From Penicillin to Penem and Carbapenem. VIII.[1] Introduction of an Allyl Group at the C-4 Position of the Azetidinone Molecule, and the Synthesis of Dethiathienamycin

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A new C_3-unit introduction reaction at the *C*-4 position of 4-acetoxy-2-azetidinone derivatives using tetraallyltin in the presence of 1/10 equiv of boron trifluoride etherate in dichloromethane is described. Dethiathienamycin was synthesized from (3*S*,4*R*)-4-allyl-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone via the ylide intermediate.

Thienamycin (**16**) and the majority of the carbapenems are extremely active antibiotics against a broad range of Gram-positive and Gram-negative bacteria and have natural stability against β-lactamases.

Naturally occurring carbapenems, however, are highly unstable compounds because of their ring strain and other factors.[2] They are sufficiently stable only in a limited pH range around neutrality. This and the fact that it has so far not been possible to increase fermentation yields by strain optimization have made their isolation in large quantities from culture filtrates difficult.

Therefore, considerable effort has been devoted to the synthesis of these compounds and the search for more stable derivatives.[2] In their syntheses a wide variety of compounds have been used as starting materials; in our case we used the azetidinone derivative **6**, which is easily obtainable from 6-APA (6-aminopenicillanic acid).

A fundamental problem for the synthesis of carbapenem derivatives from 2-azetidinone derivatives such as **6** is how to introduce a carbon substituent at the *C*-4 position of the 2-azetidinone molecule. As possible solutions several C–C bond formation methods at the *C*-4 position have been elaborated; they can be divided into the following five categories:

1. Utilization of active methylene compounds[3]
2. Utilization of organometallic reagents[4]
3. Utilization of silyl derivatives[5]
4. Utilization of carbene insertion to the C–S bond[6]
5. Utilization of potassium cyanide[7]

A common intermediate for the above reactions (excluding 4) is reasonably considered to be the azetinone (or 2-oxoazetidinium) one (**3** or its *N*-substituted one).

We took advantage of allyltin reagent for the introduction of the C_3-unit under the following working hypotheses. The properties of tin organyls are different from those of silicon and germanium in a greater tendency of Sn^{IV} to be able to coordinate in more than four centers and ionize more easily to give cationic species.[8] As shown in Chart 1 the coordination of Lewis acid would assist in the elimination of the acyloxy group to generate 2-oxoazetidinium intermediate **3**. Allyltin is apt to react with cationic derivative, and therefore under these conditions tetraallyltin should attack the acyliminium intermediate to give 4-allyl-2-azetidinone. The trialkyl(or triallyl)tin cation which is generated in this reaction process would react with the Lewis acid–acetoxy complex (e.g. $BF_3 \cdot OAc$) to generate the Lewis acid (e.g. BF_3). Under these hypotheses the reaction should proceed on inclusion of a catalytic amount of Lewis acid.

In this report we describe a mild and convenient method for the introduction of the allyl substituent at

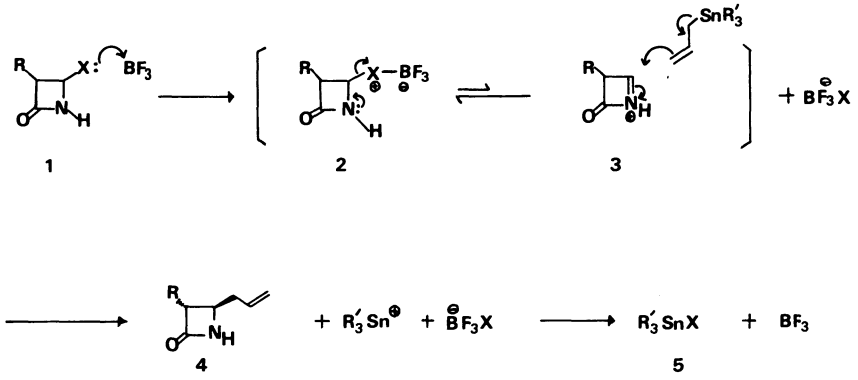


Chart 1.

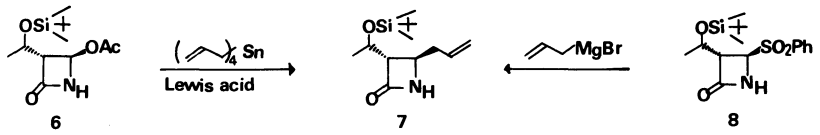


Chart 2.

Table 1. Effects of Lewis Acids

Lewis Acids	Yield/%
$SnCl_4$	30
$TiCl_4$	45
BF_3OEt_2	85
$ZnCl_2$	0
ZnI_2	0

the *C*-4 position of the azetidinone molecule, and application of this to the synthesis of dethiathienamycin (**17**).

