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Synthetic Approach to 6-Amidocarbapenem Antibiotics: Synthesis of a *dl*-6-Phthalimido-1-carbapen-2-em Derivative

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A 6-phthalimidolcarbapenem derivative was synthesized by intramolecular Wittig cyclization.

Keywords——synthesis; 6-amidocarbapenem antibiotic; 6-phthalimido-1-carbapen-2-em; intramolecular Wittig cyclization; β-lactam antibiotic

Since the isolation of thienamycin (**1**), a non-classical β-lactam antibiotic, from *Streptomyces cattleya*,[1] carbapenem antibiotics have attracted great interest with regard to both biological activity and synthesis.[2] In the light of the biological activity displayed by a derivative having an amino group at the C_6-position of carbapenem, the preparation of additional members of this class is of interest, though naturally occurring carbapenem antibiotics commonly have an alkyl substituent at the C_6-position.

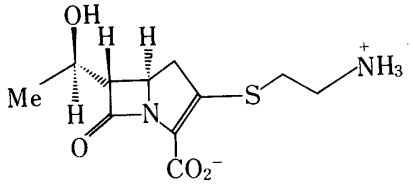

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Chart 1

Several papers[3] concerned with the synthesis of 6-amidocarbapen-2-em antibiotics have already appeared, in spite of the predominance of interest in the synthesis of naturally occurring carbapenem antibiotics. In 1978, a Shionogi group[4] attempted the synthesis of a 6-amidocarbapenem derivative using an intramolecular Wittig cyclization, but no 4,5-fused system could be isolated, though degradation products were detected.

In order to synthesize 6-amidocarbapen-2-em, we decided to adopt a Wittig cyclization procedure to construct a carbapen-2-em ring system, since the presence of an NH group at the C_3 position might cause a more favorable cyclization reaction than that of an NH group at the N_1 position during the Merck carbene insertion reaction adopted. Our synthesis of the 6-amidocarbapen-2-em nucleus began with the preparation of 3-azido-2-azetidinone. Treatment of the aldehyde (**2**)[5] with 2,4-dimethoxybenzylamine in methylene chloride in the presence of magnesium sulfate afforded the Schiff base (**3**), which, without isolation, was treated with azidoacetyl chloride in the presence of triethylamine to give the [2+2]cycloaddition product[6] (**4**) in 35% yield from (**2**). The relative stereochemistry of the C_3 and C_4 positions of (**4**) was deduced to be *trans* based on the nuclear magnetic resonance (NMR) spectral data, and none of the *cis*-isomer could be isolated under various reaction conditions.

Reduction of the azide group with zinc powder in methanol–tetrahydrofuran gave rise to

