SYNTHETIC CARBAPENEM ANTIBIOTICS I. 1-β-METHYLCARBAPENEM

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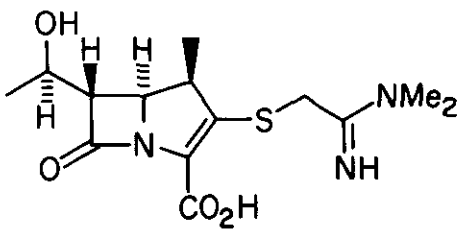
Abstract —— A total synthesis of a novel 1-β-methylcarbapenem antibiotic, (-)-(1R,5S,6S)-2-(2-N,N-dimethylamino-2-iminoethylthio)-6-[(1R)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid **1**, is reported. Compound **1** is highly resistant to renal dipeptidase-I yet retains the excellent antibacterial activities of *N-formimidoylthienamycin.*

Since the discovery of thienamycin, many naturally occurring and synthetic carbapenem antibiotics have been reported.[1] The main thrust of this structural modification work has been directed toward elaborating various new substituents at position C-2 and C-6 on the bicyclic carbapenem nucleus. Nevertheless, none of these carbapenem antibiotics has simultaneously overcome the deficiencies of thienamycin, i.e., chemical instability at high concentration and susceptibility to renal dipeptidase-I[2] while retaining its excellent antibacterial activity. In the search for a chemically and metabolically stable carbapenem antibiotic, we have undertaken a program directed toward the synthesis of 1-substituted carbapenems. Though a few 1-substituted carbapenems have been reported recently,[3] they either do not have optimal substituents at C-2 and C-6 positions of the carbapenem ring system or are devoid of the antibacterial activity of thienamycin. Herein, we wish to report the total synthesis of exceptionally stable and potent 1,2,6-trisubstituted carbapenem antibiotics, a novel 1-β-methylcarbapenem, (-)-(1R,5S,6S)-2-(2-N,N-dimethylamino-2-iminoethylthio)-6-[(1R)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid **1**.



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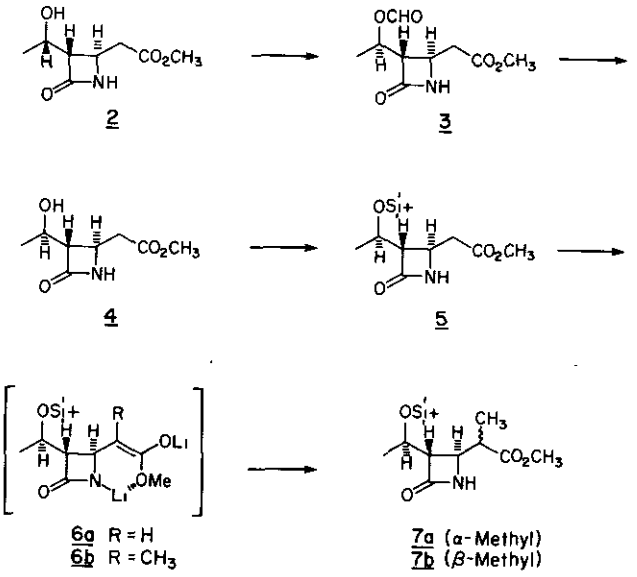
In devising a synthesis of 1-β-methylcarbapenem **1**, it was desirable to utilize intermediates readily available from the chiral synthesis of thienamycin and N-formimidoylthienamycin (MK-787).[4] (3S,4R)-3-[(1S)-1-hydroxyethyl]-4-(methoxycarbonylmethyl)-azetidin-2-one **2** has the desired chirality for the two chiral centers on the β-lactam and is also amenable to facile introduction of a methyl substituent at the pro-1 position. While the hydroxyethyl side chain has the S configuration, it can be easily inverted using a modified Mitsunobu reaction. Preparation of a key intermediate **7b** from **2** is shown in Scheme I. Treatment of **2** with triphenylphosphine, diisopropylazodicarboxylate and formic acid in THF gave the inverted formate **3** which without purification was hydrolyzed with sodium hydroxide in methanol at 0°C to give the inverted alcohol **4**. The hydroxy group of **4** was protected as the t-butyldimethylsilyl ether by treating **4** with t-butyldimethylchlorosilane and imidazole in DMF to give **5**. The overall yield from **2** was 75%.

