

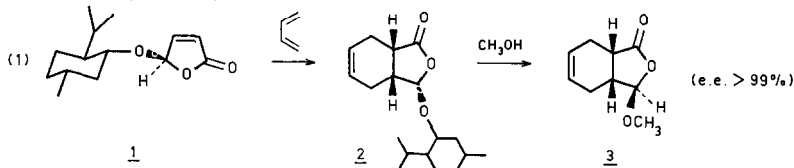
ASYMMETRIC 1,3-DIPOLAR CYCLOADDITIONS TO 5-MENTHYLOXY-2[5H]-FURANONES.

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Summary: Cycloadditions of various 1,3-dipolar reagents to chiral butenolides 1 and 5 proceed with diastereomeric excess of 20-100%.

Recently we reported a new class of C-4 and C-5 chiral synthons based on optically pure γ -alkoxy-butenolides. Examples are (1)-5-menthyloxy-2[5H]-furanone (1) and its enantiomer, which are readily prepared from 5-hydroxy-furanone and either l- or d-menthol^{1,2}. Using 1 as a chiral maleic anhydride analogue excellent diastereoselectivity was achieved in Diels Alder reactions with various dienes to yield, after methanolysis, enantiomerically pure cycloadducts (eq. 1)¹. These results prompted us to study asymmetric



1,3-dipolar cycloadditions using 1 as a dipolarophile.

In contrast to asymmetric Diels Alder reactions³ the analogous cycloadditions with 1,3-dipolar reagents have only recently been successful⁴. Intramolecular dipolar cycloadditions were applied in total syntheses of several natural products⁵ e.g. d-luciduline⁶, l-daunosamine⁷ and d-lividosamine⁸. Application of chiral dipolar reagents, such as nitrones based on glucose or α -phenylethylamine or a chiral nitrileoxide, in intermolecular cycloadditions resulted in diastereoselectivities up to 90%⁹.

More widely investigated has been the use of chiral dipolarophiles i.e. nitrileoxide additions to (S)-isopropylidene-3-butene-1,2-diol, (S)-vinylglycine and chiral acrylate esters (d.e. 4-82%)¹⁰ and nitrone additions to chiral vinylsulfoxides (d.e. 90%)¹¹. High stereocontrol (d.e. >95%) has been reached by double asymmetric induction using a chiral dipolarophile and a chiral nitrone¹².

The prospect of preparing optically active multifunctional compounds by 1,3-dipolar additions to chiral γ -alkoxybutenolides in a highly stereocontrolled fashion is particularly attractive¹³. The results of 1,3-dipolar

cycloadditions to enantiomerically pure butenolides 1 and 5 are summarized in the table.

A regioselective addition of diazomethane to butenolides 1 and 5 is found¹³. The diastereoselectivity is however poor, presumably due to the relatively unhindered attack of the small 1,3-dipolar reagent. The high regioselectivity is in accordance with earlier observations with butenolides and acrylate esters and it is mainly determined by HOMO, LUMO interactions^{13,14}. Recently a related regioselective addition of CH_2N_2 to optically active 5-hydroxymethyl-2[5H]-furanone has been found but unfortunately the diastereoselectivity was not indicated¹⁵.

The addition of ethyldiazoacetate proceeds with complete regio and diastereofacial-selection to yield enantiomerically pure 9. However, the stereochemical control by the smaller methoxy-substituent, as is present in racemic 4, is lower in this case. It should be noted that isomerization to the 2-pyrazoline structure has taken place in adducts 8 and 9.

