Stereoselective Preparation of Chiral *(E)*- Enolthioether from *L*- Threonine for Practical Syntheses of Carbapenem and Penem Intermediates

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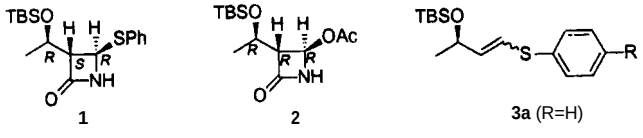
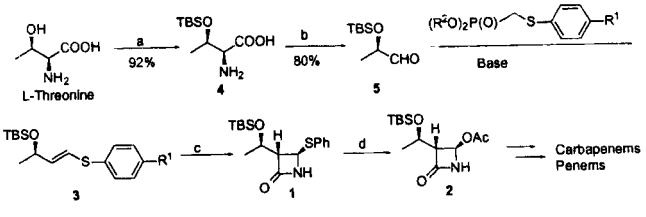
After the isolation of (+)-thienamycin in 1976,[1] carbapenems and penems have received much attention as a new generation of potent antibiotics. Their stereocontrolled total syntheses have employed (3S,4R)-4-phenylthio-3-[(1'R-*tert*- butyldimethylsilyloxy)ethyl]-2-azetidinone **(1),** (3R,4R)-4-acetoxy-3-[(1'R- *tert*- butyldimethylsilyloxy)ethyl]-2-azetidinone **(2),** or its equivalents as key intermediates to these β-lactams. The Suntory group described the synthesis of these intermediates from (R)-butane-1,3-diol,[2] or (R)-3-hydroxybutyrate[3] *via* enolthioether **(3a)** in seven or eight steps, respectively. The drawbacks of these approaches are: 1) the starting material obtained by fermentation is expensive, 2) the enolthioether is obtained as a 2.5 : 1 mixture of *E* and *Z* isomers, and it has been shown that the Z-isomer gave inferior Stereoselectivity in its nucleophilic addition to chlorosulfonyl isocyanate(CSI). Thus an alternative stereoselective preparation of the optically active *(E)*- enolthioether is needed.



Here we wish to report an efficient alternative approach to carbapenem and penem intermediates *via* stereoselective synthesis of *(E)*- enolthioether **3** from *L* -threonine as shown in Scheme 1.[4] Two key features involve the use of naturally abundant *L* -threonine as a versatile chiral template and the Horner-Wadsworth-Emmons reaction (HWE reaction) to secure the vinylsulfide, in which the sulfide group can stabilize the phosphonate anion sufficiently to give high *(E)*- Stereoselectivity. The required aldehyde **5** was prepared as follows. The hydroxy group of *L* -threonine was protected in 92% yield using TBSCl and DBU in the presence of DMAP.[5] The use of a catalytic amount of DMAP was critical to shorten the reaction time and to improve the chemical yield. Then the protected *L* -threonine was degraded by ninhydrin in aqueous methanol to give the corresponding aldehyde **5** in 80% yield,[6] which was identical in all respects with the previously prepared.[7,8] Since the aldehyde **5** was obtained from expensive (R)-(+)-lactate by silylation followed by DIBALH reduction, our synthetic approach from naturally abundant *L* -threonine seems to be an alternative practical method.



Scheme 1. a) TBSCl, DBU, cat. DMAP, CH_3CN. b) ninhydrin, MeOH/H_2O. c) CSI, $Pr^i{}_2O$. d) $Cu(OAc)_2$, AcOH.

Next the HWE reaction between aldehyde **5** and diethyl phenylthiomethylphosphonate was examined under various conditions (Table 1).

While the use of NaH or *t* -BuOK as a base gives rather inferior yield and lower *(E)* -selectivity, the lithium bases show the highest stereoselectivity. After testing various conditions, we found that the best result was obtained on using *n*- BuLi as a base in THF at − 78 °C.[9] We also examined the effect of the substituents of phosphonate on the stereoselectivity and the chemical yield.[10] The results are given in Table 2.

As expected, *(E)* -Stereoselectivity is enhanced as the phosphonate size increases (Entries 1, 4 and 7).[11] Diisopropyl phosphonate resulted in inferior chemical yields to dimethyl or diethyl phosphonate. The substrates with an electron withdrawing groups at phenylthio moiety gave higher chemical yield (Entries 2, 5 and 8) than those with an electron donating groups (Entries 3, 6 and 9).

