Synthesis of 2-(Heteroarylthiomethyl)-1β-methylcarbapenem *via* Propargylation of 4-Acetoxy-2-azetidinone with 3-Methyl-1-tributylstannylallene

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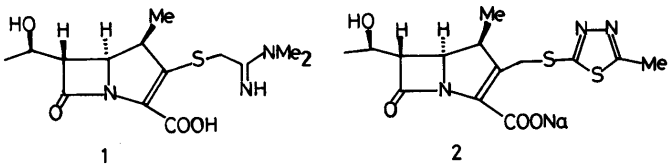
The key intermediate in the synthesis of 1β-methylcarbapenem, (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1*S*)-1-methyl-2-propynyl]-2-azetidinone (5β), was prepared by propargylation of (3*R*,4*R*)-4-acetoxy-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (3) with 3-methyl-1-tributylstannylallene (4) in the presence of a Lewis acid and successfully converted to a novel 2-(heteroarylthiomethyl)-1β-methylcarbapenem (2).

Keywords propargylation; 3-methyl-1-tributylstannylallene; 4-acetoxy-2-azetidinone; 4-[(1*S*)-1-methyl-2-propynyl]-2-azetidinone; 2-(heteroarylthiomethyl)-1β-methylcarbapenem

Since the antibiotic 1β-methylcarbapenem (**1**) exhibits high chemical stability and resistance to dehydropeptidase I (DHP-I) while retaining an extremely broad spectrum of antibacterial activities,[1] much attention has been focused on the synthesis of analogues (Fig. 1).[2] So far, however, there has been no report on the synthetic study of 1β-methylcarbapenem bearing a heteroarylthiomethyl side chain, (which has been shown to be useful in cephalosporins) at the 2-position of the carbapenem skeleton. We are interested in preparing hybrid 2-(heteroarylthiomethyl)-1β-methylcarbapenems in a search for more active and stable analogues. Here we report our synthetic work on 2-(5-methyl-1,3,4-thiadiazole-2-thiomethyl-1β-methylcarbapenem (**2**) through the propargylation of (3*R*,4*R*)-4-acetoxy-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**3**) using 3-methyl-1-tributylstannylallene (**4**).

Preparation of (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*S*)-1-methyl-2-propynyl]-2-azetidinone (5β)[3] Recently, we found that stannylallene reacted with aldehydes and ketones in the presence of $TiCl_4$ to give the corresponding homopropargylic alcohols in good yields.[4] The reaction of stannylallene as a propargylic anion equivalent was successfully applied to the introduction of the propargylic moiety at the 4-position of a readily available 4-acetoxy-2-azetidinone derivative (**3**).[5] Thus, treatment of **3** with 2 eq of **4** in CH_2Cl_2 in the presence of trimethylsilyl triflate (TMSOTf) at room temperature gave a 1 : 1 mixture of diastereomeric products (**5α** and **5β**) in 98% yield, which could not be separated either by chromatography or by recrystallization (Chart 1). When boron trifluoride etherate ($BF_3 \cdot OEt_2$) was used as a Lewis acid instead of TMSOTf, the undesired α-methyl isomer (**5α**) was obtained as a major product (**5α** : **5β** = 4 : 1) in 89% yield. The low diastereoselectivity could not be improved by employing various other Lewis acids. The ratio of **5α** and **5β** was determined by integrating the signal of the proton at the 4-position of the known alkenes (**6α** and **6β**)[6] which were quantitatively obtained by the Lindlar reduction of the mixture of diastereomers (**5α** and **5β**) (Chart 1).

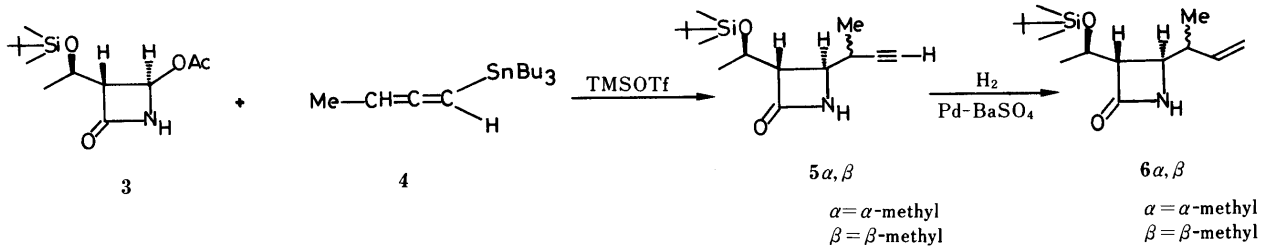


1 2

Fig. 1

Treatment of the 1 : 1 mixture of diastereomers (**5α** and **5β**) with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) in the presence of triethylamine in *N*,*N*-dimethylformamide (DMF) gave the *N*-TBDMS products (**7α** and **7β**), which were silylated with 1.1 eq of lithium diisopropylamide (LDA) and 1.1 eq of trimethylsilyl chloride (TMS-Cl) successively to produce the TMS-acetylenic compounds (**8α** and **8β**). The diastereomers (**8α** and **8β**) could be easily separated by column chromatography. The selective *N*-desilylation of **8β** was carried out with 1.1 eq of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) containing acetic acid to give the optically active β-methyl TMS-acetylenic compound (**9β**), which was converted into (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1*S*)-1-methyl-2-propynyl]-2-azetidinone (**5β**) by treatment with potassium carbonate in MeOH (Chart 2). The absolute stereochemistry of **5β** could be established by the successful transformation of **5β** into the known β-methyl alkene (**6β**).[6] The α-methyl isomer (**5α**) was also obtained in a similar manner.

