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The Stereoselective Synthesis of 4-Formyltrinem, a Key Intermediate for Novel Trinems

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Abstract: The stereoselective synthesis of a protected 4-formyltrinem **8** was accomplished in good yield. This compound is a potential intermediate in the synthesis of a wide range of 4-alkyl and alkenyl substituted trinem antibiotics, as evidenced by its reaction with a series of phosphoranes and phosphonates. © 1997 Elsevier Science Ltd.

Recently, the trinem antibiotics have been the subject of considerable study owing 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. Currently, the (4*S*)-methoxytrinem sanfetrinem **1**, and its orally active ester pro-drug sanfetrinem cilexetil **2** (**Fig. 1**) are in Phase II clinical trials.[1] The challenge of synthesising sanfetrinem on a large-scale with high stereoselectivity continues to attract the attention of several research groups.[2]

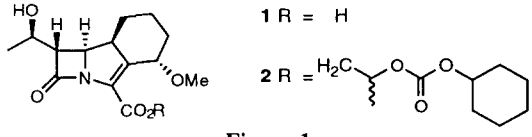
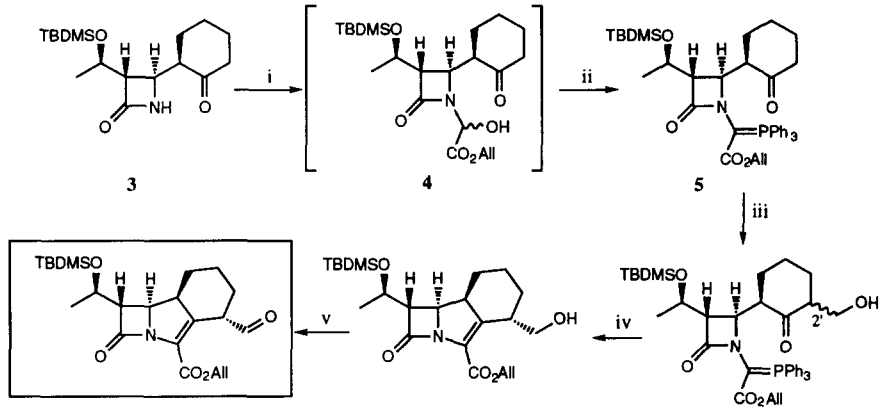


Figure 1

Following the very promising results obtained with sanfetrinem, research programmes have focused on the synthesis of other 4α- substituted trinems, such as 4-alkoxy,[3] 4-fluoro[4] and various 4-amino[5] systems, as well as derivatives having a 5-membered third ring.[6] We wished also to study the biological activity of molecules bearing carbon substituents in the 4α-position, and therefore needed to synthesise, with high selectivity, a suitably advanced intermediate to facilitate the generation of a range of derivatives. The 4α-formyl derivative **8** was considered an ideal candidate for this role, as it should be possible to then further modify the aldehyde group to give a variety of analogues for biological evaluation.

We chose to start the synthesis of aldehyde **8** from the readily available cyclohexanone derivative **3**[2] (**Scheme 1**). We wished to first generate the stabilised phosphorane **5** before introducing the formyl equivalent, and then cyclise to the trinem nucleus. We hoped that the steric hindrance of the phosphorane substituent would influence the stereoselectivity of the subsequent addition to the formyl equivalent and also that in this way we could avoid the necessity of additional protection–deprotection sequences.

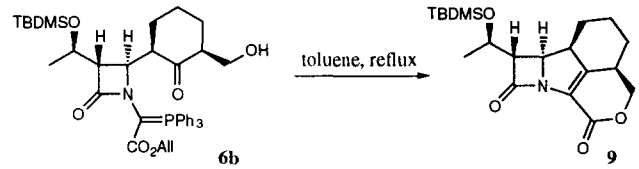


3 4 5

8 7 (and unreacted **6b**) **6a** (2'*R*), **6b** (2'*S*)

i) Allylglyoxylate (1.5eq), toluene, reflux; ii) CBr_4(2eq), PPh_3(3eq), 2,6-lutidine (2.5eq), toluene, room temp, 70%; iii) LHMDS (1.5eq), -78°C, then excess HCHO (*ca.* 0.47M in THF), -78°, 61%; iv) toluene, 80°C, 66% from mixture **6**; v) Swern oxidation, 89%

Scheme 1

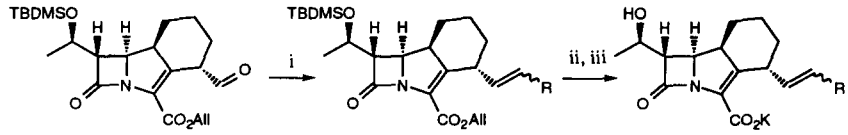


6b **9**

Scheme 2

The standard method of generating phosphoranes such as **5** involves first condensing compound **3** with allyl glyoxylate[7] under Dean and Stark conditions, chlorination of the resulting epimeric hemiaminals **4** with thionyl chloride and 2,6-lutidine and then treating the crude product with triphenylphosphine and 2,6-lutidine. Although this method has been successfully applied to the synthesis of phosphorane **5**, it suffers from some drawbacks. The hemiaminals are usually purified by column chromatography before the subsequent steps, and all traces of thionyl chloride must be removed following the chlorination of **4** before reaction with triphenylphosphine. The chloro derivatives are quite moisture sensitive and unstable, necessitating their immediate conversion to phosphorane **5**.

