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SYNTHESIS OF CARBACEPHEM ANTIBIOTICS: SYNTHESIS VIA DIECKMANN REACTION USING PHENYL ESTERS TO DIRECT THE REGIOSELECTIVITY OF THE CYCLIZATION

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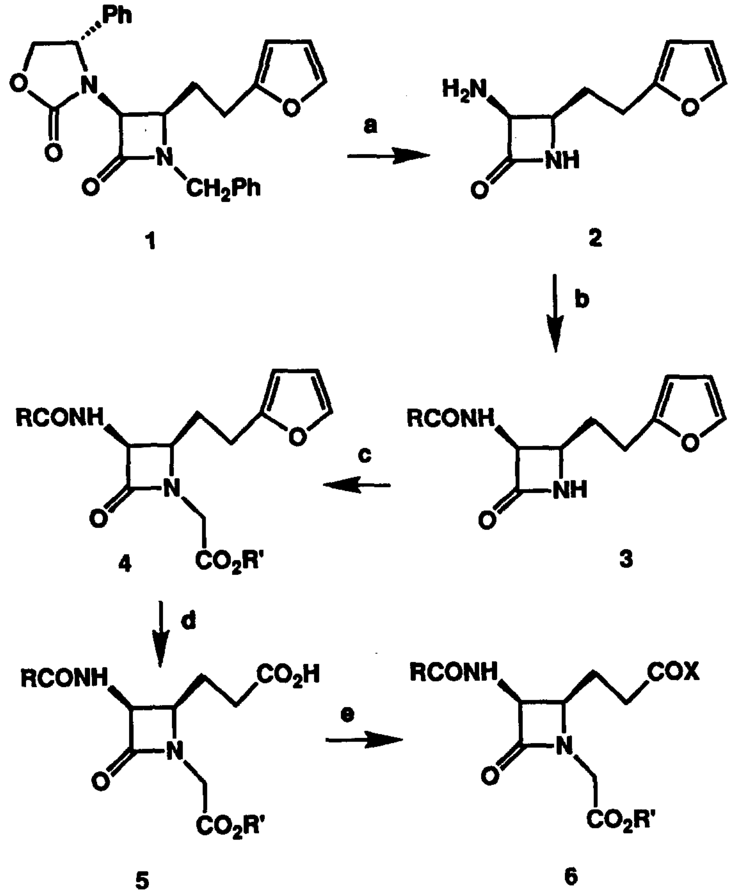
Summary: β-Ketoesters useful for elaboration to carbacephems were synthesized from a variety of enantiomerically pure diesters. Use of phenyl esters to direct the regioselectivity was demonstrated.

In the course of a study directed at various methods for forming the six-membered ring of carbacephalosporins, we examined the Dieckmann cyclization of appropriately substituted azetidinone diesters. Use of the Dieckmann reaction for synthesis of racemic carbacephems has been reported by Hatanaka and Ishimaru[1]. In that study as well as in two previously published works,[2,3] regioselectivity of the cyclization was apparently achieved through use of a thioester, taking advantage of the more nucleofugic nature of thiolate vs. alkoxide. With respect to the carbacephem-type cyclization reported by Hatanaka and Ishimaru, it is possible that the degree of regioselectivity is enhanced by having one of the esters as a t-butyl ester. A more recent publication by Nagao et al.[4] has shown that the degree of regioselectivity may depend on the nature of the base employed for the cyclization. In the work reported herein, we show that phenyl esters provide a degree of regioselectivity comparable with that obtained using thioesters, obviating the odor problems associated with use of thiols. Substrates (6) subjected to cyclization contained methyl and various aralkyl groups for substituent R'.

The diesters used in this study were enantiomerically pure, being derived from β-lactams whose syntheses were enantioselective. Thus, azetidinone 1[5] was subjected to Birch reduction using lithium in liquid ammonia affording the amine 2. Acylation of the amine with various acylating agents provided the various amides 3 used for subsequent elaboration. Alkylation of azetidinones 3 with sodium bromoacetate, followed by treatment of the resulting carboxylic acids with the appropriate halide provided the esters 4. Ozonolysis of the furyl moiety afforded the carboxylic acids 5 which were converted to diesters 6 by reaction with phenol or thiophenol, 1,3-dicyclohexylcarbodiimide and a catalytic amount of 4-dimethylaminopyridine. Cyclization of the diesters to β-ketoesters was effected with lithium hexamethyldisilazide or potassium *tert*-butoxide in tetrahydrofuran at -78°.

The resulting β-ketoesters existed predominantly as the enolic tautomer as evidenced by their NMR spectra (absence of a signal for the methine proton attached to the α-carbon and presence of a signal for the enolic hydroxyl at δ 11.2-11.4). In no cases were we able to observe formation of products arising from the alternate cyclization mode of the diesters.

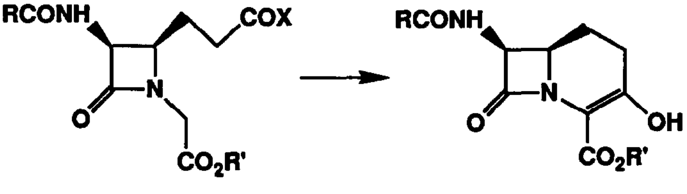
SCHEME



R, R' and X defined in table below.

(a) Li/NH_3,t-BuOH; (b) RCOCl, Et_3N, CH_2Cl_2; (c) NaH, THF, $BrCH_2CO_2Na$, R'Br (d) O_3, CH_2Cl_2/MeOH; (e) CH_2Cl_2, DCC, DMAP, C_6H_5OH or C_6H_5SH

The following table shows several examples of diesters which were prepared and subsequently caused to cyclize. Comparison of results from examples 7 - 10 indicates that very similar yields were obtained when phenyl was substituted for thiophenyl.



EXAMPLE	R	R'	X	YIELD
1.	V	PMB	SPh	87%
2.	V	PNB	SPh	42%
3.	V	CH3	SPh	77%
4.	Bz	PMB	SPh	87%
5.	Bz	PNB	SPh	34%
6.	Bz	CH3	SPh	76%
7.	CBZ	PMB	SPh	76%
8.	CBZ	PMB	OPh	77%
9.	CBZ	PNB	SPh	57%
10.	CBZ	PNB	OPh	48%
11.	CBZ	CH3	SPh	86%
12.	BOC	PMB	SPh	75%
13.	BOC	PNB	SPh	45%

Abbreviations used in table

V = phenoxyacetyl; Bz = benzoyl; CBZ = benzyloxycarbonyl; BOC = t-butyloxycarbonyl;
PNB = p-nitrobenzyl; PMB = p-methoxybenzyl; Ph = phenyl

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References and Notes

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6. Satisfactory spectral and microanalytical data were obtained for all new compounds reported in this paper.

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