Interestingly, when the 1 : 1 mixture of **5α** and **5β** was treated with 3.3 eq of LDA followed by 3.3 eq of TMS-Cl in THF, the β-methyl TMS-acetylenic compound (**9β**) was selectively obtained in 42—44% yield (α-methyl: β-methyl = 1 : > 10) and α-methyl desilyloxylated compounds

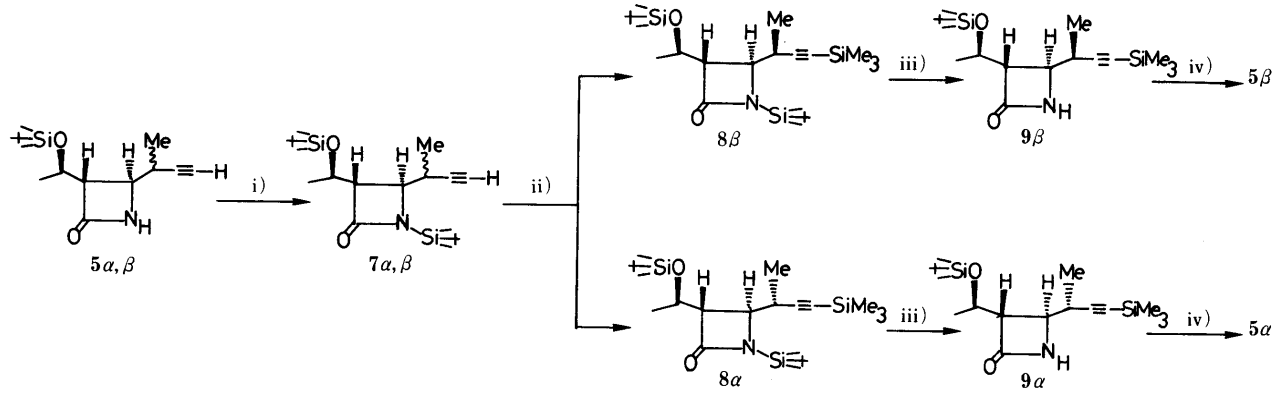


3 4 5α,β 6α,β

α = α-methyl
β = β-methyl

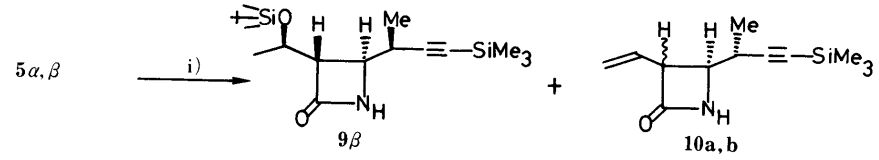
α = α-methyl
β = β-methyl

Chart 1



i) TBDMS–Cl, Et_3N, DMF; ii) 1.1 eq LDA, 1.1 eq TMS–Cl; iii) TBAF, AcOH; iv) K_2CO_3

Chart 2



i) 3.3 eq LDA, 3.3 eq TMS–Cl

Chart 3

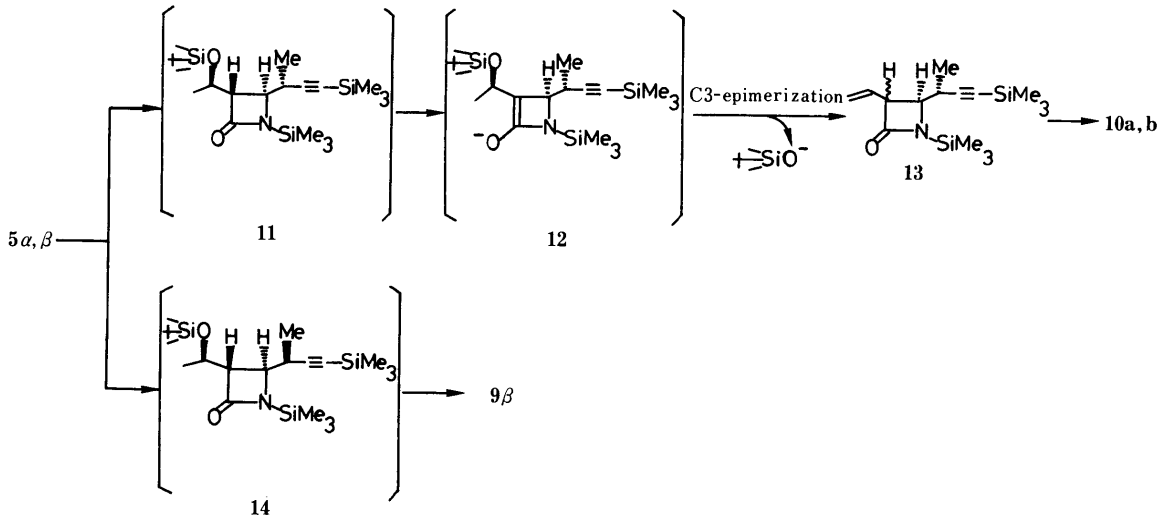
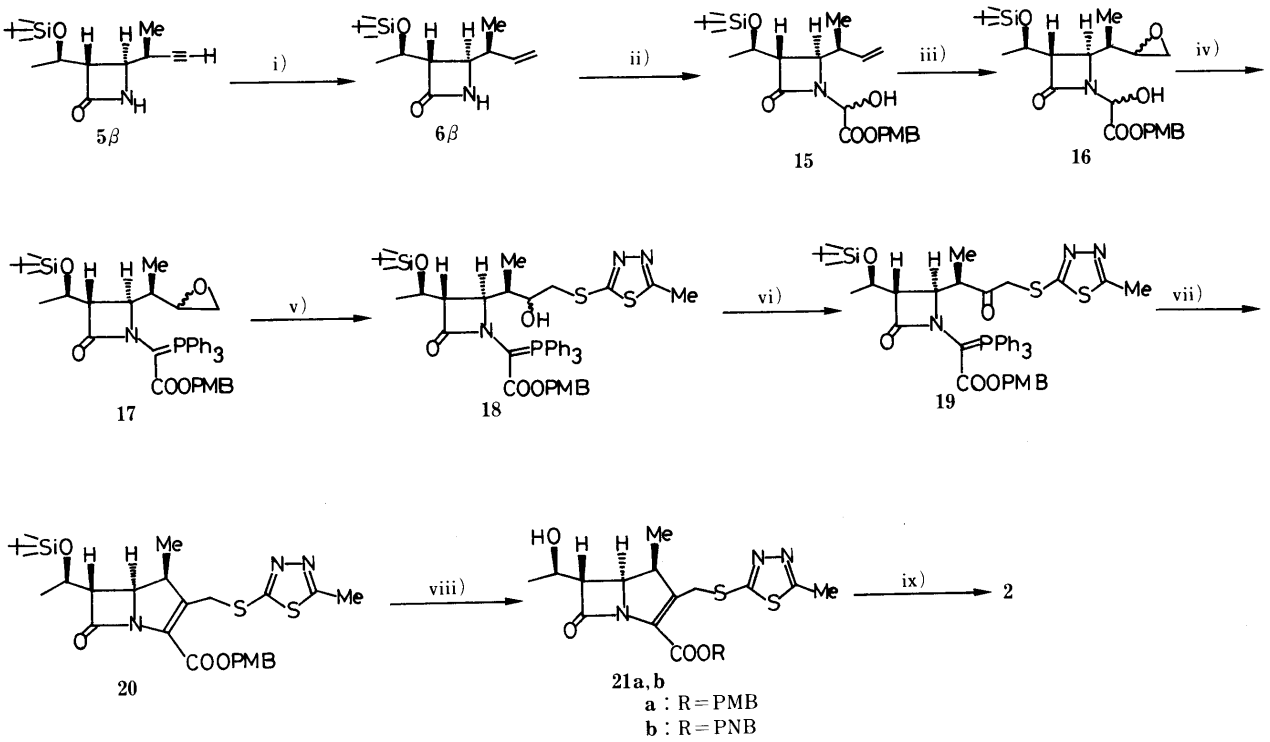