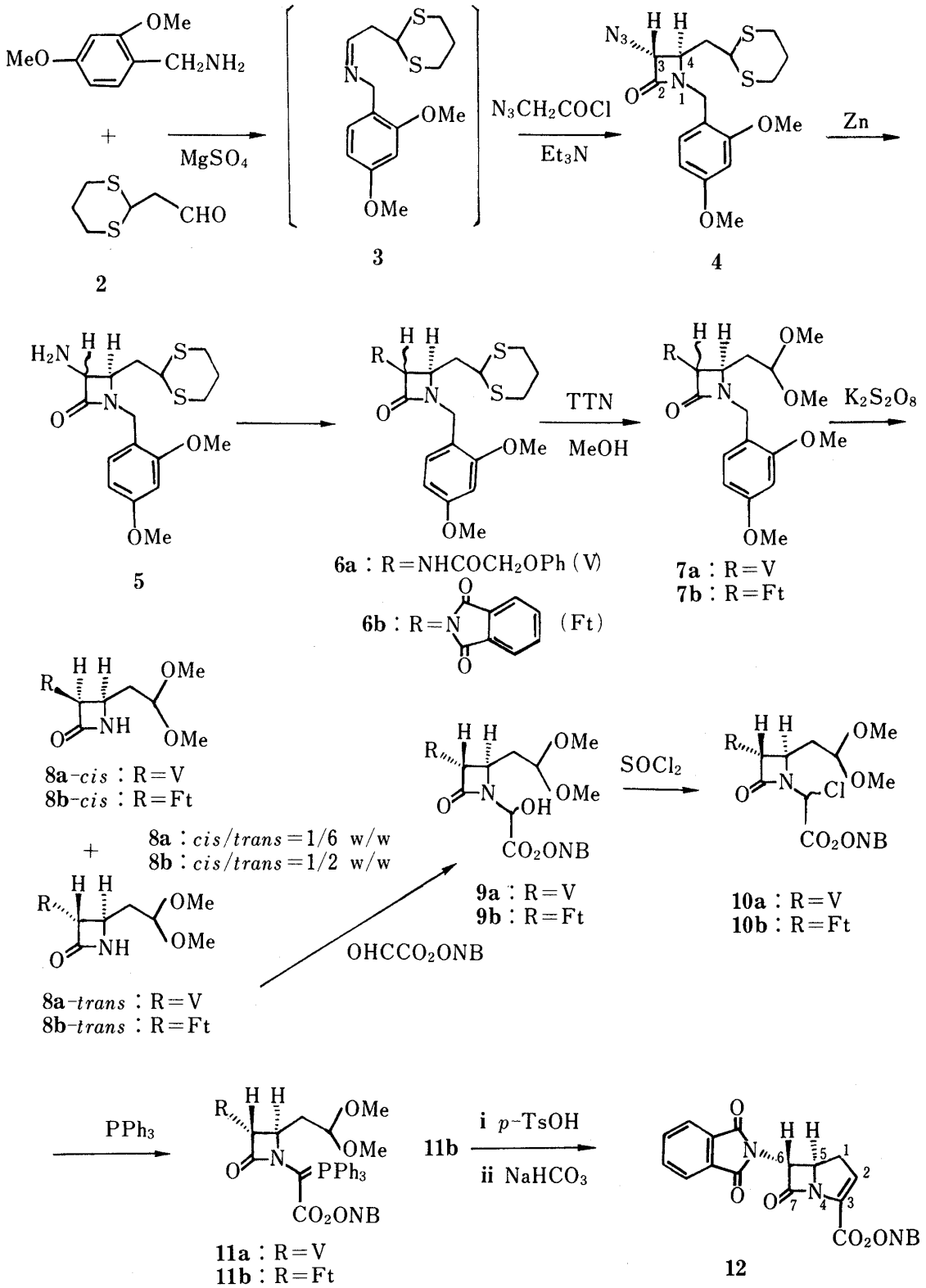

Chart 2

the corresponding amine (**5**), whose acylation with phenoxyacetyl chloride in methylene chloride furnished the amide (**6a**) as a mixture of *trans*- and *cis*-isomers in the ratio of 6 : 1 in 60.3% yield. This result indicated that epimerization of the amide group at the C_3 position of the azetidinone occurred during the transformation of (**4**) into (**6a**). The conversion of the dithioacetal (**6a**) into the dimethylacetal (**7a**) was carried out in 78% yield by using thallium

(III) nitrate[7] in methanol–benzene (3 : 1). Debenzylation of (**7a**) with 4 eq of potassium persulfate[8] in acetonitrile–water (2 : 1) at 85 °C for 1 h gave the debenzylated azetidinone (**8a**) in 57% yield. After separation of the *trans*- and *cis*-isomers (6 : 1, w/w), the major isomer (**8a**-*trans*) was converted to the phosphorane (**11a**) *via* the alcohol (**9a**) and the chloride (**10a**) according to Woodward's procedure.[9] Various attempted intramolecular Wittig cyclizations gave none of the desired product, but only decomposition products. Reinvestigation of Shionogi's and our own results suggested that Wittig cyclization would proceed to give the penem nucleus, which, however, might be too unstable to isolate for some unknown reason. We assumed that the secondary amido group might cause the destabilization of the carbapenem nucleus.

