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Diastereofacial Selectivity in the Diels-Alder Reaction of 5(*S*)-E-5,6-O-Isopropyliden-hex-3-en-2-one with Cyclopentadiene

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Dedicated to Prof. Jürgen Liebscher on the occasion of his 50th birthday

Abstract. *The effect of temperature, catalyst and pressure on the outcome of the Diels-Alder reaction of 5(S)-E-5,6-O-isopropyliden-hex-3-en-2-one with cyclopentadiene was investigated. All four possible Diels-Alder adducts were isolated and characterized on the basis of single crystal X-ray analysis and NMR experiments. Et_2AlCl was found to be the most effective catalyst to give exclusively the endo-isomers.*

The Diels-Alder reaction represents one of the most powerful reactions in organic chemistry and is of synthetic and theoretical interest. [1]

Chiral derivatives of acrylic acid obtained from 2,3-isopropylidene glyceraldehyde have been used intensively as dienophiles in asymmetric Diels-Alder reactions. [2,3] For example, it was found that the uncatalyzed Diels-Alder addition of methyl 5(*S*)-E-5,6-O-isopropylidene-pent-2-enoate to cyclopentadiene gave only *syn*-adducts with a slight preference (60:40) to the *exo*-derivative. [3] The same reaction under identical conditions (80°C, 8h), was reported to give both the *exo*- and *endo*-adducts according to a *syn*-alkoxy diastereoselection (60%:27%) as well as a mixture of the *anti*-isomers (13%). [4] However, when the reaction was performed in the presence of Et_2AlCl as a catalyst only the *syn*-derivatives were detected. [5]

It was shown by Reetz et al. in the γ-amino α,β-unsaturated carbonyl compound series that the use of enones in cycloadditions with cyclopentadiene may result in an enhanced diastereoselectivity as compared to the corresponding enoates. [6] We were interested to find out if this enhanced diastereoselectivity is also observed in the γ-alkoxy substituted series. Consequently, we studied the Diels-Alder reaction of 5(*S*)-E-5,6-O-isopropyliden-hex-3-en-2-one **1** with cyclopentadiene (Scheme 1) under different reaction conditions (Table 1) and the results are reported herein.

The uncatalyzed thermal reaction (80°C, 5h) of **1** with cyclopentadiene resulted in a mixture of the four possible Diels-Alder adducts, which could be separated by MPLC on silicagel. The identification of these

compounds was based on the X-ray analysis of compound **2a** (Figure 1), which revealed that the substituents show a *syn-endo* arrangement. In addition NOE experiments revealed an enhancement of the signal due to H7 when the H8 signal was irradiated.