Chart 4

(**10a** and **10b**) were also obtained in 10—14% yield as a 1 : 1 mixture of diastereomers of the 3-position of the β-lactam ring (Chart 3). The desired **9β** was isolated in a pure state by short column chromatography followed by recrystallization. The assignments of the configuration at the 3-position in the diastereomers (**10a** and **10b**) were based on the proton coupling constant between the C3 and C4 protons.[7] Thus, the *cis* isomer (**10a**) showed a large coupling constant of 4.9 Hz and the *trans* isomer (**10b**) showed a small coupling constant of 2.4 Hz. The assignment of the stereochemistry of the α-methyl group in **10** was based on the nuclear Overhauser effect (NOE) between the proton signal of the methyl group and that of the C4 proton.[2a,8] To get insight into the stereochemical features, the pure α-methyl isomer (**5α**) and the pure β-methyl isomer (**5β**) were subjected to the same reaction conditions as used above (LDA, TMS-Cl), independently. The β-methyl isomer (**5β**) gave the β-methyl TMS-acetylenic compound (**9β**) exclusively, although **5α** produced the α-methyl desilyloxylated compounds (**10a** and **10b**). Thus, the α-methyl isomer (**5α**) may yield an anion intermediate (**12**) through abstraction of the C3-β proton with LDA from the less sterically hindered β-face of the β-lactam ring in the α-methyl trisilylated intermediate (**11**), and the anion intermediate (**12**) would undergo elimination reaction to result in **13**, which would give **10a** and **10b** on hydrolysis (Chart 4). On the other hand, the alternative β-methyl trisilylated intermediate (**14**) is assumed to undergo hydrolysis of the N–Si bond to afford **9β** selectively, since the presence of the β-methyl group in **14** may prevent access of bulky LDA to the C3-β proton from the β-face of the β-lactam ring (Chart 4).

Synthesis of Sodium (1*R*,5*R*,6*S*)-6-[(1*R*)-Hydroxyethyl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethyl-1-methylcarbapen-2-em-3-carboxylate (2)[3,10] The ethynyl group of the



i) H_2, Pd–$BaSO_4$; ii) CHOCOOPMB, Et_3N; iii) *m*-CPBA, $NaHCO_3$; iv) 1) $SOCl_2$ 2,6-lutidine, 2) PPh_3, 2,6-lutidine; v) lithium 5-methyl-1,3,4-thiadiazole-2-thiolate; vi) DMSO, $(CF_3CO)_2O$; vii) toluene, reflux; viii) TBAF, AcOH; ix) $AlCl_3$, anisole, $NaHCO_3$

Chart 5

4-[(1*S*)-1-methyl-2-propynyl]-2-azetidinone (**5β**) is quite useful since it can be easily converted into various functional groups, *i.e.*, olefin, carboxylic acid,[3] or β-ketoester,[3,10] providing precursors for the synthesis of 1β-methylcarbapenem. In fact, the azetidinone (**5β**) can be employed as a starting material for the synthesis of a novel 1β-methylcarbapenem (**2**) (Chart 5).

Hydrogenation of **5β** with 5% palladium on $BaSO_4$ in MeOH under 1 atm pressure at room temperature gave the alkene (**6β**) quantitatively. The conversion of **6β** into the epoxy-ylide (**17**) for the intramolecular Wittig reaction was carried out without purification of the intermediates (**15** and **16**). Thus, **6β** was reacted with *p*-methoxybenzyl glyoxylate to give **15** as a mixture of two diastereomers, which was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to afford **16** as a mixture of four diastereomers. Chlorination of **16** with thionyl chloride followed by phosphoranylidenation with triphenylphosphine and 2,6-lutidine gave the epoxy-ylide (**17**) in 75% yield from **6β**. The oxirane ring of **17** was opened regiospecifically with lithium 5-methyl-1,3,4-thiadiazole-2-thiolate to give a single alcohol-ylide (**18**) in 67% yield, and **18** was oxidized to the keto-ylide (**19**). The successive intramolecular Wittig reaction of **19** was carried out in boiling toluene to afford the carbapenem (**20**) in 54% yield from **18**. Desilylation of **20** was achieved with TBAF in THF containing acetic acid to give the corresponding hydroxyethyl carbapenem (**21a**) in 50% yield. The stereochemistry of the 1β-methyl group of **21a** was confirmed by an NOE experiment.[11] The reaction conditions used above were found not to effect epimerization of the methyl group of each starting material.[12] Finally, the deprotection of the *p*-methoxybenzyl (PMB) group of **21a** was achieved by the use of $AlCl_3$-anisole, followed by purification by CHP-20P chromatography to give the desired 1β-methylcarbapenem, 2-(5-methyl-1,3,4-thiadiazole-2-thiomethyl)-1β-methylcarbapenem (**2**). Although we also synthesized a *p*-nitrobenzyl (PNB) ester of 1β-methylcarbapenem (**21b**) corresponding to **21a** according to the same procedure as used above, the reductive removal of the ester protecting group (PNB) was unsuccessful.

In conclusion, we have shown that the optically active 4-[(1*S*)-1-methyl-2-propynyl]-2-azetidinone (**5β**), which is a useful precursor for the synthesis of 1β-methylcarbapenem, can be readily prepared from the 4-acetoxy-2-azetidinone (**3**) through the propargylation using 3-methyl-1-tributylstannylallene (**4**). In addition, the utility of **5β** as a precursor for 1β-methylcarbapenem has been demonstrated by the conversion of **5β** into a novel 1β-methylcarbapenem (**2**).