Scheme I

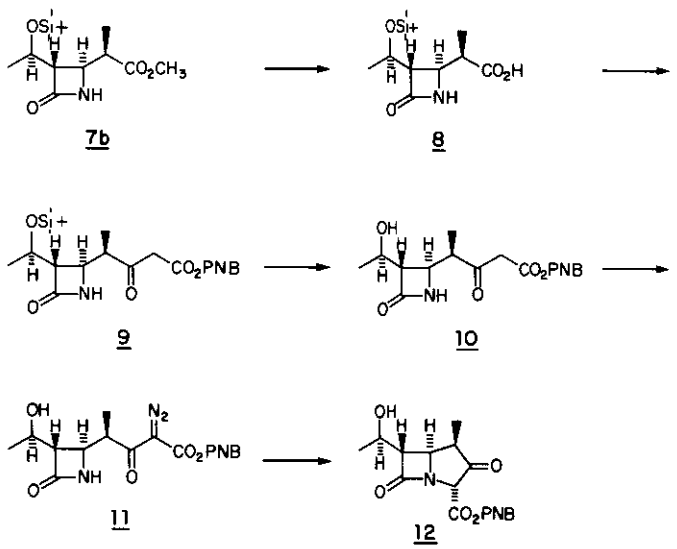


When **5** was N-silylated and treated with one equivalent of lithium diisopropylamide (LDA) in THF containing one equivalent of HMPA at -78° followed by excess methyl iodide, the product obtained had no β-lactam. Presumably the anion formed α to the carboxylate undergoes a rapid reverse Michael reaction leading to destruction of the β-lactam. Compound **5**, when treated with two equivalents of base under the above conditions, gave the desired methylation in 75% yield as a mixture of α and β isomers (**7a**:**7b**; 4:1). The formation of the dianion **6a** with a negative charge on nitrogen perhaps protects against the reverse Michael reaction, allowing the carbanion to react with methyl iodide. The dianion probably exists in the cyclic form shown in **6a**, which accounts for the predominant formation of the α-methyl isomer, the methyl group approaching **6a** from its more open α side. After separation of the isomers of **7** by preparative HPLC, the

α isomer was treated with two equivalents of LDA as described before to generate the dianion **6b**; protonation with excess acetic acid gave a 1:1 mixture of α and β isomers in 85% yield, allowing the recycling of the α isomer to the β.

The stereochemical assignments of isomers **7a** and **7b** were based on the comparison of their proton NMR spectra with those of authentic samples previously prepared via an achiral route from a crystalline intermediate whose structure has been determined by X-ray crystallography. This work will be reported separately. The intermediate **7b** has the correct absolute configuration at all centers for the synthesis of the 1-β-methylcarbapenem **1**. Scheme II summarizes the synthesis of another key intermediate, p-nitrobenzyl (1R,3R,5R,6S)-2-oxo-6-[(1R)-1-hydroxyethyl]-1-methylcarbapenam-3-carboxylate **12**, from **7b**.

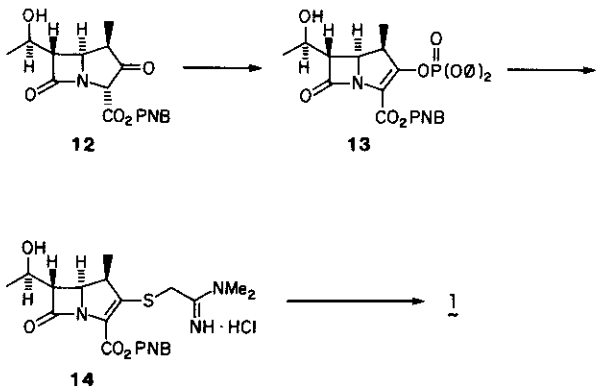
Scheme II



Saponification of **7b** with 2.5 N sodium hydroxide in aqueous methanol followed by acidification with 6 N hydrochloric acid gave 83% yield of carboxylic acid **8** without racemization of the β-methyl group. Chain extension using the Masamune condition[4b,6] provided 72% yield of **9** which was hydrolyzed with 6 N hydrochloric acid in methanol to give **10** in 89% yield. Diazotization of **10** with dodecylbenzenesulfonyl azide[7] in the presence of triethylamine gave the diazo azetidinone **11** in quantitative yield. Under the influence of 0.3% rhodium (II) octanoate catalyst, the diazo compound **11** was smoothly converted to bicyclic keto ester **12** in 95% yield in refluxing ethyl acetate/hexane (3:1) solution for 15 min or in methylene chloride at room temperature for 5 h. The 200 MHz proton NMR spectrum indicated that **12** was exclusively β-methyl isomer.[8]

The final elaboration of C-2 substituent was accomplished by displacement of vinyl phosphate with the mercaptan, 2-N,N-dimethylamino-2-iminoethylthio hydrochloride at low temperature. The p-nitrobenzyl ester of 1 was isolated as a stable crystalline solid. The synthesis of **1** from 1-β-methyl keto ester **12** is shown in Scheme III.