First, we investigated the reaction between 4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**6**) and tetraallyltin.

1) Effect of Lewis Acids. 4-Acetoxy-2-azetidinone derivative **6** was reacted with tetraallyltin in the presence of several kinds of Lewis acids. As shown in Table 1 zinc chloride and iodide failed to give the desired product. But tin tetrachloride and titanium tetrachloride gave **7** in moderate yields. Boron trifluoride etherate was the best of the five catalysts checked. 4-Acetoxy-2-azetidinone **6** was reacted with tetraallyltin in the presence of 0.1 equiv of boron trifluoride etherate in dichloromethane to give the 4-allyl-2-azetidinone (**7**) in 85% yield.

2) Effect of Amount of Tetraallyltin. Next we checked how many allyl groups in the tetraallyltin molecule could be used in this reaction. One, 0.5, and 0.25 mol of tetraallyltin was reacted with 1 mol of 4-acetoxy-2-azetidinone derivative **6** to give the desired product **7** in 85, 65, and 0% yield, respectively. These results suggest that two of the four allyl groups in the tetraallyltin molecule are effective enough in this allylation reaction. The same product **7** was also obtained using 1 equiv of allyltributyltin under the same conditions.

The 4-allyl-2-azetidinone produced was found to be identical with an authentic sample prepared from the corresponding 4-(phenylsulfonyl)-2-azetidinone derivative **8** and allylmagnesium bromide under the reported conditions.[9]

The simple 4-acetoxy-2-azetidinone (**9**) was also reacted with tetraallyltin in the presence of boron trifluoride etherate in dichloromethane to yield 4-allyl-2-azetidinone (**10**) in 74% yield.

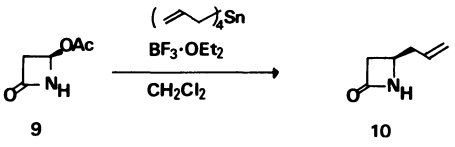


Chart 3.

In the case of tributylcrotyltin,[10] the 4-(1-methylallyl)-2-azetidinone **11** was obtained as a 1:1 mixture (^{1}H NMR, δ=1.17, 1/2 CH_3, d, J=6 Hz and 1.21, 1/2 CH_3, d, J=6 Hz) in 80% yield.

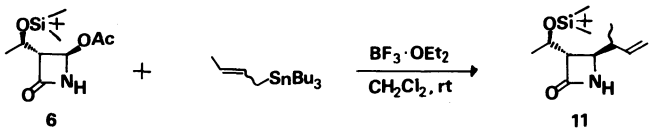


Chart 4.

It is well known that boron trifuoride etherate in chloroform is one set of conditions for the desilylation of the silyl ether.[11] Therefore the *p*-nitrobenzyloxycarbonyl (PNZ) protected azetidinone derivatives **12—14**, which are stable to the above conditions, were subjected to the above and the progress of the reaction was monitored on silica-gel TLC (UV detected). As shown in Table 2, regardless of the configurations of the *C*-4 acyloxy groups, the reaction completed in 6 h and the same 4-allyl substituted azetidinone product **15** was obtained in 93% isolated yield.

At this stage, out of interest in antibacterial activity, we turned our attention to the synthesis of dethiathienamycin (**17**) in which the sulfur atom is

Table 2. Reaction of 4-Acyloxy-2-azetidinone with Tetraallyltin

X	Isolated Yield/%
α-AcO	93
β-AcO	93
α-PhCOO	93

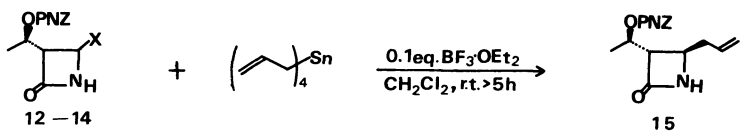
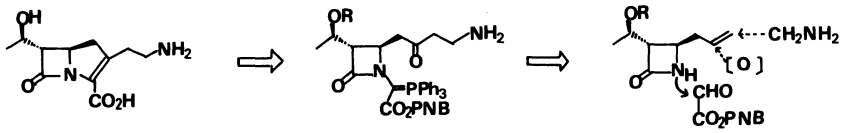


Chart 5.

16
thienamycin

17
dethiathienamycin

Chart 6.