Experimental

All melting points are uncorrected. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-22 (90 MHz) or a JEOL JNM-GX 500 (500 MHz) spectrometer (with tetramethylsilane as an internal standard unless otherwise noted). Infrared (IR) absorption spectra were recorded on a JASCO HPIR-102 spectrometer. Low- and high-resolution mass spectra (MS) were obtained with a JEOL JMS D-300 instrument, with a direct inlet system. Optical rotations were measured in a 1-dm cell of 1-ml capacity with a Perkin-Elmer 241 instrument. Extracts were dried over $MgSO_4$. For column chromatography, E. Merck silica gel (70—230 mesh ASIM) was used, unless otherwise noted.

3-Methyl-1-tributylstannylallene (4)[13] *N*-Butyllithium (10% (w/v) hexane solution, 46.7 ml) was added to a solution of 1-bromo-3-methylallene[14] (9.69 g) in 450 ml of anhydrous ether over a period of 15 min at −78 °C under a stream of nitrogen, followed by stirring at the same temperature for 1 h. After the addition of anhydrous THF (20 ml), tributylstannyl chloride (23.7 g) was added over 10 min, and then the reaction mixture was allowed to warm to room temperature, followed by stirring at room temperature for 15 min. The reaction mixture was poured

into water, and extracted with ether. The organic layer was washed with water and saturated brine, and dried. The solvent was removed under reduced pressure, and the residue was purified through column chromatography (neutral aluminum oxide containing 5% water, hexane) to give pure **4** (23.8 g, 95%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1930. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 0.7—2.0 (27H, m), 1.65 (3H, dd, J=4, 7 Hz), 4.23 (1H, dq, J=7, 7 Hz), 5.05 (1H, dq, J=4, 7 Hz). MS m/z: 344 (M^+ for Sn^{120}).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(1-methyl-2-propynyl)-2-azetidinone (5) Compound **4** (1.56 g) and TMSOTf (0.35 ml) were added to a solution of (3*R*,4*R*)-4-acetoxy-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-2-azetidinone (**3**, 653 mg) in 20 ml of anhydrous CH_2Cl_2 at 0 °C under a stream of nitrogen, followed by stirring at the same temperature for 15 min and then at room temperature for 14 h. The reaction solution was concentrated under reduced pressure, and the concentrate was diluted with ether. The ethereal solution was washed with phosphoric acid buffer (pH 7) and was added to a saturated aqueous potassium fluoride solution, followed by vigorous stirring for 1 h. The resulting precipitate was filtered off and the filtrate was dried, followed by removal of the solvent under reduced pressure. The residue was purified through column chromatography (hexane : ether = 1 : 1) to give a 98% yield (628 mg) of an inseparable mixture of α-methyl isomer (**5α**) and β-methyl isomer (**5β**) in a ratio of 1 : 1. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1755. ^{1}H-NMR ($CDCl_3$, 90 MHz): 0.08 (6H, s), 0.88 (9H, s), 1.24 (6H, d, J=6 Hz), 2.12 (1H, d, J=2.5 Hz), 2.59 (1/2H, m, α-methyl isomer), 2.70 (1/2H, m, β-methyl isomer), 2.84 (1/2H, m, α-methyl isomer), 3.00 (1/2H, m, β-methyl isomer), 3.57 (1/2H, dd, J=7.6, 1,8 Hz, α-methyl isomer), 3.67 (1/2H, dd, J=6.4, 2.0 Hz, β-methyl isomer), 4.16—4.26 (1H, m). High-resolution MS Calcd for $C_{15}H_{27}NO_2Si$–C_4H_9: 224.1108. Found: 224.1108.

$BF_3 \cdot Et_2O$ Method: When $BF_3 \cdot Et_2O$ (47% ether solution) was used instead of TMSOTf under the above reaction conditions, a 4 : 1 mixture of **5α** and **5β** was obtained in 89% yield.

Hydrogenation of a 1 : 1 Mixture of 5α and 5β with Pd–$BaSO_4$ A 1 : 1 mixture of **5α** and **5β** (500 mg), 5% Pd–$BaSO_4$ (59.2 mg), quinoline (12 mg) and MeOH (10 ml) was shaken at room temperature under H_2 gas for 10 min. The reaction mixture was filtered through Celite, which was washed with additional MeOH. The filtrate and washing were concentrated *in vacuo* and the residue was diluted with ether. The ethereal solution was washed with 0.5% HCl aqueous solution and successively with saturated brine, then dried. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to give a 99% yield (501 mg) of an inseparable mixture of α-methyl alkene (**6α**) and β-methyl alkene (**6β**) in a ratio of 1 : 1. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410, 1750. ^{1}H-NMR ($CDCl_3$) δ: 1.06 [3/2H, d, J= 6.7 Hz, –C(Me)–C=C, α-methyl isomer], 1.07 [3/2H, d, J=6.7 Hz, –C(Me)–C=C, β-methyl isomer], 1.18 (3/2H, d, J=6.1 Hz, Me–CH–OSi, β-methyl isomer), 1.23 (3/2H, d, J=6.1 Hz, Me–CH–OSi, α-methyl isomer), 3.40 (1/2H, dd, J=8.5, 1.8 Hz, H4, α-methyl isomer), 3.51 (1/2H, dd, J=7.6, 2.4 Hz, H4, β-methyl isomer).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-methyl-3-trimethylsilyl-2-propynyl]-1-*tert*-butyldimethylsilyl-2-azetidinone (8α) (α-Methyl Isomer) and β-Methyl Isomer (8β) Triethylamine (0.2 ml) and TBDMS-Cl (216.8 mg) were added to a solution of a 1 : 1 mixture of **5α** and **5β** (150 mg) in 2 ml of anhydrous DMF at room temperature under a stream of nitrogen, followed by stirring for 12 h. The reaction mixture was poured into cold 5% aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with water, then dried. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane : ether = 1 : 1) to give pure **7** (200.3 mg, 95%). Diisopropylamine (0.078 ml) was added to anhydrous THF (1.6 ml) and the stirred mixture was treated with *n*-butyllithium (10% (w/v) hexane solution, 0.356 ml) at 0 °C. After 20 min, the reaction mixture was cooled to −78 °C, and a solution of **7** in anhydrous THF (1.6 ml) was added. The mixture was stirred at the same temperature for 2 h, then TMS-Cl (0.06 ml) was added at −78 °C and the resulting solution was allowed to warm to room temperature overnight. The reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with water and saturated brine, then dried. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane : ether = 10 : 1) to give pure α-methyl isomer (**8α**, 101.3 mg) and β-methyl isomer (**8β**, 108.3 mg).