We conducted the CSI cyclization with *(E)* -thioethers to obtain the expected β -lactam **1,** which was converted into **2** in 52% overall yield according to the literature method.[12]

In summary, *(E)*- enolthioether **3** has been synthesized stereoselectively in three steps from naturally abundant *L*-threonine *via* Strecker degradation and the subsequent HWE reaction using lithium base, which was then subjected to CSI cyclization to give (3S,4R)-4-phenylthio-3-[(1'R- *tert*- butyldimethylsilyloxy)ethyl]-2-azetidinone **1.** The

Table 1. HWE Reaction of Aldehyde **(5)** with Diethyl phenylthiomethylphosphonate

Entry	Base	Solvent	Temperature (°C)	**1a** (R^1=H) E/Z ratio[a]	**1a** (R^1=H) Yield (%)[b]
1	*t*- BuOK	DMF	0	1.59/1	49
2	*t*- BuOK	DME	0	1/1.22	55
3	*t*- BuOK	Et_2O	−20	1/1	35
4	NaH(60%)	THF	0	1/1	51
5	NaH(60%)	Et_2O	0	1/1	30
6	*t*- BuLi	THF	−78	*E*	60
7	*t*- BuLi	Et_2O	−78	*E*	34
8	*n*- BuLi	THF	−78	*E*	75
9	1M-LiHMDS	THF	−78	*E*	68

[a]determined by HPLC and ^{1}H NMR (300 MHz) of the crude. [b]isolated yield.

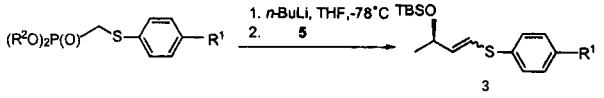


Table 2. The Effect of the Phosphonate Size and the Substituents at the Phenylthio part

Entry	R^1	R^2	Product	E/Z ratio [a]	Yield (%) [b]
1	H	Me	**3a**	97.5/2.5	77
2	Cl	Me	**3b**	97.9/2.1	78
3	OMe	Me	**3c**	*E*	67
4	H	Et	**3a**	*E*	75(93)[c]
5	Cl	Et	**3b**	*E*	77
6	OMe	Et	**3c**	*E*	67
7	H	*i*-Pr	**3a**	*E*	65
8	Cl	*i*-Pr	**3b**	*E*	69
9	OMe	*i*-Pr	**3c**	*E*	47

[a] determined by HPLC and ^{1}H NMR (300 MHz) of the crude. [b] isolated yield. [c] HPLC yield.

following substitution reaction produced (3R,4R)-4-acetoxy-3-[(1'R- *tert*- butyldimethylsilyloxy)ethyl]-2-azetidinone **2.** An alternative new approach has been developed for the synthesis of carbapenem and penem intermediates from readily available *L* -threonine.

Experimental

O- *t*- butyldimethylsilyl-L-threonine (4). Under the nitrogen atmosphere, *L* -threonine (5 g, 42 mmole) and *t* -butyldimethylsilylchloride (7.6 g, 50 mmole) were suspended in acetonitrile (50 mL) and the mixture was agitated at room temperature for 20 min. After the reaction temperature was cooled down to 0 °C, 4-dimethylaminopyridine (0.6 g) and 1,8-diazabicyclo[5 .4.0]undec-7-ene (8.4 g, 55 mmole) were slowly added to the above mixture, and the resultant mixture was agitated at 0 °C for 1 h. The reaction temperature was slowly raised up to room temperature and then a strong agitation for 16 h resulted in white precipitate. By filtering the precipitate under reduced pressure, 8.2 g of the crude product was obtained. The filtrate was concentrated and the residue was suspended with acetonitrile (20 mL) and vigorously stirred at 0 °C for 2 h to provide 1.2 g of crude product. The combined crude product was recrystallized from methanol/acetonitrile to give white pure product (9.0 g, 92%).

(R)-(+)-2- *tert*- butyMimethylsilyloxypropanal (5). O- *t*- butyldimethylsilyl- *L*- threonine (5 g, 21.4 mmole) was dissolved in mixed solvent of distilled water and methanol (1 : 1.5, 150 mL) and the mixture was heated to 50 °C. A solution containing of ninhydrin (9.9 g, 55.3 mmol) in co-solvent (50 mL) was slowly added dropwise and the resultant mixture was agitated at 50 °C for 1 h then saturated with NaCl, diluted with Et_2O/ *n* -hexane (1/1, 500 mL). After vigorous agitation, dark-brown byproduct was filtered off, the aqueous phase was extracted with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (Et_2O/ *n* -hexane=1/5) to give the aldehyde (3.2 g, 80%).

General procedure of HWE reaction. To a stirred solution of dialkylphenylthiomethyl phosphonate (1.75 mmole) **(6)** in dry THF was added a solution of 2.5 M *n*-BuLi (2 mmole) in hexane at − 78 °C under inert atmosphere. The reaction mixture was stirred for 30 min at this temperature then a solution of TBS-aldehyde **(5)** (1.59 mmole) in THF was added dropwise at − 78 °C, allowed to warm to room temperature for 2 h. The pale yellow solution was treated with aqueous NH_4Cl and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* then purified by column chromatography (Et_2O/ *n* -hexane= 1/30). The ratio was determined by HPLC and ^{1}H NMR of the crude. Coupling constants for the *trans* - and *cis* -vicinal protons of 15-16 Hz and 10-11 Hz respectively are well established.[9]

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