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A NOVEL AND EFFICIENT SYNTHESIS OF THE KEY INTERMEDIATE OF 1β-METHYLCARBAPENEM ANTIBIOTICS FROM (S)-METHYL 3-HYDROXY-2-METHYLPROPIONATE

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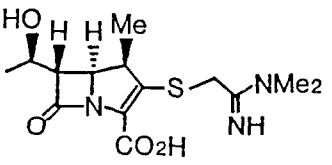
Abstract : A highly efficient synthesis of the key intermediate **2** of 1β-methylcarbapenems was accomplished in 10 steps and 30% overall yield starting from commercially available (S)-methyl 3-hydroxy-2-methylpropionate. The explored synthetic scheme features the addition reaction of diketene with a chiral imine as a key diastereoselective step.

Since the development of 1β-methylcarbapenem **1** as a synthetic carbapenem antibiotic showing excellent antibacterial activity, chemical stability, and insensitivity to renal dipeptidase-I,[1] (3S,4S)-3-[(R)-1-(t-butyldimethylsilyloxy) ethyl]-4-[(R)-1-carboxyethyl]-2-azetizinone **2** utilized as a key intermediate in the original synthesis of **1**,[1] has been the focus of current synthetic attention.[2] We wish to report an efficient and conceptionally new synthesis of **2** starting from commercially available (S)-methyl 3-hydroxy-2-methylpropionate, (S)-**5**.



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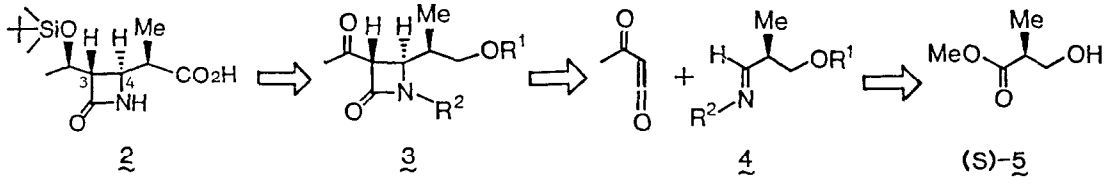
The synthetic strategy of **2** is shown in **Scheme I.** Thus, the optically active 3,4-trans-3-acetyl-β-lactam **3** is anticipated to be a reasonable precursor of **2** since the C-3 and C-4 substituents readily occupy trans configuration due to the presence of 3-acetyl group[3] and transformation of the acetyl group into 3-[(R)-1-hydroxyethyl] group can be achieved in

Scheme I



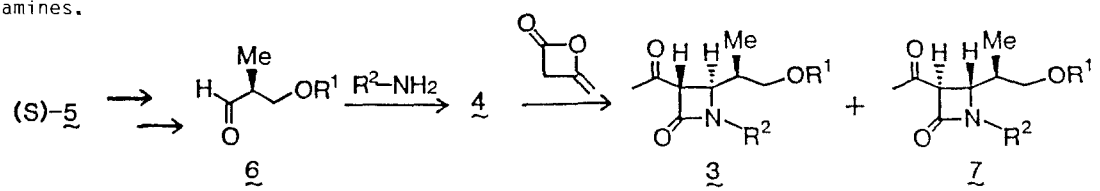
2 **3** **4** (S)-**5**

a highly stereoselective manner.[4] It is expected that **3** can be directly constructed from the chiral imine **4** obtainable from (S)-**5**, when the [2+2] cycloaddition reaction of acetylketene with **4** proceeds with a desired diastereoselectivity under influence of the adjacent chiral center and the two protective groups (R^1 and R^2).

Recent studies on β-lactam synthesis have demonstrated[5,6] that diketene can be used as an acetylketene equivalent in the reactions with imines derived from aromatic aldehydes[5] and alkyl glyoxylates,[6] resulting in a stereoselective production of 3,4-trans-3-acetyl-β-

lactams. In the latter case,[6] it was also reported that the absolute stereochemistry of C-3 and C-4 positions could be effectively controlled to give (3S, 4S)-2-azetidinone derivatives by the uses of chiral imines derived from optically active alkyl glyoxylates. However, at the outset of this work, this type of novel β-lactam formation had never been examined with an optically active aliphatic imine carrying a chiral center at the α-position.[7,8]

