

Practical Short Synthesis of 1 β -Methylcarbapenem Utilizing a New Dehydration Type Ti-Dieckmann Condensation

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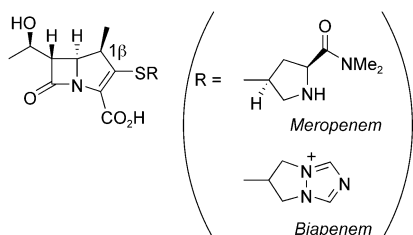
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Abstract: An efficient, practical, and stereocontrolled synthesis of 1 β -methylcarbapenems has been performed utilizing a new dehydration type of Ti-Dieckmann (intramolecular Ti-Claisen) condensation. This cyclization reaction has the advantage of direct incorporation of the thiol moiety into the target 1 β -methylcarbapenem, compared with the traditional basic Dieckmann condensation. Another advantage is the use of environmentally benign (low toxicity and safe) reagents (TiCl₄ and Et₃N or Bu₃N).

Keywords: cyclization; Dieckmann condensation; 1 β -methylcarbapenem; titanium; Ti-Claisen condensation

The discovery of 1 β -methylcarbapenem (e.g., meropenem^[1] and biapenem^[2]), which has potent and broad antibacterial activity as well as enhanced metabolic and chemical stability, has prompted many synthetic organic chemists to develop efficient methods for the stereoselective synthesis of the key carbapenem skeleton (Scheme 1). Recent reviews describe the impressive progress in this area.^[3]

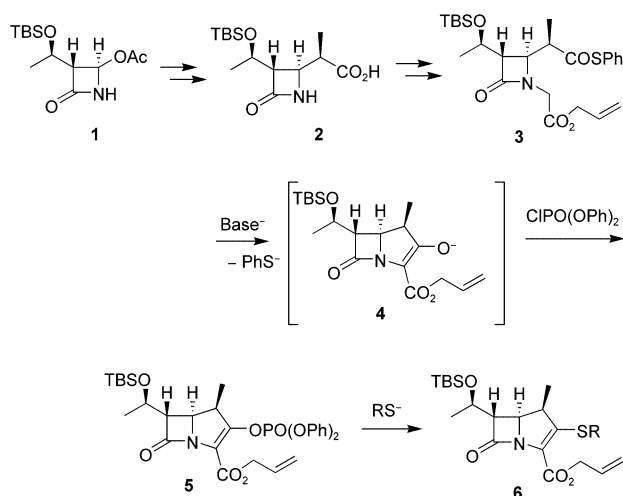
Among many synthetic methods, 1 β -methylcarboxylic acid **2** with four contiguous stereogenic centers is regarded as the most advantageous intermediate, which



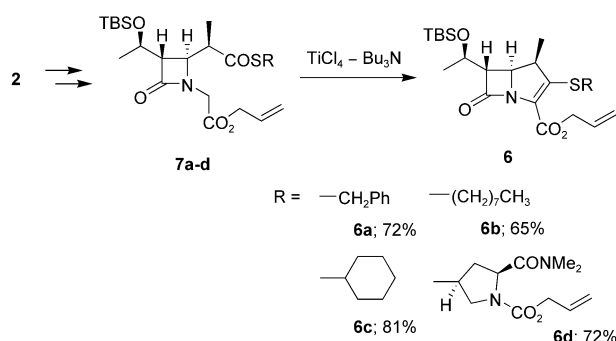
Scheme 1. 1 β -Methylcarbapenem.

was synthesized from commercially available 1-acetoxy-2-azetidinone **1** by coupling with propionic acid derivatives (Scheme 2). Some effective methods for stereoselective synthesis of the key 1 β -methyl synthon **2** have been developed, however there remains a strong need for practical methods for the subsequent construction of bicyclic framework of 1 β -methylcarbapenem **6**. Basic Dieckmann condensation,^[4] Rh-carbene insertion,^[5] and intramolecular Wittig-type reaction,^[6] are representative methodologies.^[7] Among them the Dieckmann condensation protocol seems to be the most efficient to date for the practical synthesis of a series of 1 β -methylcarbapenems. This method involves three reaction sequences; cyclization of **3** to give **4**, successive formation of enolphosphate **5**, and final substitution with thiolate to give **6** (Scheme 2).

The Ti- and Zr-Claisen and Dieckmann condensations exhibit powerful reactivity and are able to realize C–C bond formations between various carboxylic esters under mild reaction conditions.^[8] These characteristic features would be ideal for application of the reaction



Scheme 2. Synthetic route to 1 β -methylcarbapenem **6** utilizing basic Dieckmann condensation.



