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Convergent Syntheses of Oral THF 1β-Methylcarbapenems

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Convergent syntheses of oral THF 1β-methylcarbapenems **4** (OCA-983) and **5** starting from M2-phosphate **1** were developed. Reaction of the M2-phosphate **1** with THF thiols containing a requisite prodrug side chain, **9** and **10**, gave the desired oral THF 1β-methylcarbapenems **4** and **5**, respectively, in 46% and 42% overall yields.

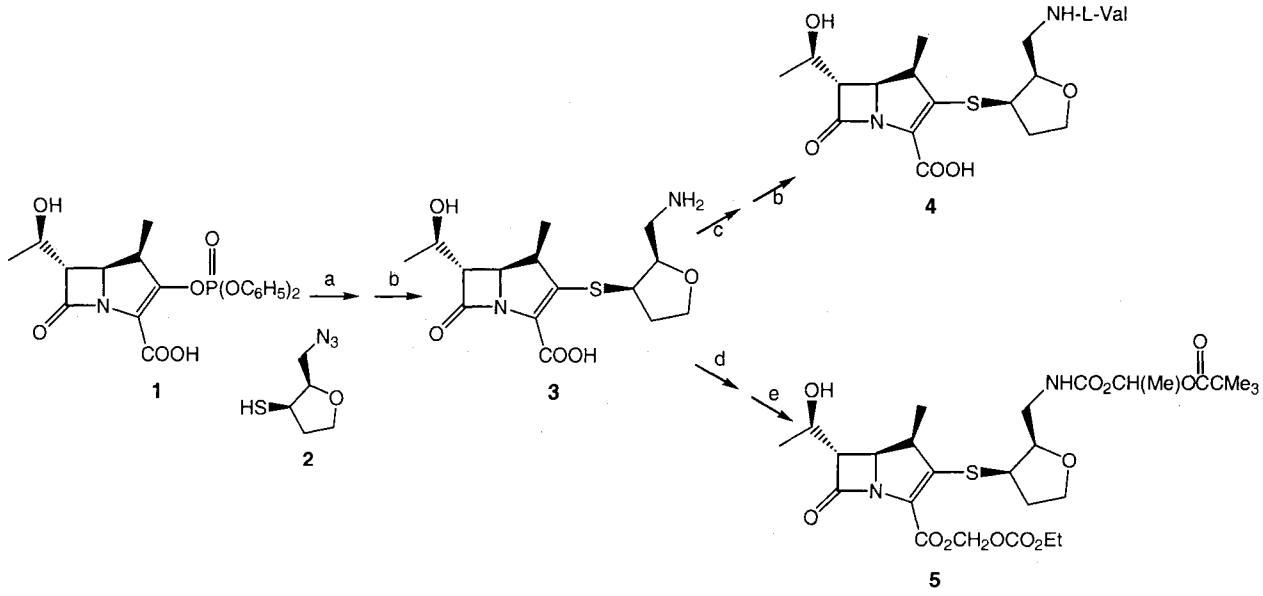
Imipenem[1,2] and meropenem[3,4] are the only carbapenems available for clinical use in the United States. Of the β-lactam antibiotics in clinical use, imipenem and meropenem have the broadest spectrum of antimicrobial activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria, including many resistant clinical isolates. Although both of these carbapenems are highly stable to hydrolysis by most serine β-lactamases, one of their significant drawbacks is that they are administered parenterally. Recently, however, novel THF 1β-methylcarbapenems have been reported, of which CL191,121 (**3**) is a representative member.[5] These THF 1β-methylcarbapenems have a spectrum of activity against Gram-positive and Gram-negative organisms comparable to those of imipenem and meropenem with the exception of decreased antipseudomonal activity. They also demonstrated some intrinsic oral activity against an *E. coli* infection in mice. Most importantly, peptidic and bis double ester prodrugs (such as **4** and **5**) of **3** demonstrated potent oral activity against Gram-positive and Gram-negative bacterial infections in mice.[6,7] As depicted in Scheme 1, syntheses of orally active THF 1β-methylcarbapenems **4** (OCA-983) and **5** were originally prepared from *p*-nitrobenzyl (1*R*, 5*R*, 6*S*)-6-[(1*R*)-1-hydroxyethyl]-2-[(dephenylphosphosphono)oxy]-1-methylcarbapen-2-em-3-carboxylate (M2-phosphate) **1** and THF thiol **2** in 4 steps in 25 and 30% overall yields.[5~7] Since the M2-phosphate **1** is an expensive intermediate, convergent syntheses of **4** and **5** starting from the M2-phosphate **1** and THF thiols containing a requisite prodrug side chain were investigated. Here we report the convergent syntheses of orally active THF 1β-methylcarbapenems **4** and **5**.