Scheme 1

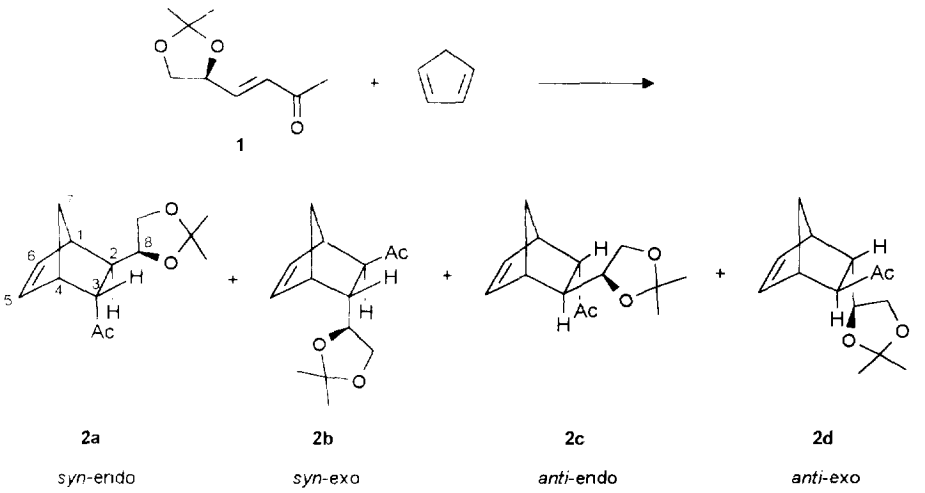

Table 1. Results of the Diels-Alder reaction of enone **1** with cyclopentadiene

entry	reaction conditions	yield	**2a** : **2b** : **2c** : **2d**	syn/anti ratio	endo/exo ratio
1	80° C, 5 h	87 %	40 : 33 : 14 : 13	2.7	1.2
2	0 °C, $Ti(O^iPr)_3Cl$, 20 h	80 %	44 : 32 : 10 : 14	3.2	1.2
3	0 °C, $Ti(O^iPr)_2Cl_2$, 20 h	90 %	31 : 21 : 32 : 16	1.1	1.7
4	0 °C, Et_2AlCl, 1.5 h	87 %	59 : 3 : 36 : 2	1.6	19.0
5	-23 °C, Et_2AlCl, 1.5h	97 %	61 : 0 : 39 : 0	1.6	*
6	-78 °C, Et_2AlCl, 2.5h	93 %	63 : 0 : 37 : 0	1.7	*
7	rt, 2d, 3 kbar	93 %	41 : 23 : 19 : 17	1.8	1.5
8	rt, 2d, 10 kbar	95 %	46 : 26 : 20 : 8	2.6	1.9

* only *syn*-isomers were found

Analogous to **2a** the *anti-endo* compound, **2c**, showed a significant NOE effect for the signal from H7 when H8 was irradiated. Additional NMR experiments (NOE measurements, coupling constant analysis) confirmed that the remaining two isomers are the *exo*-products.

However, it was not possible to distinguish between *syn*- and *anti*-orientation by means of NMR techniques because of the free rotation of the dioxolane moiety.

To determine the structures of the *exo*-isomers we used the theoretical model for diastereoface selection. The observed stereoselectivity for the major *syn-endo*-product can be explained by the antiperiplanar effect, [7] as applied for the α,β-unsaturated ester series. [3] According to this model the oxygen at the chiral centre occupies a position *anti* to the incoming diene. If we accept that the favored conformation of the enone 1 does not depend on *exo* or *endo* orientation of the incoming diene, [2h] we can establish the absolute configuration of the major *exo* adduct **2b** to be *syn* again.

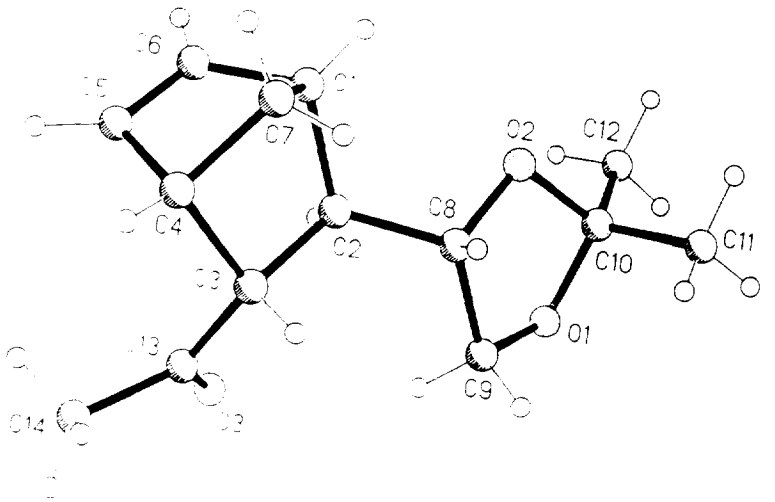

Figure 1. X-ray structure of compound **2a**

It is worth noting that, compared with the γ-alkoxyenoate series [4] the enone **1** gives the same *syn*-preference under thermal conditions. However, in our case a marginal *endo*-selectivity is observed, due to a stronger *endo*-directing effect of the acetyl group compared with the ester moiety. This is in agreement with the findings in the γ-dibenzylamino substituted series. [6]