We therefore wished to develop an alternative, more practical procedure to be used in laboratory-scale preparations. Ideally the new procedure would be milder and avoid the manipulation of moisture-sensitive substrates. We reasoned that it should be possible to treat the hemiaminal mixture **4** with a carbon tetrabromide/triphenylphosphine system[8] to give a reactive bromide which would be directly converted into a phosphonium salt by carrying out the reaction in the presence of excess triphenylphosphine. Excess base present in the reaction would then generate the stable phosphorane. Thus having formed the hemiaminals, the toluene solution was cooled before adding triphenylphosphine, lutidine and carbon tetrabromide. After 45 minutes, the resulting brown suspension was filtered through Celite®, diluted with diethyl ether, washed sequentially with 1% HCl, saturated $NaHCO_3$ and saturated brine. After removal of the solvents and flash chromatography, the phosphorane **5** was obtained in good yield. This process is used routinely in our laboratories on a 50g scale.

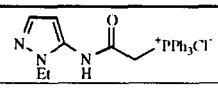
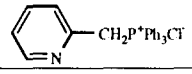
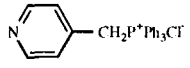
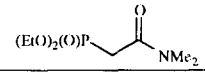
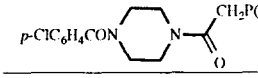
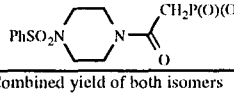


8 **12 a-h** **13 a-h**

i) $RCH_2P^+Ph_3Cl^-$ **10** or $RCH_2P(O)(OEt)_2$ **11**, base, see **Table**, ii) TBAF, AcOH, THF; iii) $Pd(Ph_3)_4$, K^+ 2-ethylhexanoate, THF

Scheme 3

Table Olefination Reactions of Aldehyde **8**

Reagent **10** or **11**(eq)		Base (eq)	Solvent	Temp.	Yield (%)
	**10a** (2)	DBU (2)	CH_2Cl_2	0°C to rt	**12a**(*E*), 75%
$Ph_3P^+CH_3Br^-$	**10b** (1.5)	^nBuLi (1.5)	THF	-78°C to rt.	**12b**, 90%
	**10c** (1.5)	DBU (1.5)	CH_2Cl_2	0°C to rt	**12c**(*E*), 29%
	**10d** (1.5)	DBU (1.5)	CH_2Cl_2	0°C to rt	**12d**(*E*)/**12e**(*Z*) 6/4, 10%*
		^nBuLi (1.5)	THF	-78°C to rt.	**12d**(*E*)/**12e**(*Z*) 6/4, 15%*
	**11a** (3)	LDA (3.7)	THF	-78°C to rt.	**12f**(*E*), 67%
	**11b** (3)	LDA (3.7)	THF	-78°C to rt.	**12g**(*E*), 65%
	**11c** (2)	LDA (2)	THF	-78°C to rt.	**12h**(*E*), 44%

* Combined yield of both isomers

It was then necessary to generate the enolate of phosphorane **5** and react it with a suitable electrophile. Despite the fact that it is possible to efficiently and selectively deprotonate the cyclohexanone ring of compound **5** with either LDA or LiHMDS, the resulting enolate proved to be quite unreactive towards ethyl chloroformate. However, the enolate could be quenched efficiently with monomeric anhydrous formaldehyde solution, readily prepared as a THF solution from α-poly(oxymethylene).[9] Thus, the epimeric alcohols **6a** and **6b** were obtained in 61% combined yield in *ca.* 8:2 ratio respectively. By heating the epimeric mixture **6** at 80°C in toluene, it was possible to selectively cyclise only the desired isomer **6a** to the corresponding protected trinem **7**, leaving the minor isomer **6b** unreacted. Attempts to cyclise **6b** at higher temperature led to the isolation of the tetracyclic lactone **9** (**Scheme 2**). We were pleased to observe that under simple Swern conditions, the desired aldehyde **8** was obtained in high yield on a gram scale. The aldehyde proved to be highly stable, and could be stored at low temperature indefinitely.

With a robust synthesis of the aldehyde **8** on a reasonable scale in hand, our next task was to explore its reactivity. We therefore selected a number of commercial, or readily available phosphoranes

or phosphonates to assess its ability to undergo Wittig or Horner-Emmons reactions,[10] and to then deprotect the resulting 4-alkenyltrinems as outlined in **Scheme 3.**

The results obtained in the Wittig or Horner-Emmons reactions are summarised in the **Table.** In most cases the yields obtained were satisfactory, although with the pyridylmethenyl phosphoranes **10c** and **10d** the yields were low.[11]

The 4-alkenyltrinems **12** were then deprotected to the target compounds **13** by standard methods.[3] The antibacterial activities of the compounds synthesised in this study will be published elsewhere.

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References and Notes

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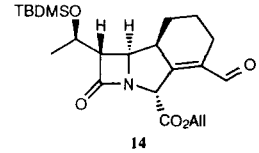
9. Rodriguez, L.; Lu, N.; Yang, N.-L., *Synlett,* **1990**, 227. Poly(oxymethylene) is sold by the Aldrich Chemical Co. Inc. Milwaukee, US.
10. The phosphoranes **10c** and **10d** were made according to; Carsky, P.; Huenig, S.; Stemmler, I.; Scheutzow, D., *Liebigs Ann. Chem.*, **1980**, *2*, 291. All other non-commercial phosphoranes were made from their corresponding chloro-derivatives and triphenylphosphine. All phosphonates were made under standard Arbuzov conditions.
11. In these cases the reactions were decidedly slower than the others studied, and significant amounts of the α,β-unsaturated aldehyde **14** were isolated, presumably formed through a competitive deprotonation–rearrangement.



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