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HETERO-DIELS-ALDER REACTIONS OF α-METHOXYMETHYLENE SUBSTITUTED 1.3-DICARBONYL COMPOUNDS WITH ENOL AND ENEDIOL ETHERS [1)]

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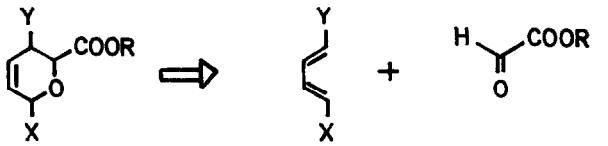
Abstract: *The inverse electron demand hetero-Diels-Alder reaction of methoxymethylene substituted 1.3-dicarbonyl compounds with enol ethers and enediol ethers results in the selective formation of 3.4-dihydro-2H-pyrans. These adducts with a high density of functional groups are versatile intermediates for natural product syntheses.*

Hetero-Diels-Alder reactions of electronrich 1.3-dienes (1.4-diacetoxy butadiene, 1.4-diacylamino butadiene, methoxybutadiene, and derivatives) with reactive carbonyl compounds (Scheme 1) lead to pseudoglycals (2H-5.6-dihydropyrans). These compounds are versatile intermediates for short syntheses of carbohydrates and related natural products such as thromboxane B_2 [2-4)].

Scheme 1

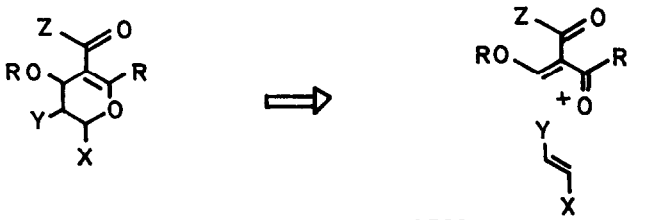


X,Y = OAc
X,Y = NHAc
X = OR, Y = H, Alkyl

Hetero-Diels-Alder reactions with inverse electron demand between α,β-unsaturated carbonyl compounds and enol ethers are an attractive route for the synthesis of 3.4-dihydro-2H-pyrans [5)]. Recent investigations have demonstrated that electron with_drawing substituents at the α-position increase the rate of this reaction strongly [6)].

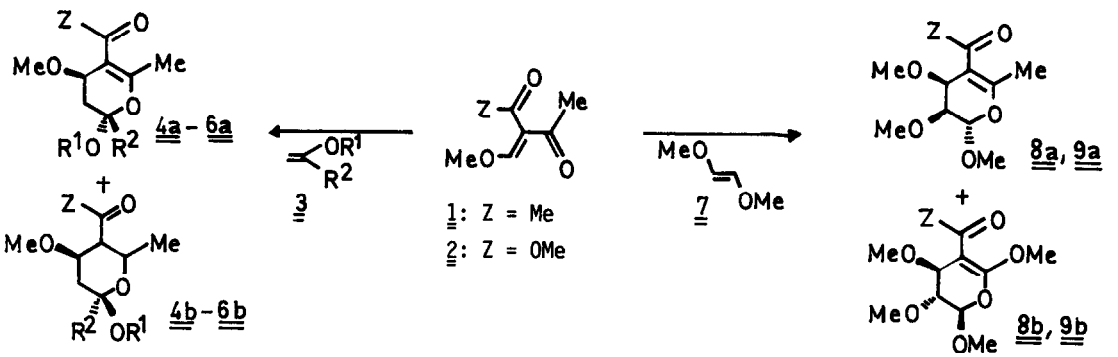
This reaction would be of great potential utility for the preparation of carbohydrates and related highly functionalised natural products, if further functional groups could be introduced into the basic starting materials (Scheme 2).