Scheme III



Practically, conversion of diazo azetidinone **11** to **14** was carried out in one pot. Thus after evaporation of the solvent, the bicyclic keto ester **11** was redissolved in acetonitrile and treated with diphenyl chlorophosphate and N,N-diisopropylethylamine at 0°C for 30 min to give vinyl phosphate. Isolation of **12** was possible but not necessary. The mixture was cooled to -35°C, then treated with one equivalent of crystalline 2-N,N-dimethylamino-2-iminoethylthiol hydrochloride and one equivalent of N,N-diisopropylethylamine in a period of 10 min. The mixture was allowed to warm to -20°C for 20 min. There was a transitory homogenous state before the product began to crystallize. The mixture was again chilled to -35°C and the solvent was removed by aspirating through a gas-dispersion tube into a vacuum trap. The crude product was washed twice with acetonitrile and once with ethyl acetate and ether at the same low temperature. The p-nitrobenzyl ester **14** was isolated as hydrochloride which was stable indefinitely in the refrigerator. The final deblocking of the ester **14** was achieved by hydrogenation at 40 psi in deionized water/n-BuOH/EtOAc solvent system in the presence of 20% $Pd(OH)_2/C$. One equivalent of sodium bicarbonate was needed to keep the pH of the solution in the 6.0 to 7.5 range. The product **1** was purified by a Dowex-50 x 4 (Na cycle) or a HP-20 column which was eluted with deionized water to give pure **1**. After concentration in vacuo to ca. 20 mg/ml, the solution was lyophilized to give a white solid product which was then crystallized from methanol to yield a white crystalline solid.

Table I. Relative in vitro antibacterial potency and DHP-I susceptibility of 1-β-methylcarbapenem **1** and MK-787 in comparison to thienamycin

	Thienamycin (MIC, μg/ml)[a]		N-Formimidoyl-thienamycin (MK-787)	1-β-Methylcarbapenem (**1**)
Staphylococcus aureus (5)[b]	1.0	(0.04)	1.2	0.5
Enterococcus (2)	1.0	(3.80)	1.3	0.8
Escherichia coli (7)	1.0	(0.36)	1.6	3.5
Enterobacter (6)	1.0	(2.04)	2.1	8.0
Klebsiella (5)	1.0	(1.77)	1.2	3.5
Serratia (2)	1.0	(2.50)	2.6	7.0
Proteus (Ind. + & -) (6)	1.0	(7.08)	1.5	4.6
Pseudomonas aeruginosa (5)	1.0	(9.13)	3.5	5.3
Methicillin resistant Staph.	1.0	(40.0)	1.5	3.5
Thienamycin resistant P. aeruginosa	1.0	(40.0)	2.0	4.0
DHP-I[c]	1.0		0.90	0.026

[a]Average MIC (μg/ml) from reference 1i
[b]Number of strains tested
[c]Ratio of susceptibility to DHP-I vs. thienamycin (hog renal)[2a]

Table II. Solubility and stability of 1-β-methylcarbapenem **1** in comparison to N-formimidoyl thienamycin (MK-787) and thienamycin[a]

Compounds	Solubility (mg/ml)[b]	t_{90} (h)[c] at pH 6.5, 0.5 M, MOPS-NaOH buffer at 22°C				
		1 mg/ml	10 mg/ml	50 mg/ml	100 mg/mg	250 mg/ml[d]
Thienamycin	N/A[e]	13.9	5.2	1.4	-	0.3
MK-787	10	19.5	9.8	-	-	0.7
1	172	36.3	36.3	36.3	36.3	36.3

[a]The materials for this study are crystalline compounds unless otherwise indicated.
[b]In sterile water at 25°C
[c]t_{90} is the time required to observe 10% decomposition of the compound as monitored by NH_2OH extinguishable uv absorption at 293 nm.
[d]Lyophilized material
[e]Crystalline material not available

Chemical modification of carbapenem antibiotics by means of total synthesis has proven very fruitful. By successfully introducing a β-methyl group onto the C-1 position of the carbapenem ring system and properly choosing a C-2 substituent,[9a] we have corrected the serious deficiencies associated with the naturally occurring carbapenems. The 1-β-methylcarbapenem antibiotic **1** is chemically stable, highly resistant to renal dipeptidase-I and most importantly, retains the excellent antibacterial activity of MK-787. Moreover, the solubility of 1-β-methylcarbapenem **1** and its stability at high concentration in water have been markedly improved over MK-787. These are important advantages for the use of this antibiotic by i.v. or i.m. injections. Tables I and II summarize in vitro antibacterial activities, renal dipeptidase-I susceptibility, solubility and stability in water of 1-β-methylcarbapenem **1** and MK-787.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. Proton nmr spectra were recorded with a Varian SC-300, XL-200 or T-60 nmr spectrometer (chemical shifts are given in ppm from internal TMS in $CDCl_3$ or TSP in D_2O; $CDCl_3$ was the solvent unless otherwise indicated), uv spectra with a Perkin-Elmer 552A or Lambda 3 uv/vis spectrophotometer, IR spectra with a Perkin-Elmer 267 spectrophotometer, and mass spectra with a LKB-9000 or Varian 731 spectrometer. Optical rotations were measured with a Perkin-Elmer 240 polarimeter and pH's with an Orion Research 301 analog pH meter. HPLC separations were performed with a Waters Associates Prep LC/System 500 using a PrepPAK-500/silica column. Microanalyses were carried out with a Perkin-Elmer 240 C, H, N elemental analyzer performed by the microanalyses laboratory. Thin-layer chromatography was performed on Analtech silica gel GF plates and column chromatography was conducted using E. Merck silica gel. All reactions were performed under a positive atmosphere of nitrogen.