Thus, we sought to prepare the phthalimidyl derivative of (**12**). Treatment of the amine (**5**) with phthalic anhydride in benzene gave rise to the imide (**6a**) as a mixture of *trans*- and *cis*-isomers in 70.5% yield in the ratio of 2 : 1. Deprotection of the thioacetal (**6b**) with thallium (III) trinitrate and subsequent debenzylation of (**7b**) with potassium persulfate were carried out as above to afford the azetidinone (**8b**). Again, after separation of the mixture (*trans*/*cis* = 2/1, w/w), the major compound (**8b**-*trans*) was converted to the phosphorane (**11b**) *via* the alcohol (**9a**) and the chloride (**10b**) in 63.9% yield. Deacetalization of (**11b**) with *p*-toluenesulfonic acid in acetone, followed by neutralization with sodium hydrogen carbonate, resulted in successful Wittig cyclization to yield the carbapenem (**12**) in 82.5% yield.

Thus, we succeeded in synthesizing the 6-phthalimio-1-carbapenem nucleus. The results suggest that the secondary amide group tends to destabilize the desired ring system. Several attempts to remove the phthaloyl group of (**12**) have unfortunately failed, presumably due to this instability.

Experimental

Infrared (IR) spectra were measured with a Hitachi 260-10 spectrophotometer, and NMR spectra with JEOL PMS-60SI and JEOL JNM-FX100 spectrometers. Ordinary and accurate mass spectra (MS) were taken with a JEOL JMS-D300 spectrometer.

***trans*-3-Azido-1-(2,4-dimethoxybenzyl)-4-(1,3-dithian-2-ylmethyl)-2-azetidinone (4)**——A solution of the aldehyde (**2**)[5] (4.82 g), 2.4-dimethoxybenzylamine (5 g), and magnesium sulfate (5 g) in dry methylene chloride (20 ml) was stirred for 1 h at ambient temperature under a current of nitrogen. After filtration of the reaction mixture, the filtrate was diluted with dry methylene chloride (100 ml). Triethylamine (5.19 ml) and a solution of azidoacetyl chloride (4.45 g) in dry methylene chloride (10 ml) were added to the above stirred solution at −78 °C under a current of nitrogen, and the reaction mixture was further stirred for 3 h at the same temperature. The reaction mixture was poured into water and the organic layer separated was dried over Na_2SO_4 and evaporated under reduced pressure at 35 °C. The resulting brownish residue was chromatographed on silica gel using benzene–ethyl acetate (95 : 5, v/v) as the eluant to give the azetidinone (**4**) [4.1 g (35%)] as a pale yellowish gum: IR ν_{max} ($CHCl_3$): 2120 (N_3), 1765 cm^{-1} (C=O). NMR ($CDCl_3$) δ: 3.48 (1H, ddd, J=0.9, 3.5 and 9.5 Hz, C_4-H), 3.81 and 3.84 (each 3H, each s, 2 × OMe), 4.0 (1H, t, J=4.6 Hz, C<u>H</u>$(S)_2$], 4.05 and 4.55 (each 1H, each d, each J=15 Hz, $ArC\underline{H}_2$), 4.31 (1H, d, J=0.9 Hz, C_3-H). MS *m/e* 394 (M^+); *m/e* 394.1113 [Calcd for $C_{17}H_{22}O_3N_4S_2$ (M^+), *m/e* 394.1134].

***trans* and *cis*-1-(2,4-Dimethoxybenzyl)-4-(1,3-dithian-2-ylmethyl)-3-phenoxyacetamido-2-azetidinone (6a)**——A mixture of the above azetidinone (**4**) (1 g), ammonium chloride (890 mg), and Zn powder (500 mg) in methanol–tetrahydrofuran (2 : 1, v/v) (60 ml) was stirred for 8 h at room temperature. After filtration of the reaction mixture, the filtrate was concentrated under reduced pressure to give the residue, which was dissolved in chloroform (100 ml). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford the crude 3-amino-2-azetidinone (**5**) [IR ν_{max} ($CHCl_3$): 1735 cm^{-1} (C=O)] which, without further purification, was used for the next reaction. Triethylamine (0.35 ml) and phenoxyacetyl chloride (0.35 ml) were added to a stirred solution of (**5**) (740 mg) in dry methylene chloride (30 ml) at 0 °C under a current of nitrogen. After being stirred for 0.5 h at 0 °C, the mixture was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using benzene–ethyl acetate (9 : 1, v/v) as the eluant to give an inseparable stereoisomeric mixture of (**6a**) (*trans*/*cis* = 6/1) [770 mg (60.3%) from (**4**)[as a yellowish gum: IR ν_{max} ($CHCl_3$): 3424 (NH), 1750 and 1688 cm^{-1} (C=O). NMR ($CDCl_3$) δ: 3.75 and 3.77 (each 3H, each s, 2 × OMe), 4.38 (2H, s, $PhOC\underline{H}_2$), 4.60 [6/7H, dd, J=0.9 and 8 Hz, C_3-H (*trans*)], 5.11 [1/7H, dd, J=5 and 8 Hz, NH). MS *m/e*: 502 (M^+); *m/e* 502.1609 [Calcd for $C_{25}H_{30}N_2O_5S_2$ (M^+), *m/e* 502.1597].

