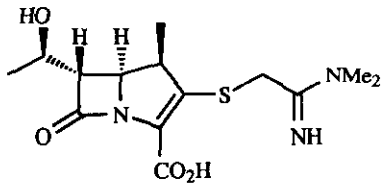
THE SYNTHESIS OF 1β-FLUOROCARBAPENEM DERIVATIVE†

Masataka Ihara,[a] Ken Satoh,[a] Yohhei Ishida,[b] Nobuaki Taniguchi,[a] Yuji Tokunaga,[a] Makoto Takemura,[b] and Keiichiro Fukumoto*[a]

a *Pharmaceutical Institute*, Tohoku University, Aobayama, Sendai 980-77, Japan
b Exploratory Research Laboratories I, Daiichi Pharmaceutical Co., Ltd., 16-13, Kitakasai 1-chome, Edogawa-ku, Tokyo 134, Japan

Abstract——The synthesis of 1β-fluorocarbapenem derivative (**16**) was carried out starting with the 4-acetoxyazetidin-2-one (**3**) through the carbapenem formation utilizing the Sankyo's procedure.

Since the presence of a 1β-methyl substituent such as **1** has been found to enhance the chemical and metabolic stability of synthetic cabapenem antibiotics,[1] the introduction of substituent(s), other than methyl group, at the C (1) position has been attracted by several groups.[2] We interested in the synthesis of 1β-fluorocarbapenems (**2**), in order to study their biological activities and stabilities, and would like to describe our findings.[3]



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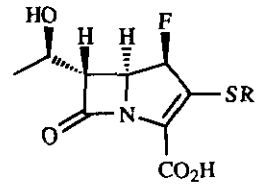
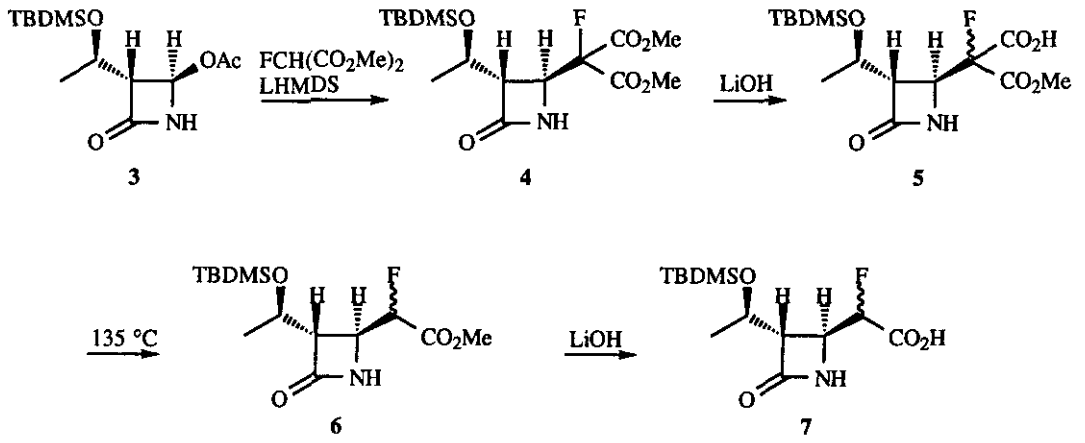