α-Methyl Isomer (**8α**): Colorless crystals. mp 64—65 °C (hexane). $[\alpha]_D^{20}$ −49.8° (c=0.55, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2170, 1740. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.09 (3H, s), 0.14 (9H, s), 0.23 (3H, s), 0.25 (3H, s), 0.89 (9H, s), 0.97 (9H, s), 1.21 [3H, d, J=7.3 Hz, –C(Me)–C≡C–], 1.23 (3H, d, J=6.1 Hz, –C(Me)–OSi), 2.81 (1H, dq, J=7.3, 4.3 Hz), 2.96 (1H, dd, J= 3.7, 3.1 Hz, H3), 3.82 (1H, dd, J=4.3, 3.1 Hz, H4), 4.21 (1H, dq, J=6.1, 3.7 Hz). *Anal.* Calcd for $C_{24}H_{49}NO_2Si_3$: C, 61.61; H, 10.55; N, 2.99. Found: C, 61.67; H, 10.53; N, 3.12.

β-Methyl Isomer (**8β**): Colorless crystals. mp 91—92 °C (hexane). $[\alpha]_D^{20}$ −54.4° (c=0.53, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2170, 1740. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.08 (3H, s), 0.13 (9H, s), 0.22 (3H, s), 0.25 (3H, s), 0.88 (9H, s), 0.98 (9H, s), 1.17 [3H, d, J=7.0 Hz, –C(Me)–C≡C–], 1.23 [3H, d, J=6.1 Hz, –C(Me)–OSi], 2.89 (1H, dq, J=7.0, 3.4 Hz), 3.12 (1H, dd, J= 6.1, 2.4 Hz, H3), 3.44 (1H, dd, J=3.4, 2.4 Hz, H4), 4.13 (1H, quint, J= 6.1 Hz). *Anal.* Calcd for $C_{24}H_{49}NO_2Si_3$: C, 61.61; H, 10.55; N, 2.99. Found: C, 61.63; H, 10.54; N, 3.14.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-methyl-3-trimethylsilyl-2-propynyl]-2-azetidinone (9α) (α-Methyl Isomer) and β-Methyl Isomer (9β) A solution of TBAF (35 mg) in 0.2 ml of anhydrous THF was added to a solution of **8α** (50.3 mg) and acetic acid (15.8 mg) in 0.2 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was poured into a solution of water and ethyl acetate (1 : 1) and extracted with ethyl acetate. The organic layer was washed successively with water, aqueous $NaHCO_3$ solution and saturated brine, and dried. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane : ether = 2 : 1) to give pure **9α** (32.4 mg, 85%) as colorless crystals, mp 95—96 °C (hexane). $[\alpha]_D^{20}$ +35.9° (c=0.56, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 2160, 1760. ^{1}H-NMR ($CDCl_3$) δ: 0.078 (3H, s), 0.08 (3H, s), 0.15 (9H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.8 Hz, α-methyl), 1.23 [3H, d, J= 6.4 Hz, –C(Me)–OSi], 2.61 (1H, quint, J=7.1 Hz, –CH–C≡C–), 2.82 (1H, dt, J=4.9, 1.7 Hz, H3), 3.55 (1H, dd, J=7.6, 2.0 Hz, H4), 4.18 (1H, dq, J=6.4, 4.9 Hz, –CH–OSi), 6.06 (1H, br, NH). *Anal.* Calcd for $C_{18}H_{35}NO_3Si_2$: C, 61.13; H, 9.97; N, 3.96. Found: C, 61.32; H, 10.00; N, 3.98.

The β-methyl isomer (**9β**) was obtained in 98% yield as colorless crystals from **8β** using the same procedure as described above, mp 147.5—148 °C (hexane). $[\alpha]_D^{20}$ −50.3° (c=0.60, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 2160, 1760. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (3H, s), 0.08 (3H, s), 0.13 (9H, s), 0.88 (9H, s), 1.21 (3H, d, J=7.1 Hz, β-methyl), 1.25 [3H, d, J=6.4 Hz, –C(Me)–OSi], 2.66 (1H, quint, J=7.1 Hz, –CH–C≡C–), 2.92—2.98 (1H, m, H3), 3.63 (1H, dd, J=2, 7.3 Hz, H4), 4.24 (1H, dq, J=3.4, 6.4 Hz, –CH–OSi), 6.37 (1H, br, NH). *Anal.* Calcd for $C_{18}H_{35}NO_2Si_2$: C, 61.13; H, 9.97; N, 3.96. Found: C, 61.15; H, 10.15; N, 3.98.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-methyl-2-propynyl]-2-azetidinone (5α) (α-Methyl Isomer) and β-Methyl Isomer (5β) A mixture of **9α** (1.7 g) and K_2CO_3 (664.4 mg) in 30 ml of MeOH was stirred at room temperature for 5.5 h, then concentrated. The residue was diluted with water and CH_2Cl_2 (1 : 1) and extracted with CH_2Cl_2. The organic layer was washed with saturated brine and evaporated *in vacuo* to give a residue, which was purified by column chromatography to give pure **5α** (1.1 g, 82%) as colorless crystals, mp 121—122 °C (hexane). $[\alpha]_D^{20}$ +20.2° (c=0.60, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 3300, 1760. ^{1}H-NMR ($CDCl_3$) δ: 0.077 (3H, s), 0.083 (3H, s), 0.88 (9H, s), 1.237 [3H, d, J= 6.1 Hz, –C(Me)–OSi], 1.241 (3H, d, J=7.3 Hz, α-methyl), 2.13 (1H, d, J= 2.4 Hz, –C≡CH), 2.58 (1H, d of quint, J=7.3, 2.4 Hz, –CH–C≡C–), 2.84 (1H, dt, J=4.9, 1.5 Hz, H3), 3.57 (1H, dd, J=7.6, 2.1 Hz, H4), 4.18 (1H, quint, J=6.1 Hz, –CH–OSi), 5.93 (1H, br, NH). *Anal.* Calcd for $C_{15}H_{27}NO_2Si$: C, 64.01; H, 9.67; N, 4.98. Found: C, 64.30; H, 9.61; N, 4.95.

The β-methyl isomer (**5β**) was obtained in 97% yield as colorless crystals from **9β** using the same procedure as described above, mp 139—139.5 °C (hexane). $[\alpha]_D^{20}$ −45.8° (c=0.77, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3300, 1760. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.24 (3H, d, J=6.8 Hz, β-methyl), 1.25 [3H, d, J=6.3 Hz, –C(Me)–OSi], 2.12 (1H, d, J=2.4 Hz, –C≡CH), 2.70 (1H, d of quint, J=2.4, 6.8 Hz, –CH–C≡C–), 2.99—3.02 (1H, m, H3), 3.67 (1H, dd, J=2.4, 6.3 Hz, H4), 4.23 (1H, dq, J=4.2, 6.3 Hz, –CH–OSi), 6.00 (1H, br, NH). *Anal.* Calcd for $C_{15}H_{27}NO_2Si$: C, 64.01; H, 9.67; N, 4.98. Found: C, 64.26; H, 9.92; N, 4.89.