Chemistry

THF thiols **9** and **10** containing a requisite prodrug side chain were prepared according to Scheme 2. Reaction of THF thioacetate **6**[5] with triethylphosphite in the presence of one equivalent of water in tetrahydrofuran, followed by saturation with dry hydrogen chloride, produced aminothioacetate **7** in 85% yield. The aminothioacetate **7** was hydrolyzed with aqueous 2 N hydrochloric acid to aminothiol **8** in 85% yield.[8] Reaction of the aminothiol **8** with *p*-nitro-carbobenzyloxy-L-valine-*N*-hydroxysuccinimide ester (PNZ-L-Val-O-Su ester)[6] in the presence of diisopropylethylamine in dichloromethane gave the desired THF thiol **9** in 93% yield. Reaction of **8** with 1-(trimethylacetoxy) ethyl *p*-nitrophenyl carbonate gave the desired THF thiol **10** in 75% yield. 1-(Trimethylacetoxy)ethyl *p*-nitrophenyl carbonate was prepared by reaction of 1-chloroethyl *p*-nitrophenyl carbonate with mercury (II) trimethylacetate in trimethylacetic acid at 80°C.

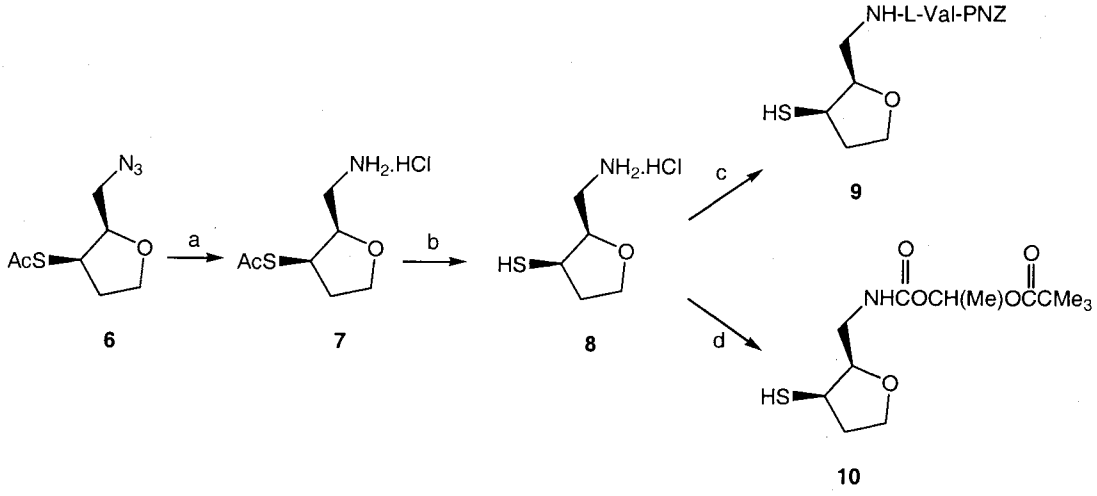
As depicted in Scheme 3, reaction of the M2-phosphate **1** with the THF thiol **9** in the presence of diisopropylethylamine in acetonitrile gave carbapenem **11** in 66% yield. The carbapenem **11** was hydrogenated over 10% palladium on carbon in a mixture of *p*-dioxane and sodium phosphate buffer (pH=6.5) in a Parr Hydrogenator to give the desired THF 1β-methylcarbapenem **4** in 70% yield. Reaction of the M2-phosphate **1** with the THF thiol **10**, followed by catalytic hydrogenation over 10% palladium on carbon in the presence of $NaHCO_3$ in a 1 : 1 mixture of *p*-dioxane and water, gave carbapenem **12** in 55% yield. The carbapenem **12** reacted with ICH_2OCO_2Et in the presence of potassium carbonate in DMF to give the desired THF 1β-methylcarbapenem 5 in 77% yield.

