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# A New Synthetic Method of 1β-Methylcarbapenems Utilizing the Eschenmoser Sulfide Contraction

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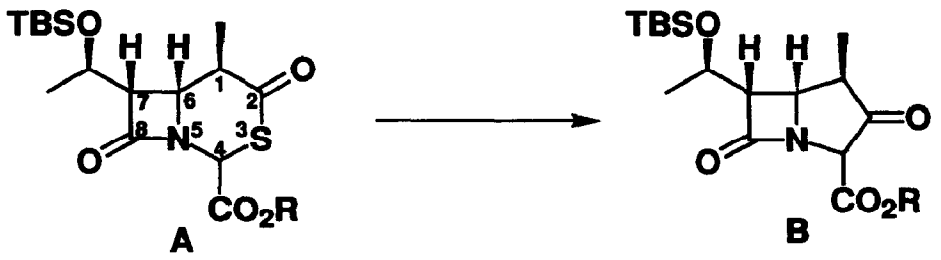
***Abstract***: 1β-Methylcarbapenems **7** were synthesized utilizing the Eschenmoser sulfide contraction as a key step in a one-pot procedure from the novel thiazinone intermediate **4** which was easily accessible from the propionic acid derivative **1**.

Since the discovery of thienamycin[1] in 1976, intensive efforts have been devoted to the synthetic studies in search of new carbapenems having potent and broad-spectrum antibiotic activities. Of these studies, the work reported by a Merck research group has given a great impetus to medicinal chemists, in that the introduction of 1β-methyl group on the carbapenem skeleton remarkably increases chemical and metabolic stability.[2] The synthesis of 1β-methylcarbapenem was stimulated increasingly by the recent findings of tstereocontrolled synthesis of the propionic acid derivatives **1** having four contiguous asymmetric centers.[3] The 1β-methycarbapenem skeleton having a bicyclic ring system has been constructed starting from **1** based on the Rh(II)-catalyzed carbene insertion,[2] the intramolecular Wittig reaction[4] and the Dieckmann reaction.[5] In this communication, we report a novel synthetic method of 1β-methylcarbapenem skeleton based on the ring contraction of a bicyclic thiazinone utilizing the Eschenmoser sulfide contraction.[6]

It is well-documented that acylthioglycolates are effectively converted to the corresponding β-ketoesters by elimination of a sulfur atom in the presence of a phosphine.[6] We anticipated that the sulfide contraction of bicyclic thiazinone A having unprecedented ring system would be initiated by the intramolecular nucleophilic attack of the anion generated at the carbon α to the ester group on the carbonyl group, leading to 1β-methylcarbapenem skeleton B (Scheme 1).

