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VINYLOGOUS vs ARYLOGOUS ISOCEPHEMS

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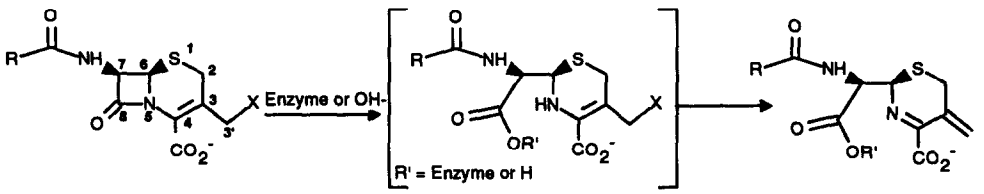
Abstract : The synthesis of 2-isocephems bearing multiple bonds between the thiazoline ring and the 3-substituent is reported. When a leaving group was present, the E-vinylogous derivatives were shown to be more active than the parent compounds, essentially against staphylococci. Insertion of an aryl group in this position, however, sharply reduces the activity against Gram-negative bacteria.

It has been shown earlier that chemical or enzymatic opening of the β-lactam ring is followed by the elimination of the 3' leaving group when it is present [1,2] (Scheme 1). The improved activity against enterobacteriaceae of cephalosporins of this type is thought to be a consequence of this mechanism. Structure activity studies of 2-isocephems [3] showed that the presence of a leaving group in the 3' position is even more important for achieving reasonable activities than in the cephem [4] series.

In the present paper we report our investigations on the effect of intercalating one or more multiple bonds between the position 3 of the isocephem nucleus and the 3' carbon bearing the leaving group.

Scheme 1

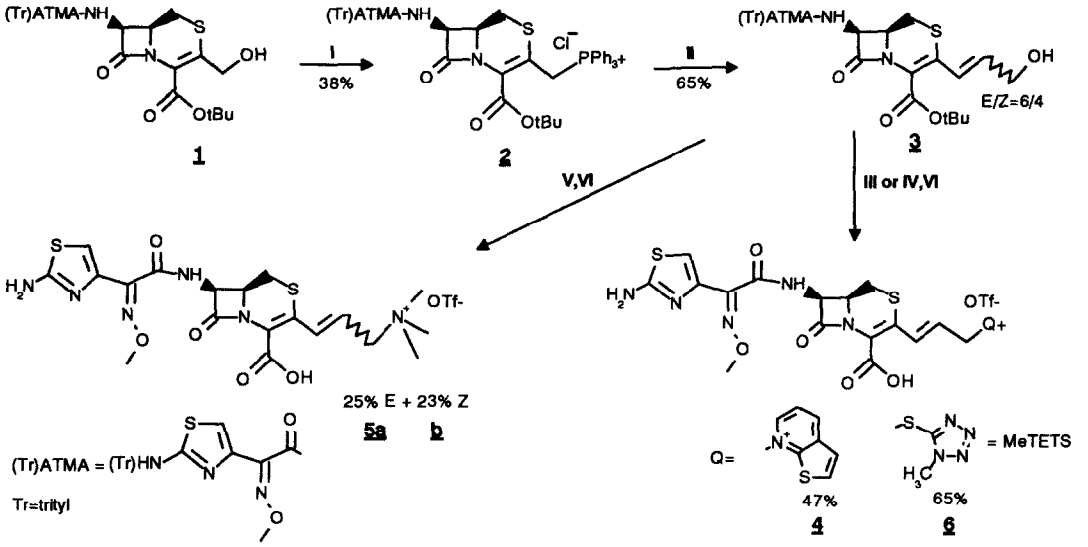


Most compounds were prepared by the Wittig reaction from readily available phosphonium salts (Scheme 2). Thus **2** was obtained from the 3'-hydroxymethyl derivative **1**[4] in two steps. Reaction with t-butyl-dimethylsilyloxy acetaldehyde in the presence of triethylamine led to **3** as a separable mixture of E and Z isomers. However for most purposes the mixture could be used without separation. When **3** was treated with trifluoromethanesulfonic anhydride in the presence of thienopyridine the quaternization was accompanied by an almost complete isomerization of the double bond, and after treatment with aqueous formic acid only the E isomer of **4** was isolated. When the thienopyridine was replaced by trimethylamine a faster reaction occurred,

and no isomerization of the double bond was observed. The two isomeric trimethylammonium salts could be separated by chromatography to give **5a** and **5b** respectively after final deprotection.