Reaction of the 1 : 1 Mixture of 5α and 5β with 3.3 eq of LDA and 3.3 eq of TMS-Cl Diisopropylamine (0.34 ml) was added to anhydrous THF (4.4 ml) under a stream of nitrogen and the stirred mixture was treated with *n*-butyllithium (10% (w/v) hexane solution, 1.6 ml) at 0 °C. After 30 min, the reaction mixture was cooled to −78 °C, a solution of the 1 : 1 mixture of **5α** and **5β** (196 mg) in anhydrous THF (4.4 ml) was added, and the resulting solution was warmed to −40 °C over 1 h period, then cooled down to −78 °C again. TMS-Cl (0.31 ml) was added to the reaction mixture at −78 °C, and the resulting solution was allowed to warm to

room temperature overnight. The reaction mixture was diluted with water and ethyl acetate (1 : 1), and the water layer was separated and extracted with ethyl acetate. The combined organic layer was washed successively with water and saturated brine, and dried. The solvent was removed under reduced pressure. The residue was purified by short column chromatography (hexane : ethyl acetate = 8 : 1) to give a mixture of **5α** and **5β**, and a mixture of **10a** and **10b**. The mixture of **5α** and **5β** was recrystallized from hexane to give pure **5β** (98.4 mg, 40%). The mixture of **10a** and **10b** was separated by preparative thin layer chromatography to give **10a** (7.6 mg, 4.9%) and **10b** (7.8 mg, 5.1%).

(3*S*,4*R*)-4-[(1*R*)-1-Methyl-3-Trimethylsilyl-2-propynyl]-3-vinyl-2-azetidinone (**10a**): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 2170, 1760. ^{1}H-NMR ($CDCl_3$) δ: 0.15 (9H, s), 1.11 (3H, d, J=6.7 Hz, α-methyl), 2.63 (1H, dq, J=9.8, 6.7 Hz, –CH–C≡C–), 3.55 (1H, dd, J=9.8, 4.9 Hz, H4), 3.87—3.91 (1H, m, H3), 5.36 (1H, d, J=10.3 Hz, CH_2=C–), 5.41 (1H, dt, J=17.1, 1.2 Hz, CH_2=C–), 5.83 (1H, ddd, J=17.1, 10.3, 8.2 Hz, –CH=CH_2), 6.02 (1H, br, NH).

(3*R*,4*R*)-4-[(1R)-1-Methyl-3-Trimethylsilyl-2-propynyl]-3-vinylazetidinone (**10b**): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 2170, 1760. ^{1}H-NMR ($CDCl_3$): 0.15 (9H, s), 1.21 (3H, d, J=7.3 Hz, α-methyl), 2.66 (1H, quint, J=7.6 Hz, –CH–C≡C–), 3.41 (1H, dd, J=7.6, 2.4 Hz, H4), 3.50 (1H, dq, J=7.3, 1.2 Hz, H3), 5.25 (1H, dt, J=10.4, 1.2 Hz, CH_2=C–), 5.32 (1H, dt, J=17.1, 1.2 Hz, CH_2=C–), 5.91 (1H, ddd, J=17.1, 10.4, 7.3 Hz, –CH=CH_2), 5.97 (1H, br, NH).

(3*S*,4*R*)-4-[(1*S*)-1-Methyl-2-propenyl]-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (6β) A solution of **5β** (302.3 mg), 5% Pd–$BaSO_4$ (40 mg) and quinoline (8 mg) in MeOH (6 ml) was shaken at room temperature under H_2 gas for 10 min. The reaction mixture was filtered through Celite, which was washed with additional MeOH. The filtrate and washing were concentrated in *vacuo* and the residue was diluted with ether. The ethereal solution was washed with 0.5% HCl aqueous solution and successively with saturated brine, then dried. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane : ethyl acetate = 5 : 1) to give **6β** (302 mg, 99%) as colorless crystals, mp 137—138.5 °C (lit.[6] mp 137—139 °C). $[\alpha]_D^{20}$ −32.9° (c=0.51, $CHCl_3$) {lit.[6] $[\alpha]_D^{20}$ −14.3° (c=0.056, $CHCl_3$)}. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410, 1750. ^{1}H-NMR ($CDCl_3$): 0.07 (6H, s), 0.88 (9H, s), 1.07 (3H, d, J=6.8 Hz, β-methyl), 1.18 [3H, d, J=6.1 Hz, –C(Me)–OSi], 2.33 (1H, br q, J=6.8 Hz, –CH–C=C–), 2.82 (1H, ddd, J=4.3, 2.4, 1.2 Hz, H3), 3.51 (1H, dd, J=7.6, 2.4 Hz, H4), 4.17 (1H, dq, J=6.1, 4.3 Hz, –CH–OSi), 5.06—5.14 (2H, m, –CH=CH_2), 5.72—5.86 (2H, m, –CH=CH_2 and NH). High-resolution MS Calcd for $C_{11}H_{20}NO_2Si$–C_4H_9: 226.126. Found: 226.128. *Anal.* Calcd for $C_{11}H_{20}NO_2Si$: C, 63.55; H, 10.31; N, 4.94. Found: C, 63.77; H, 10.22; N, 5.11.