Scheme 1.



(a) **2**/*i*-Pr_2EtN/CH_3CN/rt, 80%; (b) H_2/10% Pd/C/pH 6.5 buffer/*p*-dioxane/rt, 65%; (c) PNZ-L-Val-*OSu*/pH 8.5 buffer/*p*-dioxane/0°C, 75%; (d) *p*-$NO_2C_6H_4OCO_2CH(Me)OCOCMe_3$/*i*-$Pr_2EtN/CH_3CH$/*p*-dioxane/rt, 80%; (e) $ICH_2OCO_2Et/K_2CO_3/CH_3CN$/rt, 77%.

Scheme 2.

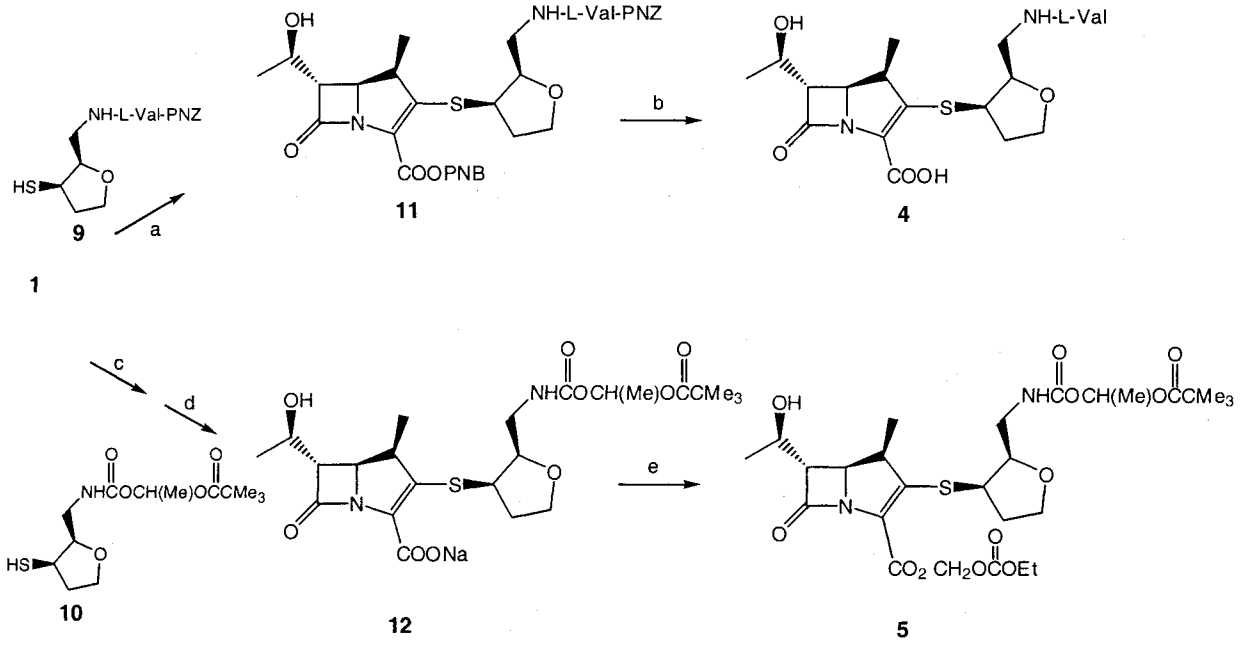


(a) (1) $(EtO)_3P/H_2O$/THF, (2) HCl/toluene, 85%; (b) H_2O/HCl, 85%; (c) PNZ-L-Val-*O*-Su/$(iPr)_2EtN/CH_2Cl_2$, 93%; (d) *p*-$NO_2C_6H_4OCO_2CHMeOCOCMe_3/(iPr)_2EtN/CH_3CN$, 75%.

