Chemistry of *O*-Silylated Ketene Acetals: a Stereoselective Synthesis of Chiral Thienamycin Intermediate

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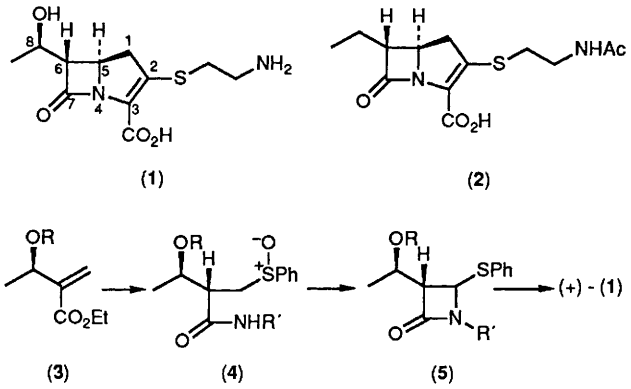
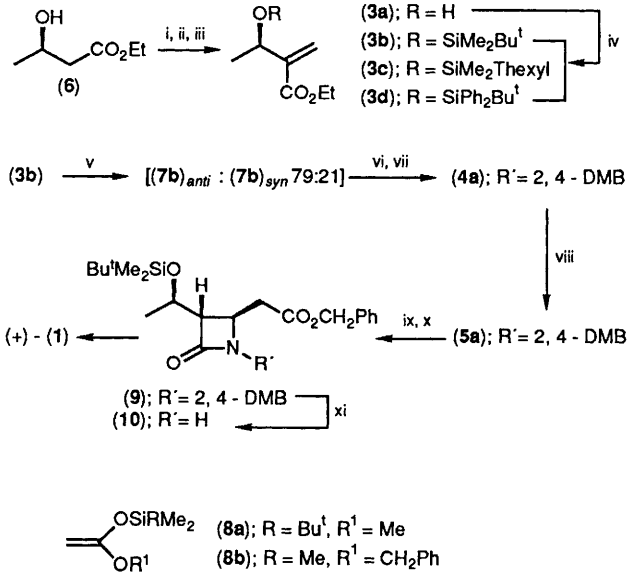
A stereoselective synthesis of chiral thienamycin intermediate (**10**) involving a diastereoselective Michael addition and a silicon-induced Pummerer-type reaction is described.

Since the discovery of the carbapenem antibiotics represented by thienamycin (**1**), much attention has been directed toward the synthesis of these compounds[1] owing to their prominent anti-bacterial activities, broad spectra, and high resistance to β-lactamases. Recently, we reported a versatile synthesis of azetidin-2-ones[2] and racemic PS-5 (**2**)[3] by our silicon-induced Pummerer-type reaction. We have now applied the method to a novel stereoselective synthesis of the chiral intermediate for (**1**).

One major difficulty in the synthesis of (+)-(**1**) is the control of the relative and absolute stereochemistry of the three contiguous chiral centres (C-5, C-6, and C-8 positions in carbapenem numbering). Our novel synthetic strategy relies on the recognition that the chiral α,β-unsaturated ester (**3**) can be utilised as a key intermediate for the optically active β-amido sulphoxide (**4**). The asymmetric centre in (**3**) directs the introduction of the correct absolute stereochemistry at the neighbouring carbon centre in the asymmetric Michael



Scheme 1



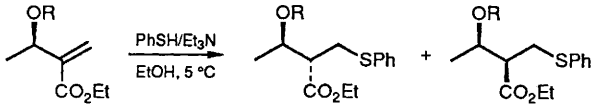
Scheme 2. *Reagents and conditions*: i, 2 equiv. lithium di-isopropylamide (LDA), $(HCHO)_n$, tetrahydrofuran (THF), −78 °C, 0.5 h, then −23 °C, 0.5 h, 67%; ii, *p*-TsCl, pyridine, 5 °C, 5 days, 82%; iii, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), toluene, 20 °C, 5 min, 92%; iv, RCl, imidazole, dimethylformamide (DMF), 20 °C, 1 day, 100% (**3b**), 89% (**3c**), 100% (**3d**); v, PhSH, Et_3N, ethanol, 5 °C, 1 day; vi, 2,4-DMBNH_2·HCl, $AlMe_3$, benzene, reflux, 3 days, 61%; vii, $NaIO_4$, methanol, 20 °C, 1 d, 89%; viii, (**8a**), cat. ZnI_2, dry MeCN, 70 °C, 8 h, 65%; ix, *m*-CPBA, methylene chloride, 0 °C, 10 min, 82%; ix, (**8b**), cat. ZnI_2, dry MeCN, 20 °C, 2 h, 75%; xi, $K_2S_2O_8$: K_2HPO_4 (2 : 1), MeCN : H_2O (1 : 1), 65 °C, 1.5 h, 56% (lit.[8] 57%).

addition reaction. The optically active (**4**) is used in the next silicon-induced Pummerer-type reaction to give the chiral β-lactam (**5**) bearing correct absolute stereochemistry at the C-6 and C-8 positions (Scheme 1).