2

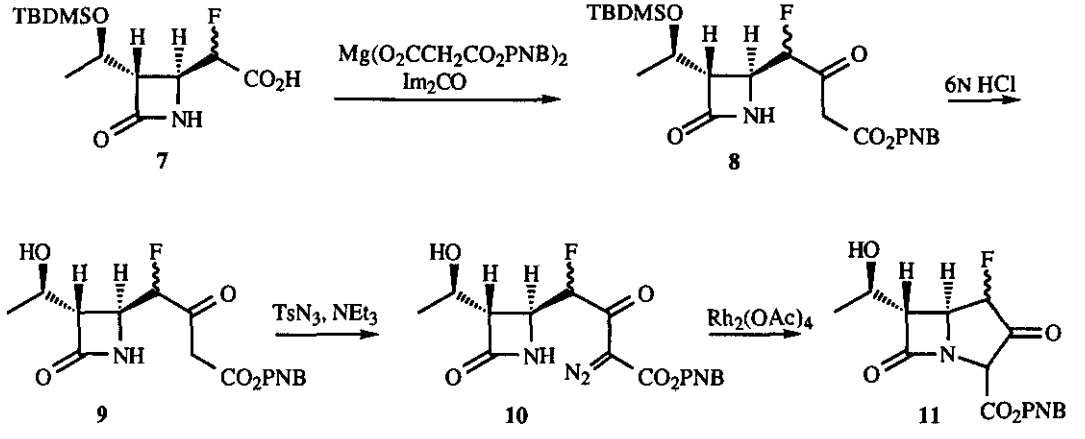
With the aim of the preparation of **7**, the substitution reaction of the commercially available **3** with fluoromalonate was examined. The desired fluoro compound (**4**) was obtained in 96% yield when the reaction was carried out in the presence of lithium hexamethyldisilazide (LHMDS). One of the methoxycarbonyl groups of **4** was removed by hydrolysis of **4** using one equivalent mole of $LiOH \cdot H_2O$ followed by decarboxylation of the resulting carboxylic acid (**5**). Heating **5** in xylene at 135 °C produced a 2 : 1 diastereoisomeric mixture of **6** in 63% overall yield from **4**. The corresponding carboxylic acids (**7**) were obtained in 96% yield by hydrolysis of **6** with $LiOH \cdot H_2O$.

† Dedicated to the memory of the late Professor Yoshio Ban.



Scheme 1

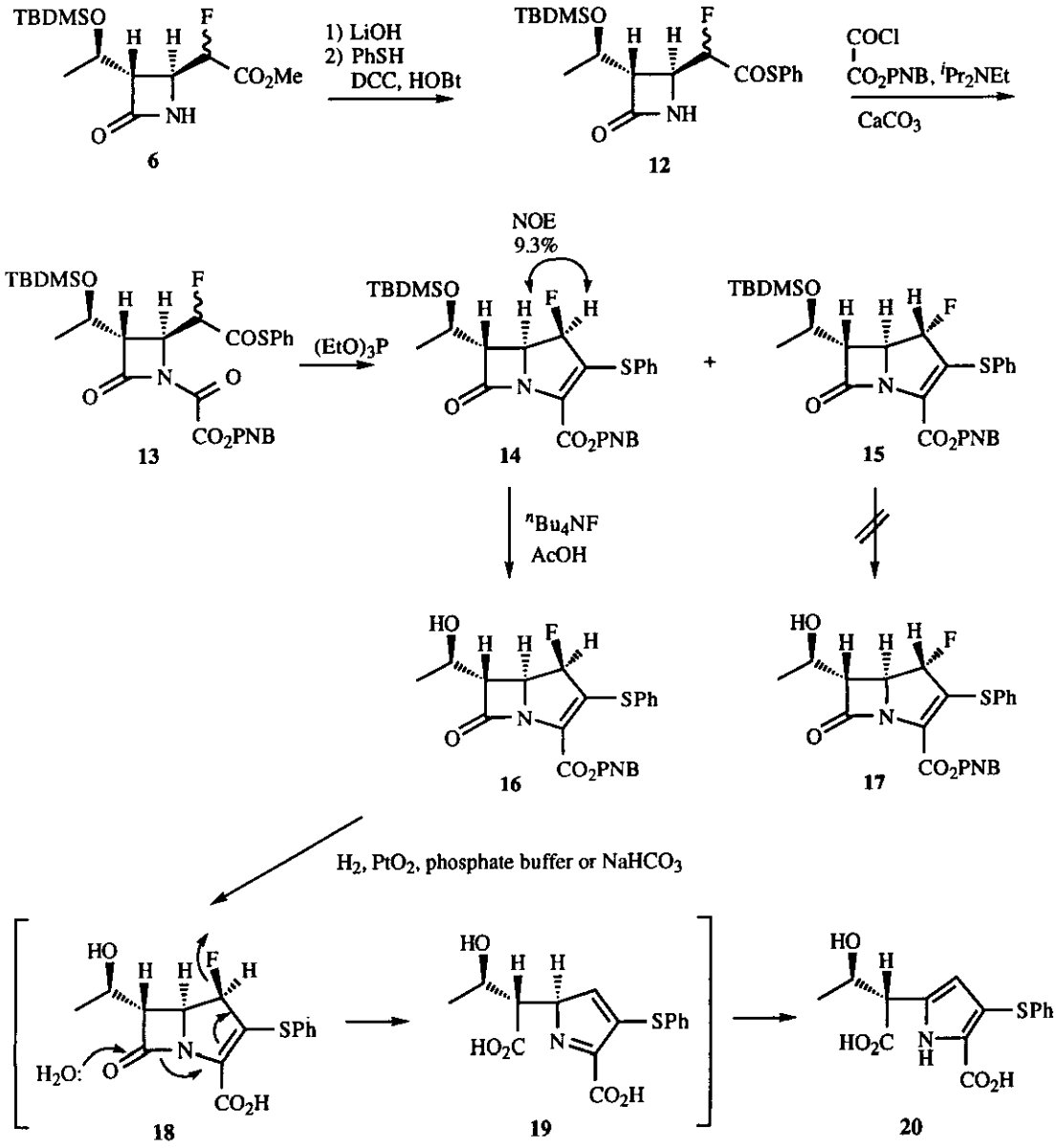
The construction of the carbapenem skeleton was first studied by the application of the Merck's method.[4] Although the side-chain extension to a β-keto ester was rather difficult, the transformation of **7** into **8** was performed in 44% yield, when MeCN was used as the reaction solvent. After the deprotection of the *tert*-butyldimethylsilyl (TBDMS) group with 6N HCl in MeOH, followed by diazoexchange with *p*-toluenesulfonyl azide in the presence of Et_3N, the formed **10** was subjected to the carbene insertion reaction using $Rh_2(OAc)_4$ in AcOEt at 80 °C. Reactions proceeded in reasonable yields, but the products (**11**) were too unstable to isolate as pure forms. Furthermore, activation of the C(2) position of **11** for the introduction of a thiol group failed. Therefore, we next focused our attention on the Sankyo's method[5] for the assembly of the carbapenem nucleus.