The great influence of Lewis acids on the stereochemical outcome of Diels-Alder reactions has been widely documented. [16,5] Hence we studied the effect of Lewis acid catalysts on the cycloaddition reactions of enone 1 with cyclopentadiene. No reaction was observed when $ZnCl_2$, titanocene dichloride and $Ti(O^iPr)_4$ were used, while $TiCl_4$ and BF_3 afforded complex polar mixtures of products. In these cases the isopropylidene moiety was probably split off. Whereas $Ti(O^iPr)_3Cl$ showed only modest catalytic activity, Et_2AlCl gave much better results compared to the uncatalyzed thermal reaction. Only the *endo*-adducts were formed at -23°C within 1.5 h. Further lowering of the reaction temperature had only very little effect on the selectivity.

The preferential formation of *endo*-adducts is often observed in Lewis acid catalyzed reactions [1b] and can be rationalized in terms of increased secondary orbital interactions. [8] In contrast to α,β-unsaturated esters giving *exo*/*endo*-mixtures, the enones afford exclusively *endo*-isomers under these conditions, but the diastereofacial selectivity is slightly lower. To explain these results, a non-chelating model for the Lewis acid complexation of **1** can be assumed, similar to that proposed by Ortuno [5] for the ester series.

Under high pressure conditions the enone **1** reacted with cyclopentadiene at room temperature to give the four diastereomers **2a-d**. The *endo*-selectivity is somewhat increased as compared to entry 1 in Table 1 and is further enhanced at higher pressures. This behavior is well known and is due to the the smaller activation volume of the *endo*-transition state. [9]

Enone **1** as well as its Z-isomer were also reacted with other dienes such as cyclohexadiene and 2,3-dimethylbutadiene. Because in all cases the stereoselectivity was low, we refrained from separating and analyzing the resulting diastereomeric mixtures.

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Experimental Section

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer at 300 MHz and 75 MHz, respectively. The samples were dissolved in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad singlet. Elemental analysis were performed with a Leco CHNS-932 apparatus. Optical rotations were measured on a Perkin Elmer 241 polarimeter using a 2 ml cell (c = 1.0; CH_2Cl_2).

Cyclopentadiene was cracked from the dimer and was freshly distilled before use. Catalysts were obtained from commercial sources. All manipulations of air-sensitive compounds were carried out in dry solvents under argon.

The diastereomeric ratios were determined from the intensities of 3 characteristic signals in the ^{13}C NMR spectra of the mixtures. The separation of the diastereomers was carried out by column chromatography over silica gel (eluent: ethyl acetate/hexane = 3 : 7).

Thermal Diels-Alder Reactions.

A mixture of the enone **1**[10] (2 mmol, 340 mg) and cyclopentadiene **2** (12 mmol, 792 mg) was heated at 80°C in an autoclave for 5 h. The reaction mixture was cooled and taken up with dichloromethane. The solvent and excess diene was evaporated under reduced pressure.

Catalyzed Diels-Alder Reactions.

A solution of the catalyst (1 mmol) was added to enone **1** (1 mmol, 170 mg) in dichloromethane (2 ml). The mixture was stirred at a particular temperature (see Table 1) for 10 min. Then cyclopentadiene (4 mmol, 264 mg) was added and the resulting solution was stirred until TLC showed the completion of the reaction. Water (2 drops) was added to destroy the Lewis acid complex and the mixture was stirred for 10 min. The

solution was filtered by suction over celite and the precipitate was washed several times with dichloromethane. The solution was dried ($MgSO_4$) and concentrated on a rotary evaporator.

High Pressure-Induced Diels-Alder Reaction.

