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SYNTHESIS OF 3-OXO-δ-LACTONES VIA HETERO-DIELS-ALDER REACTIONS

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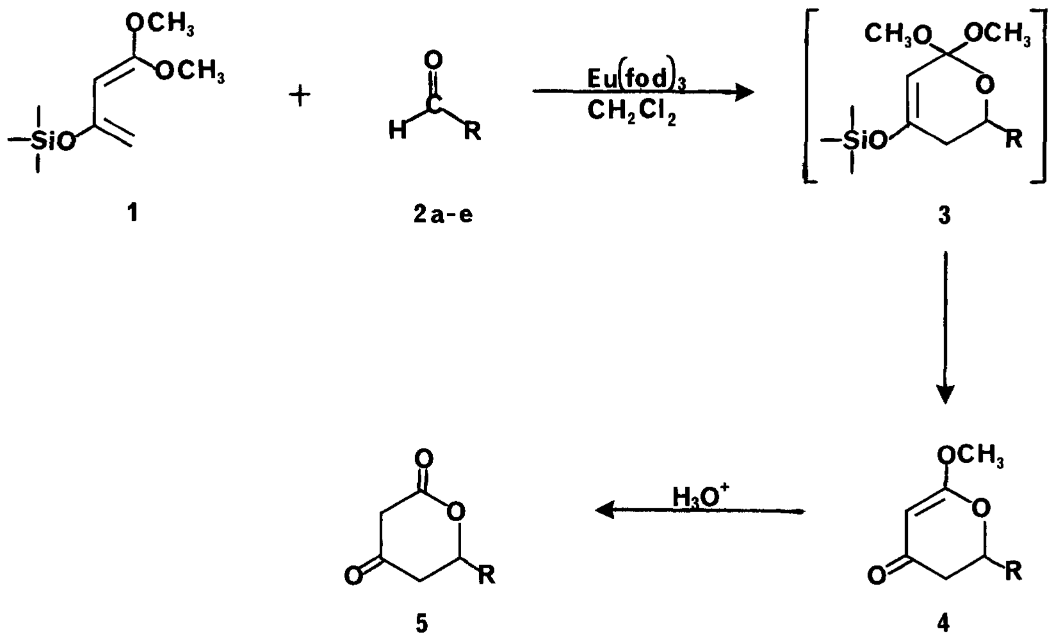
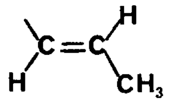
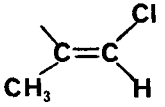
Abstract: The hetero-Diels-Alder reaction between aldehydes, 2, and bis-1,1-dimethoxy-3-trimethyl-1-siloxy-1,3-butadiene, 1, produces 2-methoxy-5,6-dihydro-γ-pyrones, 4, which are subsequently hydrolyzed to afford substituted 3-oxo-δ-lactones, 5, in high yields, providing a new and efficient approach to these synthetically useful intermediates.

The use of a carbonyl double bond as a dienophile in a Diels-Alder reaction to prepare oxygen heterocycles has met with limited success in early investigations. Using carbon substituted dienes, only carbonyl groups bearing strong electron withdrawing substituents were sufficiently activated to cyclize. Vigorous reaction conditions which require heating the solutions in sealed tubes at high temperatures give yields ranging from poor to fair.[1]

Scheeren and coworkers[2] have been successful in cyclizing oxygen substituted dienes with various aldehydes and ketones under mild conditions to produce pyrones in good yields. While the oxygen substituted dienes show greater reactivity, only activated carbonyl groups, i.e., those containing electron withdrawing substituents, react. More recently, Danishefsky and coworkers have demonstrated the utility of Lewis Acid catalysts in the hetero-Diels-Alder reaction between siloxydienes and various unactivated aldehydes to generate 5,6-dihydro-γ-pyrones.[3] Of particular interest is the application of Lanthanide shift reagents as mild Lewis Acids.[3f,g] These catalysts achieve high yields under mild reaction conditions. In this communication we wish to report the preparation of β-oxo-δ-lactones, 5, by the Eu(fod)$_3$ catalyzed hetero-Diels-Alder reaction between aldehydes, 2, and bis-1,1-dimethoxy-3-trimethylsiloxy-1,3-butadiene[4], 1, (Scheme 1).

In a typical reaction, the diene, 1, is added to a stirring solution of the aldehyde, 2, and Eu(fod)$_3$, (1-10 mole %), in CH_2Cl_2 under N_2 at room temperature. The reaction is allowed to proceed for 48 hours with stirring. Vacuum flash chromatography[5] of the crude reaction mixture affords compound 4 as the only regioisomer in good yields. The cyclic ketene acetals[6] are then hydrolyzed with dilute HCl in refluxing benzene to produce, after neutralization, crystalline δ-lactones, 5,[6] (Scheme 1), and minor amounts of the corresponding dienyl esters due to ring opening followed by elimination. While there is spectroscopic evidence to support the presence of the expected Diels-Alder adduct 3, its lability prevents isolation after chromatography.



