SYNTHESIS OF 3,5-TRANS-3-METHOXYCARBONYL-1-CARBAPENAM FROM METHYL (±)-PYROGLUTAMATE[1]

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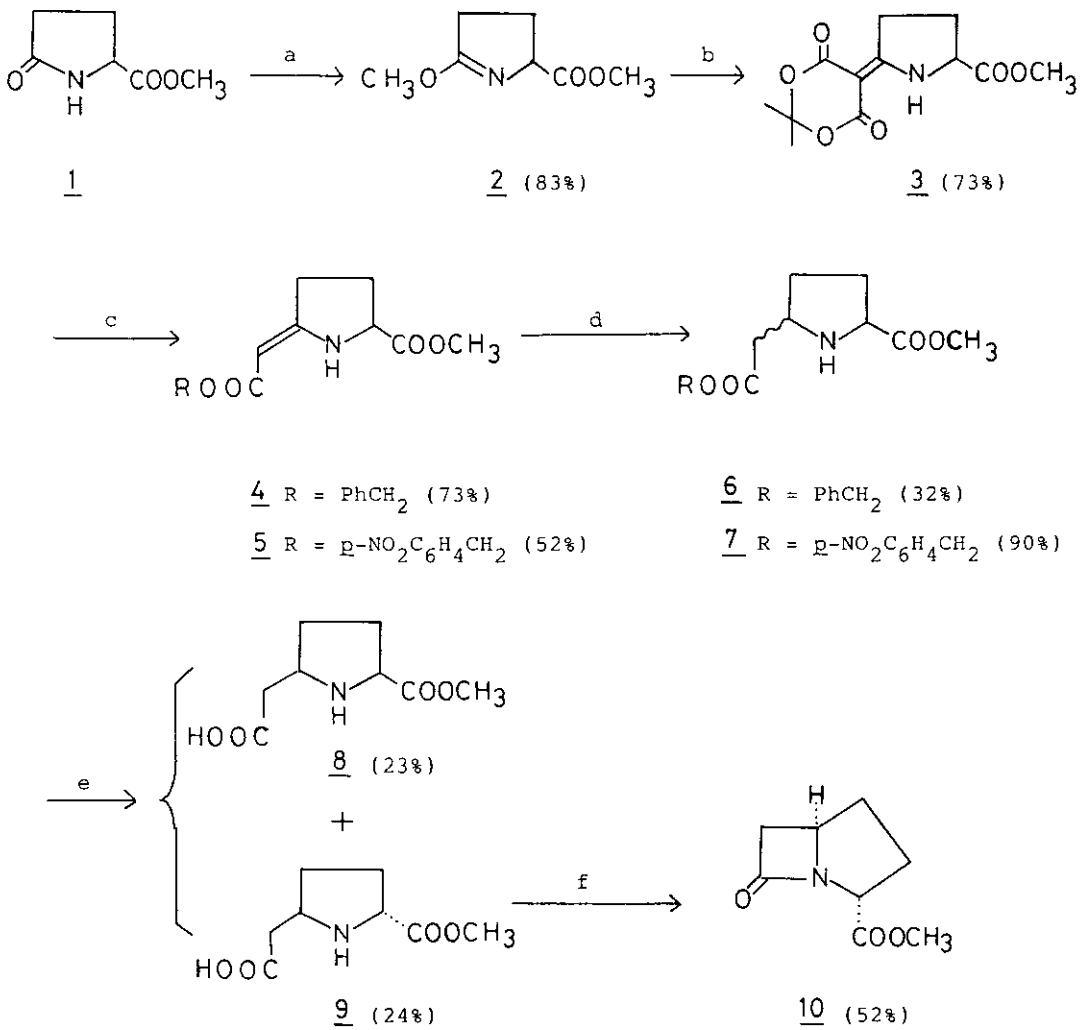
Abstract — Synthesis of 3,5-trans-3-methoxycarbonyl-1-carbapenam in six steps from methyl (±)-pyroglutamate is described.