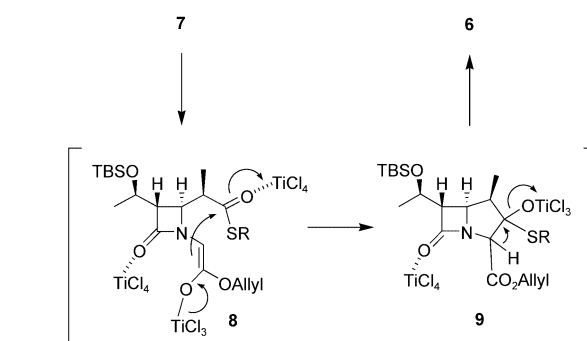
Scheme 3. Dehydration type Ti-Dieckmann condensation of thioester **7a–d**.

for the construction of the 1 β -methylcarbapenem skeleton. We present a short and efficient cyclization reaction between the α -position of allyl esters and carbonyl position of thioesters in **7a–d**, which did not yield basic reagent mediated Dieckmann-products **4** with the elimination of thiols, but yielded vinyl sulfides **6a–d** through a novel dehydration type Ti-Dieckmann condensation (Scheme 3).

Scheme 3 lists four successful results, including the precursor of meropenem, which is one of the most representative 1 β -methylcarbapenem antibiotics. Precursor **6d** could be transformed into meropenem by the known method, which involves desilylation followed by Pd-catalyzed deprotection of the allyl moiety in the ester.^[1] Optimization of the conditions revealed that 3.0 equiv. of TiCl_4 and 3.3 equiv. of Bu_3N were required. When 1.0 equiv. of TiCl_4 was used, the desired carbapenem **6** resulted in low yield ($\sim 20\%$). It should be noted that no epimerization of the 1 β -position was observed; that is, the four contiguous stereogenic centers were successfully retained, although the 1 α -diastereomer of enolate **4** was more thermodynamically stable than the 1 β one. In addition, the elimination of dummy benzenethiol and diphenyl chlorophosphate is more atom-economical.

As a proposed mechanism, this unexpected reaction comprises the following steps (Scheme 4); (i) regioselective formation of titanium allyl ester enolates intermediate **8**, (ii) cyclization to form the Ti-intermediate **9** with an sp^3 tetrahedral carbon adjacent to a chiral methyl group, and (iii) elimination of Ti(=O)Cl_2 and HCl (net process is dehydration of **7**) to give the desired vinyl sulfides **6**. In general, the thiol function of thioesters is regarded as a more easily displaced moiety, however this unusual behavior is considered to be due to the greater affinity of TiCl_4 toward oxygen than that of sulfur. Mukaiyama and his coworkers reported a related condensation reaction in which ketones were transformed into vinyl sulfides with thiols using TiCl_4 and Et_3N .^[9]

The present straightforward method is more convenient than the basic Dieckmann method and provides a



Scheme 4. Proposed mechanism of the dehydration type Ti-Dieckmann condensation.

new methodology for the synthesis of 1 β -methylcarbapenems.

Experimental Section

(3*S*,4*S*)-1-(Allyloxycarbonylmethyl)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-benzylthiocarbonylethyl]-2-azetidinone (**7a**)^[4c]

To a stirred solution of (3*S*,4*S*)-1-(allyloxycarbonylmethyl)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-carboxylethyl]-2-azetidinone^[4c] (200 mg, 0.5 mmol) in benzene (4.0 ml) was added *N,N'*-dicyclohexylcarbodiimide (206 mg, 1.0 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) at 20–25 °C under an Ar atmosphere, and the mixture was stirred for 30 min at that temperature. Benzyl mercaptan (248 mg, 2.0 mmol) was added to that mixture, followed by being stirred for 12 h. After Celite filtration, the mixture was concentrated to give the crude product, which was purified by silica-gel column chromatography (hexane : EtOAc = 5 : 1) to give the desired product **7a** as a pale yellow oil; yield: 335 mg (66%). Spectroscopic data matched with the literature.

