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THE STEREOSELECTIVE SYNTHESIS OF A KEY INTERMEDIATE OF THE TRINEM ANTIBIOTIC SANFETRINEM

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Abstract: By modulating the reactivity of the Lewis acid promoter it was possible to obtain, in a single stereoselective condensation step, the methoxyketone **7**, an advanced intermediate in the synthesis of Sanfetrinem GV104326.

Recently, the trinem antibiotic Sanfetrinem GV104326 **1** (the trinem antibiotics were formerly referred to as tribactams) and its orally active ester pro-drug GV118189 **2** (**Fig. 1**) have been the subject of considerable study[1] due to their broad spectrum antibacterial activity, resistance to β-lactamases and stability to renal dehydropeptidases, a potential problem for the penem and carbapenem classes of antibiotics.

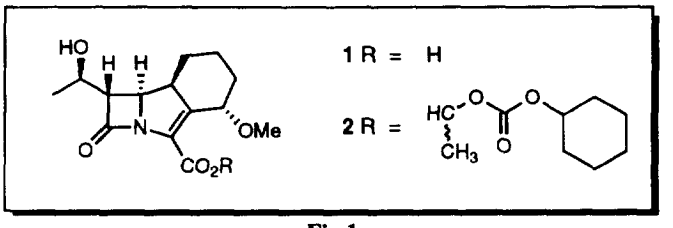
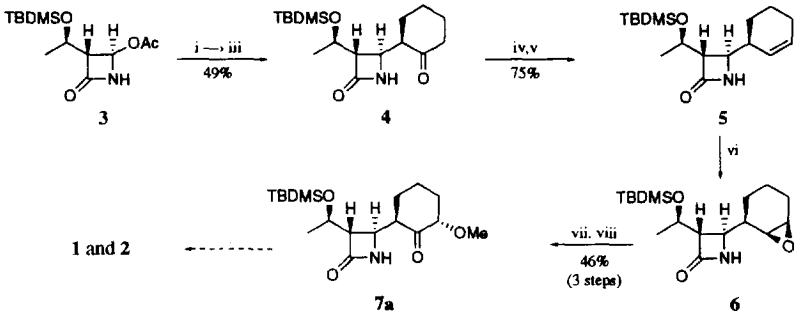


Fig 1

The abovementioned compounds, and other members of this class, also represent a considerable synthetic challenge.[2] One of the earliest routes to compounds **1** and **2**, used to make multi-kilogram quantities, is outlined in **Scheme 1**.

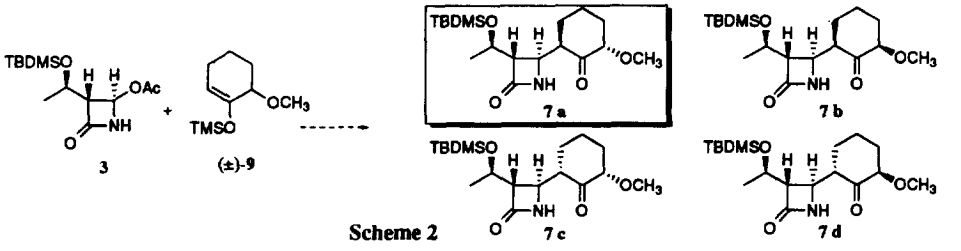


i. TMSCl, Et_3N, MeCN. ii. 1-trimethylsilyloxycyclohexene, TMSOTf, MeCN. iii. KF, MeOH. iv. $TsNHNH_2$. v. LDA, THF. vi. Mg-monoperoxyphthalate, CH_2Cl_2. vii. MeOH, PTSA. viii. Py/SO_3.

Scheme 1

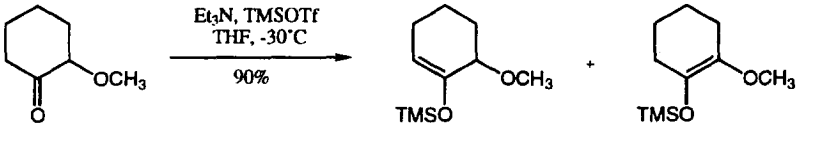
There are, however, drawbacks to this strategy, in particular the number of steps involved and the unsatisfactory yield and selectivity of the first sequence to the ketone **4**. We have recently described our work aimed at synthesising the olefin **5** in a single step from compound **3** either by using cyclohexenylboranes[2a] or an intramolecular Sakurai reaction.[2b]

We wish to report in this Letter work carried out in our laboratories on the single-step synthesis of methoxyketone **7a** by direct condensation of compound **3** with the silyl enol ether **9** of 2-methoxycyclohexanone **8**.[3] This latter route removes seven steps from the original synthesis, but poses the question of stereocontrol over the three stereogenic centres introduced onto the β-lactam nucleus. Assuming that the incoming nucleophile enters *trans* to the bulky substituent at the 3-position,[4] with racemic silyl enol ether (±)-**9** four isomers of compound **7** could be produced in the condensation reaction, as outlined in **Scheme 2**.