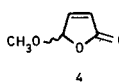
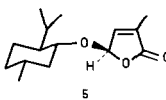
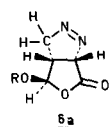
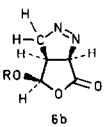
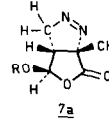
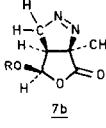
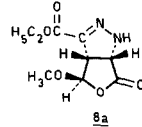
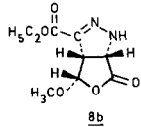
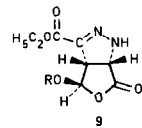

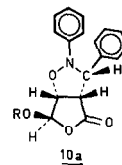
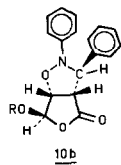
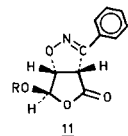
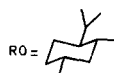
Excellent diastereofacial control is exerted by the menthyloxy-substituent in nitron- and nitrileoxide -additions to yield 10 and 11 respectively. The diphenylnitrone addition to 1 resulted in both endo-(10a) and exo-(10b) products epimeric at one of the three newly created chiral centers. The trans relationship of the acetal - and carbon-4-hydrogen atoms and consequently the π -face selectivity in 6a, 7a, 8a, 9, 10a and 11 was established by ^1H -NMR. A singlet is observed in the ^1H NMR spectrum for the acetal hydrogen atom in all cases as expected from molecular model studies of the angles between the vicinal hydrogens in a trans relationship in these bicyclic products¹⁶.

This observation is in accordance with re-face Diels Alder additions to 1¹, and trans additions of amines to 1¹⁷. The stereochemistry of the amine adducts of 1 has been proven by X-ray analysis¹⁷.

The asymmetric 1,3-dipolar cycloadditions described here show that carbon, oxygen or nitrogen functionalities are readily introduced into the α - and β -positions of the lactone moiety. In this way useful precursors for natural product synthesis are accessible. The potential applications are illustrated in the preparation of enantiomerically pure cyclopropane annelated lactone 12. One crystallization of the mixture of 6a and 6b from petroleum ether, ethylacetate gave diastereomerically pure 6a (40%, $[\alpha]_D^{20} +131.1^\circ$, C_1 , CHCl_3). Photolysis (180-300 nm) of 6a in dichloromethane in the presence of 2 equivalents of benzophenone yielded diastereomerically pure 12 (71%) and 5-menthyloxy-4-methyl-2[5H]-furanone 13 (29%).

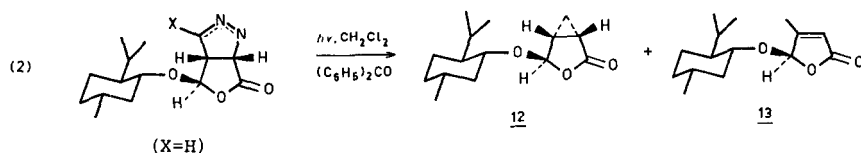
Under these conditions no cycloreversion takes place in contrast to results with pyrrolidones¹⁸. Preliminary studies indicate that the photolysis is strongly depending on the solvent and the amount of sensitizer used.

Table

butenolide	1,3-dipolar reagent	reaction conditions	product(s) ^{a,b}		yield (%)	ratio
						
<u>1</u>	CH ₂ N ₂	Et ₂ O RT, 12h			100	60 : 40
<u>5</u>	CH ₂ N ₂	Et ₂ O RT, 144h			90	55 : 45
<u>4</u>	H ₅ C ₂ O ₂ CCHN ₂	dioxane 90°C, 12h			69	91 : 9
<u>1</u>	H ₅ C ₂ O ₂ CCHN ₂	dioxane 95°C, 12h			67	100 : 0
<u>1</u>		toluene 110°C, 2h			95	65 : 35
<u>1</u>	C ₆ H ₅ C≡NO	Et ₂ O RT, 12h			92	100 : 0 ^c
						RO = 

- a. New products are fully characterized by ¹H-, ¹³C-NMR, IR and HRMS.
 b. All starting materials and products shown (except 4, 8a, 8b) are enantiomerically pure according to ¹H-NMR.
 c. Byproduct (5%), the structure of which is not established yet, was readily removed by chromatography.

Thermal conversion of the mixture of 6a and 6b in refluxing toluene resulted in the loss of nitrogen to provide enantiomerically pure 13 quantitatively. Lactone 12 is an attractive precursor for natural α-(carboxycyclopropyl)-glycines¹⁹. Investigations along these lines are in progress.



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