(3S,4R)-3-[(1R)-1-FORMYLOXYETHYL]-4-METHOXYCARBONYLMETHYL-AZETIDIN-2-ONE (3)

(3S,4R)-3-[(1S)-1-hydroxyethyl]-4-methoxycarbonylmethyl-azetidin-2-one (489 g, 2.61 M) in dry THF (4.5 L) was placed under N_2, triphenylphosphine (745 g, 2.8 M) and formic acid (130 ml, 158.6 g, 3.45 M) were added and the mixture was cooled with stirring to 0 to 5° in MeOH/ice bath. Diisopropylazodicarboxylate (575.7 g, 2.85 M) was added during 1 h, during which time the reaction temperature went to 0°. The reaction temperature was raised to 25° and stirring was continued for 2-1/2 h. IRA-68 resin (THF-washed, 800 ml, free base cycle) was added and stirred for 1 h. The resin was filtered off and washed with THF (2 x 700 ml). The filtrate and washings were evaporated under vacuum and the residue was flushed 3x with toluene to give a residue (2084 g) which was used without purification in the next step.

(3S,4R)-3-[(1R)-1-HYDROXYETHYL]-4-METHOXYCARBONYLMETHYL-AZETIDIN-2-ONE (4)

The product from the previous reaction was dissolved in MeOH (6.2 L) and cooled with stirring to -5°. A solution of sodium methoxide (27 g in 450 ml MeOH) was added over 5 min and the mixture was stirred

40 min. Dowex resin 50 x 8 (H^+ cycle, 630 ml) was added and stirred for 1 h, then filtered and washed with MeOH (2 x 600 ml). The filtrate and washings were concentrated to an oil which was dissolved in CH_2Cl_2 (6 L) and extracted with water (4 x 3 L). The aqueous extract was washed with Et_2O/hexane (1:1, 2 L) and then evaporated under vacuum. The residue was flushed with toluene (4 x 1.5 L) to give crude **4**: nmr (60 MHz) 1.2 (d, J = 7, CH_3-CH), 2.7 (m, CH_2-COO), 2.92 (dd, J = 2 and 7 Hz, H 3), 3.53 (m, H 4), 3.7 (s, -COOCH_3), 3.96 (m, CH_3-CH), 6.95 (broad s, NH); which was used without purification in the following step.

(3S,4R)-3-[(1R)-1-t-BUTYLDIMETHYLSILYLOXYETHYL]-4-METHOXYCARBONYLMETHYL-AZETIDIN-2-ONE (**5**)

The product from the previous reaction was diluted to 4.5 L with sieve-dried DMF. Imidazole (369 g, 5.42 M) and t-butyldimethylchlorosilane (393 g, 2.61 M) were added and the reaction was stirred overnight at RT under N_2. Ice water (10.0 L) was added during 1.5 h to give a crystalline precipitate which was stirred an additional 2 h, filtered and washed with H_2O (4 x 2 L). The residue was dried overnight under vacuum (20 mm) at 40-50° and then for 24 h at 50° at 0.2 mm to give **5** (583 g, 74% from **2**), mp 96-97.5; ir ($CHCl_3$): 2920 (NH), 1758 (β-lactam), 1740 (ester); nmr (200 MHz): 0.09 (s, CH_3-Si), 0.89 [s, $(CH_3)_3$C-Si], 1.22 (d, J = 5 Hz, CH_3-CH), 2.58 (dd, J = 16 and 9.5 Hz, α or β-CH_2-COO), 2.78 (dd, J = 16 and 4 Hz, α or β-CH_2-COO), 2.84 (dd, J = 2 and 7 Hz, H 3), 2.74 (s, OCH_3), 4.0 (octet, J = 2, 3.5 and 9 Hz, H 4), 4.22 (m, CH_3-CH), 6.05 (broad s, NH).