***trans* and *cis*-1-(2,4-Dimethoxybenzyl)-4-(2,2-dimethoxyethyl)-3-phenoxyacetamido-2-azetidinone (7a)**——A solution of the above dithiane (**6a**) (267 mg) in benzene (10 ml) was added to a stirred solution of thallium (III) nitrate (TTN) (590 mg) in methanol (10 ml) at ambient temperature under an atmosphere of nitrogen, and the reaction mixture was further stirred for 0.25 h at the same temperature. After filtration of the mixture through celite, the filtrate was treated with water and extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel using benzene–ethyl acetate (9 : 1, v/v) as the eluant to afford an inseparable stereoisomeric mixture of (**7a**) (*trans*/*cis* = 6/1) [420 mg (78%)] as a gum: IR ν_{max} ($CHCl_3$): 3425 (NH), 1755 and 1693 cm^{-1} (C=O). NMR ($CDCl_3$) δ: 3.35 and 3.39 (each 3H, each s, 2 × OMe), 3.94 (6H, s, 2 × OMe), 4.64 (2H, s, $PhOC\underline{H}_2$), 4.86 [6/7H, dd, J = 0.9 and 8 Hz, C_3-H (*trans*)], 5.41 [1/7H, dd, J = 5 and 8 Hz, C_3-H (*cis*)], 7.62 (1H, br d, J = 7 Hz, NH). MS *m/e*: 458 (M^+); *m/e* 458.2065 [Calcd for $C_{24}H_{30}N_2O_7$ (M^+), *m/e* 458.2053].

trans* and *cis*-4-(2,2-Dimethoxyethyl)-3-phenoxyacetamido-2-azetidinone (8a-*trans*) and (8a-*cis*)**——A stirred solution of the above azetidinone (**7a**) (190 mg), potassium persulfate (450 mg), and $Na_2HPO_4 \cdot 12H_2O$ (290 mg) in acetonitrile–water (2 : 1, v/v) (60 ml) was heated at 80 °C for 45 min. After cooling, the reaction mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using benzene–methanol (97 : 3, v/v) as the eluant, to give the *trans*-azetidinone (**8a-*trans) [52 mg (40.6%)] as an amorphous solid: IR ν_{max} ($CHCl_3$): 3420 (NH), 1770 and 1687 cm^{-1} (C=O). NMR ($CDCl_3$) δ: 3.34 (6H, s, 2 × OMe), 4.44 [1H, t, J = 5 Hz, $C\underline{H}(OMe)_2$], 4.52 (2H, s, $PhOC\underline{H}_2$), 4.66 (1H, dd, J = 1 and 8 Hz, C_3-H), 6.36 (1H, br s, NH), 7.5 (1H, br d, J = 8 Hz, NH). MS *m/e*: 309 ($M^+ + 1$).

Further elution afforded a mixture of azetidinones (**8a-*trans***) and (**8a-*cis***) [21 mg (16.4%); 1 : 1, w/w)]. The NMR spectrum of the latter compound was as follows: NMR ($CDCl_3$) δ: 5.35 [1/2H, dd, J = 5 and 8 Hz, C_3-H (*cis*)].

