A Highly Stereoselective Formal Synthesis of (±)-Thienamycin through Organocopper Enolate–Iminoester Condensation

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The conjugate addition of the Fleming silylcuprate reagent to methyl crotonate and enolate trapping by methyl 4-methoxyphenyliminoacetate produced a high yield of (1′*S**,3*R**,4*S*)-3-[1-(dimethylphenylsilyl)ethyl]-4-methoxycarbonyl-1-(4-methoxyphenyl)azetidin-2-one as a (±)-thienamycin building block.

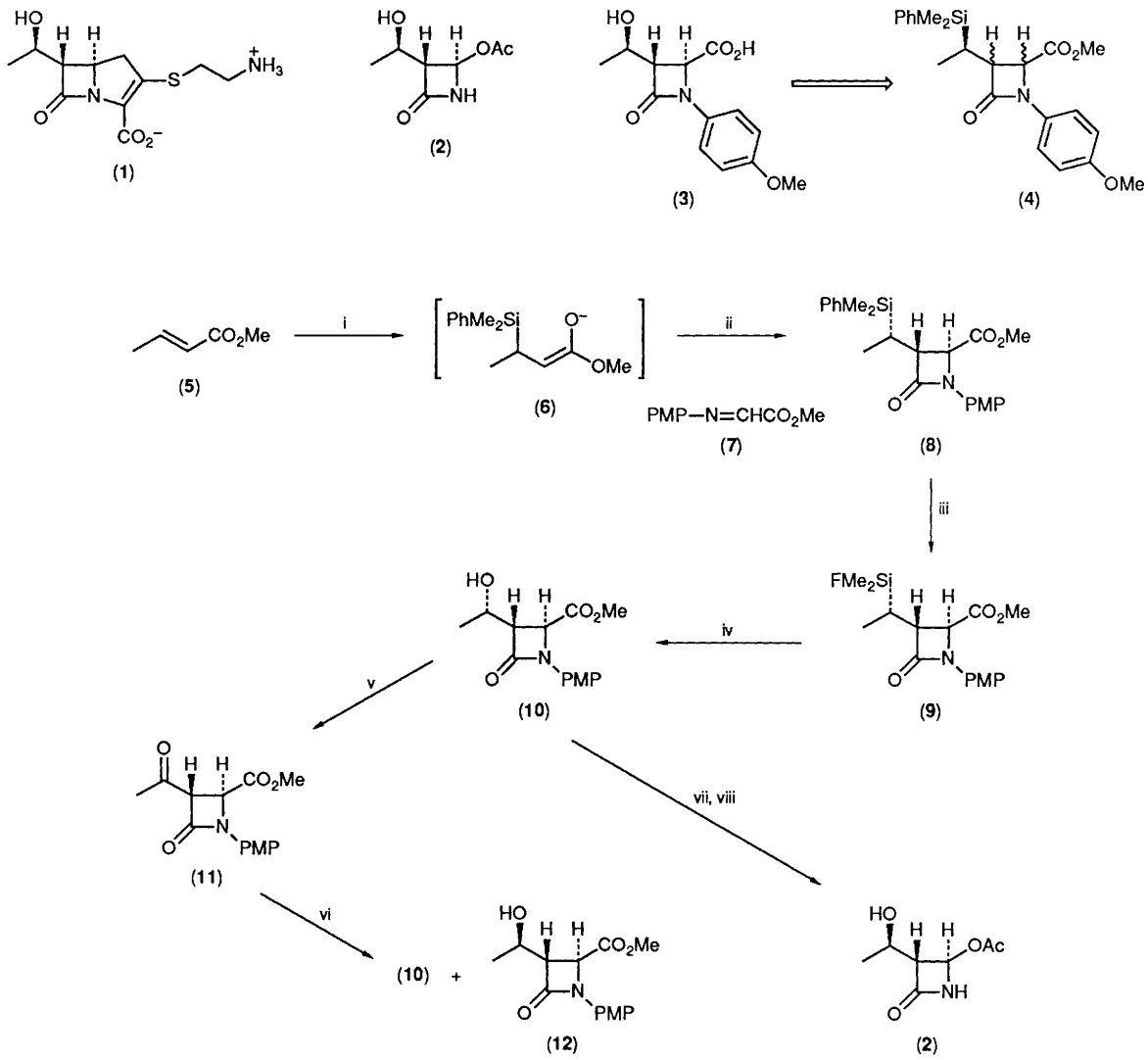
Thienamycin (**1**) and related β-lactam antibiotics comprise an interesting class of compounds, not only for their biological properties, but also for the chemistry involved in their total or formal synthesis.[1,2] Most of the reported syntheses of (**1**) require, as a key step, the formation of a 3-(1-hydroxyethyl)-4-acetoxyazetidin-2-one (**2**), usually generated from a prefunctionalised monocyclic β-lactam, such as (**3**), and further elaboration at the C-4 position following the established Merck's methodology.[3]