(3*S*,4*S*)-1-(Allyloxycarbonylmethyl)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-octylthiocarbonylethyl]-2-azetidinone (**7b**)

A similar procedure as for the preparation of **7a** using octanethiol in the place of benzyl mercaptan; yield: 98%; colorless oil; $[\alpha]_{\text{D}}^{23}$: -31.8 (c 0.32, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ = 0.079 (3H, s), 0.084 (3H, s), 0.87 (9H, s), 1.21–1.37 (17H, m), 1.51–1.58 (2H, m), 2.85 (2H, t, J = 7.4 Hz), 2.99–3.05 (2H, m), 3.90 (1H, d, J = 18.0 Hz), 4.07 (1H, dd, J = 2.8 and 2.8 Hz), 4.13–4.19 (1H, m), 4.25 (1H, d, J = 18.0 Hz), 4.62–4.64 (2H, m), 5.24–5.37 (2H, m), 5.86–5.96 (1H, m); ^{13}C NMR (100 MHz, CDCl_3): δ = -4.86 , -4.40 , 12.24, 13.94, 17.74, 22.48, 22.55, 25.68, 28.66, 28.90, 28.94, 28.99, 29.25, 31.64, 42.50, 49.46, 57.33, 61.08, 65.67, 66.47, 118.68, 131.48, 167.84, 167.88, 201.45; IR (neat): ν = 1770, 1684, 1460, 1412, 1375 cm^{-1} ; HRMS (FAB): calcd. for $\text{C}_{27}\text{H}_{49}\text{NO}_5\text{SSi}$ (M^+): 527.3101; found ($\text{M}^+ + 1$): 528.3218.

(3*S*,4*S*)-1-(Allyloxycarbonylmethyl)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-cyclohexylthiocarbonyl-2-azetidinone (7c)

A similar procedure as for the preparation of **7a** using cyclohexanethiol in the place of benzyl mercaptan; yield: 82%; pale yellow oil; $[\alpha]_D^{23}$: -33.9 (c 0.23, CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ = 0.082 (3H, s), 0.085 (3H, s), 0.88 (9H, s), 1.20–1.48 (11H, m), 1.53–1.76 (3H, m), 1.81–1.94 (2H, m), 2.95–3.02 (2H, m), 3.40–3.54 (1H, m), 3.90 (1H, d, J = 18.0 Hz), 4.07 (1H, dd, J = 2.8 and 2.8 Hz), 4.12–4.19 (1H, m), 4.26 (1H, d, J = 18.0 Hz), 4.62–4.64 (2H, m), 5.24–5.37 (2H, m), 5.86–5.96 (1H, m); ^{13}C NMR (75 MHz, CDCl_3): δ = -4.85 , -4.41 , 12.14, 17.76, 22.58, 25.35, 25.70, 32.64, 32.81, 42.43, 42.48, 49.37, 57.38, 61.01, 65.68, 66.50, 118.70, 131.47, 167.84, 167.92, 201.21; IR (neat): ν = 1766, 1680, 1450, 1412, 1375 cm^{-1} ; HRMS (FAB): calcd. for $\text{C}_{25}\text{H}_{43}\text{NO}_5\text{SSi}$ (M^+): 498.2710; found ($\text{M}^+ + 1$): 498.2689.

(3*S*,4*S*)-1-(Allyloxycarbonylmethyl)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-[(3*S*,5*S*)-1-allyloxycarbonyl-5-dimethylaminocarbonylpyrrolidin-3-yl]thiocarbonyl-2-azetidinone (7d)^[4c]

To a stirred solution of [(3*S*,5*S*)-1-allyloxycarbonyl-3-benzoylthio-5-dimethylaminocarbonylpyrrolidine (435 mg, 1.2 mmol) in CH_3CN (2.0 mL), NaOCH_3 (28% in CH_3OH , 243 mg, 1.26 mmol) was added at -15 to -10°C under an Ar atmosphere, and the mixture was stirred for 1 h at that temperature. To the mixture, phosphoric acid (85%, 145 mg, 1.26 mmol) was added, and then dried (Na_2SO_4). After Celite filtration the mixture was concentrated to a volume of ca. 2 mL, which contained (3*S*,5*S*)-1-allyloxycarbonyl-5-dimethylaminocarbonyl-3-mercaptopyrrolidine.

N,N' -Carbonyldiimidazole (195 mg, 1.20 mmol) was added to a stirred solution of (3*S*,4*S*)-1-(allyloxycarbonylmethyl)-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(1*R*)-1-carboxyethyl]-2-azetidinone^[4c] (400 mg, 1.0 mmol) in CH_3CN (8.0 mL) at 20 – 25°C under an Ar atmosphere, and the mixture was stirred for 1 h at that temperature. To the mixture, a solution of (3*S*,5*S*)-1-allyloxycarbonyl-5-dimethylaminocarbonyl-3-mercaptopyrrolidine in CH_3CN (ca. 2.0 mL) prepared above and Et_3N (121 mg, 1.20 mmol) in CH_3CN (1.5 mL) were successively added, followed by stirring for 6 h. 1 M aqueous HCl solution was added to the mixture, which was extracted by EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane:EtOAc = 1:2) to give the desired product **7d** as a colorless oil; yield: 515 mg (80%). Spectroscopic data matched with the literature.

