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A NOVEL DIELS-ALDER APPROACH TO CARBAPENEMS

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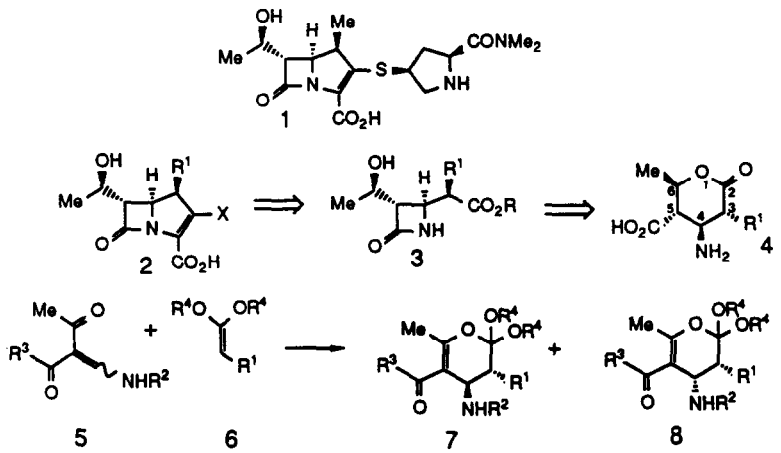
Abstract: An inverse electron demand hetero-Diels-Alder reaction between 2-acylamino-methylene-3-oxobutanoic acid derivatives (5)and ketene acetals (6)yields crystalline dihydropyrans, which are versatile intermediates in the synthesis of carbapenems.

Synthetic carbapenem analogues related to thienamycin show broad spectrum anti-bacterial activity but are rapidly metabolised by kidney dehydropeptidase (DHP-1)[1]. A second generation of 1-β-substituted carbapenems have emerged which show both improved chemical stability and resistance to DHP-1[2]. Recent publications in this area[3] have prompted us to reveal some of our synthetic work which has been directed mainly at a commercially viable route to (1)[4]. The great interest in carbapenems has produced a wide variety of synthetic approaches to the new β-lactam skeleton[5]. The azetidinones (3) have been key intermediates and our retrosynthetic analysis led, via (2) and (3), to the δ-lactones (4) which have four contiguous chiral centres. The lactone (4,R^1=H) was an intermediate in an ingenious synthesis of thienamycin[6] but the approach required the inversion of the stereochemistry at C6. Also, in a recent synthesis of 4(R^1=Me),[3b] the stereochemistry at C5 had to be inverted. In this communication we describe the facile preparation of the dihydropyrans (7) and (8) utilising a Diels-Alder reaction between the dienes (5) and the ketene acetals (6).[7] These dihydropyrans are direct precursors of the lactams (3) or the lactones (4) as described in the next paper.



Successful [4+2] cycloadditions of simple α, β–unstaurated ketones with ketene acetals have been reported[8]; some high pressure reactions of this type have also been observed[9] as well as cycloadditions in the presence of Lewis acid catalysts[10]. Intra–molecular Diels–Alder reactions between α,β–unsaturated aldehydes and ketenethioacetals have also been shown to proceed at low temparatures[11]. Molecular orbital calculations in this laboratory[12] predicted a favourable outcome of Diels–Alder reactions between the more complex dienes (5) and the ketene acetals (6).

The cycloadditions were found to proceed in high yield under extremely mild conditions and the results of a few representative reactions are shown in Table 1, demonstrating the effect of the substituents on the stereochemistry of the cis and trans adducts obtained. The dienes were either known compounds or were readily synthesised[13]. The ketene acetals were prepared by isomerisation of acrolein acetals[14] or by the dehydrohalogenation of α–halo orthoesters[15]. Lewis acid catalysts did not markedly influence the isomer ratio.

Table 1

EXAMPLE	5		6		CONDITIONS °C/HR IN TOLUENE	ISOLATED % YIELD	PRODUCT RATIO *
NO	R^2	R^3	R^1	R^4			7 : 8
a	COMe	OMe	Me	Et	20/1	90	1.2 : 1
b	COMe	OMe	H	Me	20/1	95	–
c	COMe	HN–Ph–pCl	Me	Et	90/6	90	20 : 1
d	$COCH_2Cl$	OMe	Me	Et	20/1	95	1.3 : 1
e	CO_2CH_2Ph	OMe	Me	Et	20/16	80	0.7 : 1
f	CO_2CH_2Ph	OCH_2Ph	Me	Et	20/2	95	1 : 1
g	COMe	OMe	Me	Me	20/2	95	0.8 : 1
h	COMe	(S)–NHCH(Me)Ph	Me	Et	100/6	75#	20 : 1

* Ratios were estimated by n.m.r. analysis of the crude reaction mixtures[16].