In the past several years, synthetic studies have been conducted on carbapenem and carbapenam systems related to the highly potent antibiotic thienamycin. As a continuation of our research on the chemical modifications of 2-pyrrolidinones,[2] the synthesis of a simple carbapenam derivative from pyroglutamic acid[3] was developed since glutamic acid is a precursor of 1-carbapenem antibiotic.[4] In this paper, the synthesis of 3,5-trans-3-methoxycarbonyl-1-carbapenam from methyl (±)-pyroglutamate is described (Scheme 1).

Imino ether (2) was obtained in high yield by treatment of methyl (±)-pyroglutamate (1) with dimethyl sulfate (neat) and then potassium bicarbonate. In this process, the ordinary method[5] (refluxing a lactam with dimethyl sulfate in benzene) and Bredereck's modification[6] (using dimethyl sulfate and sodium cyanide) resulted in a complicated mixture. The condensation of 2 with Meldrum's acid[7] afforded isopropylidene (2-methoxycarbonyl-5-pyrrolidinylidene)malonate (3) in 73% yield. Contrary to our expectations, the ethanolysis of 3 in the presence of sodium ethoxide[7] or acid (formic acid or hydrochloric acid) afforded decomposed products. After several experiments,[8] the desired enamine esters (4 and 5) were finally obtained by the reaction of 3 with benzyl alcohol or p-nitrobenzyl alcohol in the presence of boron trifluoride etherate in refluxing benzene. The enamine esters (4 and 5) were confirmed to be stereochemically stable Z-isomers on the basis of deshielding effects with the ^{1}H-NMR shift reagent.[7] The reduction[9] of 4 and 5 with sodium cyanoborohydride in methanol at pH 3-4 afforded diesters (6 and

Scheme 1



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2 (83%)

3 (73%)

4 R = $PhCH_2$ (73%)

5 R = p-$NO_2C_6H_4CH_2$ (52%)

6 R = $PhCH_2$ (32%)

7 R = p-$NO_2C_6H_4CH_2$ (90%)

8 (23%)

9 (24%)

10 (52%)

a: i) Me_2SO_4 (0.9 equiv.)/neat, r.t., 48 h ii) sat. $KHCO_3$

b: Meldrum's acid (isopropylidene malonate) (1 equiv.), Et_3N (1 equiv.), C_6H_6, reflux 24 h

c: ROH (3 equiv.), $BF_3 \cdot Et_2O$ (1 equiv.), C_6H_6, reflux 24 h

d: $NaBH_3CN$ (1 equiv.), MeOH-H^+ (pH 3-4), r.t., 2 h

e: 5% Pd-C, H_2 (1 atm), MeOH, 2h

f: PPh_3 (1.1 equiv.), $(PyS)_2$ (1.1 equiv.), CH_3CN, reflux 8 h

7) in 32 and 90% yields, respectively. The ^{1}H-NMR spectra of 6 and 7 indicated that both of these compounds exist as a mixture of nearly equal amount of cis- and *trans-isomers, respectively.* Their separation by column chromatography was unsuccessful.[10] The catalytic hydrogenation of 6 and 7 on 5% palladium-carbon under atmospheric hydrogen pressure afforded a mixture of amino acids (8 and 9) in 15 - 47% yield. Although these amino acids could be separated into cis-(8) and trans-isomers (9) by column chromatography, their stereochemistry could not be determined at this stage. 3,5-Trans-3-methoxycarbonyl-1-carbapenam (10) was obtained in 52% yield by applying Ohno's method[11] to the cyclization of 9. The ^{1}H-NMR spectrum of this carbapenam (10) was identical with that given in the literature.[3a, 12]

EXPERIMENTAL

All melting points were determined by micro-melting point apparatus (Yanagimoto) without corrections. IR and MS spectra were measured on a *Hitachi 200-10 and a* Hitachi M-80 spectrometer, respectively. ^{1}H-NMR spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts were recorded in ppm downfield from an *internal standard* (TMS). The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chromatographic separations were conducted on a silica gel (Wako-gel C-200) column. Thin-layer chromatography (TLC) was carried out using pre-coated silica gel plates (Kieselgel 60 F-254, Merck).

