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The Use of Zinc Enolates in the Synthesis of a Key Intermediate for the Preparation of Trinem Antibiotics.

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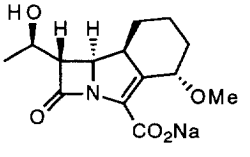
Abstract: The stereoselective preparation of **2a**, a key intermediate in the synthesis of the broad spectrum tricyclic β–lactam antibiotic GV104326 **1**, by the reaction of a zinc enolate derived from chiral non-racemic 2-methoxycyclohexanone with azetidinone **3** is described. Copyright © 1996 Elsevier 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 anti-bacterial compounds. β-lactam based agents form a large class of therapeutically significant drugs. Recently, a novel tricyclic compound **1** (GV104326) was described by these laboratories as a potent broad spectrum antibacterial agent.[1]



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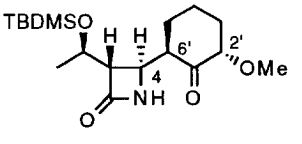
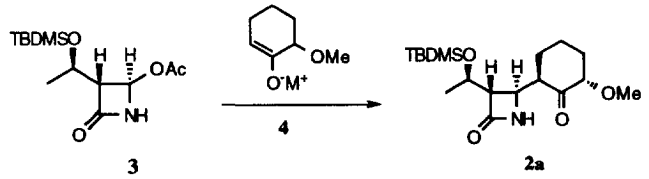


2a (2'*S*, 6'*R*) (shown); 2b (2'*R*, 6'*S*)
2c (2'*S*, 6'*S*); 2d (2'*R*, 6'*R*)

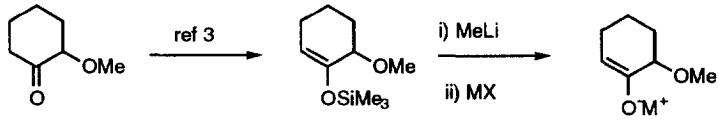
In order to further assess the potential of this molecule, it was necessary to define a route capable of giving a high degree of stereochemical control in the construction of the asymmetric carbon framework. Compound **2a** was identified as the key intermediate required for the large scale preparation of **1** and in this context the synthesis of **2a** was studied in detail.

The key reaction in the synthesis of **2a** is the stereospecific construction of the C4-C6' bond *via* the reaction of azetidinone **3** and an enolate **4** (Scheme 1); a reaction which must proceed with *syn* relative stereochemistry across the C-4 - C-6' bond in order to obtain the desired isomer.



Scheme 1

The direct formation of lithium enolate **7** by deprotonation of methoxycyclohexanone **5** using bulky lithium amide bases is not a sufficiently regioselective process and considerable amounts of the thermodynamic isomer are formed.[2] This problem has been circumvented in the preparation of GV104326 by the use of silyl enol ether **6** which is available in regiochemically pure form[3] and which reacts with the N-TMS derivative of **3** in the presence of tin tetrachloride to give good yields of the condensation product.[4] The same silyl enol ether also serves as a source of regiochemically pure lithium enolate **7** by reaction with methyl lithium[5] and of other enolates by subsequent transmetallation of **7**.



5

6 (*rac*)
6a (6*S*)

7 M = Li
8a M = ZnCl; **8b** M = ZnBr
8c M = ZnMe; **8d** M = ZnBu

Scheme 2

It is known from the literature that azetidinone **3** will react with Reformatsky reagents derived from ethyl α-bromopropionyl-oxazolidinones to give very good yields of condensation products in a highly *syn* selective reaction.[6] We decided to study the reactions of **3** with zinc enolates derived from the methoxyketone **5** based on the *syn* selectivity observed by Ito. The required zinc enolates were prepared by transmetallation of the lithium enolate **7** as outlined in scheme 2. Enolate **7** was converted to the zinc enolate at 0°C with a solution of zinc halide or alkyl zinc halide.[7] Initially, we used racemic silyl enol ether **6** in order to determine the gross diastereoselectivity of the reaction. The results of these studies are collected in **Table 1**.

Table 1

Entry	enolate M	time	ratio of 2a:2b:2c:2d[a]	Overall yield[b]
1	ZnCl	6h	6.4:5.4:1:1.6	27%
2[c]	ZnCl	1h	6.7:7:1:2.3	37%
3	ZnMe	45'	6.3:3.5:1:2.2	65%

a) ratio of **2a**:**2b**:**2c**:**2d** was measured by high field NMR; b) overall yield = yield of **2a** and **2b** measured by HPLC (see note 10) + yield of other isomers calculated from the NMR ratio; c) reaction carried out at room temperature; for general experimental procedure see note 10

It was found that 1.8 equivalents of the racemic chlorozinc enolate **8a** reacted with azetidinone **3** to give a low overall yield of condensation products with a selectivity of approximately 6:1 in favour of **2a** and **2b**. Better results were obtained with the more reactive methyl zinc enolate (entry 3). Once the favourable overall preference for *trans* isomers across the cyclohexane ring had been demonstrated, the reaction was carried out with chiral zinc enolates derived from (6*S*)-**6a**.[8] The results of the reactions of these zinc enolates are collected in **Table 2**.