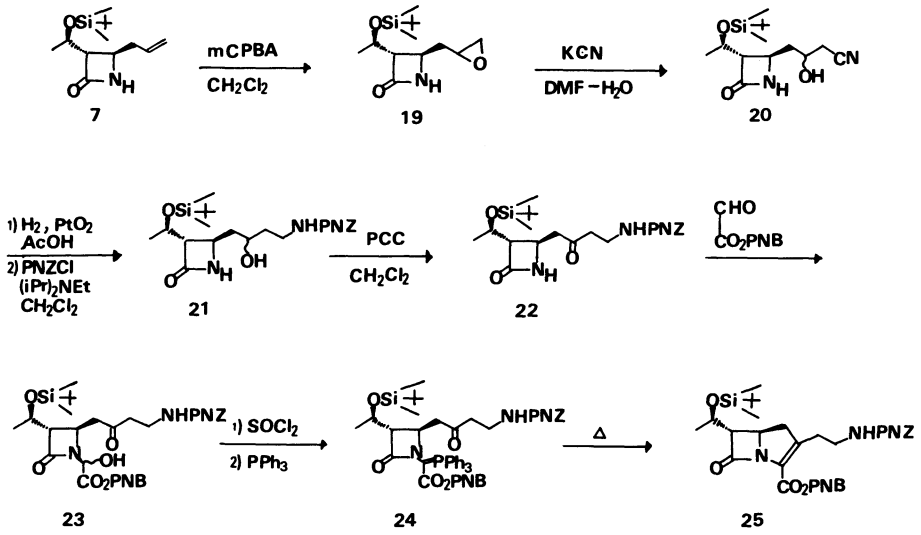
17 18

Chart 6′.

missing from the thienamycin molecule (**16**). Our strategy was as follows: i) The construction of the carbapenem skeleton was to be achieved by intramolecular Wittig reaction. ii) Compound **18** was to be synthesized from allylazetidinone **7** by the combination of 3 parts; *p*-nitrobenzyl glyoxylate, aminomethyl synthon, and the oxygen function at the 2-position of the allyl group.

We considered that the epoxidation of the double bond was useful for the introduction of the oxygen function, and the cyanide anion was taken advantage of for the aminomethyl synthon. Along these lines, the 4-allyl-2-azetidinone derivative **7** was oxidized with *m*-chloroperbenzoic acid in dichloromethane to the epoxide **19** as a mixture of two diastereomers, one of which crystallized: mp 83.5 °C $[\alpha]_D^{24}$ −18°(*c* 1, $CHCl_3$). The epoxide ring in **19** was opened regiospecifically to the cyano alcohol derivative **20**, one of the diastereomers of which also crystallized, mp 120—125 °C, on treatment with potassium cyanide in *N*,*N*-dimethylformamide–water (3:1) at room temperature for 15 h. The cyano group was then hydrogenated to the amino group using platinum oxide in acetic acid, and the succesive protection of the amino group by *p*-nitrobenzyloxycarbonyl chloride gave the compound **21** in 50% yield from **20**. The hydroxyl group in **21** was effectively oxidized to the ketone **22** with pyridinium chlorochromate in dichloromethane. Compound **22** was condensed with *p*-nitrobenzyl glyoxylate to afford the aminal derivative **23**, which was chlorinated by thionyl chloride and successively reacted with triphenylphosphine to give the ylide **24**. The intramolecular Wittig condensation reaction was easily performed by heating in benzene at 80 °C to afford the carbapenem **25**. The desilylation of this compound **25** could not be achieved under ordinary conditions (e.g. boron trifluoride etherate in acetonitrile, tetrabutylammonium fluoride and acetic acid, pyridine–acetic acid), presumably because of the instability of the carbapenem skeleton.

Therefore at the stage of **22** the silyl protective group was changed to the *p*-nitrobenzyloxycarbonyl group. The desilylation conditions, boron trifluoride



7 19 20 21 22 23 24 25

Chart 7.

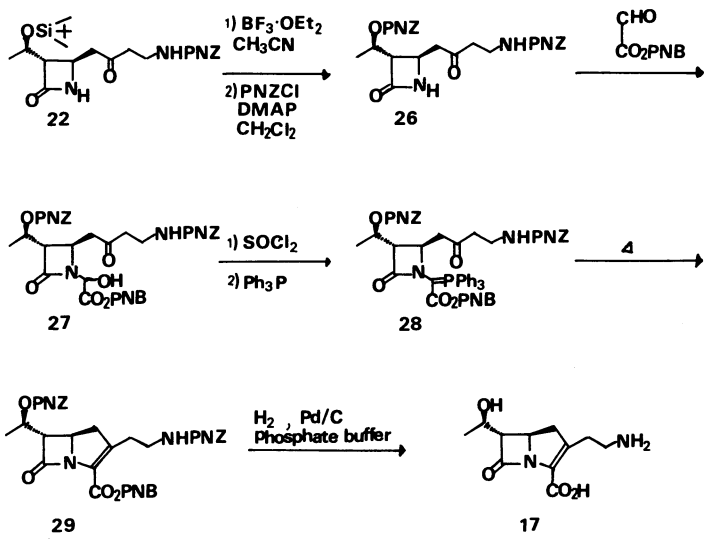


Chart 8.