2-Methoxy-5-methoxycarbonyl-1-pyrroline (2) --- A mixture of 1 (2.67 g, 18 mmol) and Me_2SO_4 (2.11 g, 16 mmol) was stirred at room temperature for 48 h, to which benzene (40 ml) and a saturated aq. $KHCO_3$ solution (15 ml) were added. The stirring was continued for an additional 30 min. Organic layer was removed, dried over $MgSO_4$, and evaporated to give 2.43 g (83%) of 2 as a colorless oil. IR ($CHCl_3$): 1730 (C=O), 1640 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$) δ: 2.00-2.80 (m, 4H), 3.60 (s, 3H), 3.80 (s, 3H), 4.30-4.70 (m, 1H).

Isopropylidene (5-Methoxycarbonyl-2-pyrrolidinylidene)malonate (3) --- A solution of 2 (7.5 g, 47 mmol), isopropylidene malonate (Meldrum's acid, 6.9 g, 47 mmol) and Et_3N (0.93 g, 47 mmol) in benzene (80 ml) was refluxed for 24 h. After evaporation of the solvent under reduced pressure, the residual solid was re-

crystallized from MeOH to give 9.25 g of 3 as colorless prisms, mp 140-142 °C. IR (KBr): 3310 (NH), 1760, 1720 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.70 (s, 6H), 2.15-2.60 (m, 2H), 3.30-3.55 (m, 2H), 3.80 (s, 3H), 4.45-4.70 (m, 1H), 10.25 (br s, 1H). MS m/z : 269 (M^+). Anal. Calcd. for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.68; H, 5.60; N, 5.15.

Benzyl (5-Methoxycarbonyl-2-pyrrolidinylidene)acetate (4) --- A solution of 3 (1.0 g, 3.5 mmol), $PhCH_2OH$ (1.13 g, 10.5 mmol), and $BF_3 \cdot Et_2O$ (0.5 g, 3.5 mmol) in benzene (25 ml) was refluxed for 24 h. After being cooled, the solution was washed with saturated $NaHCO_3$ solution (20 ml) and brine (20 ml) and dried over $MgSO_4$. Evaporation of the solvent gave an oil, which, on chromatographic separation by elution with benzene-acetone (10 : 1), gave 746 mg (73%) of 4 as a colorless oil. IR ($CHCl_3$): 3400 (NH), 1750 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.00-2.75 (m, 4H), 3.70 (s, 3H), 4.20-4.50 (m, 1H), 4.65 (s, 1H), 5.10 (s, 2H), 7.30 (s, 5H), 8.12 (br.s, 1H). MS m/z: 275 (M^+).

p-Nitrobenzyl (5-Methoxycarbonyl-2-pyrrolidinylidene)acetate (5) --- By a similar procedure as above using p-nitrobenzyl alcohol in place of $PhCH_2OH$, 5 was obtained as prisms (from benzene), mp 113-115 °C. Yield, 52%. IR (KBr): 3500 (NH), 1740 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.20-2.70 (m, 4H), 3.75 (s, 3H), 4.20-4.45 (m, 1H), 4.70 (s, 1H), 5.22 (s, 2H), 7.50 (d, J=9 Hz, 2H), 8.20 (d, J=9 Hz, 2H). MS m/z: 320 (M^+). Anal. Calcd. for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.45; H, 4.87; N, 8.63.

cis- and trans-Benzyl (5-Methoxycarbonyl-2-pyrrolidinyl)acetate (6) --- To a solution of 4 (236 mg, 0.86 mmol), $NaBH_3CN$ (56 mg, 0.9 mmol), and bromocresol green (indicator, 2 mg) in methanol was added dropwise HCl-saturated MeOH until the color of the solution remaining yellow for more than 10 min (pH 3-4). After being stirred for 30 min, the solution was neutralized with aq. $KHCO_3$ solution and evaporated to give a residual mass, followed by extraction with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to give an oil, which, on chromatographic separation by elution with $CHCl_3$-acetone (10 : 1), gave 76 mg (32%) of 6 as a colorless oil, bp 125 °C (3 mmHg). IR ($CHCl_3$): 3350 (NH), 1740, 1700 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.80-2.30 (m, 4H), 2.40-2.65 (m, 2H), 3.40-3.90 (m, 2H), 3.75 (s, 3H), 5.12 (s, 2H), 7.35 (s, 5H).