These experiments were performed in a piston-cylinder high pressure apparatus for pressures up to 14 kbar, manufactured by Andreas Hofer Hochdrucktechnik GmbH, Mülheim/Ruhr, Germany. To enone **1** (1 mmol, 170 mg) in dichloromethane (2 ml) was added cyclopentadiene (2 mmol, 132 mg). This mixture was introduced into a Teflon tube (diameter: 5 mm, length: 20 cm). After sealing the tubes were immersed into the transmitter liquid of the high pressure apparatus. The piston was inserted and the pressure was raised. The reaction mixture was kept under these conditions (see Table 1). After decompression the tubes were opened and the solvent was removed.

1(*R*), 2(*R*), 3(*R*), 4(*S*)-3-Acetyl-2-[4(*S*)-2,2-dimethyl-[1,3]-dioxolane-4-yl]-bicyclo[2.2.1]- hept-5-ene (2a): ^{1}H NMR (δ/ppm, J/Hz): 6.32 (dd, 1H, 5.6/3.2, CH=C), 5.95 (dd, 1H, 5.7/2.7, CH=C), 3.98 (m, 2H, CH_2O), 3.59 (m, 1H, H8), 3.25 (d, 1H, 3.5, H4), 3.00 (d, 1H, 1.6, H1), 2.52 (dd, 1H, 1.6/4.5, H2), 2.15 (s, 3H, CH_3CO), 2.05 (ddd, 1H, 3.5/4.5/8.4, H3), 1.69 (d, 1H, 8.7, H7), 1.50 (dd, 1H, 8.7/1.7, H7'), 1.42 (s, 3H, CH_3C), 1.36 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 207.5 (C=O), 139.4 (C6), 136.4 (C5), 109.2 (OCO), 78.9 (C8), 68.7 (CH_2O), 56.2 (C3), 46.8 (C7), 46.4 (C4), 44.7 (C1), 44.0 (C2), 26.9 (CH_3CO), 26.7, 25.9 (CH_3C); white crystals, mp 59°C; $[\alpha]_{546}^{20}$ = -33.8. Anal. Calcd. for $C_{14}H_{20}O_3$ (236.31) C: 71.16%, H: 8.53%, Found: C: 70.69%, H: 8.26%.

Crystal structure analysis of compound 2a: Crystal data $C_{14}H_{20}O_3$, M_r = 236.30, monoclinic, $P2_1$, a = 5.845 (2), b = 11.980 (2), c = 9.203 (2) Å, ß = 91.10 (2)°, Z = 2, T = -100°C. Data collection: Irregular block ca. 1.0 x 0.8 x 0.4 mm, Stoe STADI-4 diffractometer, 1743 unique intensities were measured to 2Θ = 55° (Mo Kα radiation). Structure solution and refinement: Direct methods, refinement on F^2 (programm SHELXL-93, G. M. Sheldrick, Univ. of Göttingen), H atoms as rigid methyl groups or riding. Absolute configuration at C8 assumed. Final $wR(F^2)$ 0.098, conventional $R(F)$ 0.035, for 157 parameters; S = 1.04, max. Δρ = 0.21 e Å^{-3}. Full details have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany, from where this material can be obtained on quoting the full literature citation and the reference number CSD 404027.

1(*R*), 2(*R*), 3(*R*), 4(*S*)-2-Acetyl-3-[4(*S*)-2,2-dimethyl-[1,3]-dioxolane-4-yl]-bicyclo[2.2.1]-hept-5-ene (2b): ^{1}H NMR (δ/ppm, J/Hz): 6.24 (m, 2H, CH=CH), 3.83 (m, 1H, CH_2O), 3.50 (m, 1H, CH_2O), 3.45 (dd, 1H, 9.3/5.3, H8), 3.05 (d, 1H, 1.2, H1), 2.97 (d, 1H, 3.5, H4), 2.65 (dd, 1H, 1.2/4.8, H2), 2.24 (s, 3H, CH_3CO), 1.86 (ddd, 1H, 3.5/4.8/9.3, H3), 1.49 (d, 1H, 8.7, H7), 1.41 (d, 1H, 8.7, H7'), 1.37 (s, 3H, CH_3C), 1.32 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 208.5 (C=O), 136.3 (C5), 136.3 (C6), 108.3 (OCO), 78.9 (C8), 68.4 (CH_2O), 54.9 (C3), 47.3 (C4), 46.3 (C7), 45.7 (C2), 44.5 (C1), 29.7 (CH_3CO), 26.9, 25.9 (CH_3C); colourless oil; $[\alpha]_{546}^{20}$ = -35.4. Anal. Calcd. for $C_{14}H_{20}O_3$ (236.31) C: 71.16%, H: 8.53%, Found: C: 70.30%, H: 8.64%.

