyogenes</em> C-203</td>
<td>1.8</td>
<td>0.4</td>
<td>0.8</td>
<td>0.2</td>
<td>N.D.</td>
</tr>
<tr>
<td><em>Escherichia coli</em> EC-14</td>
<td>6.3</td>
<td>12.5</td>
<td>6.3</td>
<td>25</td>
<td>0.4</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> SRL-1</td>
<td>6.3</td>
<td>12.5</td>
<td>6.3</td>
<td>25</td>
<td>0.8</td>
</tr>
<tr>
<td><em>Proteus vulgaris</em> CN329</td>
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<td>25</td>
<td>12.5</td>
<td>25</td>
<td>0.8</td>
</tr>
<tr>
<td><em>Serratia marcescens</em> 13880</td>
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<td>100</td>
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<td>50</td>
<td>1.6</td>
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<tr>
<td><em>Pseudomonas aeruginosa</em> 25619</td>
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<td>100</td>
<td>&gt;100</td>
<td>50</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* 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 epimer26).

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. 1H 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 D2O) 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)

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 (CHCl3) 2140, 1715, 1612 cm⁻¹; 1H NMR (CDCl3) 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 THE (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), tetramethylethylene diamine (302 µl, 2 mmol) and trimethylsilyl chloride (256 µl, 2 mmol) in THE (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; 1H NMR (benzene-d6) 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; 1H NMR (benzene-d6) 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 (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 (CHCl3) 3410, 2140, 1740, 1715, 1650, 1615, 1515 cm⁻¹; 1H NMR (CDCl3) 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).
**Cysteamine Derivatives 5a, b**

*N*-Acetylcysteamine 5a was prepared according to the reported procedure. 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; 'H NMR (CDCl3) S 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, IH), 6.77-7.43 (m, 4H).

**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 (CHCl3) 1780, 1767, 1750 cm⁻¹; 'H NMR (CDCl3) 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 C22H21NO4:** 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 pl, 0.51 mmol) and diisopropylethylamine (88 pl, 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 (CHCl3) 3430, 1773, 1688, 1670 cm⁻¹; 'H NMR (CDCl3) δ 1.05 (t, J=8 Hz, 1H), 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 Amax (CH2Cl2) 321 nm (s 12,300).

**Anal Calcd for C26H28N2O4S:** C 67.21, H 6.09, N 5.85, 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, 1H 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 (H₂O) 297 nm (ε 6,800).

Anal Calcd for C₁₁H₁₆N₂O₃S•0.7H₂O: 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 (H₂O) 300 nm (ε, 8,600).

Anal Calcd for C₁₃H₁₇N₂O₄SNa•H₂O: 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 (H₂O) 302 nm (ε 8,800); 1H NMR (D₂O-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=9.27 Hz, 1H).

Anal Calcd for C₁₄H₁₉N₂O₅SNa•1.4H₂O: 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 (H₂O) 298 nm (ε 6,800); 1H NMR (D₂O-TMS (ext)) δ 1.76 (s, 3H), 1.81 (s, 3H), 2.44–3.00 (m, 6H), 3.30–3.80 (m, 6H), 3.91 (d, J=9 Hz, 1H), 4.67 (td, J=9, 2.8 Hz, 1H).


9-Methoxythienamycin derivative 22a (60%): Pale yellow powder; IR (KBr) 1750, 1655, 1590 cm⁻¹; UV λ_max (H₂O) 301 nm (ε 4,800); 1H NMR (D₂O) 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 (H₂O) 299 nm (ε 6,100); 1H NMR (D₂O-TMS) δ 1.76 (s, 3H), 1.81 (s, 3H), 2.44–3.00 (m, 6H), 3.30–3.80 (m, 6H), 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 (H₂O) 301 nm (ε 3,900); 1H NMR (D₂O) 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 (H₂O) 299 nm (ε 4,600); 1H NMR (D₂O) δ 2.86–3.65 (m, 9H), 3.40 (s, 3H), 4.10–4.30 (m, 2H). Compound 22e (29%): Pale yellow powder; IR (KBr) 1755, 1660, 1610 cm⁻¹; UV λ_max (H₂O) 301 nm (ε 3,900); 1H NMR (D₂O) 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).