etherate in acetonitrile were effectively applied to compound **22** to give the 1-hydroxyethyl compound, mp 115—116 °C. The hydroxyl group was reprotected with the *p*-nitrobenzyloxycarbonyl group using *p*-nitrobenzyloxycarbonyl chloride-4-(dimethylamino)-pyridine in dichloromethane to give the compound **26** in 50% isolated yield. The aminal formation reaction between **26** and *p*-nitrobenzyl glyoxylate (water was removed azeotropically before use) was smoothly performed in benzene in the presence of a catalytic amount of triethylamine at 40 °C for 5 min to afford the expected compound **27**. Chlorination and the ylide formation were performed under the standard conditions[12] to afford the ylide **28**. The intramolecular Wittig reaction was successfully applied to the ylide **28** by refluxing in benzene for 5 h to yield the desired carbapenem derivative **29**: IR(neat): 3400, 1775, 1745, 1720 cm^{-1}. The final stage of the synthesis; the deprotection of the *p*-nitrobenzyloxycarbonyl and *p*-nitrobenzyl group of the carbapenem derivative **29**, was achieved hydrogenetically by 10% palladium on carbon in phosphate buffer (pH 7.0), and the purification of the crude product was performed carefully on CHP 20P (75—150 μ) chromatography (water elution) to give the desired dethiathienamycin **17**. The antibacterial activity of dethiathienamycin (**17**) thus obtained is as follows: M.I.C. (μg/ml), Staphylococcus aureus FDA 209P JC 0.01, *Staphylococcus aureus* 56 (PCase+) 0.01, *Escherichia coli* NIHJ JC-2 0.2, *Escherichia coli* 609 (PCase+) 0.4, *Pseudmonas aeruginosa* 1001 12.5, *Klebsiela pneumoniae* 806 0.4. These activities are about one half of those of thienamycin (**16**).

Experimental

General. All melting points are uncorrected. Specific rotations were measured using a Perkin-Elmer 241 polarimater. IR spectra were recorded on JASCO A102 and A320 Infrared spectrometers. NMR spectra were taken using a Varian EM 360L spectrometer (60 MHz) and the chemical shifts are expressed in ppm units using TMS as internal standard: s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; t, triplet; q, quartet; dq, doublet of quartet; m, multiplet. Mass spectra (MS) were measured on JMS 01SG and JMS D300 mass spectrometers. (Preparative) TLC was carried out on Merck TLC-plates silica gel F_{254} Pre-coated, layer thickness: (2 mm) 0.25 mm and spots were made visible by ultraviolet irradiation.

(3*S*,4*R*)-4-Allyl-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (7) Reaction of 6 with Tetraallyltin. General Procedure: To a stirred solution of 1 g (3.484 mmol) of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**6**) in 20 ml of anhydrous dichloromethane was added 1.46 g (5.166 mmol) of tetraallyltin and 49.5 mg (0.3484 mmol) of boron trifluoride etherate under a nitrogen atmosphere. The resulting yellow solution was stirred at room temperature (rt) for 15 h. Dichloromethane was added and the mixture was washed three times with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. Purification of the oil residue by flash column chromatography (cyclohexane-ethyl acetate, 2:1 v/v) afforded 800 mg (85%) of allylazetidinone (**7**):mp 70—77 °C; ^1H NMR ($CDCl_3$) δ=0.06 (6H, s), 0.87 (9H, s), 1.19 (3H, d, J=6 Hz), 2.2—2.5 (2H, m), 2.74 (1H, ddd, J=1.5, 3, and 5 Hz) 3.5—3.85 (1H, m), 3.95—4.35 (1H, m), 4.8—5.9 (3H, m).

Found: C, 62.47; H, 10.05; N, 5.20%. Calcd for $C_{14}H_{27}NO_2Si$: C, 62.40; H, 10.10; N, 5.20%.

Reaction of 6 with Allyltributyltin: To a solution of 60 mg (0.2091 mmol) of **6** in 6 ml of anhydrous dichloromethane was added 200 mg (0.6050 mmol) of allyltributyltin and 10 mg (0.0704 mmol) of boron trifluoride etherate under a nitrogen atmosphere. The resulting yellow solution was stirred at rt for 16 h. Dichloromethane was added and the mixture was washed three times with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified

by TLC (cyclohexane–ethyl acetate, 2:1 v/v) to give 40 mg (71%) of the desired product (**7**).

4-Allyl-2-azetidinone (9): To a solution of 550 mg (4.264 mmol) of 4-acetoxy-2-azetidinone in dichloromethane (10 ml) was added 1.4 g (4.95 mmol) of tetraallyltin and 60 mg (0.42 mmol) of boron trifluoride etherate under a nitrogen atmosphere. The resulting yellow solution was stirred at rt for 15 h. Dichloromethane was added and the mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by TLC (cyclohexane–ethyl acetate, 2:1 v/v) to give 350 mg (74%) of the desired product **9**: mp 76—77 °C; ^{1}H NMR ($CDCl_3$) δ=2.2—2.5 (2H, t like), 2.4—2.75 (1H, m), 2.82—3.21 (1H, m), 3.45—3.8 (1H, m), 4.8—6.05 (3H, m), 6.9 (1H, br s).