Fleming and Kilburn[4] reported a formal synthesis of (±)-thienamycin (**1**) by using the β-dimethylphenylsilyl group as a masked form of the hydroxy group, and recently we have reported[5] that β-dimethylphenylsilylbutanoyl chloride–iminoester condensation could be an efficient alternative to the above approach leading to the corresponding β-lactam (**4**) in good yield, although with moderate stereoselectivity. Among other methods for the preparation of monocyclic β-lactams, the lithium enolate–imine condensation has received considerable attention in thienamycin synthesis.[6] Following this approach, Hart *et al.*[7] reported that the lithium enolate of ethyl β-(dimethylphenylsilyl)butyrate reacts with imines to afford β-lactams with modest to excellent stereoselectivity. Unfortunately, this approach fails when iminoesters are used as imino components of the reaction.† In general, the metal enolate–iminoester approach[8] only works well with tin(II) enolates, silyl ketene acetals, and boron enolates,‡ to give the corresponding β-aminothiolesters or β-amino acids, which then were cyclised by standard procedures.[10] In recent years, organocopper enolate chemistry[11] has found wide applicability in organic synthesis but, to our knowledge, no applications in β-lactam synthesis have been published.

We present here a concise formal synthesis of (±)-thienamycin (**1**) through an organocopper enolate–imine condensation, which involves a one-step preparation of a 3-(1-dimethylphenylsilylethyl)-β-lactam of type (**8**), followed by further transformation of the dimethylphenylsilyl group into the required hydroxy functionality present in thienamycin. The key of the method is that addition of Fleming's

† Reaction of the lithium enolate of ethyl β-(dimethylphenylsilyl)-butyrate with methyl 4-methoxyphenyliminoacetate did not lead to the desired β-lactam. See also ref. 16.

‡ For a recent study on the reaction of α-iminoesters with organometallic compounds, see ref. 9.



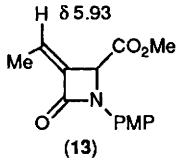
Scheme 1. *Reagents and conditions*: i, $(PhMe_2Si)_2CuCNLi_2$, tetrahydrofuran (THF), 0 °C, 20 min; ii, THF, 0 → 20 °C, 3 h; iii, HBF_4·Et_2O, CH_2Cl_2, 0 °C → room temp., 20 h; iv, $MeCO_3H$ (32%), NEt_3, room temp., 3 h; v, NDC, CH_2Cl_2, room temp., 8 h, vi, $NaBH_4$, MeOH, 0 °C, 10 min; vii, PPh_3, diethyl azodicarboxylate (DEAD), HCO_2H, 0 → 25 °C, 1.5 h, then MeOH, HCl, 25 °C, 1 h; viii, ref. 16. PMP = *p*-methoxyphenyl.

Table 1. Preparation of β-lactams (**15**)—(**17**).[a]

			^{1}H NMR data[d]			
			trans		*cis*	
Compound[b]	Yield (%)[c]	*trans* : *cis*	$J_{1',3}$	$J_{3,4}$	$J_{1',3}$	$J_{3,4}$
(**15**)	77	85 : 15	10.5	2.4	13.5	5.7
(**16**)	80	92 : 8	10.2	2.4	13.4	5.5
(**17**)	85	100 : 0	—	2.5	—	—

[a] Reactions conducted on a 10 mmol scale by addition of the cuprate to the α,β-unsaturated ester at 0 °C. [b] All compounds are racemic and were characterized by their physical and analytical data. [c] Yields based on weight of product isolated by column chromatography. [d] Determined by 300 MHz NMR spectroscopy; *J* values in Hz.