Antimicrobial Activity

The antimicrobial activity of prodrugs **4** and **5** and their parent compound **3** is summarized in Table 1.[5~7] As is evident from the *in vitro* data (MIC=minimum inhibitory concentration), the peptidic prodrug **4** (OCA-983) is nearly as active as the parent compound **3** against *S. aureus* and *E. coli* microorganisms, and the double-ester prodrug **5** is virtually inactive. However, the peptidic prodrug **4** and the double-ester prodrug **5** improved the oral activity of the parent compound **3** by 9 and 6 fold against *S. aureus* Smith bacterial infection and by 12 and 9 fold against

Scheme 3.



(a) **9**/(iPr)$_2$EtN/CH_3CN, 66%; (b) H_2/10% Pd/C/pH 6.5 buffer/p-dioxane/rt, 70%; (c) **10**/(iPr)$_2$EtN/CH_3CN, 64%; (d) H_2/10% Pd/C/$NaHCO_3$/p-dioxane/H_2O/rt, 86%; (e) ICH_2OCO_2Et/K_2CO_3/DMF, 77%.

Table 1. Biological activity of THF carbapenems, **3**, **4** and **5** against acute lethal bacterial infections in mice.

Compound	MIC (μg/ml)		ED_{50} (mg/kg)			
			S. aureus Smith		*E. coli* #311	
	S. aureus[a]	*E. coli*[b]	*SOD*[c]	*SSC*[d]	*SOD*[c]	*SSC*[d]
3	≤0.06	≤0.06	0.88	0.04	3.8	0.34
4	0.25	≤0.06	0.10	0.07	0.31	0.29
5	128	4.0	0.15	0.07	0.42	0.46
Primaxin[e]	—	—	33	0.03	79	0.70
Imipenem	≤0.06	0.12	—	—	—	—

[a] ATCC 25922; [b] ATCC29213; [c] Single oral dose; [d] Single subcutaneous dose; [e] A 1 : 1 combination of imipenem and cilastatin.

E. coli #311 bacterial infection, both in mice. The oral activity of both prodrugs is superior (about 200 fold better) to that of Primaxin against bacterial infections in mice.

As indicated by our previous reports, the peptidic prodrug **4** is most likely orally absorbed by the dipeptide and tripeptide transport system and the double-ester prodrug **5** through the phospholipid bilayer.[5~7]

In summary, reaction of M2-phosphate **1** with THF thiols containing a requisite prodrug side chain, **9** and **10**, gave the desired oral THF 1β-methylcarbapenems **4** (OCA-983) and **5**, respectively, in 46% and 42% overall yield. Peptidic and bis double ester prodrugs, **4** and **5**, of CL191,121 (**3**) both demonstrated much improved oral activity against *S. aureus* Smith and *E. coli* acute lethal bacterial infections in mice.

Experimental

NMR spectra were determined with a NT-300 WB (^{1}H at 300 MHz, ^{13}C at 75 MHz) and a GE-500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) Spectrometers, and chemical shifts (δ) are expressed in part per million relative to internal tetramethylsilane. IR spectra were measured on a Nicolet 20-SXB FT-IR spectrometer. Mass spectra were recorded on a VG ZAB-SE spectrometer (for fast atom bombardment spectra-FAB). The FAB matrix was dithiothreitol/dithioerythritol (5/1 w/w). Chromatographic separations were done using either thin layer plates (Analtech silica gel GF), flash column-silica gel or reversed phase thin layer or preparative plates (Analtech RPS-F).

2,5-Anhydro-1-amino-1,4-dideoxy-3-thio-D-threo-pentitol 3-acetate Hydrochloride (**7**)

To a solution of 15.62 g (77.61 mmol) of **6** in a mixture of 1.39 ml (77.61 mmol) of water and 77.6 ml of tetrahydrofuran at room temperature was added 13.31 ml (77.61 mmol) of triethyl phosphite dropwise. The reaction mixture was stirred 30 minutes at room temperature, then 2 hours at 45°C. The reaction mixture was concentrated *in vacuo* to give an oil which was dissolved in 77.6 ml of anhydrous toluene at 0°C. Hydrogen chloride was bubbled into the solution for 30 minutes. The mixture was stored overnight at room temperature to give 14.0 g (85.0%) of **7** as white crystals.