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-(1-methyl-2-propenyl)-2-azetidinone (11): To a solution of 100 mg of **6** in 2 ml of dichloromethane was added 248 mg of 2-butenyltributyltin and 5 mg of boron trifluoride etherate. The mixture was stirred for 5 h and dichloromethane was added. The solution was washed with aqueous sodium hydrogencarbonate and water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by flash column chromatography (cyclohexane–ethyl acetate, 2:1 v/v) to give 78.9 mg (80%) of the desired product **11**: ^{1}H NMR ($CDCl_3$) δ=0.08 (6H, s), 0.78 (9H, s), 1.05 (3H, d, J=6 Hz), 1.17 (3/2H, d, J=6 Hz), 1.21 (3/2H, d, J=6 Hz), 2.6—2.9 (1H, m), 3.2—3.6 (1H, m), 4.12 (1H, quintet, J=6 Hz), 4.8—5.3 (2H, m), 5.3—6.0 (1H, m), 6.0—6.7 (1H, m).

(3*S*,4*R*)-4-Allyl-3-[(*R*)-1-(*p*-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (15): To a solution of 115 mg (0.327 mmol) of (3*R*,4*S*)- or (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*p*-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (**12**, **13**) in 5 ml of anhydrous dichloromethane was added 115 mg (0.407 mmol) of tetraallyltin and 4.64 mg (0.0327 mmol) of boron trifluoride etherate under a nitrogen atmosphere. The resulting yellow solution was stirred at rt for 5 h. Dichloromethane was added and the mixture was washed 3 times with water, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by TLC (cyclohexane–ethyl acetate, 2:1 v/v) to give 101 mg (92.6%) of the desired product **15**: IR (neat): 3300 and 1740 cm^{-1} (lactam carbonyl); ^{1}H NMR ($CDCl_3$) δ=1.42 (3H, d, J=6.5 Hz), 2.36 (2H, t, J=6.5 Hz), 3.00 (1H, dd, J=2.5 and 7.5 Hz), 4.9—6.1 (4H, m), 5.20 (2H, s), 6.25 (1H, br s), 7.4—8.3 (4H, A_2B_2 type).

The same procedure with (3*R*,4*S*)-4-benzoyloxy-3-[(*R*)-(*p*-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (**14**) gave **15** in 93% yield.

(3*S*,4*R*)-4-(2,3-Epoxypropyl)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (19): To a solution of 800 mg (2.97 mmol) of 4-allylazetidinone **7** in 20 ml of anhydrous dichloromethane was added 780 mg (4.52 mmol) of *m*-chloroperbenzoic acid in an ice bath. The mixture was stirred at rt for 15 h. The reaction mixture was washed with 5% aqueous sodium hydrogenecarbonate and water successively, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 650 mg of the desired product **19**. One of the diastereomers was recrystallized from petroleum ether: mp 83.5 °C; R_f= 0.45 (cyclohexane–ethyl acetate 1:2 v/v); IR (nujol) 3140, 3080, 1760, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.08 (6H, s), 0.89 (9H, s), 1.19 (3H, d, J=6 Hz), 1.5—2.1 (2H, m), 2.3—3.1 (5H, m), 3.6—4.4 (2H, m).

Found: C, 59.02; H, 9.45; N, 4.89%. Calcd for $C_{14}H_{27}NO_3Si$: C, 58.91; H, 9.53; N, 4.90%.

(3*S*,4*R*)-4-(3-Cyano-2-hydroxypropyl)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (20): To a solution of 500 mg (1.75 mmol) of **19** in 3 ml of DMF and 1 ml of water was added 250 mg (3.85 mmol) of potassium cyanide. The mixture was stirred at rt for 15 h. Ethyl acetate was added and the reaction mixture was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. Purification of an oily residue by flash column chromatography (cyclohexane–ethyl acetate, 1:2 v/v) afforded 420 mg (77%) of the desired product **20**. One of the diastereomers crystallized from petroleum ether and ethyl acetate: mp 120—125 °C; IR (nujol) 3330, 2240(CN), 1700 cm^{-1} (lactam C=O); ^{1}H NMR ($CDCl_3$) δ=0.08 (6H, s), 0.89 (9H, s), 1.21 (3H, d, J=6 Hz), 1.7—2.1 (2H, m), 2.45—3.0 (3H, m), 3.5—4.4 (3H, m), 6.6 (1H, br s).