silylcuprate reagent to methyl crotonate[2] (**5**), followed by trapping of the *in situ*-generated enolate (**6**) by the iminoester (**7**) (molar ratio 1.5 : 1) in tetrahydrofuran as solvent, afforded the β-lactam (**8**) in 80% yield as the single diastereoisomer [δ 3.34 (dd, 3-H, $J_{1',3}$ 5.1, $J_{3,4}$ 2.4 Hz) and 4.16 (d, 4-H, $J_{3,4}$ 2.4 Hz)]. Conversion of the β-lactam (**8**) into the (±)-thienamycin building block (**10**) was easily accomplished in two steps. Accordingly, reaction between (**8**) and HBF_4·Et_2O followed by peracetic acid oxidation of the resulting fluoride (**9**) afforded (1'*S**,3*R**,4*S**)-3-(1-hydroxyethyl)-4-methoxycarbonyl-1-(4-methoxyphenyl)azetidin-2-one (**10**) in 90% overall yield [δ 3.39 (dd, 3-H, $J_{1',3}$ 5.4, $J_{3,4}$ 2.4 Hz) and 4.43 (d, 4-H, $J_{3,4}$ 2.4 Hz)]. We assigned the relative stereochemistry between C-1' and C-3 in two ways. First, oxidation of (**10**) by 3-carboxypyridinium dichromate (NDC reagent)[13] followed by sodium borohydride reduction of the resulting methylketone (**11**) afforded a mixture of the 1'-hydroxyethyl compound (**10**) and its epimer (**12**) in a 60 : 40 ratio. The ^{1}H NMR spectrum [δ 3.35 (dd, 3-H, $J_{1',3}$ 4.1, $J_{3,4}$ 2.7 Hz) and 4.60 (d, 4-H, $J_{3,4}$ 2.7 Hz)] of the 1'*R**-isomer showed a smaller coupling constant for 1-H and 3-H.[14] Alternatively, epimerisation at C-1 was successfully accomplished by the Mitsunobu reaction,[15] using formic acid as the nucleophile, to afford the corresponding formate of (**12**), which, upon acid hydrolysis,[16]



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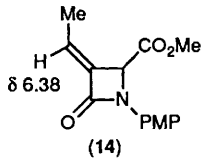

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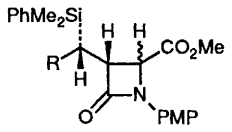
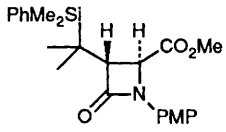


(15) R = Ph
(16) R = 4-MeC$_6$H$_4$



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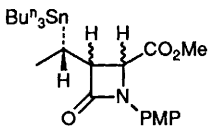

(18)

furnished the desired hydroxy compound in nearly quantitative yield. Conversion of both epimers (**10**) and (**12**) into their corresponding methanesulphonates and further stereospecific elimination[17] provided the respective *Z*-(**13**) and *E*-(**14**) alkenes, thus confirming unambiguously the above stereochemical assignment. Since both N-1 and C-4 groups in the β-lactam (**12**) can be easily elaborated to the β-lactam (**2**), our procedure constitutes a highly stereoselective formal synthesis of (±)-thieneamycin.

In order to determine the scope of the stereoselectivity of the reaction, we extended the method to other α,β-unsaturated esters and the results are summarized in Table 1. As can be seen, apart from the good yields obtained, the high degree of stereoselectivity seems to be the most important feature of the reaction. Further application of the present organocopper –enolate methodology is shown in the tributylstannylcuprate[18] addition to methyl crotonate (**5**) and enolate trapping by the iminoester (**7**) to give the corresponding stannyl β-lactams (**18**) in 65% yield, as a mixture of *cis–trans*-isomers at the 3- and 4-positions of the β-lactam ring in a 40:60 ratio.§

From the results reported here,¶ the methodology developed could be readily extended to other synthetic applications in the β-lactam field and, consequently, in the chemistry that employs β-lactams as starting materials.

§ Although we have not assigned the relative configuration at C-3, the ^{1}H NMR spectra showed a $J_{1',3}$ 10.5 Hz and $J_{1',3}$ 3.9 Hz for the *trans*- and *cis*-isomers respectively.

¶ All compounds prepared in this work are racemic, only one diastereoisomer is drawn.

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