The use of tetrabutylammonium iodide in the presence of 2,6-lutidine led to the formation of the 3-iodo derivative which was transformed *in situ* to the tetrazolylthio analogue. Formic acid treatment afforded **6.**

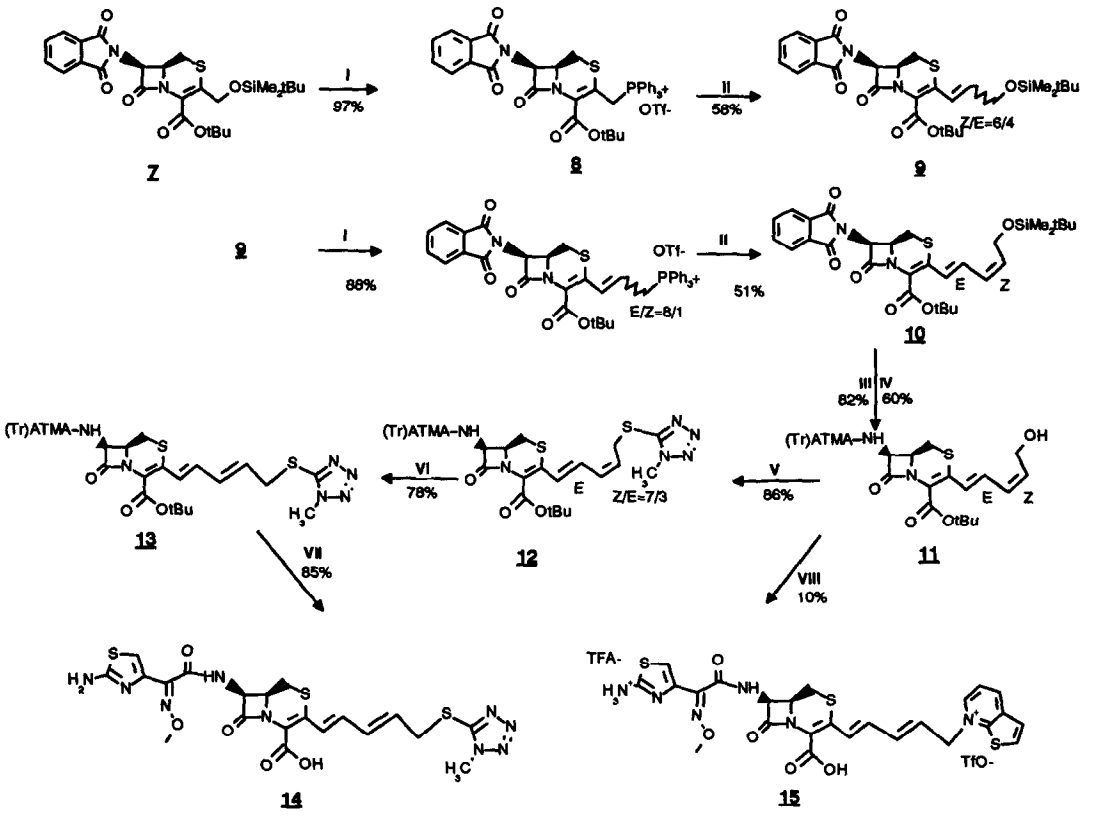
Scheme 2



I: 1, $SOCl_2$, pyridine, 2, Ph_3P, SiO_2; II: $Me_2tBuSiOCH_2CHO$, Et_3N, CH_2Cl_2, 2, HCl acetone; III: Tf_2O, thienopyridine, CH_2Cl_2, -70°C; IV: 1, Tf_2O, 2,5-lutidine, (E-isomer of 3), Bu_4NI, CH_2Cl_2, -70°C, 2, MeTETSNa, DMF; V: Tf_2O, Me_3N, CH_2Cl_2, -70°C; VI: aq. HCO_2H, 50°C

Bis-vinylogous compounds were prepared from the phthalimido derivative **7** [5] (Scheme 3) by removal of the silyl protecting group followed by a one step transformation of the resulting alcohol to the phosphonium salt **8**. Reaction with t-butylsilyloxy acetaldehyde gave rise to **9** as a mixture of E and Z isomers. This compound was transformed by repeating this procedure to the double vinylogous compound **10** as a single isomer after chromatographic purification Removal of the phthalimido and silyl protecting groups followed by coupling with the (Tr)ATMA side-chain afforded alcohol **11**. Introduction of the N-methyl tetrazolyl function was achieved in a one pot reaction to yield **12** as an isomeric mixture which was further transformed to the E,E isomer **13** by iodine treatment. Deprotection in aqueous formic acid afforded the desired compound **14**. The coupling of **11** with thienopyridine was accompanied by a complete isomerisation of the Z double bond, and **15** was obtained as a TFA salt of a single isomer after treatment with trifluoroacetic acid.