Scheme 2



X = OR, Y = H,Z = OR, Alkyl
X,Y = OR, Z = OR, Alkyl

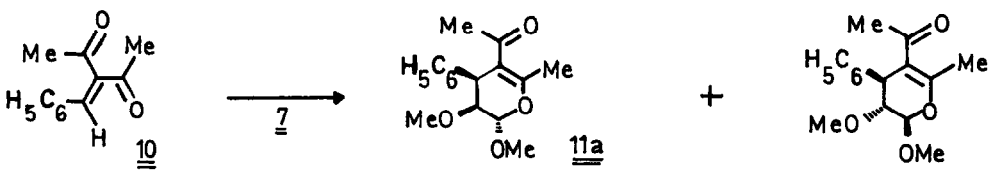
Scheme 3 *



4a,b: Z = Me, R^1 = Et, R^2 = H
5a,b: Z = Me, R^1 = Me; R^2 = Me
6a,b: Z = OMe, R^1 = Et; R^2 = H

8a,b: Z = Me
9a,b: Z = OMe

Scheme 4 *



* Only one enantiomer is depicted.

Table 1. Cycloadducts 4a - 6a, 4b - 6b, 8a,b, 9a,b, 11a,b

Starting Materials	Reaction Conditions [a] Temp. [°C]	Time [h]	Products [b]	Yield [c] [%]	R_F [d] (TLC/Silica Gel)
1 +	140	14	4a . b ≈1:2	87	4a · 0.48 4b 0.41
1 +	100	12	5a b ≈1·1	74	5a · 0.54 6b . 0.20
2 +	130	14	6a . b ≈1 2	96	6a . 0.42 6b : 0.30
1 + 7	150	14	8a : b ≈1 1	71	8a 0.58 8b : 0.40
2 + 7	140	14	9a : b ≈1·1	69	9a 0.48 9b . 0.36
10 + 7	140	14	11a,b [e] ≈ 1.1	84	11a,b . 0.53

[a] Equimolar amounts of starting material without solvent, trace of hydroquinone.
[b] All compounds gave correct elemental analyses.
[c] Isolated yields
[d] Petroleum ether/ethyl acetate = 1 1 (4a,b, 5a,b, 8a,b, 9a,b), 2 1 (6a,b, 11a,b).
[e] Chromatographic separation not performed.

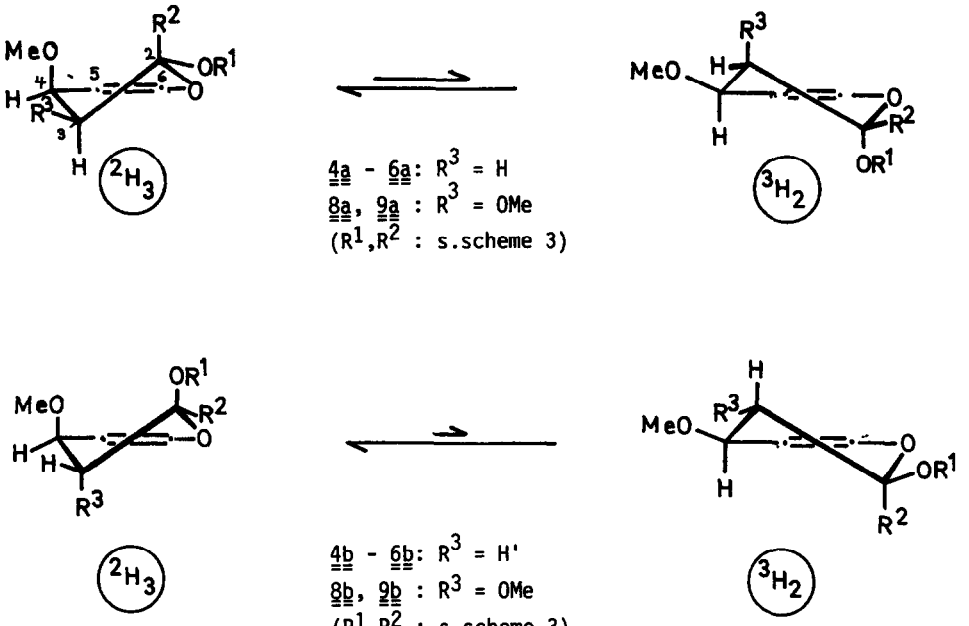


Table 2: ^{1}H-NMR-Data [a]