cis- and trans-p-Nitrobenzyl (5-Methoxycarbonyl-2-pyrrolidinyl)acetate (7) --- Using the above method, 7 was obtained from 5 in 90% yield as an oil. IR ($CHCl_3$):

3350 (NH), 1770, 1720 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.80-2.70 (m, 4H), 2.40-2.70 (m, 2H), 3.40-3.90 (m, 2H), 3.70 (s, 3H), 5.25 (s, 2H), 7.50 (d, J=8 Hz, 2H), 8.20 (d, J=8 Hz, 2H). MS m/z: 322 (M^+). A portion of trans-7 was recovered on the tert-butoxycarbonylation of 7 (mixture) with Boc-S reagent (tert-butyl S-4,6-dimethylpyrimidin-2-ylthiocarbonate): ^{1}H-NMR ($CDCl_3$) δ: 1.6-2.4 (m, 4H), 2.5 (d, J=6 Hz, 2H), 2.76 (s,, 1H, NH), 3.7 (s, 3H), 3.75 (m, 2H), 5.25 (s, 2H), 7.50 (d, J=8 Hz, 2H), 8.20 (d, J=8 Hz, 2H).

cis- and trans-(5-Methoxycarbonyl-2-pyrrolidinyl)acetic Acid (8 and 9) --- Catalytic hydrogenation of 7 (1.0 g, 3 mmol) on 5% Pd-C (200 mg) in MeOH (10 ml) gave an oil which was separated into a cis-amino acid (8) (23%) and a trans-amino acid (9) (24%) on chromatography by elution of $CHCl_3$-MeOH (5 : 1). 8, colorless needles from isopropanol, mp 155-158°C. IR ($CHCl_3$): 1750 cm^{-1} (C=O). ^{1}H-NMR (CD_3OD) δ: 1.6-2.6 (m, 4H), 2.75 (d, J=6 Hz, 2H), 3.85 (s, 3H), 4.0 (m, 1H), 4.55 (t, J=7.5 Hz, 1H). Anal. Calcd. for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.23; H, 6.96; N, 7.36. MS (CI) m/z: 188 (M^++1). 9, colorless needles from isopropanol, mp 154-155°C. IR ($CHCl_3$): 1750 cm^{-1} (C=O). ^{1}H-NMR (CD_3OD) δ: 1.6-2.5 (m, 4H), 2.55 (m, 2H), 3.83 (s, 3H), 3.8 (m, 1H), 4.43 (t, J=7.5 Hz, 1H). MS (CI) m/z: 188 (M^++1). Anal. Calcd. for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.54; H, 7.03; N, 7.78.

3,5-trans-3-Methoxycarbonyl-1-carbapenam (10) --- A solution of 9 (133 mg, 0.71 mmol), PPh_3 (223 mg, 0.85 mmol), and $(PyS)_2$ (187 mg, 0.85 mmol) in CH_3CN (100 ml) was refluxed for 8 h. After being cooled, the solvent was evaporated to give a residual mass which, on chromatographic separation by elution with benzene-acetone (20 : 1), gave 62 mg (52%) of 10 as a colorless oil. IR (neat): 1765, 1742 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.1-2.6 (m, 4H), 2.65 (dd, J=2 Hz, J=16 Hz, 1H), 3.16 (dd, J=5 Hz, J=16 Hz, 1H), 3.74 (s, 3H), 3.7-4.0 (m, 1H), 4.45 (t, J=7 Hz, 1H). ^{13}C-NMR (CDC13) δ: 31.1 (t), 35.4 (t), 42.5 (t), 52.4 (d), 53.0 (q), 59.0 (d), 171.8 (s), 176.1 (s). MS m/z: 169 (M^+).

REFERENCES AND NOTES

1 This work was presented at the 5th Niigata Conference of the Kanto Branch, Yuki Gosei Kagaku Kyokai, Nov. 1984 (Abst. p.54).