1(*R*), 2(*S*), 3(*S*), 4(*S*)-2-Acetyl-3-[4(*S*)-2,2-dimethyl-[1,3]-dioxolane-4-yl]-bicyclo[2.2.1]-hept-5-ene (2c): ^{1}H NMR (δ/ppm, J/Hz): 6.23 (dd, 1H, 5.5/3.2, CH=C), 5.94 (dd, 1H, 5.6/2.7, CH=C), 4.07 (m, 1H, CH_2O), 4.05 (m, 1H, H8), 3.60 (m, 1H, CH_2O), 3.23 (d, 1H, 4.1, H1), 3.00 (d, 1H, 1.5, H4), 2.54 (dd, 1H, 4.6/4.0, H2), 2.18 (s, 3H, CH_3CO), 2.01 (ddd, 1H, 4.2/1.5/8.0, H3), 1.73 (d, 1H, 8.5, H7), 1.45 (d, 1H, 7.0,

H7'), 1.38 (s, 3H, CH_3C), 1.33 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 208.5 (C=O), 138.1 (C5), 133.4 (C6), 109.0 (OCO), 79.3 (C8), 69.2 (CH_2O), 55.5 (C2), 47.0 (C7), 46.1 (C1), 46.1 (C4), 44.6 (C3), 29.3 (CH_3CO), 26.7, 25.6 (CH_3C); colourless oil; $[\alpha]_{546}^{20}$ = +40.3, Anal. Calcd. for $C_{14}H_{20}O_3$ (236.31) C: 71.16%, H: 8.53%, Found: C: 70.69%, H: 8.59%.

1(*R*), 2(*S*), 3(*S*), 4(*S*)-3-Acetyl-2-[4(*S*)-2,2-dimethyl-[1,3]-dioxolane-4-yl]-bicyclo[2.2.1]-hept-5-ene (2d): ^1H NMR (δ/ppm, J/Hz): 6.26 (dd, 1H, 5.5/3.2, CH=C), 6.05 (dd, 1H, 5.6/2.8, CH=C), 4.03 (dd, 1H, 8.0/5.9, CH_2O), 3.67 (dd, 1H, 8.0/5.9, CH_2O), 3.50 (m, 1H, H8), 2.94 (d, 1H, 3.3, H1), 2.67 (d, 1H, 1.8, H4), 2.40 (dd, 1H, 3.2/4.6, H2), 2.35 (ddd, 1H, 1.8/4.6/10.2, H3), 2.30 (s, 3H, CH_3CO), 1.60 (d, 1H, 8.5, H7), 1.40 (m, 1H, H7'), 1.34 (s, 3H, CH_3C), 1.29 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 210.7 (C=O), 137.5 (C5), 134.8 (C6), 108.8 (OCO), 80.3 (C8), 68.7 (CH_2O), 55.1 (C4), 47.9 (C1), 47.2 (C7), 46.2 (C3), 44.2 (C2), 30.1 (CH_3CO), 26.0, 25.0 (CH_3C), colourless oil; $[\alpha]_{546}^{20}$ = -55.9, Anal. Calcd. for $C_{14}H_{20}O_3$ (236.31) C: 71.16%, H: 8.53%, Found: C: 70.39%, H: 8.46%.

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