(3*S*,4*R*)-4-[(1*S*)-1-Methyl-2-propenyl]-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-1-(*p*-methoxybenzyloxycarbonyl)hydroxymethyl-2-azetidinone (15) A solution of **6β** (258.7 mg), *p*-methoxyglyoxylate monohydrate[15] (271.1 mg) and a trace of triethylamine in dry benzene (40 ml) was heated to reflux for 10 h with the use of a Dean-Stark trap containing Molecular Sieves 4A to remove traces of water. The reaction mixture was then cooled and concentrated. The residue was diluted with ethyl acetate, and this solution was washed with water, dried and concentrated to give crude **15** (507.8 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 1755, 1745. ^{1}H-NMR ($CDCl_3$ 90 MHz) δ: 0.04 (6H, s), 0.81 (9H, s), 0.96 (3H, d, J=7 Hz), 1.16 (3H, d, J=6 Hz), 2.25—2.83 (2H, m), 3.75 (3H, s), 3.57—4.23 (2H, m), 4.84—6.03 (6H, m), 6.82 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-(*p*-methoxybenzyloxycarbonyl)hydroxymethyl-4-[(1*R*)-1-methyl-2,3-epoxypropyl]-2-azetidinone (16) A mixture of the crude **15** (507.8 mg), *m*-CPBA (80%, 590.5 mg), and $NaHCO_3$ (230 mg) in CH_2Cl_2 (8 ml) was stirred at room temperature for 16 h under a stream of nitrogen. The reaction mixture was diluted with ethyl acetate, washed with 10% aqueous $Na_2S_2O_3$ solution, aqueous $NaHCO_3$ and saturated brine, then dried. The solvent was removed under reduced pressure to give crude **16** (513 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 1755, 1745. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 0.02 (3H, s), 0.04 (3H, s), 0.84 (9H, s), 2.34—3.05 (5H, m), 3.77 (3H, s), 3.54—4.31 (3H, m), 5.13 (2H, s), 6.84 (2H, d, J=8 Hz), 7.28 (2H, d, J=8 Hz).

(3*S*,4*R*)-3-[(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-methyl-2,3-epoxypropyl]-1-(*p*-methoxybenzyloxycarbonyl)triphenylphosphoranediylmethyl-2-azetidinone (17) 2,6-Lutidine (0.266 ml) and thionyl chloride (0.1 ml) were added to a solution of the crude **16** (513 mg) in anhydrous THF (3.5 ml) at −40 °C under a stream of nitrogen, and the reaction mixture was stirred at the same temperature for 3 h. The resulting solution was filtered through Celite, and the filtrate was concentrated. The residue was dissolved in anhydrous THF (3.5 ml) and treated with triphenylphosphine (239.4 mg) and 2,6-lutidine (0.159 ml) at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with water, dried, and concentrated. The residue was purified by column chromatography (hexane : ethyl acetate = 3 : 1) to give pure **17** (508 mg, 75% from **6β**). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735, 1615. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 0.76 and 0.78 (9H, s × 2, *tert*-Bu), 3.80 and 3.81 (3H, s × 2, –OMe), 6.81—6.92 (2H, m, arom), 7.22—7.33 (2H, m, arom), 7.37—7.88 (15H, m, arom). Other signals could not be assigned.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-(*p*-methoxybenzyloxycarbonyl)triphenylphosphoranediylmethyl-4-[(1*R*)-2-hydroxy-1-methyl-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propyl]-2-azetidinone (18) *n*-Butyllithium (10% (w/v) hexane solution, 0.3 ml) was added to a solution of 5-methyl-1,3,4-thiadiazole-2-thiol (243.6 mg) in anhydrous THF (3 ml) with ice cooling, and the reaction mixture was stirred for 30 min at room temperature under a stream of nitrogen. A solution of **17** (680 mg) in anhydrous THF (4 ml) was added and the resulting solution was stirred at room temperature for 15 h, then diluted with ethyl acetate, concentrated, washed with water and dried. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane : ethyl acetate = 1 : 1) to give pure **18** (538 mg, 67%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1735, 1610. ^{1}H-NMR ($CDCl_3$)δ: 0.07 (6H, s), 0.78 (9H, s), 2.70 (3H, s, –N=C–Me), 7.28—7.91 (17H, m, arom). Other signals could not be assigned.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-(*p*-methoxybenzyloxycarbonyl)triphenylphosphoranediylmethyl-4-[(1*R*)-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)-2-oxopropyl]-2-azetidinone (19) Trifluoroacetic anhydride (0.162 ml) was added to a solution of dimethyl sulfoxide (0.122 ml) in CH_2Cl_2 (1.5 ml) at −72 °C under a stream of nitrogen and the mixture was stirred for 20 min. Then a solution of **18** (500 mg) in CH_2Cl_2 (2.5 ml) was added and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (0.336 ml) was added, and the reaction mixture was stirred for 1 h at the same temperature, then diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried and concentrated to give crude **19** (489 mg) containing a trace of **18**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735, 1610. ^{1}H-NMR ($CDCl_3$)δ: 1.25 (3H, J=7.3 Hz, β-melthyl), 1.26 [3H, J=6.7 Hz, –C(Me)–OSi], 2.69 (3H, s, –N=C–Me), 3.72 (3H, s, –OMe), 6.89 (2H, d, J=8 Hz, arom), 7.29—7.79 (17H, m, arom). Other signals could not be assigned.

***p*-Methoxybenzyl (1*S*,5*R*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-methyl-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (20)** A solution of the crude **19** (489 mg) in toluene (25 ml) was refluxed for 1.5 h, then concentrated. The residue was purified by column chromatography (hexane : ethyl acetate = 2 : 1) to give pure **20** (181.2 mg, 54% from **18**). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775, 1725. ^{1}H-NMR ($CDCl_3$)δ: 0.05 (3H, s), 0.06 (3H, s), 0.87 (9H, s), 1.20 (3H, d, J=7.3 Hz, 1β-methyl), 1.23 [3H, d, J=6.1 Hz, –C(Me)–OSi], 2.71 (3H, s, –N=C–Me), 3.23 (1H, dd, J=3.1, 5.5 Hz, H6), 3.26—3.34 (1H, m, H1), 3.80 (3H, s, –OMe), 4.10 and 4.87 (2H, ABq, J=14 Hz, –CH_2–S–), 4.16 (1H, dd, J=3.1, 10.4 Hz, H5), 4.21 (1H, quint, J=6.1 Hz, H8), 5.22 (2H, s, –O–CH_2–), 6.87 (2H, d, J=8.6 Hz, arom), 7.38 (2H, d, J=8.6 Hz, arom).

***p*-Methoxybenzyl (1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-methyl-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (21)** Acetic acid (0.262 ml) and TBAF (1 M THF solution, 1.53 ml) were added to a solution of **20** (180 mg) in anhydrous THF (5.8 ml) under a stream of nitrogen, and the reaction mixture was stirred for 29 h at room temperature. The resulting mixture was diluted with ethyl acetate, washed with cold water, 10% $NaHCO_3$ and saturated brine, then dried. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane : ethyl acetate = 1 : 3) to give pure **21** (72.4 mg, 50%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1775, 1715, 1610. ^{1}H-NMR ($CDCl_3$)δ: 1.21 (3H, d, J=7.3 Hz, 1β-methyl), 1.32 [3H, d, J=6.1 Hz, –C(Me)–O–], 2.71 (3H, s, –N=C–Me), 3.27 (1H, dd, J=2.4, 6.2 Hz, H6), 3.32—3.45 (1H, m, H1), 3.80 (3H, s, –OMe), 4.07 and 4.85 (2H, ABq, J=14 Hz, –CH_2–S–), 4.18 (1H, dd, J=2.4, 9.8 Hz, H5), 4.17—4.28 (1H, m, H8), 5.19 and 5.27 (2H, ABq, J=12 Hz, –CH_2–O–), 6.88 (2H, d, J=8.6 Hz, arom), 7.38 (2H, d, J=8.6 Hz, arom).