	H-2	H-3	H-3'	H-4	$J_{2,3}$	$J_{2,3'}$	$J_{3,3'}$	$J_{3,4}$	$J_{3',4}$
4a	5.00(dd)	2.30(ddd)	1.64(ddd)	4.20(m)	10.6	2.2	14.0	2.2	3.7
5a	-	2.20(dd)	1.96(dd)	4.33(dd)	-	-	13.4	6.4	6.4
6a	5.05(dd)	2.22(ddd)	1.59(ddd)	4.25(m)	10.6	2.2	13.6	2 2	3.4
8a	5.10(d)	3.35(dd)	-	4.46(d)	8.0	-	-	3.0	-
9a	5.18(d)	3.35(dd)	-	4.56(d)	8.0	-	-	3.0	-
4b	5.15(dd)	2.35(ddd)	1.96(ddd)	4.23(dd)	3.5	3.6	14.7	3.6	5.4
5b	-	2.48(dd)	1 76(dd)	4.12(dd)	-	-	14.9	1.8	5.5
6b	5.18(dd)	2.31(ddd)	1.88(ddd)	4.20(mc)	3.7	3.0	14.3	3.0	5.5
8b	5.05(dd)[b]	3.65(dd)	-	4.10(mc)[c]	3.0	-	-	1.5	-
9b	5.02(dd)	3.58(dd)	-	4.04(mc)	2.0	-	-	1.0	-
11a, b[d]	4.88(d) 4.76(d)	3.5 3.5	- -	3.90(m) 4.10(d)	4.3 6.2	- -	- -	e 4.3	- -

[a] 80- and 250-MHz spectra, internal TMS, δ-values in ppm, multiplicity in parentheses, coupling constants in Hz.

[b] Long range-coupling with H-4.

[c] Long range-coupling with H-4 and 6-CH_3

[d] Structural assignment not reliable on the basis of these data

[e] Not assigned.

This paper demonstrates, that α,β-unsaturated carbonyl compounds with an electron releasing methoxy substituent form cycloadducts with enol and enediol ethers regiospecifically (Scheme 3) [7]. Methoxymethylene acetylacetone (1) and methyl methoxymethylene acetoacetate (2), react with ethylvinylether (3 · R^1 = Et, R^2 = H) and isopropenyl methylether (3 : R^1, R^2 = Me) to give the 2.4-dialkoxy-3.4-dihydro-2H-pyrans 4a,b, 5a,b, and 6a,b in a high yielding cis addition (Table 1). 1 and 2 react in an analogous manner with trans-1.2-dimethoxyethylene (7) to yield the 2 3. 4-trimethoxy-3.4-dihydro-2H-pyrans 8a,b and 9a,b, respectively. The stereoisomers were separated chromatographically and the structures assigned on the basis of the ^{1}H-NMR data (Table 2). Because of the anomeric and/or allylic effect [2,8] the 2-OR^1-endo adducts 4b - 6b, 8b, and 9b prefer the $^2H_3$-conformation. The same arguments favor an equilibrium between the $^2H_3$- and $^3H_2$-conformers for the 2-OR^1-exo adducts 4a - 6a, 8a, and 9a. However, the observed high $J_{2,3}$ - coupling suggests that the $^2H_3$-conformation predominates.

The corresponding 3.4-dihydro-2H-pyrans 11a,b (Scheme 4) were obtained by the cycloaddition of phenylmethylene substituted acetylacetone 10 with 7 (see Table 1 and 2).

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1) De novo-Synthesis of Carbohydrates and Related Natural Products, Part 10. - This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. - Part 9, see ref. 4c.

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