9-Methoxythienamycin derivative 22a (60%): Pale yellow powder; IR (KBr) 1750, 1655, 1590 cm⁻¹; UV λ_max (H₂O) 301 nm (ε 4,800); 1H NMR (D₂O) 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).

Hydroxycarboxylic Acid 9

To a solution of disopropylamine (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 (CHCl₃) 3450, 3075, 1738, 1602 cm⁻¹; 1H NMR (CDCl₃) δ 0.15 (s, 3H), 0.30 (s, 3H), 0.98 (s, 3H), 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); [α]D⁰⁻⁴⁵.₃±0.₄° (c 1.0, MeOH).

Anal Calcd for C₁₅H₂₅NO₃Si: 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 ethyl chloroformate (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 (CHCl3) 3380, 1730, 1600 cm⁻¹; ¹H NMR (CDCl3) 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 (dd, J=9, 4, 2.5 Hz, 1H), 6.93 (br s, 2H); [α]D 50.0±0.9° (c 1.0, MeOH).

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 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. Usual workup gave the crude product 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 (CHCl3) 3410, 2150, 1762, 1718, 1652, 1620 cm⁻¹; ¹H NMR (CDCl3) 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) 3400, 3395, 1780, 1688, 1662, 1603 cm⁻¹; UV λmax (MeOH) 226 nm (ε 13,800), 275 (3,900), 282 (4,400), 319 (12,100); [α]D 35.8±1.4° (c 0.5, MeOH); ¹H NMR (CDCl3) 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_{2}O_{6}S·0.8H_{2}O:  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-methoxybenzyloxy carbonyl 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}) 1753, 1705 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}) 1750, 1700 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-butyldimethylsilyle 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, 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_{5}Si:  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 (CHCl₃) 3425, 3500~2400, 1779, 1755 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₃H₂₅NO₅Si·0.5H₂O (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 (CHCl₃) 3410, 1785, 1742 cm⁻¹; ¹H NMR (CDCl₃) δ 0.08 (s, 6H), 0.86 (s, 9H), 2.08 (s, 3H), 3.35 (s, 3H), 3.35~3.57 (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 C₁₄H₂₇NO₅Si: 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 (CHCl₃) 3410, 1783, 1740 cm⁻¹; ¹H NMR (CDCl₃) δ 0.13 (s, 6H), 0.87 (s, 9H), 2.08 (s, 3H), 3.33 (s, 3H), 3.35~3.57 (m, 1H), 3.39 (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 C₁₄H₂₇NO₅Si: C 52.96, H 8.59, N 4.41.
Found: C 52.95, H 8.65, N 4.39.

Diazo Keteoster 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 (CHCl₃) 3410, 2140, 1758, 1710, 1648 cm⁻¹; ¹H NMR (CDCl₃) 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 (CHCl₃) 3410, 2140, 1760, 1710, 1650 cm⁻¹; ¹H NMR (CDCl₃) 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).

Diazo Ketoster 19b

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. 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 (CHCl₃) 3530, 1770, 1748, 1610 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₈H₂₁NO₇: C 59.49, H 5.84, N 3.86.
Found: C 59.19, H 5.82, N 3.93.

Compounds 20b was prepared by the same procedure (68.6%): Colorless prisms; mp 108°C; IR
(CHCl₃) 3500, 1768, 1745, 1610 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₈H₂₁NO₇: 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 with 10% methanol in ethyl acetate and afforded 49 mg (20.2%) of 21a: Pale yellow foam; IR (CHCl₃) 3440, 1775, 1672, 1608, 1508 cm⁻¹; ¹H NMR (CDCl₃) 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 (CHCl₃) 3425, 1772, 1715, 1702, 1608, 1505 cm⁻¹; ¹H NMR (CDCl₃) 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 (CHCl₃) 3445, 3350, 1778, 1673, 1612, 1510 cm⁻¹; ¹H NMR (CDCl₃) 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 (CHCl₃) 3430, 1778, 1715, 1612, 1510 cm⁻¹; ¹H NMR (CDCl₃) 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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