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A Simple and Highly Diastereoselective Synthesis of A 1β-Methylcarbapenem Key Intermediate by Deallyloxycarbonylation Using Palladium Complexes

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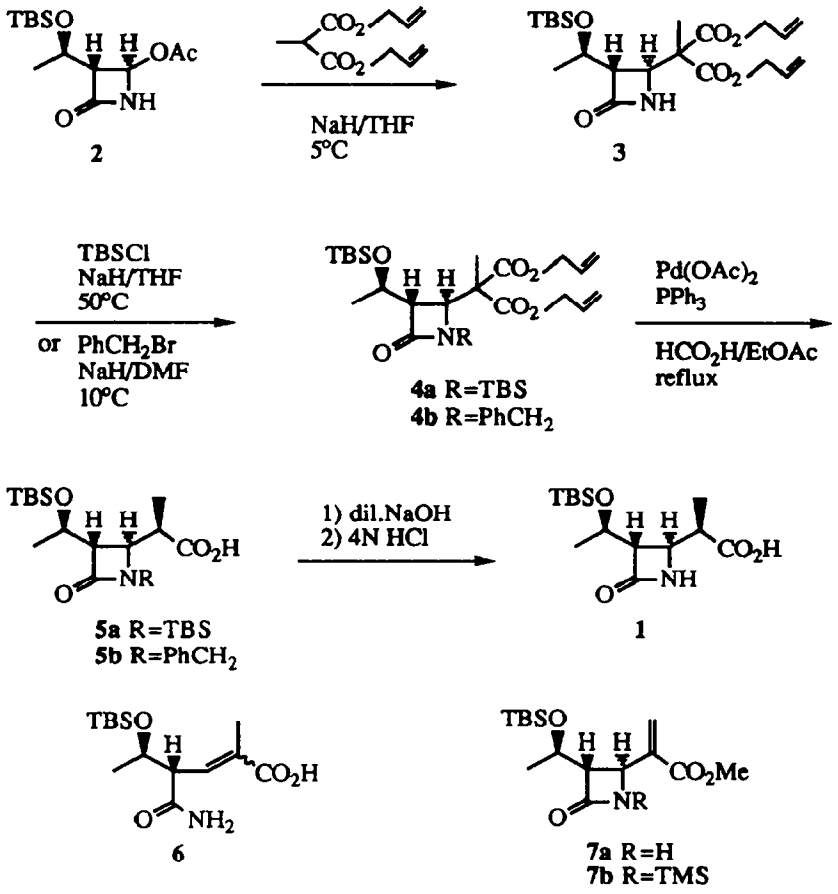
Abstract: A Simple, highly diastereoselective synthesis of the key 1β-methylcarbapenem intermediate **1** has been accomplished via a palladium catalyzed deallyloxycarbonylation of diallyl malonate derivative **4a** which was readily prepared from (3S,4R)-4-acetoxy-3-[(R)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone **2** in two steps.

Since the report that introduction of a β-methyl substituent at the 1-position of the carbapenem nucleus leads to dramatically improved chemical and metabolic stability[1], considerable effort has been devoted to the development of stereoselective methodology for the synthesis of (3S,4S)-3-[(R)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone **1**[2], a key precursor to more elaborate carbapenem systems. The most popular and successful entries to this key intermediate have relied on aldol-type reactions of (3S,4R)-4-acetoxy-3-[(R)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone **2** with properly designed chiral[2a-d] and achiral metal enolates.[2e-g]

It has long been known that decarboxylation of malonic ester derivatives is a very important method for the preparation of substituted carboxylic acids. However, this methodology typically required harsh conditions for the decarboxylation reaction and no reports regarding the preparation of 1β-methylcarbapenem intermediates via this methodology have appeared. Recently, Tsuji and co-workers reported a mild, useful method for the direct transformation of substituted allyl malonates to the corresponding substituted carboxylic acid derivatives by a palladium catalyzed deallyloxycarbonylation with ammonium formate.[3] We report herein a simple and highly diastereoselective preparation of key intermediate **1** via application of the Tsuji deallyloxycarbonylation technology to diallyl malonate **4a** (prepared in two steps from 4-acetoxyazetidinone **2**).