Scheme 3

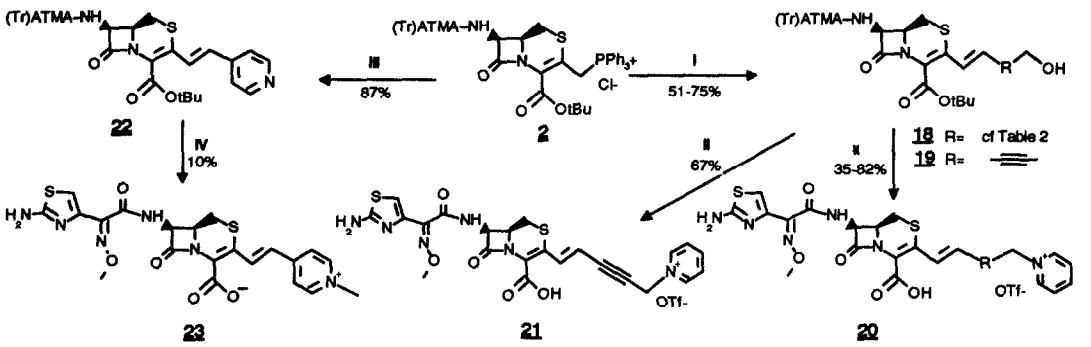


I: HF aq., MeCN, r.t., 2, Tf_2O, Ph_3P, CH_2Cl_2, -70°C; II: $Me_2tBuSiO$-CH_2-CHO, tBuOLi, THF, -70°C, III: 1, hydrazine hydrate, DMF, 2, HCl; IV: (Tr)ATMA-OH, TsCl, $NaHCO_3$, acetone, water; V: 1, Tf_2O, 2,5-lutidine, Bu_4NI, CH_2Cl_2, -70°C, 2, MeTETSNa, DMF; VI: I_2 cat., benzene; VII: aq. HCO_2H, 50°C; VIII: 1, Tf_2O, thienopyridine, CH_2Cl_2, -70°C, 2, TFA

In the following examples, the second double bond of the bis-vinylogous compounds was replaced by a triple bond or various aromatic rings (Scheme 4). Phosphonium salt **2** was reacted with various hydroxymethyl aromatic aldehydes (**16**) [6] in dichloromethane in the presence of potassium carbonate to give arylogous compounds (**18**) as single isomers. This reaction did not need protection of the hydroxyl function. Alternatively the use of 4-(t-butyldimethylsilyloxy)but-2-yl-1-al (**17**) [7] gave rise to **19** after removal of the silyl protecting group. One step quaternization with trifluoromethanesulfonic anhydride and pyridine followed by formic acid treatment afforded **20** and **21** respectively.

The Wittig reaction of **2** with 4-pyridine carboxaldehyde gave rise to **22** which was transformed to the pyridinium derivative **23** in two steps.

Scheme 4



I: HO-CH_2-R-CHO (16) or $Me_2tBuSiO$-CH_2-C≡C-CHO (17) (+ HCl treatment after the Wittig reaction), K_2CO_3, CH_2Cl_2, H_2O, r.t.; II: 1, Tf_2O, pyridine, CH_2Cl_2, -70°C, 2, aq. HCO_2H, 50°C; III: 4-pyridine carboxaldehyde, K_2CO_3, CH_2Cl_2, H_2O, r.t.; IV: 1, MeI, MeCN, r.t.; 2, TFA, r.t., HPLC.

All these compounds have been evaluated against Gram-positive and Gram-negative bacteria by using a broth macrodilution test. The antibacterial activity is represented as the geometric mean of MIC's (μg/ml) against 3 staphylococci ($\overline{M}$ staph) and 16 enterobacteriaceae ($\overline{M}$ ent). Table 1 shows that the vinylogous thienopyridinium derivative (4) displays 4-6 fold higher overall activity than the reference compound. For 5a and 6 this improvement is limited to staphylococci. [8] The presence of a Z double bond (5b), however reduces the antibacterial potency against both Gram-positive and Gram-negative bacteria. In these respects amonium substituted isocephems (4, 5a, 5b) are comparable to their cephem counterparts [9,10], however the vinylogous tetrazolyl derivative (6) does not show a loss of activity as was reported in the cephem series. [11] In the presence of two double bonds, the *in-vitro* activity drops to the level of the reference compound in the case of the amonium derivative (15) but the Gram-negative potency is impared for the tetrazolyl analogue 14.