***trans* and *cis*-1-(2,4-Dimethoxybenzyl)-4-(1,3-dithian-2-ylmethyl)-3-phthalimido-2-azetidinone (6b)**——A mixture of (**5**) (1.25 g) and phthalic anhydride (632 mg) in benzene (70 ml) was stirred under reflux for 3 h in an apparatus equipped with a Dean–Stark water trap. After cooling, the reaction mixture was diluted with benzene. The organic layer was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using benzene–ethyl acetate (9 : 1, v/v) as the eluant to give an inseparable stereoisomeric mixture of (**6b**) [1.25 g (70.5%)] (*trans*/*cis* = 2/1) as a yellowish gum: IR ν_{max} ($CHCl_3$): 1770 (sh), 1753 and 1722 cm^{-1} (C=O). NMR ($CDCl_3$) δ: 3.79 and 3.85 (each 3H, each s, 2 × OMe), 4.2 and 4.53 (each 1H, each d, each J = 14 Hz, $ArC\underline{H}_2$), 4.89 (2/3H, d, J = 2.4 Hz, C_3-H (*trans*)], 5.2 [1/3H, d, J = 5 H, C_3-H (*cis*)]. MS *m/e*: 498 (M^+); *m/e* 498.1296 (M^+) [Calcd for $C_{24}H_{26}N_2O_5S_2$ (M^+), *m/e* 498.1283].

***trans* and *cis*-1-(2,4-Dimethoxybenzyl)-4-(2,2-dimethoxyethyl)-3-phthalimido-2-azetidinone (7b)**——A solution of (**6b**) (500 mg) in benzene (20 ml) was added to a stirred solution of TTN (1.025 g) in methanol (20 ml) at ambient temperature under a current of nitrogen, and the reaction mixture was further stirred for 0.25 h at the same temperature. The same work-up and purification procedures as in the case of (**7a**) gave an inseparable stereoisomeric mixture of (**7b**) (*cis*/*trans* = 1/2) [285 mg (62.5%)] as a gum: IR ν_{max} ($CHCl_3$): 1772 (sh), 1758 and 1728 cm^{-1} (C=O). NMR ($CDCl_3$) δ: 3.05 and 3.07 [each 1H, each s, 2 × OMe (*cis*)], 3.14 and 3.21 [each 2H, each s, 2 × OMe (*trans*)], 3.78 and 3.81 (each 3H, each s, 2 × OMe), 5.06 [2/3H, d, J = 2.2 Hz, C_2-H (*trans*)], 5.21 [1/3H, d, J = 4.6 Hz, C_3-H (*cis*)]. MS *m/e*: 454 (M^+); *m/e* 454.1721 [Calcd for $C_{24}H_{26}N_2O_7$ (M^+), *m/e* 454.1738].

trans* and *cis*-4-(2,2-Dimethoxyethyl)-3-phthalimido-2-azetidinone (8b-*trans*) and (8b-*cis*)**——A stirred mixture of (**7b**) (420 mg), potassium persulfate (1 g), and $Na_2HPO_4 \cdot 12H_2O$ (665 mg) in acetonitrile–water (2 : 1, v/v) (60 ml) was heated at 80 °C for 45 min. After the same work-up as in the case of (**8a**), the residue was purified by column chromatography on silica gel using benzene–methanol (9 : 1, v/v) as the eluant to give the *trans*-azetidinone (**8b-*trans) [57 mg (20.3%)] as an amorphous solid: IR ν_{max} ($CHCl_3$): 3440 (NH), 1790, 1775 and 1732 cm^{-1} (C=O). NMR ($CDCl_3$) δ: 2.05 (2H, dd, J = 5.2 and 7 Hz, C_2-$C\underline{H}_2$), 3.22 and 3.26 (each 3H, each s, 2 × OMe), 4.07 (1H, dt, J = 2.4 and 7 Hz, C_4-H), 4.38 [1H, t, J = 5.2 Hz, $C\underline{H}(OMe)_2$], 4.95 (1H, d, J = 2.4 Hz, C_3-H), 6.56 (1H, br s, NH), 7.67 and 7.73 (each 2H, each br s, Ar-H). MS *m/e*: 305 ($M^+ + 1$); *m/e* 305.1112 (Calcd for $C_{15}H_{17}N_2O_5$ ($M^+ + 1$), *m/e* 305.1137.