(3S,4S)-3-[(1R)-1-t-BUTYLDIMETHYLSILYLOXYETHYL]-4-(1-METHOXYCARBONYLETHYL)-AZETIDIN-2-ONE (**7**)

To THF (70 ml, distilled from LAH), cooled to -78° under N_2, was added diisopropylamine (3.2 ml, 23.3 mmol) and the stirred mixture treated wtih n-butyllithium (10.1 ml of a 2.3 M solution in hexane). After 5 min, hexamethylphosphine triamide (HMPA) (4.2 ml, 23.3 mmol) was added followed 10 min later with a solution of the ester **5** (3.2 g, 10.6 mmol) in 20ml THF, added over 2 min. The golden yellow solution was stirred 40 min then treated with methyl iodide (2.5 ml, 24 mmol) and the reaction was stirred at -78° for 1-1/2 h. Saturated NH_4Cl solution (50 ml) and ether (200 ml) were added and the organic phase was separated and washed with water (4 x 50 ml), dried and evaporated. The crystalline residue was purified by preparative HPLC (silica gel, 60% Et_2O/petroleum ether) to give (3S,4S)-3-[(1R)-1-t-butyldimethylsilyloxyethyl]-4-[(1S)-1-methoxycarbonylethyl]-azetidin-2-one (**7a**, 2.1 g, 63%), mp 133-134°C; $[\alpha]_D^{22}$ +6.0 (c 2.0, CH_2Cl_2); ir ($CHCl_3$): 2920 (NH), 1758 (β-lactam), 1735 (ester); nmr (200 MHz): 0.09 (s, CH_3-Si), 0.9 (s, CH_3-C-Si), 1.26 (2 overlapping d, J = 7 Hz), 2.56 (m, CH_3-CH-C=O), 2.8 (dt, J = 5.2 and 1.5 Hz, H 3), 3.72 (dd, J = 6 and 2 Hz, H 4), 3.75 (s, OMe), 4.21 (m, CH_3-CH-O), 6.02 (broad s, NH); and (3S,4S)-3-[(1R)-1-t-butyldimethylsilyloxyethyl]-4-[(1R)-methoxycarbonylethyl]-azetidin-2-one (**7b**, 0.40 g, 12.1%), mp 120-121°C; $[\alpha]_D^{22}$ -21.0 (c 2.09, CH_2Cl_2); ms: m/e 300 (M^+-15), 258 (M^+-57); ir ($CHCl_3$): 2920 (NH), 1758 (β-lactam), 1737 (ester); nmr (100 MHz): 0.08

(s, CH_3-Si), 0.88 (s, CH_3-C-Si), 1.18 and 1.24 (2d, J = 7, CH_3-CH), 2.73 (m, CH_3-CH-COO), 3.0 (d of d, J = 2.5 and 4, H 3), 3.72 (s, OCH_3), 3.9 (d of d, J = 2.5 and 5, H 4), 4.23 (m, CH_3-CH-O), 5.83 (broad s, NH). Anal. Calcd for $C_{15}H_{29}NO_4Si$: C, 57.11; H, 9.26; N, 4.44. Found: C, 57.22; H, 9.32; N, 4.23.

EQUILIBRATION OF **7a** TO A MIXTURE OF **7a** AND **7b**

To THF (50 ml, distilled from LAH), cooled to -78° under N_2 was added diisopropylamine (2.1 ml, 15.2 mmol), and the stirred mixture was treated with n-butyllithium (6.9 ml of a 2.3 M solution in hexane). After 5 min HMPA (2.8 ml, 15.2 mmol) was added followed 10 min later with a solution of the ester **7a** (2.1 g, 6.7 mmol) in THF (20 ml) added over 2 min. The reaction was stirred at -78° for 0.5 h and treated with acetic acid (2.8 ml, 46.6 mmol) in THF (10 ml) added as rapidly as possible. The reaction mixture was stirred 5 min and worked up as described for the previous reaction, to give after HPLC separation **7a** (1.2 g) and **7b** (0.603 g). On a large-scale run on 108 g of **7a** the yield was 78% with a ratio of **7a** to **7b** of 1:1.

(3S,4S)-3-[(1R)-1-t-BUTYLDIMETHYLSILYLOXYETHYL]-4-[(1R)-1-CARBOXYETHYL]-AZETIDIN-2-ONE (**8**)

The ester **7b** (200 mg, 0.63 mmol) was dissolved in MeOH (2 ml) and water (0.5 ml), NaOH (2.5 N, 0.26 ml) was added, and the mixture was stirred at RT for 0.5 h and at 50° for 1 h. The reaction mixture was diluted with water, extracted twice with ether, and the aqueous phase was acidified and extracted with EtOAc. The organic phase was dried and evaporated to give the acid **8** (159 mg, 83%), mp 140-143° (dec); ir ($CHCl_3$): 2920 (NH), 3000-4300 (broad COOH), 1742 (β-lactam and acid); nmr (200 MHz): 0.08 (s, CH_3-Si), 0.7 (s, CH_3-C-Si), 1.24 (d, J = 7, CH_3-C-H), 1.3 (d, J = 7.5, CH_3-C-H), 2.78 (m, CH_3-CH-C=O), 3.06 (dd, J = 2 and 4.5, H 3), 3.98 (dd, J = 2 and 5, H 4), 4.24 (m, CH_3-CH-O), 6.37 (broad s, NH); ms: m/e 286 (M^+-15), 244 (M^+-57). Anal. Calcd for $C_{14}H_{27}NO_4Si$: C, 55.78; H, 9.03; N, 4.65. Found: C, 56.06; H, 9.05; N, 4.49.