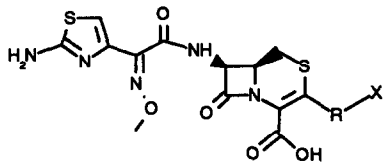
When a double bond is combined with a triple bond (21), the overall antibacterial potency though somewhat reduced, remains at a level comparable to that of the non-vinylogous derivative.

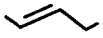
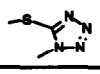
The situation is quite different when an aryl group is inserted between the cephem nucleus and the potential leaving group. Although the p-isomer 20c is topologically comparable to 21 the MIC's of the former compound are of one order of magnitude higher against enterobacteriaceae than those of the triple bond containing counterpart. While the level of anti-Gram-negative activity seems to be quite independent of the nature of the aromatic ring and the position of the substituents, the antistaphyloccocal potency increases when the polar substituent is getting closer to the isocephem nucleus. The decrease of *in-vitro* activity against Gram-negative strains might be rationalized by the impossibility of the potential leaving group to assist β-lactam opening :

With multiple double bonds the ring opening could be assisted by the departure of the pyridinium substituent (Scheme 5) [1,2] to give 25 and/or a more stable acyl enzyme intermediate could be formed as was shown for a DD-transpeptidase/carboxypeptidase. [14]

Table 1

In-vitro activity of vinylogous compounds



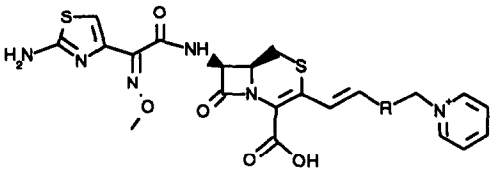
X	R	CH_2*				
	Compound	**				21
	M staph	2.5				5
	M ent	0.2				0.4
	Compound		4		15	
	M staph	0.76	0.12		0.38	
	M ent	0.12	0.03		0.12	
	Compound	**	5a	5b		
	M staph	10	1.2	10		
	M ent	0.28	0.19	1		
	Compound	**	6		14	
	M staph	15.9	2.5		5	
	M ent	0.4	0.14		1.5	

* Reference compounds [3]

** Racemic compounds, MIC's are uncorrected.

Table 2

In-vitro activity of arylogous compounds

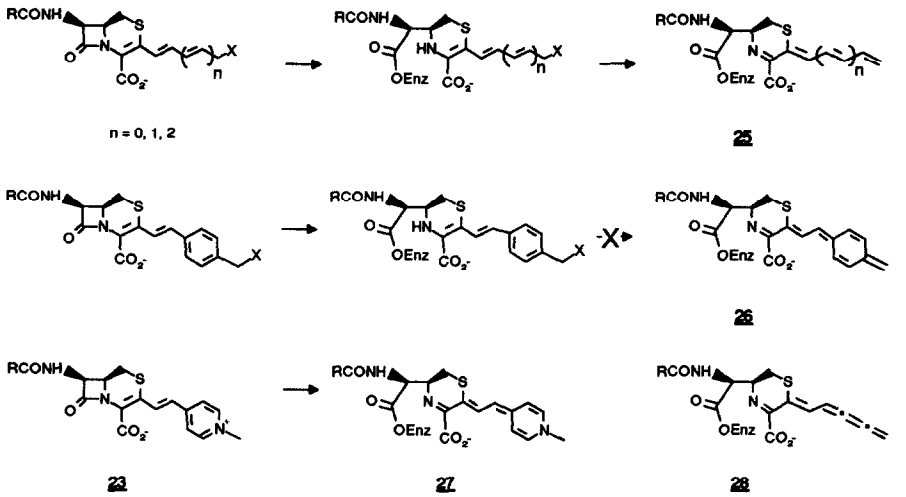


R =							
	21	20c	20b	20a	20d	20e	23
M staph	5	6.3	2.5	0.95	3.1	6.3	0.8
M ent	0.4	3.9	8	7.3	3.8	5.9	0.3

The same mechanism is conceivable with a triple bond too (28). In the case of the arylogous analogue 20c, however, the formation of 26 though theoretically conceivable would not be energetically favourable and probably no elimination of the 3' substituent occurs as shown by an almost identical antibacterial profile between the p- and m-isomers (20b and 20c), for the latter the elimination being impossible.

The lack of leaving group can be compensated for by a properly placed positive charge. Compound **23** shows a well balanced and reasonable level of antibacterial potency. In this case, however, the formation of **27** might assist ring opening, and/or stabilize the acyl-enzyme complex. Penems tend to show a similar behaviour [12], even though in their case the role of the pyridinium leaving group seems to be less important . [13]

Scheme 5



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