IR (KBr) 2877, 1693 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 2.02~1.9 (m, 1H); 2.36 (s, 3H); 2.6~2.43(m, 1H); 3.17~2.85 (m, 2H); 3.9~3.81 (m, 1H), 4.04~3.96 (m, 1H); 4.17~4.1 (m, 1H); 4.5~4.44 (m, 1H); 8.49 (bs, 3H). ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 30.02, 31.93, 40.31, 42.93, 65.84, 75.67, 193.94. LRFAB-MS *m/z* 176.1 $(M+H)^+$, 198.1 $(M+Na)^+$.

2,5-Anhydro-1-amino-1,4-dideoxy-3-thio-D-threo-pentitol Hydrochloride (**8**)

A solution of 12.12 g (57.25 mmol) of **7** in 172 ml of 2 N HCl was heated 16 hours at 45°C. The reaction mixture was evaporated to dryness *in vacuo* to give 9.71 g (~100%) of **8** as a white solid, which was recrystallized from MeOH/Et_2O to give 8.25 g (85.0%) of **8** as white crystals.

IR (KBr) 2889 cm^{-1}. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 1.95 (d, J=8.1 Hz, 1H); δ 2.03~1.95 (m, 1H); 2.6~2.4 (m, 1H, obscured by DMSO); 3.22~3.08 (m, 1H); 3.44~3.31 (m, 1H), 3.65~3.59 (m, 1H); 3.88~3.81 (m, 1H); 4.11~4.03 (m, 1H); 4.39~4.33 (m, 1H); 8.42 (bs, 3H). ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 35.32, 38.49, 40.51, 65.56, 76.66. LRFAB-MS *m/z* 134.1 $(M+H)^+$, 156.1 $(M+Na)^+$. Rotation $[\alpha]_D^{25}$ +42.1° (*c* 1.11, H_2O).

Anal Calcd. for $C_5H_{11}NOSHCl$: C, 35.4; H, 7.13; Cl, 20.9; N, 8.26; S, 18.9. Found: C, 35.4; H, 7.14;; Cl, 21.0; N, 8.19; S, 18.9.

2,5-Anhydro-1-[[[(4-nitrophenyl)methoxy]carbonyl]-L-valyl]amino-1,4-dideoxy-3-thio-D-threo-pentitol (**9**)

In a 300 ml, 3-neck, flame-dried flask kept in an ice bath under argon the solution of 2,5-anhydro-1-amino-1,4-dideoxy-3-thio-D-threo-pentitol hydrochloride (**8**) (4 g; 23.57 mmol) and diisopropylethylamine (5.3 ml; 30.7 mmol; 1.3 equivalents) in dichloromethane (100 ml) was prepared. The solution of (*S*)-[1-[(2,5-dioxo-1-pyrrolidinyl)oxy] carbonyl-2-methylpropyl]carbamic acid (4-nitrophenyl) methyl ester (9.3 g; 23.57 mmol) in dichloromethane (70 ml) was added slowly *via* addition funnel. The ice bath was removed and the solution stirred at room temperature for 6 hours. A bright yellow spot (Rf=~0.5; SH stain) appeared on a silica gel thin layer chromatography plate eluted with ethyl acetate. The spot was also UV-positive. The solution was evaporated to dryness. The residue was treated with EtOAc (200 ml) and the crystalline suspension was stored in the refrigerator for one hour. The crystals were collected to give 9.05 g (93.3%) of **9**.

^{1}H NMR ($CDCl_3$) δ 0.9~1.0 (m, 6H); 3.8~4.0 (m, 3H); 3.7~3.8 (m, 2H); 3.4~3.5 (m, 1H); 3.3~3.4 (m, 1H); 2.4~2.5 (m, 1H); 2.1~2.2 (m, 1H); 1.9~2.0 (m, 1H); 1.6 (d, 1H, SH, J=8.1 Hz); 0.97 (d, 3H, Me, J=6.8 Hz); 0.93 (d, 3H, Me, J=6.8 Hz).

[1(*S*),3[4*R*,5*S*,6*S*(*R*)]]-1-[[[[2-(4-nitrophenyl)methoxy]-carbonyl]amino-3-methyl-1-oxobutyl]amino]-2,5-anhydro-3-*S*-[6-(1-hydroxyethyl)-4-methyl-2-[[(4-nitrophenyl)-methoxy]carbonyl]-7-oxo-1-azabicyclo[3.2.0.]hept-2-en-3-yl]-1,4-dideoxy-3-thio-D-threo-pentitol (**11**)

A mixture of M2-phosphate **1** (9.4 g; 15.8 mmol), acetonitrile (120 ml), diisopropylethylamine (3.7 ml; 21.0 mmol; 1.3 equivalents) and **9** (6.5 g; 15.8 mmol) was stirred at room temperature overnight. The reaction mixture was evaporated to dryness and silica gel chromatographed to give 7.82 g (65.5%) of **11**.