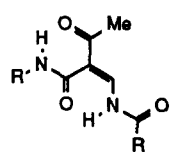
the 75% yield is the sum of the two trans diastereoisomers obtained in almost equal amounts.

Examples (c) and (h) with acidic N–H groups at R^3 gave high yields of the required trans adduct (7), whereas all the others which had esters at R^3 afforded approximately equal mixtures of cis and trans isomers. The reason for this stereoselectivity became clear when the olefin geometries of the dienes (5) were determined by ^{13}C n.m.r.

The dienes in examples (c) and (h) were shown to have Z-geometry whereas the others in Table 1 were predominantly E; this structural preference is probably determined in the synthesis of the dienes by the hydrogen bonding depicted in (9) and (10)[17]. The essentially planar nature of the heterodiene system allows the dienophile to approach from either side but the Z-geometry of the dienes in examples (c) and (h) (cf. 9) provide a sterically free region for the methyl group of the ketene acetal (6,R^1=Me) only if it approaches in the exo-fashion (cf.11). With E-dienes (cf. 10), the choice between exo-and endo-approach was less clear and mixtures of cis and trans isomers resulted.

The effects of solvents, temperature, catalysts, pressure and sonication were tried in an effort to influence the trans/cis isomer ratios in Diels-Alder reactions involving E-dienes. The best trans isomer yields were obtained using DMSO at 50°C; thus, using these conditions, the trans/cis ratio for example (e) rose from 0.7:1 to 2.3:1.

Example (h) illustrated that chiral dihydropyrans (7) could be readily obtained using this cycloaddition reaction. When the diene prepared from (S)-α-methylbenzylamine (cf. example h) was reacted with the ketene acetal (6, R^1=Me, R^4=Et), very little chiral induction was observed but the mixture of the two trans diastereoisomers, 12 (S-3S, 4S, mp 158°C) and 13(S-3R,4R, mp 212°C) were easily separated by crystallisation. The structures of these diastereoisomers were confirmed by X-ray crystallography.



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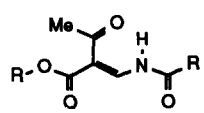

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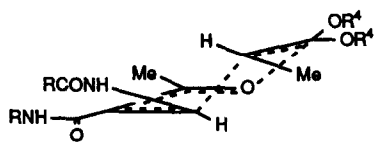

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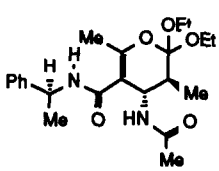

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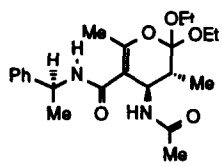

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This paper presents a simple synthesis of the dihydropyrans (7) and (8) in which substituents can be varied and the stereochemistry can be controlled. Chiral dihydropyrans can be readily obtained. In the following paper, the conversion of (7) into 5-keto-esters, δ-lactones and azetidinone intermediates for carbapenems is described.

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7. cf. European Patent EP 230,771. We discovered that the dihydropyrans could be prepared in lower yields by heating the dienes with ortho-esters like $(EtO)_3$-CCH_2CH_3 which acted as precursors of ketene acetals.
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16. eg. Example a, structure 7 (trans isomer) had mp 153°C, NMR ($CDCl_3$) δ 0.97 (d,3H), 1.22 (t,3H), 1.29 (t,3H), 1.92 (s,3H), 2.30 (d,3H), 2.31(dq,1H), 3.58(q,2H), 3.65(q,2H) 3.71(s,3H), 4.85(ddq,1H), 6.08(d,1H). The signal at 4.85 showed $J_{3,4}$=1.5; $J_{4,NH}$=9.8; J4,C6Me (Allylic coupling)0.9Hz. Example (a), structure 8(cis isomer) had mp 87°C, NMR ($CDCl_3$) δ 1.04 (d,3H), 1.20(t,3H), 1.25(t,3H), 1.94(s,3H), 2.25(d,3H), 2.26(dq,1H), 3.70(S,3H), 3.5-3.9(m,4H), 5.12(ddq,1H), 5.98(d,1H). The signal at 5.12(H4) showed $J_{3,4}$f=5.4; $J_{4,NH}$=10.2; $J_{4,C6Me}$ (allylic coupling)=0.9 Hz. Despite the low $J_{3,4}$ coupling constant for the trans isomer, its structure was confirmed by an NOE between H4 and the C3 methyl group and by an X-Ray analysis.
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