Scheme 2

After conversion of **6** into thioester (**12**) (87% overall yield), reaction of **12** with *p*-nitrobenzyl chlorooxalate in the presence of $^iPr_2NEt$ and $CaCO_3$ provided the oxalimides (**13**) in 86% yield. Cyclization of **13** was achieved

by heating with $(EtO)_3P$ in refluxing xylene for 1 h. Two stereoisomers (**14**) and (**15**) were isolated in 45 and 33% yields, respectively, after chromatographical separation. Stereostructures of products were determined by the nOe experiment: 9.3% nOe was observed between hydrogens at C(1) and C(5) positions. The assigned stereochemistry was further supported by their chemical behaviors. Treatment of **14** with $^nBu_4NF$ in the presence of AcOH produced **16** in 31% yield; 64% yield based on the consumed starting material (**14**), while



Scheme 3

the deprotection of TBDMS group of **15** to **17** was not successful under various conditions. It was reported that 1α-methylcarbapems were unstable comparing with the corresponding 1β-isomers.[6] The rule could be applied to this case. Unfortunately, attempts to deblock the *p*-nitrobenzyl ester resulted in failure. Only the pyrrole derivative (**20**) was obtained by deprotection procedures carried out under a variety of conditions. It is assumed that the formed acid (**18**) is readily attacked with H_2O at the lactam carbonyl group to expel the fluorine atom to afford **20** *via* **19**. This result suggests the necessity of further elaboration for isolation of deprotected 1-fluorocarbapenems.

EXPERIMENTAL

(3*S*,4*S*)-3-[(1'*R*)-1'-(*tert*-Butyldimethylsiloxy)ethyl]-4-bis(methoxycarbonyl)fluoromethylazetidin-2-one (4). To a stirred solution of dimethyl fluoromalonate (5.0 g, 33.3 mmol) in dry THF (50 ml) at –78 °C was added 1 M LHMDS-hexane (31.8 ml, 31.8 mmol). After being stirred for 30 min at –78 °C, a solution of **3** (8.7 g, 30.3 mmol) in dry THF (90 ml) was added to it. The mixture was stirred for 3 h at –78 °C and for 9 h at ambient temperature. After neutralization with 1N HCl under ice cooling, the mixture was concentrated under reduced pressure and the residue was taken up into AcOEt. The extract was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica gel with $CHCl_3$–MeOH (99 : 1 v/v) as eluent gave **4** (11.0 g, 96%) as crystals, mp 158–160 °C, $[\alpha]_D^{29}$ –47.7 ° (c = 1.1, $CHCl_3$): νmax ($CHCl_3$, cm^{-1}) 3440 (NH), 1755 (C=O); δH ($CDCl_3$, 500 MHz) 0.07 (6H, s, $SiMe_2$), 0.88 (9H, s, ^{t}Bu), 1.06 (3H, d, *J* = 6.1 Hz, 1'-Me), 3.29 (1H, br s, 3-H), 3.87 and 3.88 (each 3H, each s, 2 × OMe), 4.25–4.30 (1H, m, 1'-H), 4.41 (1H, dd, *J* = 20.8 and 1.8 H, 4-H), 5.85 (1H, br s, NH); HRms *m/z* calcd for $C_{15}H_{25}NO_6FSi$ (M^+ –Me): 362.1436, found: 362.1411. Anal. Calcd for $C_{16}H_{28}NO_6FSi$: C, 50.91; H, 7.48; N, 3.71. Found: C, 50.99; H, 7.52; N, 3.69.