Found: C, 57.87; H, 9.05; N, 8.92%. Calcd for $C_{15}H_{28}N_2O_3Si$: C, 57.66; H, 9.03; N, 8.96%.

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*p*-nitrobenzyloxycarbonylamino)-2-hydroxybutyl]-2-azetidinone (21): A mixture of 821 mg (2.63 mmol) of **20** and 42 mg of platinum oxide in 8 ml of glacial acetic acid was stirred under a hydrogen atmosphere at 1 atm for 5 h. The mixture was filtered through Celite and evaporated to give the desired amino derivative.

To a solution of the amino derivative thus obtained in 5 ml of dichloromethane was added 850.7 mg (3.95 mmol) of *p*-nitrobenzyl chloroformate and 1.02 g (7.91 mmol) of *N*,*N*-diisopropylethylamine. The mixture was stirred at rt overnight. Ethyl acetate (50 ml) was added and the mixture was washed with water two times and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. Purification of a residue by flash column chromatography (cyclohexane–ethyl acetate, 1:10 v/v) afforded 612.7 mg (47%) of the desired product **21** as a 3:5 mixture of diastereomers. Diastereomer I: R_f=0.55 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ=0.12 (6H,s), 0.89 (9H, s), 1.25 (3H, d, J=6 Hz), 1.4—2.0 (4H, m), 2.7—3.1 (1H, m), 2.0—4.4 (6H, m), 5.13 (2H, s), 5.63 (1H, t, J=6 Hz), 6.69 (1H, s), 7.3—8.3 (4H, m). Diastereomer II: R_f=0.50 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ=0.08 (6H, s), 0.88 (9H, s), 1.22 (3H, d, J=6 Hz), 1.4—2.1 (4H, m), 2.6—3.0 (1H, m), 3.0—4.1 (5H, m), 3.9—4.3 (1H, m), 5.16 (2H, s), 5.66 (1H, t, J=6 Hz), 6.65 (1H, s), 7.3—8.2 (4H, m).

(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[4-(*p*-nitrobenzyloxycarbonylamino)-2-oxobutyl]-2-azetidinone (22): To a solution of 368.6 mg (0.754 mmol) of **21** in 25 ml of dichloromethane was added 1.12 g (5.20 mmol) of pyridinium chlorochromate. The mixture was stirred at rt for 3 h and filtered through Celite. Dichloromethane was added to the filtrate and the solution was washed with water two times and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by TLC (cyclohexane–ethyl acetate, 1:2 v/v) to give 242.9 mg (66%) of the desired product **22**: R_f=0.6

(cyclohexane–ethyl acetate, 1:2 v/v); ^{1}H NMR ($CDCl_3$) δ= 0.07 (6H, s), 0.86 (9H, s), 1.19 (3H, d, J=5.4 Hz), 2.4—3.0 (4H, m), 3.42 (2H, q like, J=6 Hz), 3.7—4.1 (1H, m), 3.9—4.4 (1H, m), 5.13 (2H, s), 5.70 (1H, br t, J=6 Hz), 6.52 (1H, br s), 7.3—8.2 (4H, m).

***p*-Nitrobenzyl 2-[(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)-ethyl]-4-[4-(*p*-nitrobenzyloxycarbonylamino)-2-oxobutyl]-2-oxo-1-azetidinyl]-2-hydroxyacetate (23):** A mixture of 242.9 mg (0.4297 mmol) of **22** and 250 mg (1.10 mmol) of *p*-nitrobenzyl glyoxylate monohydrate in 100 ml of benzene was refluxed overnight. Triethylamine was added to this solution and the mixture was refluxed for 6 h. The solvent was removed under reduced pressure. A residue was purified by TLC (hexane–ethyl acetate–acetone, 8:6:3 v/v) to give 258.1 mg (86%) of the desired product **23** as a mixture of two diastereomers: R_f=0.55, 0.50 (hexane–ethyl acetate–acetone, 8:6:3 v/v); ^{1}H NMR ($CDCl_3$) δ=0.02 (3H, s), 0.05 (3H, s), 0.84 (9H, s), 1.22 (3H, d, J=6.4 Hz), 1.7—2.1 (1H, m), 2.4—3.2 (4H, m), 3.2—4.5 (5H, m), 5.0—6.0 (6H, m), 7.2—7.8 (4H, m), 7.9—8.5 (4H, m).

***p*-Nitrobenzyl 2-[(3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)-ethyl]-4-[4-(*p*-nitrobenzyloxycarbonylamino)-2-oxobutyl]-2-oxo-1-azetidinyl]-2-triphenylphosphoranylideneacetate (24):** To a solution of 258.1 mg (0.3677 mmol) of **23** in 22 ml of THF was added 0.064 ml of 2,6-lutidine. The mixture was cooled to −30 °C and 0.04 ml of thionyl chloride was added. The reaction mixture was stirred for 1 h and the precipitate formed was filtered through Celite. The solvent was removed under reduced pressure to give a crude chloro derivative.