^{1}H NMR ($CDCl_3$) δ 8.2 (m, 4H); 7.65 (d, 2H, J=8.8 Hz); 7.5 (d, 2H, J=8.7 Hz); 6.29 (m, 1H); 5.52 (d, 1H, J=13.9 Hz); 5.23 (d, 1H, J=13.9 Hz); 5.19 (s, 2H); 3.8~4.3 (m, 9H); 3.25~3.5 (m, 3H); 2.35~2.5 (m, 2H); 2.0~2.2 (m, 1H); 1.37 (d, 3H J=6.3 Hz); 1.28 (d, 3H, J=7.3 Hz); 0.96 (d, 3H, J=6.8 Hz); 0.92 (d, 3H, J=6.8 Hz).

[1(*S*),3[4*R*,5*S*,6*S*(*R*)]]-1-[(2-amino-3-methyl-1-oxobutyl)amino]-2,5-anhydro-3-*S*-[2-carboxy-6-(1-hydrox-yethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0.]hept-2-en-3-yl]-1,4-dideoxy-3-thio-D-threo-pentitol (**4**)

A solution of **11** (5 g, 6.6 mmol) in *p*-dioxane (85 ml) was prepared. To the solution was added sodium phosphate buffer (pH 6.5; 0.1 M; 85 ml) and 10% palladium on charcoal (1.05 g). The mixture was hydrogenated in the Parr Hydrogenator at 49 lb per square inch for 5.5 hours. The *p*-dioxane was removed under reduced pressure and the aqueous mixture was washed with ethyl acetate (2×50 ml) and chromatographed (CHP-20P resin; eluting with water, followed by 10% acetonitrile/water) to give 1.9 g (65%) of **4**.

^{1}H NMR (D_2O) δ 4.1~4.17 (m, 3H); 3.96 (q, 1H); 3.78 (m, 2H); 3.58 (d, 1H, J=6.0 Hz); 3.2~3.4 (m, 4H); 2.34 (m, 1H); 2.0~2.1 (m, 2H); 1.27 (d, 3H, J=6.3 Hz); 1.18 (d, 3H, J=7.2 Hz); 0.99 (d, 6H, J=6.9 Hz).

HRFAB-MS *m/z* Calculated for $C_{20}H_{31}N_3O_6S$ $(M+H)^+$ 442.2012; Found 442.2022.

LRFAB-MS *m/z* 442.3 $(M+H)^+$.

Mercury (II) Trimethylacetate

Mercury(II) oxide (43.2 g; 199.5 mmol) and 100 ml of trimethyl acetic acid (100 ml) was placed in a 250 ml three-necked round-bottomed flask equipped with a mechanical stirrer and a reflux condenser. The reaction mixture was stirred at 60°C. Trimethyl acetic anhydride (41 ml; 37.2 g; 199.7 mmol) was added slowly. After addition was complete, heating was continued at 120°C overnight. After cooling and addition of ethyl ether (300 ml) into the flask, 63.4 g (80% yield) of mercury (II) trimethylacetate was obtained as white solid.

^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9H).

1-Chloroethyl *p*-Nitrophenyl Carbonate

A mixture of *p*-nitrophenol (27.8 g), pyridine (17 ml) and anhydrous chloroform (1 liter) in a 2 liter flame-dried round bottom flask was cooled in an ice-bath. To the reaction mixture was added chloroethyl chloroformate (34.0 g) dropwise *via* an addition funnel. The ice-bath was removed after one hour. The reaction mixture was stirred at room temperature for 16 hours, washed with water (200 ml×3), 0.5% aqueous sodium hydroxide (200 ml×3) and water (200 ml×3). The organic layer was dried over sodium sulfate and filtered. After removal of the solvents, 47.9 g (97%) of 1-chloroethyl *p*-nitrophenyl carbonate was obtained.