(3*S*,4*S*)-3-[(1'*R*)-1'-(*tert*-Butyldimethylsiloxy)ethyl]-4-methoxycarbonyl(fluoro)methylazetidin-2-one (6). To a solution of **4** (90 mg, 0.24 mmol) in MeOH (5 ml) was added a solution of $LiOH·H_2O$ (10 mg, 0.24 mmol) in H_2O (2 ml), and the mixture was stirred for 2 h at ambient temperature. After concentration under reduced pressure, the residue was partitioned between Et_2O (15 mL) and H_2O (5 ml). The ethereal layer was washed with saturated $NaHCO_3$ (3 ml). The combined aqueous layer was acidified with 1N HCl under ice cooling and then thoroughly extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and evaporated to give a 2 : 1 diastereoisomeric mixture of the acids (**5**) (71 mg, 82%) as a powder: δH ($CDCl_3$, 500 MHz) 0.05 and 0.07 [each 3H, each s, $SiMe_2$], 0.87 and 0.88 [9H (2 : 1), each s, ^{t}Bu], 1.07 and 1.13 [3H (1 : 2), each d, each *J* = 6.1 Hz, 1'-Me], 3.33 and 3.38 [1H (1 : 2), each br s, 3-H], 3.88 and 3.89 [3H (2 : 1), each s, OMe], 4.24–4.30 (1H, m, 1'H), 4.44 and 4.46 [1H (2 : 1), each dd, each *J* = 19.0 and 1.8 Hz, 4-H], 6.45 and 6.93 [1H (2 : 1), each s, NH], which was used in the next reaction without purification. The starting material (**4**) (16 mg) was obtained from the above ethereal solution.

A mixture of the above acids (**5**) (100 mg, 0.28 mmol) in xylene (5 ml) was heated for 3 h at 135 °C. After evaporation of the solvent, the residue was taken up into CH_2Cl_2. The extract was washed with brine, dried

($MgSO_4$), and evaporated to afford a residue, which was subjected to flash chromatography on silica gel. Elution with hexane–AcOEt (7 : 3 v/v) yielded a 2 : 1 diastereoisomeric mixture of **6** (68 mg, 77%) as a solid, mp 136–138 °C: νmax ($CHCl_3$, cm^{-1}) 3405 (NH), 1764 (C=O); δH ($CDCl_3$, 400 MHz) 0.06 and 0.07 (each 3H, each s, $SiMe_2$), 0.86 (9H, s, ^{t}Bu), 1.13 and 1.15 [3H (2 : 1), each d, each J = 6.4 H, 1'-Me], 3.23 and 3.26 [1H (1 : 2), each br s, 3-H], 3.83 and 3.84 [3H (1 : 2), each s, OMe], 4.00–4.15 (1H, m, 4-H), 4.20–4.30 (1H, m, 1'-H), 4.91 (1/3 × 1H, dd, J = 48.3 and 5.6 Hz, CHF), 4.97 (2/3 × 1H, dd, J = 48.3 and 4.9 Hz, CHF), 5.85 and 5.90 [1H (2 : 1), each br s, NH]; HR ms *m/z* calcd for $C_{13}H_{23}NO_4FSi$ (M^+ –Me): 304.1381, found: 304.1378. Anal. Calcd for $C_{14}H_{26}NO_4FSi$: C, 52.64; H, 8.20; N, 4.38. Found: C, 52.63; H, 8.18; N, 4.24.

