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Alkyl Groups on the Metal Enhance the Reactivity of the "Classical" Zirconium Enolate of 1-Methoxycyclohexanone

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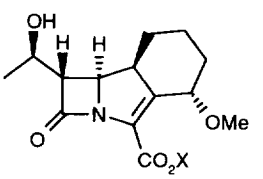
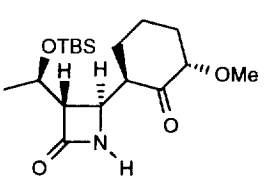
Abstract: Compound **2** is the key intermediate in the preparation of our lead trinem antibiotic sanfetrinem **1a**. In this communication it is described how a modified "Evans" zirconium enolate of 1-methoxycyclohexanone is able to react with azetidinone **3** in the presence of LiHMDS under strict kinetic conditions, giving **2** with good yield and selectivity. Copyright © 1996 Elsevier Science Ltd

The emergence of bacterial strains that are resistant to standard chemotherapeutic agents provides a constant driving force for the discovery and development of novel antibacterial compounds. β-Lactams form a large class of therapeutically significant drugs widely used for their high potency, breadth of antibacterial spectrum and superior safety profile.[1]

We recently reported on the trinems[2] as extremely potent antibacterial agents endowed with remarkable stability to β-lactamases. In particular, compound **1a** (GV104326) and its metabolically labile ester **1b** (GV118819) were selected for development studies due to their excellent microbiological profile.[3] Because of the length of the original route to compounds **1a,b**, a major effort was undertaken in order to identify a more convenient process applicable to their industrial preparation. Compound **2** was identified as the key intermediate *en route* to **1a,b**, and its one step synthesis from commercially available 3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-4-acetoxy-azetidin-2-one[4] **3** and (2S)-2-methoxycyclohexanone studied in detail.



1a X=Na
1b X=OCH(Me)OC(O)OCyHex



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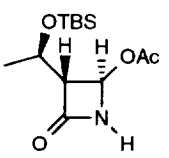
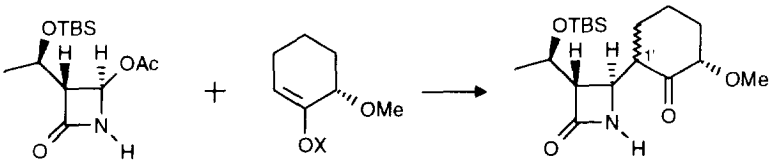


3

Figure 1

The substitution reaction of the C-4 acetoxy group in azetidinone **3** by nucleophiles has been extensively used in the preparation of several penem and carbapenem antibiotics.[5] The reaction occurs under both acidic and basic conditions via an elimination-addition process that goes through the intermediacy of either an acyliminium or acylimine species respectively.[6] The bulk of the substituent at C-3 directs the approach of the nucleophile from the less-hindered *re* face of the planar and reactive intermediate, whereas the stereochemistry at the newly generated C-1' stereogenic center has been found to depend upon the nature of the enolate, its geometry, the nature of the counterion and the reaction conditions.[7] In our particular case, following examples from aldol chemistry, the counterion of the enolate and the reaction conditions must be chosen so that the coupling with **3** occurs in a *syn* selective manner. In this regard, Zr(IV) enolates are generally known to give good *syn* selectivities in classical aldol reactions irrespective of their initial configuration.[8] Furthermore, they have been shown to react with **3** in the presence of a suitable Lewis acid (i.e. through an acyliminium intermediate) with the desired selectivity,[9] although results from Endo[10] have shown that the same reaction could not be performed at low temperature in the absence of a Lewis acid (i.e. through an acylimine intermediate), possibly because a Zr enolate is not sufficiently reactive under these conditions.[11] In spite of these adverse precedents, it was decided to investigate the possibility of increasing the reactivity of the "classical" zirconium enolate of (2S)-2-methoxycyclohexanone **7a** either by modifying the nature of the ligands on the metal, or by adding to the reaction mixture an appropriate, non-nucleophilic base. The preliminary results we have obtained are the subject of the present communication.

It was known to us that the most commonly used lithium bases are not able to give with sufficient selectivity the desired regioisomeric enolate **6**.[12,13] The corresponding trimethylsilyl enol ether **5**, on the other hand, can be obtained from enantiomerically pure α-methoxycyclohexanone **4**[14] by a known procedure;[15] from **5**, the lithium enolate **6** was obtained by treatment with a slight excess of MeLi in THF at -10°C, and the desired Zr enolate **7a** by a second transmetallation with neat zirconocene dichloride at -78°C.[16]



3 | **5** X=TMS, **6** X=Li, **7a-d** X=Cp_2Zr-R | **2** C1'=β, **9** C1'=α

Scheme 1

The results obtained in the reaction of the different Zr enolates **7a-d** with **3** under different conditions are reported in Table 1, and shown in Scheme 1. No reaction was observed when two equivalents of the "classical" Zr enolate **7a** were reacted with **3** in the temperature range between -78°C and 0°C (Table 1, entry 1), whereas at higher temperature complete decomposition was observed. This is in full agreement with results previously reported by Endo.[10] The observation that the reaction did not proceed to any extent even in the presence of one equivalent of LHMDS (used in order to activate **3**) (Table 1, entry 2) clearly showed that the enolate itself

was not sufficiently reactive, and therefore it was decided to modify its reactivity by replacing the chlorine atom on the metal center with a more electron releasing alkyl group.