^{1}H NMR ($CDCl_3$) δ 8.29 (d, 2H, J=9.0 Hz); 7.70 (d, 2H, J=9.0 Hz); 6.50 (q, 1H, J=5.4 Hz); 1.85 (d, 3H, J=5.4 Hz).

1-(Trimethylacetoxy)ethyl *p*-Nitrophenyl Carbonate

A mixture of 1-chloroethyl *p*-nitrophenyl carbonate (6.14 g, 25 mmol), mercury (II) trimethylacetate (12.09 g, 30 mmol) and trimethyl acetic acid (60 ml) in a 250 ml of three-necked round-bottomed flask was heated at 80°C in an oil bath overnight. After filtration, the filtrate was concentrated to an oil. The oil was silica gel chromatographed to give 6.65 g (86%) of 1-(trimethylacetoxy)ethyl *p*-nitrophenyl carbonate.

^{1}H NMR ($CDCl_3$) δ 8.29 (d, 2H, J=9 Hz); 7.70 (d, 2H, J=9 Hz); 6.82 (q, 1H, J=5.4 Hz); 1.62 (d, 3H, J=5.4 Hz); 1.24 (s, 9H).

LRFAB-MS *m/z* 312 $(M+H)^+$.

2,5-Anhydro-1-[[1-(trimethylacetoxy)ethoxy]carbonyl]-amino-1,4-dideoxy-3-thio-D-threo-pentitol (**10**)

To a suspension of **8** (5.80 g, 34.2 mmol) in acetonitrile (180 ml) was added diisopropylethylamine (7.8 ml, 44.4 mmol) under nitrogen. A clear solution was formed. To the solution at 0°C was added 1-(trimethylacetoxy)ethyl *p*-nitrophenyl carbonate (10.64 g, 34.2 mmol) in acetonitrile (60 ml) *via* an addition funnel. The reaction mixture was stirred at room temperature for 2 hours and then evaporated to a thick oil. This oil was then dissolved in ethyl acetate (250 ml), washed with 1 M sodium carbonate (4×50 ml), saturated aqueous sodium chloride (2×50 ml) and dried over sodium sulfate. After removal of the ethyl acetate, the residue was silica gel chromatographed to give 7.81 g (75%) of **10** as a light yellow oil.

^{1}H NMR ($CDCl_3$) δ 6.71 (q, 1H, J=5.4 Hz); 5.12 (br, 1H); 4.01 (m, 2H); 3.81 (m, 1H); 3.52 (m, 2H); 3.34 (m, 1H); 2.51 (m, 1H); 1.94 (m, 1H); 1.62 (m, 1H); 1.45 (d, 3H, J=5.4 Hz); 1.19 (s, 9H).

LRFAB-MS *m/z* 306 $(M+H)^+$.

(4*R*, 5*S*, 6*S*)-3-((2*R*, 3*R*)-2-{[1-(2,2-Dimethyl-propionyl-oxy)ethoxycarbonylamino]-methyl}-tetrahydro-furan-3-yl-sulfanyl)-6-((1*R*-hydroxyethyl)-4-methyl-7-oxo-1-aza-bicyclo[3.2.0.]hept-2-ene-2-carboxylic Acid Sodium Salt (**12**)

To a suspension of M2-phosphate **1** (15.1 g, 25.38 mmol) in acetonitrile (180 ml) at 0°C under nitrogen was added diisopropylethylamine (6.20 ml, 35.54 mmol) and a solution of **10** (7.75 g, 25.38 mmol) in acetonitrile (50 ml). The reaction mixture was stirred at room temperature overnight. After removal of the volatile materials, the residue was silica gel chromatographed to give 10.53 g (64%) of (4*R*, 5*S*, 6*S*)-3-((2*R*, 3*R*)-2-{[1-(2,2-dimethyl-propionyloxy)ethoxy-carbonylamino]-methyl}-tetrahydro-furan-3-ylsulfanyl)-6-((1*R*-hydroxyethyl)-4-methyl-7-oxo-1-aza-bicyclo[3.2.0.]-

hept-2-ene-2-carboxylic acid 4-nitrophenymethyl ester as a light yellow solid.