(3*S*,4*S*)-3-[(1'*R*)-1'-(*tert*-Butyldimethylsiloxy)ethyl]-4-[1-carboxy-1-fluoromethyl]azetidin-2-one (7). To a solution of **6** (62 mg, 0.19 mmol) in MeOH (3 ml) was added a solution of $LiOH·H_2O$ (8.1 mg, 0.19 mmol) in H_2O (2 ml), and the mixture was stirred for 1 h at ambient temperature. After concentration under reduced pressure, the residue was partitioned between Et_2O (10 ml) and H_2O (4 ml). The ethereal layer was extracted with saturated $NaHCO_3$. The combined aqueous layer was acidified with 1N HCl under ice cooling and then thoroughly extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and evaporated to provide a 2 : 1 mixture of **7** (57 mg, 96%) as an amorphous powder: νmax ($CHCl_3$, cm^{-1}) 3405 (NH), 1760 (C=O); δH ($CDCl_3$, 500 MHz) 0.10 and 0.11 (2/3 × 6H, each s, $SiMe_2$), 0.11 and 0.12 (1/3 × 6H, each s, $SiMe_2$), 0.90 and 0.91 [9H (2 : 1), each s, ^{t}Bu], 1.18 (2/3 × 3H, J = 6.7 Hz, 1'-Me), 1.24 (1/3 × 3H, J = 6.1 Hz, 1'-Me), 3.22–3.24 and 3.24–3.26 [1H (2 : 1), each m, 3-H)], 4.10–4.17 (1H, m, 4-H), 4.25–4.32 (1H, m, 1'-H), 5.15 (1/3 × 1H, dd, J = 48.8 and 3.1 Hz, CHF), 5.25 (2/3 × 1H, dd, J = 48.8 and 4.9 Hz, CHF), 7.30 and 7.49 [1H (2 : 1), each br s, NH]; HRms *m/z* calcd for $C_{12}H_{21}NO_4FSi$ (M^+ –Me): 290.1224, found: 290.1244.

(3*S*,4*S*)-3-[(1'*R*)-1'-(*tert*-Butyldimethylsiloxy)ethyl]-4-[(1-fluoro-3-(*p*-nitrobenzyloxy-carbonyl)-2-oxopropyl]azetidin-2-one (8). To a solution of **7** (367 mg, 1.2 mmol) in MeCN (10 ml) was added a solution of *N,N'*-carbonyldiimidazole (234 mg, 1.44 mmol) in MeCN (5 ml), and the mixture was stirred for 30 min at ambient temperature. After addition of a solution of magnesium *p*-nitrobenzyl malonate (661 mg, 1.32 mmol) in MeCN (5 ml), the resulting mixture was stirred for 12 h at ambient temperature. Concentration of the mixture under reduced pressure gave a residue, which was taken up into AcOEt. The organic extract was washed with 10% HCl, H_2O, saturated $NaHCO_3$, and brine. After being dried ($MgSO_4$), evaporation of the solvent afforded a residue, which was subjected to flash chromatography on silica gel. Elution with benzene–acetone (92 : 8 v/v) provided **8** (253 mg, 44%) as an oil: νmax ($CHCl_3$, cm^{-1}) 3400 (NH), 1765 (C=O), 1520 and 1350 (NO_2); δH ($CDCl_3$, 500 MHz) 0.06 (6H, s, $SiMe_2$), 0.86 (9H, s, ^{t}Bu), 1.15 and 1.18 [3H (2 : 1), each d, each J = 6.1 Hz, 1'-Me], 3.18–3.23 (1H, m, 3-H), 3.69–3.87 (2H, m, $COCH_2CO$), 4.05–4.10 (1H, m, 4-H), 4.20–4.27 (1H, m, 1'-H), 4.90 and 4.98 [1H (2 : 1), each dd, each J = 47.6 and 6.1 Hz, CHF], 5.28 and 5.31 [2H (2 : 1), each s, CH_2Ar], 5.90 and 5.97 [1H (2 : 1), each br s, NH], 7.52 and 7.53 (2H, each d, J = 8.6 Hz, 2 × ArH), 8.23 and 8.24 (2H, each d, J = 8.6 Hz, 2 × ArH); HRms m/z calcd for $C_{18}H_{22}N_2O_7FSi$ (M^+ –^{t}Bu): 425.1180, found: 425.1153.