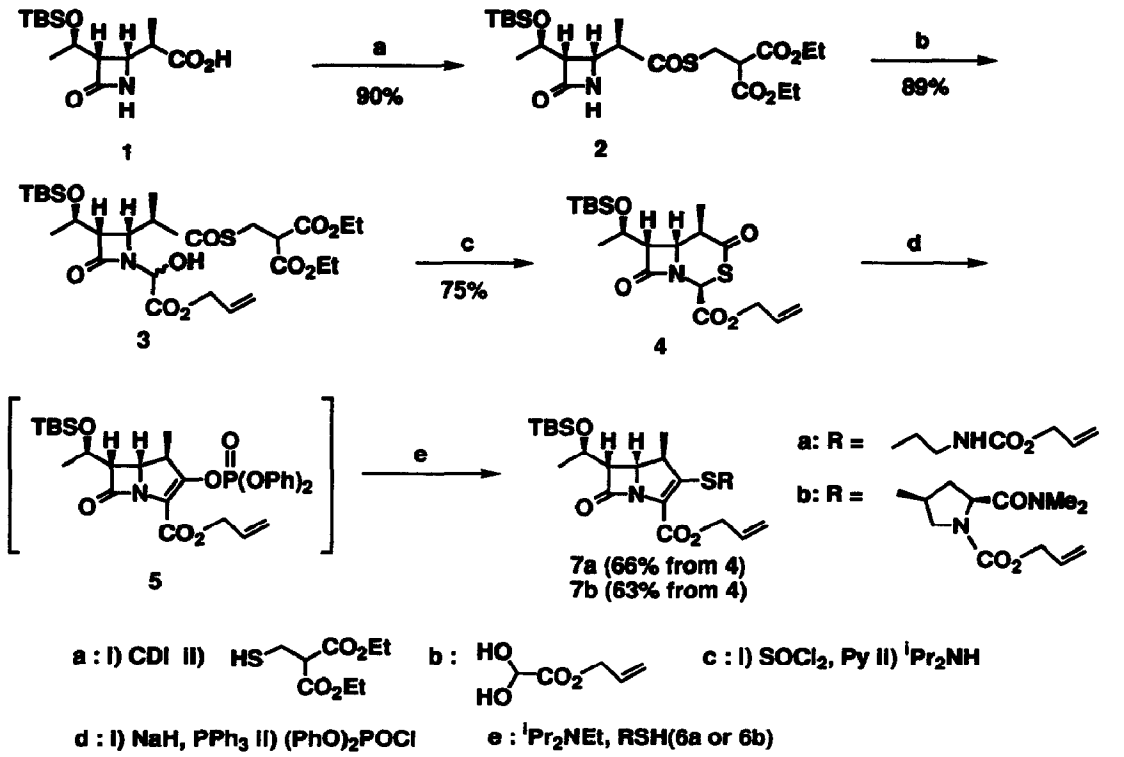
**Scheme 1**




**TBS: *tert*-butyldimethylsilyl**

Thus, we first examined the effective synthesis of thiazinone 4 starting from the propionic acid derivative 1 based on the strategy involving the formation of the C4-S bond of 4 (Scheme 2).

**Scheme 2**

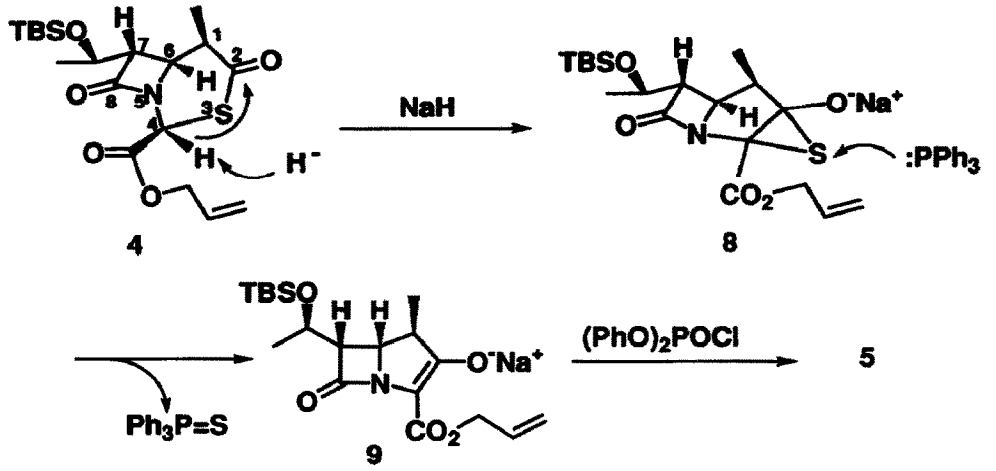



The propionic acid derivative **1** was converted to thioester **2** by the usual method.[7] Compound **2** was condensed with allyl glyoxylate in hot toluene to give **3** in a good yield. Compound **3** was treated with $SOCl_2$ and pyridine[8] to afford the corresponding chloride. Without isolation of the chloride, the crude chloride was treated with $^iPr_2NH$ in $CH_3CN$ to afford thiazinone **4**[9] in 75% yield; the nucleophilic attack of the thiocarboxylate anion generated by elimination of 2,2-bis(carboethoxy)ethyl group[10] under basic conditions effectively took place on the carbon attached to the Cl atom. The stereochemistry of **4** was unambiguously determined by NOE experiment.[11]