(3S,4R)-3-[(1R)-1-t-BUTYLDIMETHYLSILYLOXYETHYL]-4-[(1R)-1-METHYL-3-p-NITROBENZYLOXYCARBONYL-2-OXOPROPYL]-2-AZETIDIN-2-ONE (**9**)

A 1-liter, three-necked, round-bottomed flask equipped with a mechanic stirrer, nitrogen inlet tube and a thermometer, was charged with acetonitrile (588 ml), azetidinone carboxylic acid **10** (14.0 g, 46.5 mmol), and carbonyldiimidazole (9.1 g, 55.8 mmol). The reaction mixture became homogeneous in a minute. After stirring 30 min at RT, the solution was mixed with anhydrous magnesium p-nitrobenzyl malonate (23.3 g, 46.5 mmol) and heated at 60°C for 18 h, then evaporated in vacuo to give an oil residue. The crude product was taken up in ethyl acetate and washed with 1.0 N HCl, water, 10% K_2CO_3, and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, then evaporated in vacuo to give 23.60 g of an oil which was purified by a silica gel column (23 x 4.4 cm) eluting with ethyl acetate to give 22.30 g of white solid **11**, mp 76-78°C; ir ($CHCl_3$): 1750 cm^{-1}; ms: m/e 421 (M^+-57); nmr (200 MHz): 0.06 (s, 6 H, CH_3Si), 0.87 (s, 9 H, CH_3C-Si), 1.10 (d, J = 6.8 H, 3 H, (CH_3CH), 1.23 (d, J = 7.6 Hz, 3 H, CH_3CHOH), 2.92 (dd, J = 2.8 Hz, 1 H,

H 3), 2.96 (m, 1 H, $CH_3C\underline{H}$), 3.66 (s, 2 H, $C\underline{H_2}CO_2$-), 3.96 (dd, J = 2.8 and 4.5 Hz, 1 H, H 4), 4.20 (m, 1 H, $CH_3C\underline{H}O$), 5.30 (s, 2 H, $OC\underline{H_2}$), 5.92 (s, 1 H, NH), 7.56 and 8.26 (d, J = 8.0 Hz, 2 H, aromatic protons).

(3S,4R)-3-[(1R)-1-HYDROXYETHYL]-4-[(1R)-1-METHYL-3-p-NITROBENZYLOXYCARBONYL-2-OXOPROPYL]-AZETIDIN-2-ONE (**10**)

The O-t-butyldimethylsilyl keto ester **9** (13.0 g, 27.2 mmol) was dissolved in methanol (130 ml) and treated with 6 N HCl (13.6 ml, 81.6 mmol). The solution was stirred at RT for 2 h, then treated wtih 0.1 N Na_2HPO_4 (30 ml) and 10% K_2CO_3. The mixture was evaporated to half of the original volume under reduced pressure then extracted with ethyl acetate. The organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated in vacuo to give an oil which was crystallized from ether to give 8.5 g (85%) of white solid product, mp 94-96°C; $[\alpha]_D^{21}$ -8.0°(c 2.5, CH_2Cl_2); nmr (300 MHz): 1.25 (d, J = 7.0 Hz, 3 H, $C\underline{H_3}CH$), 1.30 (d, J = 6.4 Hz, 3 H, $C\underline{H_3}CHOH$), 2.90 (dd, J = 2.2 and 6.4 Hz, 1 H, H 3), 2.94 (quintet, J = 7.0 Hz, 1 H, $C\underline{H}CH_3$), 3.66 and 3.68 (ABq, J = 15 Hz, 2 H, $C\underline{H_2}CO_2$PNB), 3.84 (dd, J = 2.2 and 7.0 Hz, 1 H, H 4), 4.14 (m, 1 H, $C\underline{H}OH$), 6.10 (s, 1 H, N$\underline{H}$), 7.55 and 8.27 (d, J = 6.6 Hz, 2 H, aromatic protons). Anal. Calcd for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53; N, 7.69. Found: C, 55.98; H, 5.55; N, 7.43.