Table 2

Entry	enolate M	time	ratio of 2a:2c[a]	yield of 2a[b]
1	ZnCl	6h	8:1	24%
2	ZnBr	o.n.	6.9:1	55%
3[c]	ZnBr	<5'	7:1	69%
4	ZnBu	60'	3.3:1	46%

a) ratio of 2a:2c measured by high field NMR; b) yield of **2a** measured by HPLC analysis of crude product of reaction (note 10); c) reaction carried out at room temperature with 2.6 equivalents of enolate.

Again the chloro zinc enolate (2'S)-**8a** gave a low yield in its reaction with **3** whereas the bromozinc and the butyl zinc species gave much better results. The overall yield of the reaction was further improved by using 2.6 equivalents of bromozinc enolate **8b** with respect to **3** (entry 3). No isomerization appeared to occur under the conditions of the reaction since the isomers **2b** and **2d** were not observed by NMR when (6*S*)-**6a** was used.

The presence of amide bases in the reactions of lithium enolates has been reported to exert an effect on the stereochemical course of such reactions[9] therefore we looked at the possibility of influencing the selectivity and the reactivity of these zinc enolates by adding the amide bases LDA or LHMDS. The results of these studies are collected in **Table 3**.

Table 3

Entry	silyl enol ether	M	amide base (eq)	time	ratio of 2a:2b:2c:2d[a]	Overall yield[b]
1	**6**	ZnCl	LDA (1.0)	120'	4.4:4.4:1:1	42%
2	**6a**	ZnCl	LHMDS (1.0)	80'	6:-:1:-	40%
3	**6a**	ZnCl	LHMDS (2.0)	20'	1.7:-:1:-	60%
4	**6a**	ZnMe	LHMDS (1.0)	<5'	3:-:1:-	67%
5	**6**	ZnBu	LHMDS (1.0)	<5'	3.4:3.7:1:1	68%

a), b) for footnotes see table 1

The use of LDA in the presence of enolate **8a** (entry 1) increased the rate of reaction and gave an improvement in the yield but reduced the selectivity to 4:1 (entry 1) whereas 1 equivalent of LHMDS with respect to the azetidinone increased the reaction rate but did not appear to greatly affect the selectivity.

Increasing the amount of LHMDS to 2 equivalents with respect to **3** led to a loss of selectivity (entry 3) although the overall conversion was higher. In general, a loss of selectivity was observed when the alkyl zinc enolates were used in conjunction with 1 equivalent of LHMDS, although the reactions appeared to be much faster in these cases.

The mechanism of the activation of **3** in this reaction remains unclear although we found that it was unstable in the presence of LHMDS alone at $0^{o}C$ and this leads us to suspect the involvement of complex aggregates between the base and the enolate.

In summary, the condensation reaction between a zinc enolate derived from methoxycyclohexanone and azetidinone **3** appears to be stereoconvergent in that the reaction of the racemic enolate with chiral non-racemic **3** favours the formation of **2a** and **2b** in approximately equal quantities over formation of the other diastereomers. The same reaction carried out with the (6*S*)-enolate gives desired product **2a** and smaller amounts of unwanted **2c**, the ratio between the two being maintained.

References and Notes

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10. *General experimental procedure exemplified for entry 2, table 2*: Methyl lithium (1.1ml of a 1.6M solution in Et_2O) was added slowly to a stirred solution of (6*S*)-methoxycyclohexanone (0.41g, 0.42ml, 2.0mmol) in dry THF (4ml) at $0^{o}C$ under N_2. The mixture was stirred for 15' after which time a solution of $ZnBr_2$ (0.453g, 2.0mmol) in THF (3ml) was added. The mixture was stirred for a further 10' prior to the addition of THF (4ml) and **3** (0.275g, 0.96mmol). When no **3** remained (TLC: 2:1 cyclohexane: ethyl acetate) the mixture was poured into a saturated solution of NH_4Cl (10ml) and extracted into ethyl acetate (50ml). The organic layer was dried over Na_2SO_4 and the solvent removed to give a crude residue which was assayed for **2a** by HPLC (Hypersil ODS2 (25x 0.40cm) x 5μm; $(NH_4)H_2PO_4$ 50mM / acetonitrile 45/55 %v/v; 1.0mlmin^{-1} /UV detection 205nm) (external standard); 55% and for the ratio of **2a**:**2c** by NMR (6:1). NMR data: Marchioro, C., *et al.*, *Mag. Chem. Res.*, submitted.

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