(3*S*,4*S*)-3-[(1*R*')-1'-(*tert*-Butyldimethylsiloxy)ethyl]-4-[1-fluoro-1-(phenylthiocarbonyl)-methyl]azetidin-2-one (12). The esters (**6**) (735 mg, 2.3 mmol) was converted, by the same procedure as above, into the acids (**7**), which was used in the reaction without purification. To a stirred solution of the crude acids (**7**), thiophenol (0.236 ml, 2.30 mmol) and 1-hydroxybenzotriazole (HOBt) (31 mg, 0.23 mmol) in THF (30 ml) was added DCC (712 mg, 3.45 mmol) under ice cooling. The mixture was stirred for 20 min at 0 °C and for 18 h at ambient temperature. Evaporation of the solvent gave a residue, which was taken up into AcOEt. After filtration, the filtrate was washed with H_2O, dried (Na_2SO_4), and evaporated to afford a residue, which was chromatographed on silica gel. Elution with hexane–AcOEt (85 : 15 v/v) provided **12** (792 mg, 87% form **6**) as an oil: ν_{max} ($CHCl_3$, cm^{-1}) 3405 (NH), 1770 and 1690 (C=O); δ_H ($CDCl_3$, 400 MHz) 0.07 and 0.08 [6H (2 : 1), each s, $SiMe_2$], 0.86 and 0.87 [9H (2 : 1), each s, ^{t}Bu], 1.16 and 1.17 [3H (1 : 2), each d, each J = 5.9 Hz, 1'-Me], 3.25–3.35 (1H, m, 3-H), 4.10–4.20 (1H, m, 4-H), 4.23–4.30 (1H, m, 1'-H), 5.04 and 5.07 [1H (1 : 2), each dd, each J = 48.3 and 4.9 Hz, CHF], 5.95 and 6.00 [1H (2 : 1), each br s, NH], 7.38–7.48 (5H, m, 5 × ArH); HR ms *m/z* calcd for $C_{18}H_{25}NO_3FSSi$ (M^+ –Me): 382.1308, found; 382.1309.

***p*-Nitrobenzyl (1*R* and 1*S*,5*S*,6*S*)-6-[(1'*R*)-1'-(*tert*-Butyldimethylsiloxy)ethyl]-1-fluoro-2-(phenylthio)carbapen-2-em-3-carboxylate (14 and 15).** To a solution of **12** (792 mg, 1.99 mmol) in CH_2Cl_2 (40 ml) were added $ClCOCO_2PNB$ (970 mg, 3.98 mmol), $^i Pr_2NEt$ (0.69 ml, 3.98 mmol) and $CaCO_3$ (399 mg, 3.98 mmol) under ice cooling, and the mixture was stirred for 1 h at the same temperature. After evaporation, the residue was taken up into AcOEt. The extract was washed with H_2O, dried ($MgSO_4$), and evaporated to give a residue, which was purified by flash chromatography on silica gel. Elution with $CHCl_3$–MeOH (99 : 1 v/v) provided **13** (1.04 g, 86%) as an oil.

A mixture of **13** (1.04 g, 1.72 mmol) and $(EtO)_3P$ (1.47 ml, 8.57 mmol) in xylene (50 ml) was heated for 1 h under reflux. Evaporation of the solvent afforded a residue which was subjected to flash chromatography on silica gel. Elution with hexane–AcOEt (95 : 5 v/v) gave **14** (438 mg, 45%) as an oil: ν_{max} ($CHCl_3$, cm^{-1}) 1790 and 1720 (C=O), 1520 and 1340 (NO_2); δ_H ($CDCl_3$, 400 MHz) 0.05 and 0.06 (each 3H, each s, $SiMe_2$), 0.84 (9H, s, ^{t}Bu), 1.13 (3H, d, J = 6.4 Hz, 1'-Me), 3.46 (1H, t, J = 2.9 Hz, 6-H), 4.19 (1H, ddd, J = 29.3, 6.4 and 2.9 Hz, 5-H), 4.30–4.40 (1H, m, 1'H), 5.03 (1H, dd, J = 54.2 and 6.4 Hz, 1-H), 5.37 and 5.50 (each 1H, each d, J = 14.2 Hz, OCH_2Ar), 7.35–7.60 (3H, m, 3 × ArH), 7.62 (2H, d, J = 6.8 Hz, 2 × ArH), 7.68 (2H, d, J = 8.8 Hz, 2 × ArH), 8.23 (2H, d, J = 8.8 Hz, 2 × ArH); HRms *m/z* calcd for $C_{28}H_{33}N_2O_6FSSi$ (M^+): 572.1813, found: 572.1799.