The chloro derivative was dissolved in 14 ml of dioxane and 192 mg (0.733 mmol) of triphenylphosphine and 0.09 ml of 2,6-lutidine was added to this solution. The mixture was stirred at rt overnight. Ethyl acetate was added and the solution was washed with water two times and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. A residue was purified by TLC (hexane–ethyl acetate–acetone, 10:6:3 v/v) to give 93.5 mg (27%) of the desired product **24** and 24.7 mg (8%) of the desilylated phosphorane.

***p*-Nitrobenzyl (5*R*,6*S*)-6-[(*R*)-1-(*t*-Butyldimethylsilyloxy)-ethyl]-3-[2-(*p*-nitrobenzyloxycarbonylamino)ethyl]-7-oxo-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (25):** To a solution of 165.8 mg (0.175 mmol) of **24** in 80 ml of dry benzene was added catalytic amount of hydroquinone. The mixture was refluxed for 5 h. The solvent was removed under reduced pressure and a residue was purified by medium pressure liquid chromatography on silica gel (cyclohexane–ethyl acetate, 2:3 v/v) to give 85 mg (73%) of the desired product **25**: R_f=0.4 (cyclohexane–ethyl acetate, 2:3 v/v); ^{1}H NMR ($CDCl_3$) δ=0.09 (6H, s), 0.86 (9H, s), 1.23 (3H, d, J=6.6 Hz), 2.4—3.7 (7H, m), 3.8—4.5 (2H, m), 4.8—5.4 (1H, m), 5.08 (2H, s), 5.1—5.4 (2H, m), 7.2—7.8 (4H, m), 7.8—8.4 (4H, m); IR(neat) 3380, 1765 (lactam C=O), 1715(NHC=O) cm^{-1}.

Found: C, 57.66; H, 6.15; N, 8.38%. Calcd for $C_{32}H_{40}N_4O_{10}Si$: C, 57.47; H, 6.03; N, 8.38%.

(3*S*,4*R*)-3-[(*R*)-1-Hydroxyethyl]-4-[4-(*p*-nitrobenzyloxycarbonylamino)-2-oxobutyl]-2-azetidinone: To a solution of 248.9 mg (0.5049 mmol) of **22** in 6 ml of acetonitrile was added 0.125 ml of boron trifluoride etherate under ice cooling. The mixture was stirred for 18 min in an ice bath and then cooled aqueous sodium hydrogencarbonate was added. The organic layer was extracted with ethyl acetate. The extracts were washed with water two times and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and a residue was purified by medium pressure liquid chromatography on silica gel (dichloromethane–ethanol, 10:1 v/v) to give 165.5 mg (90%) of the desired product as white crystals: mp 115—116 °C; R_f=0.1 (ethyl acetate); IR (KBr pellet) 3340, 1755 (lactam C=O), 1700, 1680 cm^{-1}; ^{1}H NMR (aceton-d_6) δ=1.18 (3H, d, J=6.2 Hz), 2.5—3.0 (4H, m), 2.89 (2H, d, J=6.2 Hz), 3.1—3.6 (2H, m), 3.6—4.2 (3H, m), 5.14 (2H, s), 7.3—7.8 (2H, m), 8.0—8.4 (2H, m).

Found: C, 53.69; H, 5.54; N, 11.07%. Calcd for $C_{17}H_{21}N_3O_7$: C, 53.75; H, 5.70; N, 11.06%.

(3*S*,4*R*)-4-[4-(*p*-Nitrobenzyloxycarbonylamino)-2-oxobutyl]-3-[(*R*)-1-(*p*-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (26): A solution of 471.5 mg (1.292 mmol) of the hydroxy derivative in 3 ml of dichloromethane was cooled in an ice bath and 315.9 mg (2.589 mmol) of 4-(dimethylamino)pyridine was added. A solution of 1.39 g (6.45 mmol) of *p*-nitrobenzyl chloroformate in 5 ml of dichloromethane was added slowly for 6.5 h and stirred for 30 min. The reaction mixture was washed with water, dil hydrochloric acid, and dil aqueous sodium hydrogencarbonate successively and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by medium pressure liquid chromatography on silica gel (ethyl acetate) to give 465.2 mg (66%) of the desired product **26**: ^{1}H NMR ($CDCl_3$) δ=1.42 (3H, d, J=6 Hz), 2.3—4.1 (9H, m), 5.10 (2H, s), 4.2—4.7 (1H, m), 6.50 (1H, br s), 7.2—7.7 (4H, m), 7.9—8.4 (4H, m).