^{1}H NMR ($CDCl_3$) δ 8.22 (d, 2H, J=8.7 Hz); 7.66 (d, 2H, J=8.7 Hz); 6.75 (q, 1H, J=5.4 Hz); 5.51 (d, 1H, J=13.8 Hz); 5.22 (d, 1H, J=13.8 Hz); 5.20 (m, 1H); 4.20 (m, 5H); 3.85 (m, 2H); 3.60 (m, 1H); 3.45 (m, 1H); 3.30 (m, 2H); 2.49 (m, 1H); 2.05 (m, 1H); 1.45 (d, 3H, J=5.4 Hz); 1.37 (d, 3H, J=6.3 Hz); 1.27 (d, 3H, J=7.0 Hz); 1.18 (s, 9H).

LRFAB-MS m/z 649 $(M)^+$.

A solution of (4*R*, 5*S*, 6*S*)-3-((2*R*, 3*R*)-2-{[1-(2,2-dimethyl-propionyloxy)ethoxycarbonylamino]-methyl}-tetrahydro-furan-3-ylsulfanyl)-6-((1*R*-hydroxyethyl)-4-methyl-7-oxo-1-aza-bicyclo[3.2.0.]hept-2-ene-2-carboxylic acid 4-nitrophenymethyl ester (5.20 g; 8 mmol) in a mixture of *p*-dioxane (85 ml) and water (85 ml) was prepared. To the solution was added sodium bicarbonate (0.86 g; 10.24 mmol) and 10% Pd/C (0.90 g). The reaction mixture was hydrogenated with the Parr Hydrogenator at 45 lbs per square inch for 5.5 hours. Catalyst was removed by filtration. The filtrate (pH=7.8) was adjusted to pH=7.1 with 1 N HCl, concentrated to approximately 60 ml of volume, and extracted with ethyl acetate (3×50 ml). The aqueous phase was then concentrated to about 40 ml of volume and chromatographed (CHP-20P resin, eluting with water, followed by 20% acetonitrile/water) to give 3.72 g (86 %) of **12**.

^{1}H NMR (D_2O) δ 6.70 (q, 1H, J=5.4 Hz); 4.23 (m, 3H); 4.11 (m, 1H); 3.80 (m, 2H); 3.41 (m, 4H); 2.44 (m, 1H); 2.10 (m, 1H); 1.45 (d, 3H, J=5.4 Hz); 1.25 (3H, d, J=5.4 Hz); 1.20 (m, 4H); 1.18 (s, 9H).

LRFAB-MS m/z 537.1 $(M+H)^+$.

(4*R*, 5*S*, 6*S*)-3-((2*R*, 3*R*)-2-{[1-(2,2-Dimethyl-propionyl-oxy)ethoxycarbonylamino]-methyl}-tetrahydro-furan-3-ylsulfanyl)-6-((1*R*-hydroxyethyl)-4-methyl-7-oxo-1-aza-bicyclo[3.2.0.]hept-2-ene-2-carboxylic Acid (Ethoxy-carbonyloxy)methyl Ester (**5**)

To a suspension of **12** (2.68 g, 5.0 mmol), 1.11 g of potassium carbonate (1.11 g, 8.0 mmol) in acetonitrile (70 ml) at 0°C under nitrogen was added 1.73 g of ethyl iodomethyl carbonate (1.72 g, 7.5 mmol) in acetonitrile (10 ml). The reaction mixture was then stirred at room temperature overnight. After filtration, the filtrate was concentrated to a thick oil. The oil after silica gel chromatography gave 2.38 g (77%) of **5**.

^{1}H NMR ($CDCl_3$) δ 6.75 (q, 1H, J=5.4 Hz); 5.93 (d, 1H, J=5.7 Hz); 5.86 (d, 1H, J=5.7 Hz); 5.16 (br, 1H); 4.25 (m, 6H); 3.75 (m, 2H); 3.62 (m, 1H); 3.42 (m, 4H); 2.48 (m, 1H); 2.01 (m, 2H); 1.45 (d, 3H, J=5.4 Hz); 1.32 (m, 8H); 1.18 (s, 9H).

HRFAB-MS m/z Calculated for $C_{27}H_{40}N_2NaO_{12}S$ $(M+Na)^+$ 639.2200; Found 639.2210.

FAB-MS m/z 639.4 $(M+Na)^+$.

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