Further elution with hexane–AcOEt (9 : 1 v/v) furnished **15** (322 mg, 33%) as an oil: δ_H ($CDCl_3$, 400 MHz) 0.05 and 0.06 (each 3H, each s, $SiMe_2$), 0.84 (9H, s, ^{t}Bu), 1.18 (3H, d, J = 6.3 Hz, 1'-Me), 3.18 (1H, t, J = 3.9 Hz, 6-H), 4.17 (1H, dt, J = 33.7 and 3.9 Hz, 5-H), 4.20–4.30 (1H, m. 1'-H), 5.34 and 5.49 (each 1H, each d, J = 14.2 Hz, OCH_2Ar), 5.58 (1H, dd, J = 54.2 and 3.9 Hz, 1-H), 7.30–7.45 (3H, m, 3 × ArH), 7.61 (2H, d, J = 7.8 Hz, 2 × ArH), 7.67 (2H, d, J = 8.6 Hz, 2 × ArH), 8.22 (2H, d, J = 8.6 Hz, 2 × ArH).

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1'*R*)-1'-Hydroxyethyl]-1-fluoro-2-(phenythio)carbapen-2-em-3-carboxylate (16).** A mixture of **14** (236 mg, 0.42 mmol), AcOH (0.24 ml, 4.10 mmol) and 1 M Bu_4NF-THF (1.24 ml, 1.24 mmol) in THF (20 ml) was stirred for 24 h at ambient temperature. After concentration

under reduced pressure, the residue was subjected to flash chromatography on silica gel. Elution with $CHCl_3$-MeOH (99 : 1 v/v) gave **14** (122 mg) and further elution with $CHCl_3$–MeOH (99 : 1 v/v) provided **16** (59 mg, 31%; 64% based on the consumed **14**) as an oil: $[\alpha]_D^{21}$ +145.6 ° (c = 0.49, $CHCl_3$); ν_{max} ($CHCl_3$, cm^{-1}) 1790 and 1710 (C=O), 1520 and 1350 (NO_2); δ_H ($CHCl_3$, 400 MHz) 1.29 (3H, d, *J* = 6.3 Hz, 1'-Me), 3.49 (1H, dd, *J* = 5.4 and 2.9 Hz, 6-H), 4.12 (1H, ddd, *J* = 28.3, 6.4 and 2.9 Hz, 5-H), 4.25–4.40 (1H, m, 1'-H), 5.06 (1H, dd, *J* = 54.2 and 6.4 Hz, 1-H), 5.34 and 5.56 (each 1H, each d, *J* = 13.7 Hz, OCH_2Ar), 7.40–7.50 (3H, m, 3 × ArH), 7.61 (2H, d, *J* = 7.3 Hz, 2 × ArH), 7.69 (2H, d, *J* = 8.6 Hz, 2 × ArH), 8.24 (2H, d, *J* = 8.6 Hz, 2 × ArH); HRms *m/z* calcd for $C_{22}H_{19}NO_4FS$ ($M^+ - NO_2$): 412.1019, found 412.0996.

(1'*S*,2'*R*)-5-(1'-Carboxy-2'-hydroxypropyl)-3-(phenylthio)pyrrole-2-carboxylic Acid (20). A mixture of **16** (53 mg, 0.11 mmol) and PtO_2 (10 mg) in THF–1/15 M phosphate buffer (pH 7) (1 : 1 v/v, 10 ml) was shaken for 30 min at ambient temperature under H_2 (4 kg/cm^2). After filtration, followed by concentration of the filtrate under reduced pressure, the residue was purified by chromatography using DIAION HP-20 with H_2O and THF-H_2O (5 : 95 v/v) as eluent. Elution with H_2O provided **20** (15 mg, 41%) as a powder: δ_H (D_2O, 400 MHz) 1.20 (3H, d, *J* = 6.4 Hz, Me), 3.36 (1H, d, *J* = 8.3 Hz, 1'-H), 4.18 (1H, dq, *J* = 8.3 and 6.4 Hz, 2'-H), 5.90 (1H, s, 4-H), 7.25 - 7.55 (5H, m, Ph).

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