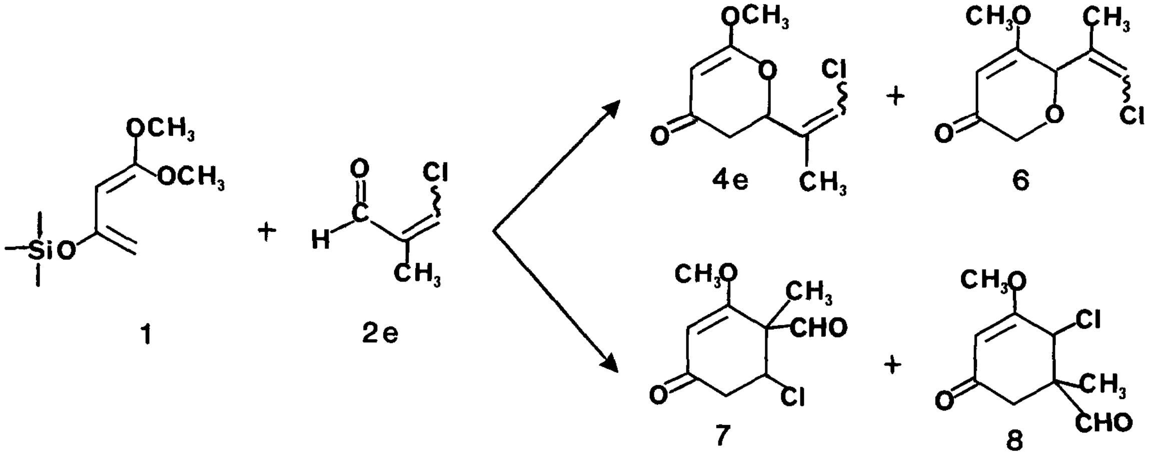
entry	R	% yield of 4[a]	% yield of 5[a]
a[7]	$-COOCH_3$	73[b]	78
b[8]	$-C_6H_5$	85	95
c[8]	$-CH(CH_3)_2$	69	89
d[8]		70	93
e		87	90

a-isolated yields

b-no Eu(fod)3 catalyst

Scheme 1

Aldehyde 2e contains two potential dienophiles, the carbonyl double bond and a very dienophilic carbon-carbon double bond. Therefore, four products could potentially be expected from the cyclization of 2e and 1 (Scheme 2). Under $Eu(fod)_3$ catalysis, compound 4e is the sole product. When the reaction is carried out without the catalyst a 1.35:1 mixture of compounds 7 and 4e is isolated in 29% yield. Dienophile 2a undergoes cyclization without catalysis to give exclusive addition at the aldehyde double bond. Attempts at the cyclization of 1 with 2-butanone were not successful.



Scheme 2

In conclusion, the methodology presented offers a new and different approach to highly functionalized δ-lactones. We are continuing to investigate the scope of this reaction and are involved in its application toward the total synthesis of natural products.

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6. All structures were completely characterized by infared, ^{1}H-NMR (200 or 300 MHz), ^{13}C-NMR (50 or 75 MHz), and mass spectroscopy. Representative NMR data: 4d ^{1}H-NMR (200 MHz, CDCl$_3$) δ 2.65 (AB, 2H), 1.75 (ddd, J=6.5, 1.5, and 1 Hz, 3H), 3.80 (s, 3H), 4.95 (m, 1H), 4.90 (s, 1H), 5.64 (ddq, J=15, 6.8, and 1.5 Hz, 1H), and 5.89 (dqd, J=15, 6.5 and 0.7 Hz, 1H). ^{13}C-NMR (50 MHz, CDCl$_3$) δ 17.7(q), 40.6(t), 55.7(q), 80.5(d), 82.5(d), 127.0(d), 131.8(d), 173.9(s), and 192.1(s). 5d ^{1}H-NMR (200 MHz, CDCl$_3$) δ 1.78 (ddd, J=6.5, 1.5, and 1.0 Hz, 3H), 2.61 (dd, J=18.3 and 8.5 Hz, 1H), 2.77 (dd, J=18.3 and 4 Hz, 1H), 3.50 (AB, 2H), 5.58 (ddq, J=15, 6.8, and 1.5 Hz, 1H), 5.91 (dqd, J=15, 6.5, and 0.7 Hz, 1H), and 5.11 (m, 1H). ^{13}C-NMR (50 MHz, CDCl$_3$) δ 17.3(q), 43.4(t), 46.9(dd), 75.5(d), 126.5(d), 131.8(d), 167.0(s), and 199.8(s).
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9. 2e, a mixture of Z and E isomers, was prepared from the Wittig reaction between pyruvic aldehyde dimethyl acetal (Aldrich) and chloromethylenetriphenylphosphorane (S. Miyano, Y. Izumi, K. Fujii, Y. Ohno, and H. Hashimoto, Bull. Chem. Soc. Japan., 1979, 1197).

Note added in proof: After submission of this communication a paper appeared, S. Danishefsky, D. F. Harvey, G. Quallich, B. J. Uang, J. Org. Chem. 1984, 49, 392, describing the synthesis of 4b via the same method as herein.

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