Initially, we examined the deallyloxycarbonylation of diallyl malonate **3**, which was readily prepared in 95% yield by treatment of 4-acetoxyazetidinone **2** with diallyl malonate and sodium hydride in THF. A solution of **3** and triethylammonium formate in THF containing catalytic amounts of palladium acetate and



triphenylphosphine was heated at reflux for 2 h to afford the carboxylic acid **1** as a mixture of two diastereomer (β:α=15:85) in 53% yield accompanied by formation of the ring opened amide **6** as a by-product. Based on a report by Kim that the selectivity of the catalytic hydrogenation of olefinic esters **7a** and **7b** was dramatically dependent on the nitrogen substituent (**7a**; β:α=35:65, **7b**; β:α=75:25),[2e] we decided to to investigate the deallyloxycarbonylation of the analogous *N*-TBS substituted diallyl malonate **4a**. *N*-Silylation of malonate **3** under the standard conditions (TBSCl, triethylamine in DMF at room temperature for 6 days) gave the *N*-TBS malonate **4a** in 74% yield. Alternatively, treatment of **3** with TBSCl and sodium hydride in THF at 50°C for 2 h afforded **4a** in 93% yield.[4] Deallyloxycarbonylation of **4a** under the above conditions proceeded in highly stereoselective manner to afford **5a** in 60% yield in addition to a considerable amount of the ring opened amide **6**. In order to suppress the formation of amide **6** the reaction conditions were modified as illustrated in Table 1. Improved yields of **5a** were obtained by substitution of formic acid for ammonium formate (82-85%, run 3-5) as the acid source and the use of ethyl acetate as the solvent (85%, run 4).[5] Interestingly, when *N*-benzylmalonate **4b** (prepared from the reaction of **3** with benzyl bromide and sodium hydride in DMF) was subjected to the deallyloxycarbonylation, the diastereoselectivity was

Table 1 The Deallyloxycarbonylation of Malonates (3 and 4) Catalyzed by Palladium Complexes

run	Malonate	Solv.	(°C)	(min.)	Product (%)[d]	β:α (%)
1[a]	3	THF	reflux	120	1 (53)	15:85
2[a]	4a	THF	reflux	120	5a(60)	96:4
3[b]	4a	THF	reflux	80	5a(82)	96:4
4[b]	4a	EtOAc	reflux	70	5a(85)	96:4
5[c]	4a	EtOAc	reflux	210	5a(82)	95:5
6[b]	4a	Toluene	82	390	5a(82)	93:7
7[b]	4b	EtOAc	reflux	90	5b(90)	77:23

a. $Pd(OAc)_2$ 1%, PPh_3 5%, HCO_2H 3.3 equiv., Et_3N 3.3 equiv.
b. $Pd(OAc)_2$ 1%, PPh_3 5%, HCO_2H 3.3 equiv.
c. $Pd(OAc)_2$ 0.5%, PPh_3 2%, HCO_2H 3.5 equiv.
d. Isolated yield.

suppressed (run 7).

Finally, transformation of **5a** to the key intermediate **1** was readily achieved as follows. An ethereal solution of **5a** was added to dilute sodium hydroxide solution and the mixture was stirred for 30 minutes. After separation of the organic layer, the aqueous solution was carefully acidified to pH 5 with 4N HCl at 5°C to precipitate white solids, which were filtered, washed with water, and dried to give the desired key intermediate **1** in 93% yield as a mixture of two diastereomers (β:α=96:4).

In conclusion, we have demonstrated a simple, practical, and highly stereoselective synthesis of **1** via the palladium complex catalyzed deallyloxycarbonylation of **4a**. The process is anticipated to be one of great value due to its high diastereoselectivity, mild reaction conditions and the use of readily available reagents.

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4. The silylation of **3** was carried out in the following way.
To a stirred suspension of sodium hydride (0.51g, 21.3 mmol) in THF (10 ml) was added dropwise a solution of **3** (8.50 g, 20.0 mmol) and TBSCl (3.16 g, 21.0 mmol) in THF (30 ml) at 50°C. The mixture was stirred for 2 h. The reaction was quenched with saturated ammonium chloride solution. After the usual workup, the oily product was purified by silica gel column chromatography to give pure **4a** (10.03 g, 93%).

5. A typical deallyloxycarbonylation procedure is as follows:
To a solution of palladium acetate (22.1 mg, 1 mol%) and triphenylphosphine (131.5 mg, 5 mol%) in ethyl acetate (15 ml) was added a solution of formic acid (1.50 g, 32.6 mmol) in ethyl acetate (5 ml) at room temperature. The mixture was heated at reflux for 30 minutes. Then **4a** (5.39 g, 10 mmol) was added dropwise over a period of 20 minutes and the mixture was heated at reflux for 2 h. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel to give **5a** (3.52 g, 85%) as a 96:4 ratio of β:α isomers.

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