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3 Only a few syntheses of 3-alkoxycarbonyl-1-carbapenam from pyrrolidine derivatives have been reported: e.g., a) S. R. Berrghill, T. Price, and M. Rosenblum, J. Org. Chem., 1983, 48, 158. b) M. D. Bachi, R. Breiman, and H. Meshulam, J. Org. Chem., 1983, 48, 1439. c) Synthesis of 3,5-trans-3-p-nitrobenzyloxycarbonyl-1-carbapenam was presented at the 106th Annual Meeting of Pharmaceutical Society of Japan, Chiba, Apr. 1986 (Abst. p.218) by T. Ohta, A. Hosoi, and S. Nozoe (Tohoku University).

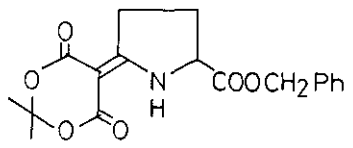
4 S. W. Queener and N. Neuss, "Chemistry and Biology of β-Lactam Antibiotics", ed. by R. B. Morin and M. Gorman; Academic Press Inc., 1982, Vol 3, p.71.

5 S. Peterson and E. Tietze, Chem. Ber., 1957, 90, 909.

6 H. Bredereck, G. Simchen, and W. Kantlehner, Chem. Ber., 1971, 104, 924.

7 J-P. Célérier, E. Deloisy, G. Lhommet, and P. Maitte, J. Org. Chem., 1979, 44, 3089.

8 When 3 was warmed with sodium (1 equiv.) in benzyl alcohol (120°C, 26 h), the ester (11) was obtained in 28% yield. Refluxing 3 in benzyl alcohol gave the dibenzyl ester (12) in 20% yield. 11: Colorless needles (EtOAc-hexane), mp



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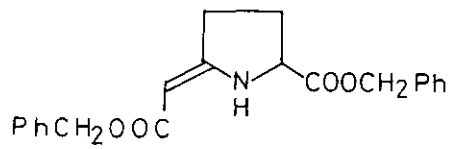

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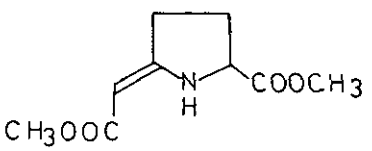
152-154°C. IR (KBr): 3280 (NH), 1740, 1710 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.70 (s, 6H), 2.20-2.60 (m, 2H), 3.25-3.60 (m, 2H), 4.45-4.80 (m, 1H), 5.20 (s, 2H), 7.45 (s, 5H), 10,40 (br s, 1H). MS m/z: 345 (M^+). Anal. Calcd. for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.18; H, 5.51; N, 4.08. 12: Colorless needles (hexene), mp 83-85°C. IR (KBr): 3290 (NH), 1710 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.05-2.80 (m, 4H), 4.25-4.45 (m, 1H), 5.10 (s, 2H), 5.18 (s, 2H), 7.30 (s, 10H), 8.15 (br s, 1H). MS m/z: 351 (M^+). Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.20; N, 3.99. Found: C, 71.60; H, 5.86; N, 3.83.

9 Catalytic hydrogenation (on palladium-carbon or platinum oxide) of 3 with acid (hydrochloric acid and/or acetic acid) was attempted for the direct synthesis of amino acids (8 and 9), but resulted in failure. A reaction of 4 with sodium borohydride in methanol gave the di-ester (13) in 38% yield. The catalytic

hydroganation of 4 on 5% palladium-carbon in methanol under 3 atm hydogen pressure gave the cis-5-methylproline ester (14) in 58% yield, which is described as hydrochloride in the literature (C. G. Overberger, K. H. David,



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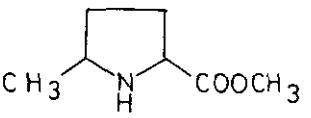