At first this was done prior to formation of the enolate. Thus, hydrozirconation of 1-hexene with Schwartz' reagent Cp_2ZrHCl gave $Cp_2Zr(Hex)Cl$, which was in turn reacted with **6** to give **7b** (R=Hex) (Method A).[17,18] This novel enolate alone showed a notable increase in reactivity (Table 1, entry 3), affording **2** in 25% yield after 4 hours at -78°C. When the reaction was repeated in the presence of one equivalent of LHMDS (Table 1, entry 4), **2** was obtained in 42% yield, and with a good selectivity (85:15) over the undesired stereoisomer **9**.

A simpler, one-pot procedure was next devised, whereby the "classical" enolate **7a** was treated at -78°C with n-BuLi for 1 hour prior to addition of **3** and LHMDS (Method B).[19,20] As entry 5 (Table 1) shows, the enolate **7c** (R=n-Bu) obtained by this procedure behaved similarly to the one prepared by Method A, giving **2** with the same selectivity and comparable yield (46%). However, when MeLi was used instead of n-BuLi (Table 1, entry 6), no unreacted **3** was recovered after 6 h and the isolated yield of **2** increased to 60%. Thus, substitution of the chlorine atom in **7a** with a small, electron-releasing methyl group sharply increases the overall reactivity of the enolate: this, together with the use of LHMDS for the activation of **3**, leads to **2** in good yield and selectivity.

With this simple procedure we have for the first time succeeded in reacting a zirconium enolate with **3** at low temperature and in the absence of Lewis acid catalysts. Further studies are needed in order to identify the mechanism of this complex reaction, where formation of an "ate" complex between the base and the enolate most certainly plays a major role.[21]

Table 1

Entry	Base (eq.)	Enolate 7a-d	Rxn time (Temp)	Isolated Yield of (2)	d.r. 2:9 (a)
1	none	**7a** R=Cl	3 h (-78°C+0°C)	No Reaction	
2	$LiN(Me_3Si)_2$ (1)	**7a** R=Cl	4 h (-78°C)	No Reaction	
3	none	**7b** R=Hex (b)	4 h (-78°C)	25%	N.D.
4	$LiN(Me_3Si)_2$ (1)	**7b** R=Hex (b)	6 h (-78°C)	42% (d)	86:14
5	$LiN(Me_3Si)_2$ (1)	**7c** R=Bu (c)	6 h (-78°C)	46% (d)	85:15
6	$LiN(Me_3Si)_2$ (1)	**7d** R=Me (c)	6 h (-78°C)	60%	86:14

(a) The diastereomeric ratio (d.r.) was calculated by NMR analysis of the crude mixture.
(b) Enolate prepared by route A.
(c) Enolate prepared by route B.
(d) 10% of unreacted **3** was recovered

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16. Since we never observed products derived from attack of the regioisomeric enolate onto azetidinone **3**, we assume that both transmetallations proceed with retention of configuration of the enolate.
17. **Method A**. In a pear-shaped flask, **10** (175 µl, 1.4 mmol) was dissolved in dry THF (7 ml) and treated for min with neat $Cp_2Zr(Cl)H$ (360 mg, 1.4 mmol). The resulting yellow solution was added at -78°C to a round-bottomed flask where **5** (120 mg, 1.4 mmol) in THF (8 ml) had been treated at -10°C with MeLi (1.4 mmol, 1 ml) for 15 min. The mixture was stirred for 1 hr, then neat **3** (200 mg, 0.7 mmol) followed by the appropriate amount of base were added, as indicated in Table I. Quenching was done by pouring the mixture into 60 ml of a 1/1.5 mixture of 1M citric acid and CH_2Cl_2, stirring for a 20 min, separating the two phases and repeating the same operation twice with saturated NH_4Cl (20 ml). After standard crude isolation, pure **2** was isolated by column chromatography (Cyclohexane/Ethyl acetate 6/4).
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20. **Method B**. A solution of **5** (476 mg, 2.8 mmol) in THF (30 ml) was treated at -10°C with MeLi (2.8 eq, 2 ml) for 15 min. After cooling to -78°C neat zirconocene dichloride (820 mg, 2.8 mmol) was added and stirring continued for 1 h. MeLi (2.8 eq, 2 ml) was then added very slowly so that the temperature of the solution never increased above -65°C; after stirring for 1h, neat **3** (400 mg, 1.4 mmol) followed by the appropriate amount of base were added, as indicated in Table I. For quenching and workup see ref 17.
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