Based on our synthetic strategy delineated above, various chiral aldehydes **6** were first prepared from (S)-**5** by sequential protection of the hydroxy group,[9] reduction of the methyl ester to an alcohol with lithium aluminum hydride , and Swern oxidation.[10] As for **6i** which gave the most successful result (*vide infra*), it could be prepared from (S)-**5** in 87% overall yield according to the reported procedure with some modifications.[11,12] Preparation of **4** was simply achieved in a quantitative yield by stirring a mixture of **6** and an amine in toluene in the presence of magnesium sulfate. Taking into account the reported results,[6] p-anisidine (PMP-NH_2) and di-p-anisylmethylamine (DAM-NH_2) were utilized as amines.



a : R^1=Si*t*-BuMe$_2$, R^2=PMP ; **b** : R^1=Si*t*-BuPh$_2$, R^2=PMP ; **c** : R^1=$CH_2O(CH_2)_2OMe$, R^2=PMP
d : R^1=CH_2SMe, R^2=PMP ; **e** : R^1=CH_2Ph, R^2=PMP ; **f** : R^1=CPh_3, R^2=DAM
g : R^1=CH_2OMe, R^2=DAM ; **h** : R^1=CH(OEt)Me, R^2=DAM ; **i** : R^1=CH_2Ph, R^2=DAM
j : R^1=*t*-Bu, R^2=DAM

Table I Cycloaddition Reaction of Diketene with Chiral Imines **4**[a]

Run	**4**	Time (h)	Yield[b] (%)	Ratio of **3** to **7**[c]
1	**a**	64	33	0.25 : 1
2	**b**	15	10	0 : 1
3	**c**	60	41	1.5 : 1
4	**d**	24	38	1.5 : 1
5	**e**	60	58	1.6 : 1
6	**f**	34	12	0.25 : 1
7	**g**	77	44	1.7 : 1
8	**h**	120	32	2.2 : 1
9	**i**	60	47	2.5 : 1
10	**j**	60	26	3.3 : 1

a) All reactions were performed at -30 °C in THF using diketene (5.0-8.0 equiv.) and imidazole (1.1 equiv.). b) Combined yield of **3** and **7**. c) Determined by ^{1}H-NMR spectrum of the mixture of **3** and **7**.

Table II Effects of Solvent and Catalyst on Cycloaddition Reaction of Diketene with the Chiral Imine **4i**[a]

Run	Solvent	Catalyst	Time (h)	Yield[b] (%)	Ratio of **3** to **7**[c]
1	DMF	Imidazole	60	12	1.1 : 1
2	Hex-THF[d]	Imidazole	60	36	3.0 : 1
3	$CHCl_3$	Imidazole	39	25	3.0 : 1
4	Et_2O	Imidazole	39	38	4.7 : 1
5	Toluene	Imidazole	39	33	6.7 : 1
6	Toluene	4-Me-ImH[e]	60	52	11 : 1
7	Toluene[f]	4-Me-ImH[e]	90	49	15 : 1
8	Toluene	Benz-ImH[g]	96	<10[h]	-[i]
9	Toluene	Pyridine	80	<10[h]	-[i]
10	Toluene	NEt_3	80	0	-

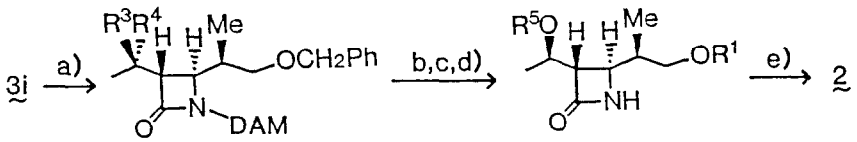
a) All reactions were performed at -30 °C using diketene (5.0 equiv.) and catalyst (1.1 equiv.). b,c) See, **Table I** footnotes b,c). d) Hexane:THF =5:1. e) 4-Methylimidazole. f) 2.0 equiv. of diketene was used. g) Benzimidazole. h) Roughly estimated by TLC. i) Not determined.

