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SYNTHESIS OF 1-β-METHYLCARBAPENEM KEY INTERMEDIATES INVOLVING THE LABILE ACYL AUXILIARY 4,4-DIMETHYL-1,3-OXAZOLIDINE-2-THIONE

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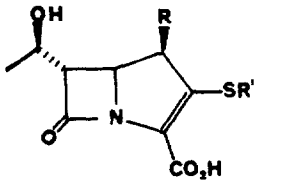
SUMMARY: A convenient synthesis of 1-β-methylcarbapenem key intermediates based on the facile displacement of the 4,4-dimethyl-1,3-oxazolidine-2-thione auxiliary of 5 is described

Since Merck researchers demonstrated that the introduction of a β-methyl substituent at C-1 position of the carbapenem nucleus resulted in a considerable increase of chemical and metabolic stability (1 vs 2)[2], many synthesis of 1-β-methylcarbapenem intermediates have been reported[3]. Although the diastereoselective introduction of the β-methyl substituent has succesfully been achieved, several chemical transformations such as removal of an auxiliary and refunctionalization are often required to access key intermediates.

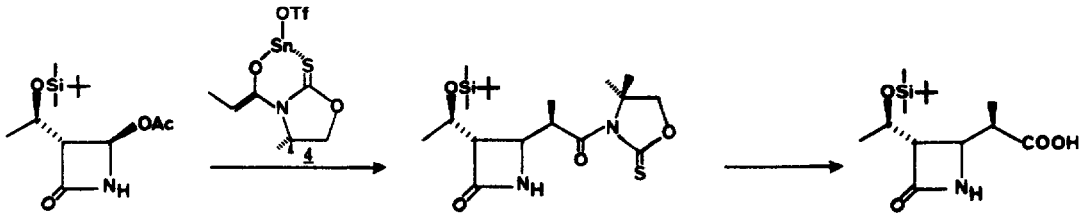
We recently reported a simple and diastereoselective synthesis of the precursor 6 (scheme involving an aldol-type reaction of the tin (II) enolate of 3-propanoyl-4,4-dimethyl-1,3-oxazolidine-2-thione 4 (3-propanoyl DMOT) with the readily available (+)-4-acetoxy-2-azetidione 3[3c]