Sodium (1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethyl-1-methylcarbapen-2-em-3-carboxylate (2) A solution of **21** (35 mg) in a mixture of anisole (0.42 ml) and CH_2Cl_2 (0.1 ml) was added to a solution of $AlCl_3$ (39.3 mg) in a mixture of anisole (0.97 ml) and CH_2Cl_2 (0.15 ml) at −60 °C under a stream of nitrogen, and the resulting mixture was stirred for 2.5 h at −60 °C. A solution of $NaHCO_3$ (111.3 mg) in phosphate buffer (0.05 M, pH 7, 3 ml) was added, and the reaction mixture was stirred for 30 min under ice cooling, then filtered. The filtrate was washed with CH_2Cl_2. The separated aqueous layer was chromatographed on a CHP-20P column (H_2O—H_2O–8% MeOH). Fractions con-

taining the product were combined, concentrated under reduced pressure at 25 °C, and freeze-dried to give pure **2** (8.9 mg, 32%) as an amorphous powder. UV $\lambda_{max}^{H_2O}$ nm: 214 (sh), 278. ^{1}H-NMR (D_2O, DOH at 4.80) δ: 1.18 (3H, d, J=7.2 Hz, 1β-methyl), 1.31 [3H, d, J=6.2 Hz, –C(Me)–O–], 2.78 (3H, s, –N=C–Me), 3.38—3.46 (1H, m, H1), 3.47 (1H, dd, J=2.8, 6.2 Hz, H6), 3.79 and 4.48 (2H, ABq, J=14.5 Hz, –CH_2–S–), 4.17 (1H, dd, J=2.8, 9.8 Hz, H5), 4.26 (1H, quint, J=6.2 Hz, H8).

References and Notes

1) D. H. Shih, F. Baker, L. Cama and B. G. Christensen, *Heterocycles*, **21**, 29 (1984).

2) *a*) J. G. de Vries and G. Sigmund, *Tetrahedron Lett.*, **26**, 2765 (1985); *b*) T. Shibata, K. Iino, T. Tanaka, T. Hashimoto, Y. Kameyama and Y. Sugimura, *ibid.*, **26**, 4739 (1985); R. N. Guthikonda, L. D. Cama, M. Quesada, M. F. Woods, T. N. Salzmann and B. G. Christensen, *J. Med. Chem.*, **30**, 871 (1987); S. M. Schmitt, T. N. Salzmann, D. H. Shih and B. G. Christensen, *J. Antibiotics*, **41**, 780 (1988); the precursor for 1β-heteroatom-substituted carbapenem, see: Y. Nagao, T. Kumagai, T. Abe, M. Ochiai, T. Taga, K. Machida and Y. Inoue, *J. Chem. Soc., Chem. Commun.*, **1987**, 602.

3) This work was the subject of a patent application (Japan. Patent Appl. 52816/87, March 6, 1987) and was presented at the 108th Annual Meeting of the Pharmaceutical Society of Japan, Hiroshima, April 1988, Abstracts, p. 79. A similar preparation of **5**β, see: J. S. Prasad and L. S. Liebeskind, *Tetrahedron Lett.*, **28**, 1857 (1987).

4) This work was presented at the Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, December 1987, Poster Abstracts, p. S226.

5) After our patent application,[3] an analogous reaction was reported, see: J. S. Prasad and L. S. Liebeskind, *Tetrahedron Lett.*, **29**, 4257 (1988).

6) H. Fliri and C.-P. Mak, *J. Org. Chem.*, **50**, 3438 (1985).

7) The *trans* and *cis* isomers were readily distiguishable by the value of $J_{3,4}$, the value for the *cis* isomer always being larger than that for the *trans* one in such compounds: F. A. Bouffard and B. G. Christensen, *J. Org. Chem.*, **46**, 2208 (1981).

8) A positive NOE (6%) in **10a** could be obtained between the proton signal of the α-methyl group at 1.11 ppm (d, J=6.7 Hz) and that of H4 at 3.55 ppm (dd, J=9.8, 4.9 Hz), and a positive NOE (4%) in **10b** could be obtained between the proton signal of the α-methyl group at 1.21 ppm (d, J=7.3 Hz) and that of H4 at 3.41 ppm (dd, J=7.6, 2.4 Hz): C. U. Kim, B. Luh and R. A. Partyka, *ibid.*, **28**, 507 (1987); L. M. Fuentes, I. Shinkai, A. King, R. Purick, R. A. Reamer, S. M. Schmitt, L. Cama and B. G. Christensen, *J. Org. Chem.*, **52**, 2563 (1987).

9) H. Ona, S. Uyeo, T. Fukao, M. Doi and T. Yoshida, *Chem. Pharm. Bull.*, **33**, 4382 (1985).

10) M. Shibasaki, A. Nishida and S. Ikegami, *Tetrahedron Lett.*, **23**, 2875 (1982).

11) The hydroxyethyl carbapenem (**21a**) showed a positive NOE (+7.3%) between the 1β-methyl group and C6 proton, and also a positive NOE (+3.5%) between the C1 and C5 protons.

12) R. N. Guthikonda, L. D. Cama, M. Quesada, M. F. Woods, T. N. Salzmann and B. G. Christensen, *J. Med. Chem.*, **30**, 871 (1987).

13) K. Ruitenberg, H. Westmijze, J. Meijer, C. J. Elsevier and P. Vermeer, *J. Organomet. Chem.*, **241**, 417 (1983).

14) S. R. Landor, A. N. Patel, P. F. Whiter and P. M. Greaves, *J. Chem. Soc.* (*C*), **1966**, 1223; G. Linstrumelle and D. Michelot, *J. Chem. Soc., Chem. Commun.*, **1975**, 561.

15) E. G. Brain, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, R. Southgate and P. Tolliday, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2479; I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler and R. B. Woodward, *J. Am. Chem. Soc.*, **100**, 8214 (1978).