(3S,4R)-3-[(1R)-1-HYDROXYETHYL]-4-[(1R)-1-METHYL-3-DIAZO-3-p-NITROBENZYLOXYCARBONYL-2-OXOPROPYL]-AZETIDIN-2-ONE (**11**)

At RT under nitrogen atmosphere, the crystalline keto ester **10** (14.7 g, 40.0 mmol) was dissolved in anhydrous acetonitrile (92 ml). To the solution was added dodecylbenzenesulfonyl azide (48.05 ml, 33% in hexane, 48.5 mmol) and triethylamine (6.62 ml, 48.5 mmol). The mixture was stirred for 3 h, then evaporated in vacuo to give an oil which was purified by a silica gel column (250 ml bed column, 4 cm diameter) eluting with ethyl acetate to give diazo azetidinone **11** as a white solid (15 g, 95%), nmr (300 MHz): 1.22 (d, J = 6.0 Hz, 3 H, 1-β-methyl), 1.32 (d, J = 6.0 Hz, 3 H, $C\underline{H_3}CHOH$), 2.38 (d, J = 3.2 Hz, 1 H, O$\underline{H}$), 2.92 (dd, J = 2.4 and 7.6 Hz, 1 H, H 3), 3.77 (quintet, J = 6.0 Hz, 1 H, $C\underline{H}CH_3$), 3.86 (dd, J = 2.4 and 6.0 Hz, 1 H, H 4), 4.15 (m, 1H, $C\underline{H}OH$), 5.38 (s, 2 H, CO_2CH_2), 5.90 (s, 1 H, N$\underline{H}$), 7.57 and 8.30 (d, J = 6.6 Hz, 2 H, aromatic protons); ir (film): 2140, 1750, 1720 and 1650 cm^{-1}; $[\alpha]_D^{21}$ -50.4°(c 2.5, CH_2Cl_2).

p-NITROBENZYL (1R,5S,6S)-2-(2-N,N-DIMETHYLAMINO-2-IMINOETHYLTHIO)-6-[(1R)-1-HYDROXYETHYL]-1-METHYLCARBAPEN-2-EM-3-CARBOXYLATE HYDROCHLORIDE (**14**)

A 500-ml round-bottomed flask equipped with a reflux condenser was charged with diazo keto ester **11** (5.0 g, 12.82 mmol) and 30 ml of 75% ethyl acetate/hexane. The solution was first heated to reflux, then treated with rhodium (II) octanoate (15 mg). Vigorous gas evolution occurred immediately. After refluxing for 15 min, the mixture was evaporated in vacuo to give 1-β-methyl bicyclic keto ester **12** as a foam, nmr (200 MHz): 1.23 (d, J = 8.0 Hz, 3 H, 1-β-methyl), 1.39 (d, J = 6.4 Hz, 3 H, $C\underline{H_3}CHOH$), 2.86 (quintet,

J = 8.0 Hz, 1 H, H 1), 3.30 (dd, J = 2.3 and 6.4 Hz, 1 H, H 6), 4.27 (dd, J = 2.3 and 8.0 Hz, 1 H, H 5), 4.36 (quintet, J = 6.4 Hz, CHOH), 4.78 (s, 1 H, H 3), 5.28 and 5.39 (ABq, J = 12 Hz, 2H, CO_2CH_2), 7.58 and 8.28 (d, J = 8.0 Hz, 2 H, aromatic protons); ir ($CHCl_3$): 1760 cm^{-1}; ms: m/e 362 (M^+), 334, 316, 305; $[\alpha]_D^{23}$ +89.2°(c 2.5, CH_2Cl_2).

The bicyclic keto ester **12** was dissolved in 50 ml of acetonitrile (distilled from P_2O_5) and kept in an ice-bath under nitrogen atmosphere. To the solution was simultaneously added N,N-diisopropylethylamine (2.35 ml, 13.5 mmol) and diphenyl chlorophosphate (2.80 ml, 13.5 mmol) over a period of 5 min. The mixture was stirred for an additional 30 min to give 1-β-methyl vinyl phosphate **13** which can be isolated by tlc, nmr (200 MHz): 1.24 (d, J = 7.2 Hz, 3 H, 1-β-methyl), 1.35 (d, J = 6.5 Hz, 3 H, CH_3CHOH), 3.35 (dd, J = 3.0 and 6.5 Hz, 1H, H 6), 3.52 (m, 1 H, H 1), 4.26 (dd, J = 3.0 and 10.0 Hz, H 5), 4.30 (m, 1H, H 8), 5.24 and 5.40 (ABq, J = 13.2 Hz, 2 H, CO_2CH_2), 7.29 (m, 10 H, C_6H_5), 7.58 and 8.18 (d, J = 8.0 Hz, 2 H, p-NO_2-C_6H_4).