1 R = CH_3 , R' = $\sim NH_2$

2 R = H , R' = $\sim$ (NH, NMe_2)

Scheme I



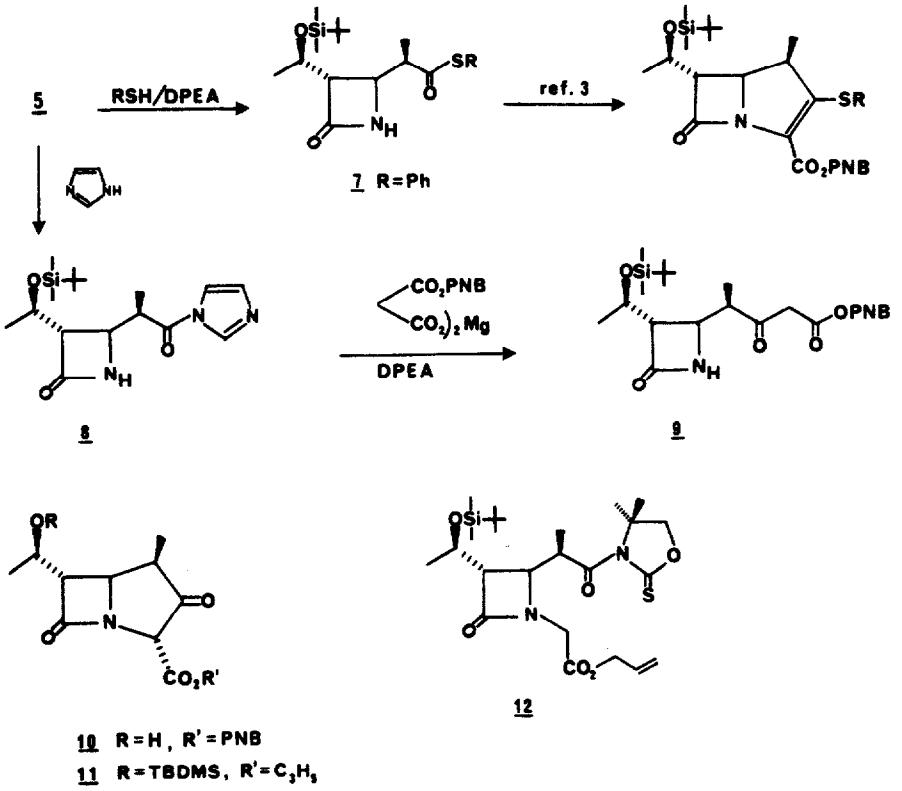
3 5 6

The resulting DMOT intermediate 5 was next treated with diluted sodium hydroxide to give 6 in very good yield. We now wish to report our recent results showing that 5 is a very useful and versatile precursor of many 1-β-methylcarbapenem intermediates. Like other auxiliaries of this type[4], the DMOT moiety proved to be an efficient active acyl and it is smoothly displaced by nucleophiles.

In the first instance we were interested in preparing thiol esters from 5 since they were found to be valuable precursors of carbapenems by employing the oxalimide cyclization reaction[5]. Accordingly, 5 was treated with thiophenol (1.1 eq) and diisopropylethylamine (1.1 eq) in acetonitrile to give the desired thiol ester 7 in 90% yield while retaining the integrity of the β-methyl (scheme II)[6]. Another useful synthetic transformation of 5 is its straightforward conversion into 9, a precursor of the useful bicyclic ketoester 10 , utilizing Masamune's procedure . Thus, 5 was treated with imidazole (1.1 eq) in refluxing acetonitrile to give the acylimidazole derivative 8, which without isolation was treated with p-nitrobenzyl magnesium malonate (1.2 eq) and diisopropylethylamine (1.15 eq) at r.t. to give 9 in 83% yield after purification[8].

Since it has already been demonstrated that the construction of the carbapenem skeleton could be achieved *via* a Dieckmann-type cyclization[3k,9] , we decided to investigate this way. Accordingly the allyl ester 12 was prepared in 80% yield by treating 5 with lithium hexamethyldisilazide at -78°C in THF followed by the addition of allyl bromoacetate (1.1 eq, -78°C → 0°C). The Dieckmann cyclization required particular conditions; treatment of 12 with lithium hexamethyldisilazide (LiHMDS) at low temperature in THF gave 11 in low yield.

Scheme II



However, when 12 was treated with NaHMDS (2 eq) at -78°C in THF the cyclization occured within 2 min, then the mixture was quenched with 1N HCl. At that stage no epimerization of the C-1 methyl took place as evidenced by ^{1}H NMR (200 MHz). Attempts to purify 11 by chromatography resulted in substantial epimerization to the α-methyl isomer. Best results were obtained when the crude product was quickly 'filtered' through a silica gel pad with vacuum elution with CH_2Cl_2: hexane (3:1), in this manner 11 was obtained in 60% yield along with 5% of the α-methyl epimer [10].

As it has been exemplified not only the DMOT auxiliary serves to achieve high diastereoselectivity but it also acts as a very good active acyl providing a very straightforward entry to key intermediates of 1-β-methylcarbapenems.

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6) Spectral data of 7: NMR (200 MHz, $CDCl_3$) δ: 0.07 (s, 6H) 0.87 (s, 9H), 1.18 (d, J=6.3Hz, 3H), 1.32 (d, j=7.0 Hz, 3H), 2.99 (m, 1H), 3.03 (dd, j=4.4, 2.0 Hz, 1H), 3.93 (dd, J=5.6, 2.2 Hz, 1H), 4.2 (m, 1H), 6.04 (m, 1H), 7.41 (m, 5H). IR ($CHCl_3$) 3420, 1760, 1695 cm^{-1}. m.p. 89-90°C.

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10) Spectral data of 11: NMR (200 MHz, $CDCl_3$) δ: 0.087 (s, 6H), 0.88 (s, 9H), 1.19 (d, J=7.8 Hz, 3H), 1.26 (d, J=6.18 Hz, 3H), 2.31 (m, α-isomer, 5%), 2.77 (m, 1H), 3.20 (dd, J=5.4, 2.4 Hz, 1H), 4.24 (dd, J=4.9, 2.4 Hz, 1H), 4.27 (m, 1H), 4.63 (s,1H), 4.65 (m,2H), 5.30 (m, 2H), 5.87 (m, 1H). IR ($CHCl_3$) 1765, 1750 cm^{-1}.

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