***p*-Nitrobenzyl 2-Hydroxy-2-[(3*S*,4*R*)-4-[4-(*p*-nitrobenzyloxycarbonylamino)-2-oxobutyl]-3-[(*R*)-1-(*p*-nitrobenzyloxycarbonyloxy)ethyl]-2-oxo-1-azetidinyl]acetate (27):** A mixture of 387.9 mg (1.709 mmol) of *p*-nitrobenzyl glyoxylate (water was removed azeotropically before use), 465 mg (0.855 mmol) of **26**, and 1 drop of triethylamine in 100 ml of benzene was stirred at 40 °C for 5 min. The solvent was removed under reduced pressure and a residue was purified by medium pressure liquid chromatography (dichloromethane–THF, 7:1 v/v) to give the desired products as a mixture of diastereomers. Diastereomer I: 208 mg (32%); R_f=0.4 (dichloromethane–THF, 7:1 v/v); ^{1}H NMR ($CDCl_3$) δ=1.39 (3H, d, J=6 Hz), 2.2—4.7 (11H, m), 5.10 (2H, s), 5.17 (2H, s), 5.21 (2H, s), 4.7—5.4 (1H, m), 7.2—7.6 (6H, m), 7.9—8.3 (6H, m). Diasteromer II: 322.1 mg (49%); R_f=0.3 (dichloromethane–THF, 1:1 v/v); ^{1}H NMR ($CDCl_3$) δ=1.39 (3H, d, J=6 Hz), 2.4—4.6 (11H, m), 5.10 (2H, s), 4.7—5.8 (3H, m), 5.17 (2H, s), 7.1—7.8 (6H, m), 7.8—8.4 (6H, m).

***p*-Nitrobenzyl 2-[(3*S*,4*R*)-4-[4-(*p*-Nitrobenzyloxycarbonylamino-2-oxobutyl]-3-[(*R*)-1-(*p*-nitrobenzyloxycarbonyloxy)-ethyl]-2-oxo-1-azetidinyl]-2-phosphoranylideneacetate (28):** To a solution of 530 mg (0.691 mmol) of **27** in 7 ml of THF was added 0.14 ml of 2,6-lutidine. The mixture was cooled to −20 °C and 0.07 ml of thionyl chloride was added. The reaction mixture was stirred for 30 min and the precipitate formed was filtered through Celite. The solvent was removed under reduced pressure to give a crude chloro derivative.

The crude chloro derivative was dissolved in 7 ml of dioxane, and 540.6 mg (2.063 mmol) of triphenylphosphine and 0.25 ml of 2.6-lutidine was added to this solution. The

mixture was stirred at rt for 3 h and at 40 °C for 13 h. After cooling, ethyl acetate was added and the solution was washed with water two times and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by medium pressure liquid chromatography (cyclohexane–ethyl acetate, 1:10 v/v) to give 481 mg (69%) of the desired product **28**: R_f=0.3 (cyclohexane–ethyl acetate, 1:10 v/v); ^{1}H NMR ($CDCl_3$) δ=1.12 (3H, d, J=6.2 Hz), 2.3—3.0 (5H, m), 3.0—3.7 (4H, m), 4.5—4.9 (1H, m), 4.9—6.3 (6H, m), 7.1—8.0 (21H, m), 7.9—8.3 (6H, m).

***p*-Nitrobenzyl (5*R*,6*S*)-3-[2-(*p*-Nitrobenzyloxycarbonyl amino)ethyl]-6-[(*R*)-1-(*p*-nitrobenzyloxycarbonyloxy)ethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (29):** To a solution of 503.3 mg (0.4973 mmol) of **28** in 100 ml of dry benzene was added catalytic amount of hydroquinone. The mixture was refluxed for 5 h and the solvent was removed under reduced pressure. A residue was purified by flash column chromatography (dichrolomethane–ether, 20:1 v/v) to give 194.5 mg (54%) of the desired product **29**: R_f=0.2 (dichrolomethane–ether, 20:1 v/v); IR(neat) 3400, 1775, 1745, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.46 (3H, d, J=6.2 Hz), 2.3—3.7 (7H, m), 3.7—4.5 (1H, m), 4.7—5.4 (8H, m), 7.1—7.8 (6H, m), 7.8—8.4 (6H, m).

(5*R*,6*S*)-3-(2-Aminoethyl)-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (Dethiathienamycin) 17: A mixture of 194.5 mg (0.2705 mmol) of **29** and 58.3 mg of 10% palladium on carbon in 3.8 ml of THF and 3.8 ml of phosphate buffer (pH 7.0) was stirred under a hydrogen atmosphere (1 atm) for 2 h. The mixture was filtered through Celite and evaporated and the residue was chromatographed on CHP-20P (75—150 μ) (water elution) to give 14.9 mg (23%) of the desired product **17**: UV (water) 267 nm; ^{1}H NMR (D_2O, DSS) δ=1.22 (3H, d, J=6 Hz).

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