Scheme 2

In order to study the direct condensation reaction it was necessary to prepare the corresponding trimethylsilyl enol ether of 2-methoxycyclohexanone **8**. The reaction of 2-methoxycyclohexanone **8** with a base and silylating agent can provide both the desired "kinetic" product **9** and the "thermodynamic" regioisomer **10**. We found that deprotonation of ketone **8** with lithium 2,2,6,6-tetramethylpiperidide, quenching with TMSCl at -78°C gave a disappointing 2.5 : 1 ratio of isomers **9** and **10** in 48% yield.[5] However, an adaptation of a procedure employed for a similar substrate, using a combination of triethylamine and trimethylsilyl triflate,[6] gave a high yield of the desired isomer **9** with no traces of compound **10** detectable in the crude mixture by high field NMR. At the conclusion of the reaction, the solution was diluted with hexanes, causing precipitation of the triflate salts as an oil. The upper hexane phase was passed through a pad of alumina, eluting with further hexane, and the fractions containing the silyl enol ether **9** collected. (**Scheme 3**)

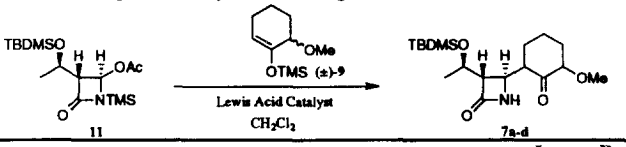


8 **9** **10**

Scheme 3 Ratio **9** : **10** = >20 : <1

In order to eliminate the possibility of closed transition states in the condensation reaction of silyl enol ether **9** with acetoxyazetidinone **3**, involving the azetidinone nitrogen, which would lead to isomers **7c** and **7d**, it was decided to protect the nitrogen with a trimethylsilyl group giving compound **11**.[7] To prevent the formation of isomers **7b** and **7d** it would simply be necessary to carry out the condensation reaction with optically pure silyl enol ether **9**. However, in the initial

catalyst screening phases of the study we carried out the reaction using the more readily available racemic **9**. The results of this preliminary screen are given in **Table 1**.

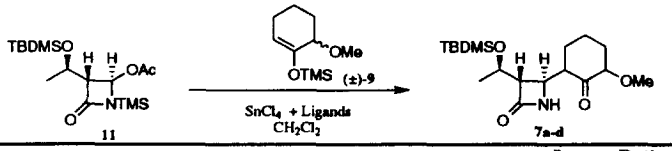


Entry	Catalyst (eq)	Temp (°C)	Time (h)	Yield*	Isomer Ratio 7a	7b	7c	7d
1	TMSOTf	0	5	51%	1.5	4	2	1
2	$ZnCl_2$	0 to 23	27	60%	1.7	1.7	1	3.3
3	$TiCl_4$	0 to 5	2.5	dec	-	-	-	-
4	$TiCl(O^iPr)_3$	0 to 5	3	dec	-	-	-	-
5	$CeCl_3$	23	24	n. r.	-	-	-	-
6	$SnCl_4{\cdot}2Et_2O$	0 to 5	1	30%	1.5	n.d.	n.d.	1
7	$SnCl_4{\cdot}2Et_2O$	23	0.16	45%	1.5	n.d.	n.d.	1

dec = decomposition, n.r. = no reaction observed, n.d. = not detectable by high field NMR of crude reaction mixture * The yields quoted are combined isolated yields of all isomers.

Table 1

With both trimethylsilyl triflate and zinc chloride as catalysts (**Entries 1** and **2**) we obtained encouraging global yields but the stereoselectivity was poor. Titanium tetrachloride and titanium chlorotriisopropoxide (**Entries 3** and **4**) caused extensive degradation of the starting materials whereas cerium trichloride failed to promote the reaction to any appreciable extent. A considerable improvement in stereoselectivity was observed with tin tetrachloride etherate, and by carrying out the reaction at room temperature we were able to increase the yield to 45%. However, the reaction was virtually instantaneous. In order to modulate the reactivity of the tin tetrachloride we studied the effect of varying the Lewis base ligands.[8] A summary of the results is given in **Table 2**.