However, purification of **13** was not necessary. The vinyl phosphate **13** in the same pot was chilled to -35°C by a cooling bath (dry ice in 1:1 ethylene glycol/water). To the solution was added in portions, N,N-diisopropylethylamine (2.35 ml, 13.5 mmol) and crystalline 2-N,N-dimethylamino-2-iminoethyl thiol hydrochloride (2.08 g, 13.5 mmol) over a period of 10 min. The mixture was allowed to warm to -20°C and stirred for 20 min. After a transitory homogenous state, a crystalline product formed. The mixture was again chilled to -35°C, then solvents were removed by a gas dispersion tube which was connected to a vacuum trap. The crude product was washed twice with 5 ml acetonitrile and once with ethyl acetate and ether. After drying in vacuo, the product **14** was obtained as off-white powder (5.23 g, 81.3%), nmr (200 MHz, D_2O): 1.29 (d, J = 8.0 Hz, 1-β-methyl), 1.34 (d, J = 7.0 Hz, 3 H, CH_3CHOH), 3.16 (s, 3 H, NCH_3), 3.27 (m, 1 H, H 1), 3.30 (s, 3 H, NCH_3), 3.62 (dd, J = 2.3 and 7.0 Hz, 1 H, H 6), 4.10 (d, J = 6.8 Hz, 2 H, exchangeable, SCH_2), 4.30 (quintet, J = 7.0 Hz, 1 H, H 8), 4.36 (dd, J = 2.3 and 9.5 Hz, H 5), 5.41 and 5.54 (ABq, J = 13 Hz, 2 H, CO_2CH_2), 7.72 and 8.31 (d, J = 8.0 Hz, 2 H, aromatic protons); ir (Nujol mull): 1758 cm^{-1}; uv $\lambda_{max}^{H_2O}$ 310 nm (ε 10,750) and 272 nm (ε 10,438); $[\alpha]_D^{21}$ +12.8°(c 2.8, 1:1 dioxane/water).

(1R,5S,6S)-2-(2-N,N-DIMETHYLAMINO-2-IMINOETHYLTHIO)-6-[(1R)-1-HYDROXYETHYL]-1-METHYLCARBAPEN-2-EM-3-CARBOXYLIC ACID (**1**)

(A) The p-nitrobenzyl ester hydrochloride **14** (5.20 g, 10.42 mmol), n-butanol (252 ml), ethyl acetate (126 ml), pH 6.8, 0.5 M N-methylmorpholine buffer (252 ml), deionized water (126 ml), sodium bicarbonate (1.01 g, 12.02 mmol), and 20% $Pd(OH)_2/C$ (1.90 g) were placed in a 2-liter flask and hydrogenated under 40 psi of hydrogen at RT for 2 h. The aqueous layer was separated, extracted with ethyl acetate (500 ml), then concentrated in vacuo to 90 ml. The solution was charged on a HP-20 column (200 ml bed

column, 4.3 cm in diameter) eluting with deionized water at 2.5 ml/min in the cold room (4°C) and monitoring with a 285 nm uv detector to collect 1.75 g (51%) of product in 2.5 L of water. The solution was concentrated in vacuo to 100 ml, then lyophilized to give a white solid product.

(B) The same scale hydrogenation has also been carried out in the absence of N-methylmorpholine buffer and the crude product was purified by a Dowex 50 x 4 (Na cycle) column eluting with deionized water to give a 45% yield of product in 0.6 L of water. The lyophilized solid **1** (1.78 g) was mixed with 20 ml of methanol at RT quickly to give a homogenous solution. Crystallization occurred within less than a minute. The mixture was stirred at RT for 20 min, then filtered to collect a white crystalline product (1.50 g), mp 237°C (dec); uv $\lambda_{max}^{H_2O}$ 293 nm (ε 8,077); $[\alpha]_D^{23}$ -11.37°(c 1.58, H_2O); nmr (200 MHz, D_2O): 1.20 (d, J = 7.5 Hz, 3 H, 1-β-methyl), 1.30 (d, J = 6.1 Hz, 3 H, CH_3CHOH), 3.15 (s, 3 H, NCH_3), 3.31 (s, 3 H, NCH_3), 3.33 (dq, J = 7.5 and 9.6 Hz, 1 H, H 1), 3.53 (dd, J = 3.0 and 6.1 Hz, 1 H, H 6), 3.86 and 3.97 (ABq, J = 15.0 Hz, 2 H, exchangeable, SCH_2), 4.26 (dd, J = 3.0 and 9.6 Hz, 1 H, H 5), 4.27 (quintet, J = 6.1 Hz, 1 H, CH_3CHOH); ir (Nujol mull): 1753 and 1710 cm^{-1}. Anal. Calcd for $C_{14}H_{21}N_3O_4S$: C, 51.37; H, 6.47; N, 12.84. Found: C, 51.60; H, 6.49; N, 12.73.

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