Allyl (4*R*,5*S*,6*S*)-3-Benzylthio-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (6a)^[4c]

TiCl_4 (1.0 M solution in CH_2Cl_2 ; 0.60 mL) was added to a stirred solution of **7a** (101 mg, 0.2 mmol) and Bu_3N (122 mg, 0.66 mmol) in CH_2Cl_2 (0.5 mL) at -45 to -40°C under an Ar atmosphere, and the mixture was stirred for 1 h. Water was

added to the mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane:EtOAc = 40:1) to give the desired product **6a** as a pale yellow oil; yield: 71 mg (72%). Spectroscopic data matched with the literature.

Allyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-methyl-3-octylthio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (6b)

A similar procedure as for the preparation of **6a** using **7b** in the place of **7a**; yield: 65%; pale yellow oil; $[\alpha]_D^{23}$: $+54.0$ (c 0.13, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ = 0.079 (6H, s), 0.88 (9H, s), 1.22–1.46 (19H, m), 1.61–1.68 (2H, m), 2.75–2.88 (2H, m), 3.18 (1H, dd, J = 6.6 and 2.4 Hz), 3.25–3.33 (1H, m), 4.12–4.14 (1H, dd, J = 9.2 and 2.6 Hz), 4.19–4.26 (1H, m), 4.66–4.81 (2H, m), 5.21–5.25 (1H, m), 5.42–5.47 (1H, m), 5.90–6.00 (1H, m); ^{13}C NMR (75 MHz, CDCl_3): δ = -5.02 , -4.28 , 13.97, 16.82, 17.85, 22.52, 25.62, 28.68, 29.00, 29.59, 31.49, 31.66, 42.92, 55.98, 59.96, 65.33, 66.31, 117.95, 123.98, 131.68, 151.15, 160.71, 172.49; IR (neat): ν = 1718, 1655, 1462, 1379 cm^{-1} ; HRMS (FAB): calcd. for $\text{C}_{27}\text{H}_{47}\text{NO}_5\text{SSi}$ (M^+): 509.2995; found ($\text{M}^+ + 1$): 510.2889.

Allyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3-cyclohexylthio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (6c)

A similar procedure as for the preparation of **6a** using **7c** in the place of **7a**; yield: 81%; pale yellow oil; $[\alpha]_D^{23}$: $+85.0$ (c 0.15, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ = 0.082 (3H, s), 0.087 (3H, s), 0.88 (9H, s), 1.19–1.52 (11H, m), 1.59–1.71 (1H, m), 1.76–1.86 (2H, m), 1.91–2.02 (2H, m), 3.03–3.11 (1H, m), 3.19 (1H, dd, J = 5.6 and 2.8 Hz), 3.24–3.32 (1H, m), 4.15 (1H, dd, J = 9.6 and 2.4 Hz), 4.21–4.27 (1H, m), 4.65–4.82 (2H, m), 5.21–5.25 (1H, m), 5.42–5.47 (1H, m), 5.91–6.00 (1H, m); ^{13}C NMR (75 MHz, CDCl_3): δ = -5.02 , -4.32 , 17.15, 17.89, 22.39, 25.33, 25.64, 26.04, 32.08, 35.94, 43.11, 43.84, 55.64, 60.11, 65.33, 65.98, 117.93, 125.11, 131.70, 149.39, 160.58, 172.66; IR (neat): ν = 1718, 1464, 1450, 1381 cm^{-1} ; HRMS (FAB): calcd. for $\text{C}_{25}\text{H}_{41}\text{NO}_5\text{SSi}$ (M^+): 527.2526; found ($\text{M}^+ + 1$): 528.2478.

Allyl (4*R*,5*S*,6*S*)-3-[1-Allyloxycarbonylpyrrolidin-(3*S*,5*S*)-5-dimethylaminocarbonyl-3-ylthio]-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (6d)^[4c]

A similar procedure as for the preparation of **6a** using **7d** in the place of **7a**; yield: 72%; pale yellow oil. Spectroscopic data matched with the literature.