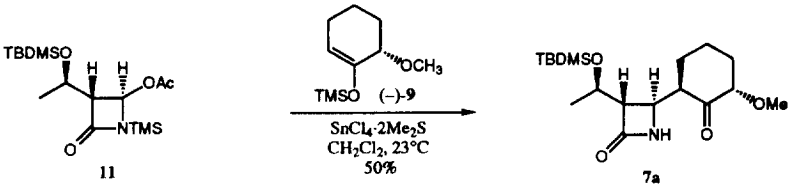
Entry	$SnCl_4$ + 2 eq of	Eq. of cat.	Temp (°C)	Time (h)	Yield	Isomer Ratio 7a	7b	7c	7d
1	Et_2O	1.5	23	0.16	45%	1.5	n.d.	n.d.	1
2	THF	2	23	2	30%	3	1	n.d.	3
3	1,4-dioxane	2	23	3	39%	1	n.d.	n.d.	1
4	MeCN	2	0 to 23	3	31%	1	n.d.	n.d.	1
5	$^iPr_2NEt$	2	23	12	40%	1.5	n.d.	n.d.	1
6	Et_3N	2	23	n.r.	0	-	-	-	-
7	DMSO	2	23	n.r.	0	-	-	-	-
8	Me_2S	2	23	2	50%	1	n.d.	n.d.	1
9	Et_2S	2	23	0.3	40%	1	n.d.	n.d.	1
10	$^iPr_2S$	2	23	0.3	45%	1.5	1	traces	1.5

dec = decomposition, n.r. = no reaction observed, n.d. = not detectable by high field NMR of crude reaction mixture * The yields quoted are combined isolated yields of all isomers.

Table 2

In changing the tin tetrachloride ligands from diethyl ether to tetrahydrofuran we were able to observe a clear increase in reaction time (**Table 2, Entries 1** and **2**). However, this improvement was accompanied by a fall in both yield and stereoselectivity. With 1,4-dioxane and acetonitrile (**Entries 3** and **4**) we were able to recover the stereoselectivity but the yields were not acceptable. Diisopropylethylamine (**Entry 5**) significantly suppressed the reactivity of the tin tetrachloride, the reaction needing 12 hours to go to completion. Despite the unsatisfactory yield of 40% we observed an interesting, if not necessarily useful, selectivity between the desired isomer **7a** and **7d**. More nucleophilic ligands such as triethylamine and dimethylsulphoxide (**Entries 6** and **7**) caused complete inhibition of the reaction. We then screened a series of dialkyl sulphides as potential ligands. The most promising in terms of yield, reaction time and stereoselectivity, being dimethylsulphide (**Entry 8**).

This system was then studied using enantiomerically pure silyl enol ether **9** prepared from (*S*)-(–)-2-methoxycyclohexanone (–)-**8**. Compound (–)-**8** was prepared in large scale *via* the enzymatic resolution of (±)-*trans*-2-methoxycyclohexanol[9] and subsequent Swern oxidation. Conversion to the silyl enol ether (–)-**9** was achieved as shown in **Scheme 3** without detectable racemisation. Using optically active (–)-**9** it was possible to obtain, in a single step, the methoxyketone **7a** with a yield of 50% and with high diastereoselectivity (**Scheme 4**). Further work on the optimisation of this reaction will be published in due course.



Scheme 4

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References and Notes

1. Di Modugno, E; Erbetti, I.; Ferrari. L; Galassi, G; Hammond, S.H.; Xerri, L.; *Antimicrob. Agents Chemother.*, **1994**, *38*, 2362.
2. For the most recent references to the synthesis of trinem GV104326 see: a) Rossi, T., Biondi, S., Contini, S., Thomas, R. J. and Marchioro C.; *J. Am. Chem. Soc.*, **1995**, *117*, 9604. b) Bismara, C., Donati, D., Di Fabio, R., Rossi, T., and Thomas, R. J.; *Tetrahedron Lett.*, **1995**, *36*, 4283.
3. Part of this work was presented in a poster at the OMCOS8 conference, Santa Barbara, California, August 1995.
4. The only reported example of a *C*-nucleophile entering *cis*- to the hydroxyethyl side chain of compound **3** is given in reference 2a.
5. For the formation of compound **10** using LDA and TMSCl see Kowalski, C., Creary, X., Rollin, A. J. and Burke, C. M.; *J. Org. Chem.*, **1978**, *43*, 2601.
6. Rossi, L. and Pecunioso, A.;*Tetrahedron Lett.* **1994**, *35*, 5285.
7. Initial experiments also indicated that under these conditions significantly improved yields and selectivity in the condensation were obtained with the *N*-TMS protected **11** with respect to both the unprotected **3** and the *N*-TBDMS derivative.
8. In a further preliminary experiment we noted that under these conditions using tin tetrachloride without ligands an extremely rapid reaction occured with a low yield of the desired compound **7a**.
9. Stead, P., Rossi, T., Roberts, S. M. *et al.*, forthcoming publication.

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