We next examined the ring transformation of **4** to carbapenem **7** under a variety of reaction conditions using the Eschenmoser sulfide contraction. As a result, we found that the use of NaH in DMF as a base-solvent system made the reaction proceed smoothly. Thus, treatment of **4** with NaH (1.1eq) in the presence of $PPh_3$ (1.0 eq) in DMF at -20°C followed by addition of $(PhO)_2POCl$ to the reaction mixture gave **5**; in this reaction, substantial formation of triphenylphosphine sulfide was observed even at -20°C,[12] clearly indicating the occurrence of efficient sulfur extrusion from the thiazinone ring. Without isolation of **5**, the addition of mercaptans **6a, b** to the reaction mixture afforded[13] the corresponding carbapenems **7a, b** in good yields in a one-pot procedure from **4**.

This sulfide contraction is probably initiated by abstraction of the proton on the 4-position of 4 by NaH; this hydrogen atom on C4 would be exposed on the convex side of carbapenem skeleton.[11] The resulting anion would attack intramolecularly on the carbonyl group of thiazinone to form thiirane 8. Subsequently, 8 would be subject to the sulfur extrusion by aid of $Ph_3P$ to be converted into Na salt 9 which is effectively trapped in situ by $(PhO)_2POCl$ to give 5 (Scheme 3).

**Scheme 3 Plausible Mechanism of Ring Contraction**




In summary, we established a new method for the synthesis of 1β-methylcarbapenems from the propionic acid derivative **1** utilizing the Eschenmoser sulfide contraction. This method should find application in the construction of other types of β-lactams such as penems and cephalosporins.

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**References and Notes**

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9. Spectral data of **4**: IR (neat) 1779, 1744, 1690 $cm^{-1}$; $^1H$-NMR (200 MHz, $CDCl_3$) δ: 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.21 (d, $J$ = 6.2 Hz, 3H), 1.23 (d, $J$ = 6.7 Hz, 3H), 2.93 (dd, $J$ = 4.7, 3.0 Hz, 1H), 3.55 (m, 1H), 4.22 (m, 1H), 4.55 (dd, $J$ = 7.2, 2.9 Hz, 1H), 4.72 (m, 2H), 5.36 (m, 2H), 5.84 (s, 1H), 5.94 (m, 1H); MS m/e 398 ($M^+$-15), 356 ($M^+$-57).
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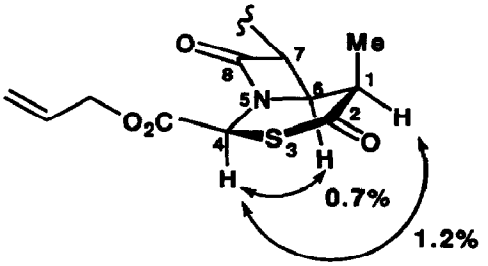
11. NOE was observed between H1 and H4, and between H4 and H6 depicted as below (the substituent group on C7 was omitted to clarify).




12. A. Eschenmoser et al. reported that the higher temperature (50~70°C) was usually needed for completion of the sulfide contraction. See ref. 6.
13. A typical procedure is as follows.
To a solution of **4** (300mg, 0.726mmol) and $Ph_3P$ (186mg, 0.726mmol) in DMF (6ml) was added 60%NaH (32mg, 0.798mmol) with stirring at -20°C under $N_2$ atmosphere. After the reaction mixture was stirred for 2h, $(PhO)_2POCl$ (0.165ml, 0.709mmol) and DMAP (9mg, 0.07mmol) were added to the mixture and stirring was continued at 0°C. After stirred for 2h, *N*-allyloxycarbonylcysteamine (**6a** ) (152mg, 0.944mmol) and $^iPr_2NEt$ (0.165ml, 0.944mmol) were added and the mixture was stirred for 3 days at 0°C. The reaction mixture was poured into $H_2O$ (30ml) and AcOEt (30ml). The organic layer was separated and the aqueous layer was reextracted with AcOEt (30ml). The combined organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with n-hexane:AcOEt = 3:1) to afford **7a** (250mg, 66%) as a gummy syrup.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