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References

- [1] a) M. Sunagawa, H. Matsumura, T. Inoue, M. Funasaka, M. Kato, *J. Antibiot.* **1990**, *43*, 519; b) M. Sunagawa, A. Sasaki, *Heterocycles* **2001**, *54*, 497.
- [2] a) P. J. Petersen, N. V. Jacobus, W. J. Weiss, R. T. Testa, *Antimicrob. Agents Chemother.* **1991**, *35*, 203; b) G. J. Malonski, L. Collins, C. Wennerstein, R. C. Moellering, G. M. Eliopoulos, *Antimicrob. Agents Chemother.* **1993**, *37*, 2009.
- [3] a) A. H. Berks, *Tetrahedron* **1996**, *52*, 331; b) M. Sunagawa, A. Sasaki, *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 761.
- [4] a) M. Sunagawa, A. Sasaki, H. Matsumura, K. Goda, K. Tamoto, *Chem. Pharm. Bull.* **1994**, *42*, 1381; b) M. Seki, K. Kondo, T. Iwasaki, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2851; c) K. Kondo, M. Seki, T. Kuroda, T. Yamanaka, T. Iwasaki, *J. Org. Chem.* **1997**, *62*, 2877; d) D. K. Pyun, W. J. Jeong, H. J. Jung, J. H. Kim, J. S. Lee, C. H. Lee, B. J. Kim, *Synlett* **2001**, 1950; e) M. Seki, T. Yamanaka, K. Kondo, *J. Org. Chem.* **2000**, *65*, 572.
- [5] a) R. W. Ratcliff, T. N. Salzmann, B. G. Christensen, *Tetrahedron Lett.* **1980**, *21*, 31; b) D. H. Shih, F. Baker, L. Cama, B. G. Christensen, *Heterocycles* **1984**, *21*, 29; c) T. J. Sowin, A. I. Meyers, *J. Org. Chem.* **1988**, *53*, 4154; d) M. A. Williams, M. J. Miller, *Tetrahedron Lett.* **1990**, *31*, 1807; e) M. Kume, H. Ooka, H. Ishitobi, *Tetrahedron* **1997**, *53*, 1635; f) N. Yasuda, C. Yang, K. M. Wells, M. S. Jensen, D. L. Hughes, *Tetrahedron Lett.* **1999**, *40*, 427.
- [6] a) L. D. Cama, B. G. Christensen, *J. Am. Chem. Soc.* **1978**, *100*, 8006; b) A. J. G. Baxter, P. Davis, R. J. Ponsford, R. Southgate, *Tetrahedron Lett.* **1980**, *21*, 5071; c) A. Yoshida, Y. Tajima, N. Takeda, S. Oida, *Tetrahedron Lett.* **1984**, *25*, 2793; d) T. Sibata, Y. Sugimura, *J. Antibiot.* **1989**, *42*, 374; e) K. Oda, A. Toshida, *Chem. Pharm. Bull.* **1997**, *45*, 1439; f) X. E. Hu, T. P. Demuth, Jr., *J. Org. Chem.* **1998**, *63*, 1791; g) P. Bitha, Y. I. Lin, *Synth. Commun.* **2001**, *31*, 587; h) M. Mori, S. Oida, *Chem. Pharm. Bull.* **2000**, *48*, 126.
- [7] Other methods: a) O. Sakurai, H. Horikawa, *Tetrahedron Lett.* **1996**, *37*, 7811; b) O. Sakurai, T. Ogiku, M. Takahashi, M. Hayashi, T. Yamanaka, H. Horikawa, T. Iwasaki, *J. Org. Chem.* **1997**, *62*, 7889; c) R. Hayakawa, I. Fuseya, T. Konagaya, M. Shimizu, T. Fugisawa, *Chem. Lett.* **1998**, 49; d) J. C. Galland, S. Roland, J. Malpart, M. Savignac, J. P. Genet, *Eur. J. Org. Chem.* **1999**, *3*, 621; e) M. Mori, S. Oida, *Chem. Pharm. Bull.* **2000**, *48*, 126; f) Y. Kozawa, M. Mori, *Tetrahedron Lett.* **2002**, *43*, 111.
- [8] a) Y. Tanabe, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917; b) Y. Yoshida, R. Hayashi, H. Sumihara, Y. Tanabe, *Tetrahedron Lett.* **1997**, *38*, 8727; c) Y. Yoshida, N. Matsumoto, R. Hamasaki, Y. Tanabe, *Tetrahedron Lett.* **1999**, *40*, 4227; d) R. Hamasaki, S. Funakoshi, T. Misaki, Y. Tanabe, *Tetrahedron* **2000**, *56*, 7423; e) Y. Tanabe, R. Hamasaki, S. Funakoshi, *Chem. Commun.* **2001**, 1674; f) Y. Tanabe, A. Makita, S. Funakoshi, R. Hamasaki, T. Kawakusu, *Adv. Synth. Catal.* **2002**, *344*, 507.
- [9] T. Mukaiyama, K. Saigo, *Chem. Lett.* **1973**, 479.