The starting chiral α,β-unsaturated esters (**3a—d**) were obtained from readily available (*R*)-(+)-ethyl 3-hydroxybutanoate (**6**)[4] by the standard method as outlined in Scheme 2. Based on the recent result of a diastereoselective nucleophilic conjugated addition of benzylamine to 2-hydroxyalkylpropenoates,[5,6] we examined the nucleophilic addition of thiophenol to (**3a—d**) bearing a chiral substituent at the C-2 position and found that the bulky silyl ethers (**3b—d**) gave highly diastereoselective Michael addition products (**7b—d**). Typically, a mixture of (**3b**) (474 mg, 1.84 mmol), thiophenol (404 mg, 3.67 mmol), and triethylamine (0.7 ml) in ethanol (7 ml) was stirred at 5 °C overnight. The mixture was concentrated and purified by silica gel column chromatography to give a mixture of *anti*- and *syn*-adducts [670 mg, 99% $(7b)_{anti}$: $(7b)_{syn}$ 79 : 21]. The assignment of the stereochemistry of (**7**) was made by 500 MHz ^1H NMR spectroscopic measurement based on a similar method reported by Kurihara.† While the details of the diastereoselective addition of thiophenol to (**3b—d**) remain unknown, a plausible transition state is given in Figure 1. The *anti*-selectivity can be explained by the preferential protonation to the face of the alkenic bond opposite to that of the pre-existing bulky siloxy group.[7]

Amidation of [$(7b)_{anti}$: $(7b)_{syn}$ 79 : 21] with 2,4-dimethoxybenzylamine hydrochloride (2,4-DMBNH_2·HCl) followed by oxidation with sodium periodate gave (**4a**), which was cyclised with 1-(dimethyl-t-butylsiloxy)-1-methoxyethylene (**8a**)[2,3] to give the 4-phenylthioazetidin-2-one (**5a**) (65%, 4*R* : 4*S* 4 : 1). Oxidation of the mixture (**5a**) with *m*-chloroperbenzoic acid (*m*-CPBA) followed by reaction with (**8b**) afforded the *anti*-azetidin-2-one ester (**9**) {62%, $[\alpha]_D^{22}$ −3.68° (*c* 0.816, $CHCl_3$)}, selectively. Deprotection of (**9**) by the known method[8] gave the known (**10**)[9,10] {m.p. 91—92 °C, $[\alpha]_D^{24}$ +14.5° (*c* 0.588, $CHCl_3$), lit.[8] m.p. 92—93 °C, $[\alpha]_D^{24}$ +17.4° (*c* 1.75, $CHCl_3$)}, which had already been correlated with (**1**).[11,12]

Table 1.



	α,β-Unsaturated ester R	Yield (%)	Ratio[a] *anti* : *syn*
(**3a**)	H	100	50 : 50
(**3b**)	$SiMe_2Bu^t$	99	79 : 21
(**3c**)	$SiMe_2$Thexyl[b]	97	79 : 21
(**3d**)	$SiPh_2Bu^t$	96	89 : 11

[a] The ratios were determined by ^1H NMR spectroscopy. [b] Thexyl = 1,1,2-trimethylpropyl.

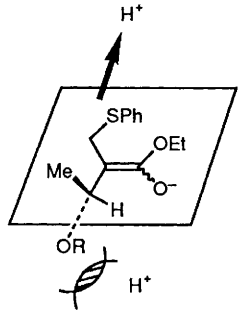


Figure 1

† Y. Matsubara, R. Yoneda, S. Harusawa, and T. Kurihara, *Heterocycles*, 1988, **27**, 667. Lithium aluminium hydride reduction of each Michael adduct followed by treatment with 2,2-dimethoxypropane in the presence of toluene-*p*-sulphonic acid gave 1,3-dioxane derivatives. Since the major product has a smaller vicinal coupling constant ($J_{4,5}$ 2.4 Hz) than that ($J_{4,5}$ 9.8 Hz) of the minor product, the major product is *anti*-(**8**) and the minor one is *syn*-(**8**).

In the present method, three asymmetric centres were constructed in a novel highly stereocontrolled way and all steps were performed in moderate to good yield.

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