Further elution gave an inseparable mixture of (**8b-*trans***) and (**8b-*cis***) (1 : 1) [97 mg (34.5%)] as an amorphous solid. The NMR spectrum of the latter (**8b-*cis***) was as follows: NMR ($CDCl_3$) δ: 4.03 [1/2H, dt, J = 5.2 and 7 Hz, C_4-H (*cis*)], 4.34 [1/2H, t, J = 5.2 Hz, $C\underline{H}(OMe)_2$ (*cis*)], 5.33 [1/2H, d, J = 5.2 Hz, C_3-H (*cis*)].

trans*-*o*-Nitrobenzyl 6-Phthalimido-1-carbapen-2-em-3-carboxylate (12)**——A solution of *o*-nitrobenzyl glyoxylate (21 mg) in dry dimethylformamide (1 ml) was added to a stirred solution of the above azetidinone (**8b-*trans) (50 ml) in dry dimethylformamide–benzene (1 : 2, v/v) (15 ml) at room temperature under a current of nitrogen. The mixture was stirred for 5 h, then the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography using benzene–ethyl acetate (8 : 1, v/v) as the eluant to afford the alcohol (**9b**) [75 mg (89.3%)] as an amorphous solid: IR ν_{max} ($CHCl_3$): 1785 (sh), 1772 and 1732 (C=O), 1345 cm^{-1} (NO_2). NMR ($CDCl_3$) δ: 3.22 and 3.27 (each 3H, each s, 2 × OMe), 5.10 (1H, d, J = 2.8 Hz, C_3-H).

A solution of thionyl chloride (13.6 mg) in dry tetrahydrofuran (0.5 ml) was added to a stirred solution of the above alcohol (**9b**) (45 mg) and 2,6-lutidine (12.2 mg) in dry tetrahydrofuran (3 ml) at −20 °C under a current of nitrogen, and the reaction mixture was stirred for 30 min. After filtration, the filtrate was evaporated under reduced

pressure. The residue was dissolved in dry dioxane–dry dimethylformamide (1 : 1, v/v) (4 ml), and 2,6-lutidine (14 mg) and triphenylphosphine (35 mg) were added to the solution at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred for 10 h at 60 °C. After filtration, the filtrate was evaporated to afford a yellowish caramel, which was chromatographed on silica gel using benzene–ethyl acetate (20 : 1, v/v) as the eluant to give the phosphorane (**11b**) [45.5 mg (68.5%)] as a caramel: IR ν_{max} ($CHCl_3$): 1783 (sh), 1758 and 1728 (C=O), 1620 (ylide), 1345 cm^{-1} (NO_2). NMR ($CDCl_3$) δ: 3.12 (6H, s, 2 × OMe).

A solution of the above phosphorane (40 mg) and *p*-toluenesulfonic acid (25 mg) in acetone (7 ml) was stirred for 1 h at ambient temperature. After removal of the solvent, the resulting residue was dissolved in methylene chloride and the organic layer was washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was rapidly chromatographed on silica gel using benzene–ethyl acetate (93 : 7, v/v) as the eluant to afford the *trans*-6-phthalimido-1-carbapen-2-em derivative (12) [47 mg (82.5%)] as an amorphous solid: IR ν_{max} ($CHCl_3$): 1798, 1783 and 1734 (C=O), 1350 cm^{-1} (NO_2). NMR ($CDCl_3$) δ: 2.9 and 3.08 (each 1H, each d, each J = 3.2 Hz, C_1-C$\underline{H}_2$), 4.72 (1H, dt, J = 3.3 and 9.2 Hz, C_5-H), 5.35 (1H, d, J = 3.3 Hz, C_6-$\underline{H}$), 5.59 and 5.89 (each 1H, each d, each J = 15.6 Hz, Ar-C$\underline{H}_2$), 6.54 (1H, t, J = 3.2 Hz, C_2-H), 7.48—8.19 (8H, m, Ar-$\underline{H}$). MS *m/e*: 433 (M^+); *m/e* 433.0888 [Calcd for $C_{22}H_{15}N_3O_7$ (M^+), *m/e* 433.0909].

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