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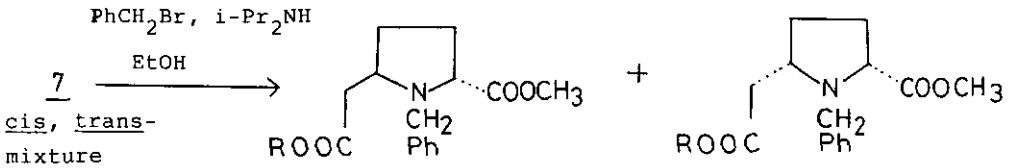
and J. A. Moore, Macromolecules, 1972, 5, 368). 13: Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.80-2.20 (m, 2H), 2.45-2.70 (m, 2H), 3.30-4.40 (m, 1H), 3.58 (s, 6H), 4.50 (s, 1H), 8.00 (br s, 1H). 14 (HCl salt): mp 176-177°C (acetone) [lit. mp 176°C (dec)]. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (d, J=6 Hz, 3H), 2.05-2.55 (m, 4H), 3.70-4.10 (m, 1H), 3.81 (s, 3H), 4.30-4.60 (m, 1H), 9.10-10.20 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 17.64 (q), 27.79 (t), 30.96 (t), 53.39 (q), 56.91(d), 59.21 (d), 169.3 (s). MS (CI) m/z: 144 (M^++1). Anal. Calcd. for $C_7H_{13}NO_2 \cdot HCl$: C, 46.80; H, 7.85; N, 7.80. Found: C, 46.84; H, 7.81; N, 7.90.

10 When 7 (cis-, trans-mixture) was subjected to tert-butyloxycarbonylation at the 1-position, unreacted trans-7 was recovered and from which, amino acid (9) was obtained by catalytic hydrogenation. The N-benzylation of 7 (mixture) afforded trans- and cis-products (15 and 16) in 24 and 46% yields, respectively. Each could be separated by column chromatography. The catalytic hydrogenation of 15 and 16 failed to give amino acids (8 and 9), but acids (17 and 18) were obtained in 23 and 51% yields, respectively. The stereochemistry



15 R = p-$NO_2C_6H_4CH_2$ (24%) → 17 R = H (23%)

16 R = p-$NO_2C_6H_4CH_2$ (46%) → 18 R = H (51%)

of these compounds was determined by the benzylation of trans-9 to 17. 15:

yellow oil. IR ($CHCl_3$): 1725 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.62-2.42 (m, 4H), 2.20-2.80 (m, 2H), 3.55 (m, 2H), 3.65 (s, 3H), 3.71 (d, J=13.5 Hz, 1H), 3.95 (d, J=13.5 Hz, 1H), 5.17 (s, 2H), 7.27 (s, 5H), 7.46 (d, J=8 Hz, 2H), 8.17 (d, J=8 Hz, 2H). MS (CI) m/z:413 (M^++1) 16: Yellow oil. IR ($CHCl_3$): 1725 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.60-2.15 (m, 4H), 2.25-2.80 (m, 2H), 3.30 (m, 2H), 3.50 (s, 3H), 3.72 (d, J=13.5, Hz, 1H), 3.88 (d, J=13.5 Hz, 1H), 5.17 (s, 2H), 7.27 (s, 5H), 7.47 (d, J=8 Hz, 2H), 8.17 (d, J=8 Hz, 2H). MS (CI) m/z: 413 (M^++1). 17: ^{1}H-NMR ($CDCl_3$) δ: 1.65-2.65 (m, 4H), 2.60 (m, 2H), 3.70 (s, 3H), 3.7 (m, 2H), 3.83 (d, J=12 Hz, 1H), 4.05 (d, J=12 Hz, 1H), 7.30 (s, 5H), 10.55 (s, 1H). 18: ^{1}H-NMR ($CDCl_3$) δ: 1.60-2.30 (m, 4H), 2.55 (m, 2H), 3.23 (m, 1H), 3.50 (s, 3H), 3.55 (m, 1H), 3.70 (d, J=12 Hz, 1H), 4.0 (d, J=12 Hz, 1H), 7.3 (s, 5H), 12.68 (s, 1H).

11 S. Kobayashi, T. Iimori, T. Izawa, and M. Ohno, J. Am. Chem. Soc., 1981, 103, 2406.

12 In the literature (3a), a mixture of 3,5-cis- and 3,5-trans-3-methoxycarbonyl-1-carbapenams is described accompanying with the complete ^{1}H-NMR spectrum of only the trans-isomer (10). The stereochemical assignments are made by comparison of the ^{1}H-NMR spectrum of the product with those of the related stereoisomeric benzyl and tert-butyl esters (S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen, J. Org. Chem., 1980, 45, 1135) and the trans-form (10) is suggested to be a more stable isomer by the thermodynamically controlled experiments.

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