With various structural types of **4** in hand, the cycloaddition reactions of diketene with **4** were examined in tetrahydrofuran in the presence of imidazole.[6] Some representative results were shown in **Table I.** As expected, the chemical yields and stereoselectivity of the addition reactions were found to highly depend upon the nature of R^1 and R^2 groups. The favorable results could be realized for **4h-j** (Runs 8-10). With an aim to obtain the more improved result, the cycloaddition reactions of **4i** were further attempted by employing various solvents and catalysts. As shown in **Table II**, it became evident that the use of toluene as a reaction solvent affords the better stereoselectivity (Run 5) and 4-methylimidazole is usable as a more effective catalyst than imidazole (Runs 6,7).

Based on these studies, it was finally established that a mixture of **3i** and **7i** (11-15 : 1) could be obtained in 49-52% yield when **4i** was treated with diketene (2.0-5.0 equiv.) in toluene at -30 °C in the presence of 4-methylimidazole (1.1 equiv.) (**Table II**, Runs 6, 7). The desired major isomer **3i**, mp 90-91 °C and $[\alpha]_D^{20}$ -58.1° (c=0.53, $CHCl_3$), was isolated in a pure state by column chromatography (SiO_2, CH_2Cl_2:acetone=98.5:1.5) followed by separation with TLC (SiO_2, Et_2O:hexane=3:1). The optical purity of **3i** was determined as >95% ee based on the ^{1}H-NMR spectrum measured in the presence of chiral shift reagent, Eu(hfc)$_3$. On the other hand, direct recrystallization of the mixture of **3i** and **7i** from isopropyl ether gave optically pure **3i**, mp 92-93 °C and $[\alpha]_D^{20}$ -59.0° (c=0.62, $CHCl_3$).

Since it is quite ambiguous whether the true reactant of the cycloaddition reaction is diketene, acetylketene, or 1-(acetoacetyl)imidazole derivative, and the β-lactam formation is concerted, stepwise, or the mixture of both processes, full rationalization of the obtained results seems to be quite difficult. However, it is worth noting that the methyl and the benzyloxymethyl groups of **4i** can effectively control the stereoselectivity of cycloaddition reaction even if the difference of their steric bulkiness is very small.

Transformation of **3i** into **2** was readily achieved in 5 steps. Reduction of the acetyl group of **3i** was effected in a highly stereoselective manner according to the reported method,[4] giving a mixture of the two epimeric alcohols (**8** and **9**, **8**:**9**=16:1). These epimeric alcohols could be separated by TLC (SiO_2, CH_2Cl_2:acetone=9:1) to yield **8** in a pure state, $[\alpha]_D^{20}$ -55.1° (c=0.85, $CHCl_3$). The di-*p*-anisylmethyl group of **8** was oxidatively removed with cerium(IV) ammonium nitrate (CAN),[13] yielding the N-unprotected β-lactam **10**, $[\alpha]_D^{20}$ -5.0° (c=0.44, $CHCl_3$). Selective protection of the alcoholic function of **10** with *t*-butyldimethylsilyl group followed by reductive removal of the benzyl group produced the primary alcohol **11**, mp 90-91° C and $[\alpha]_D^{20}$ -21.7° (c=0.46, $CHCl_3$). Oxidation of **11** with



8 : R^3=OH, R^4=H
9 : R^3=H, R^4=OH

10 : R^1=CH_2Ph, R^5=H
11 : R^1=H, R^5=Si*t*-BuMe$_2$

a) KBH(*s*-Bu)$_3$, KI, THF, 0 °C, 99% b) CAN, aq.CH_3CN, 0 °C, 91% c) *t*-BuMe_2SiCl, Imidazole, DMF, rt, 91% d) H_2, Pd-C, AcOEt, rt, 100% e) PDC, DMF, rt, 91%.

pyridinium dichromate (PDC)[14] furnished **2**, mp 146-147 °C and $[\alpha]_D^{20}$ -34.6° (c=0.26, MeOH) (lit.,[1] mp 140-143 °C). The spectral data of **2** were identical with those reported.[1] The overall yield of **2** from **3i** was 76%.

In summary, a novel and efficient synthesis of **2** was developed employing the cycloaddition reaction of diketene with chiral imine as a key step. Among various synthetic routes to **2** so far explored,[1,2] the present process may hold promise as one of the most practical methods due to short synthetic steps (overall 10 steps from (S)-**5**), high yield (30% overall yield from (S)-**5**), high selectivity in the key diastereoselective reaction (11-15:1), and the use of the readily available starting material ((S)-**5**).

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