Pergamon

Tetrahedron Vol. 51, No. 6, pp. 1631-1640, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01049-8

Diastereofacial Selectivity of the Cycloaddition of Diazo Compounds to Enones

G. Galley and M. Pätzel*

Humboldt-Universität Berlin, Fachbereich Chemie, Hessische Str. 1-2, D-10115 Berlin, Germany

P. G. Jones

Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Postfach 3329, D-38023 Braunschweig, Germany

Abstract: Chiral α,β-unsaturated γ-alkoxy- or γ-amino-ketones (enones) **1** react with diazo compounds in a stereoselective manner affording conjugated Δ^2-pyrazolines **5** and **6**. In all cases *syn*-selectivity for the cycloaddition was observed. The diastereomeric ratio is improved at lower temperatures, but no significant influence of high pressure is observed. Carrying out this reaction with (E) and (Z) derivatives of the same enone **1** leads to identical products.

Introduction

Recently we reported on the 1,3-dipolar cycloaddition of azomethine ylides to enantiomerically pure enones **1** with an amino- or alkoxy-substituent in γ-position, leading to the regio- and stereospecific formation of pyrrolidines. [1]

These results prompted us to investigate the addition of diazo compounds **2** to substrates **1**. Apart from selectivity aspects, the pyrazolines formed should be of interest as precursors for the synthesis of cyclopropane derivatives.

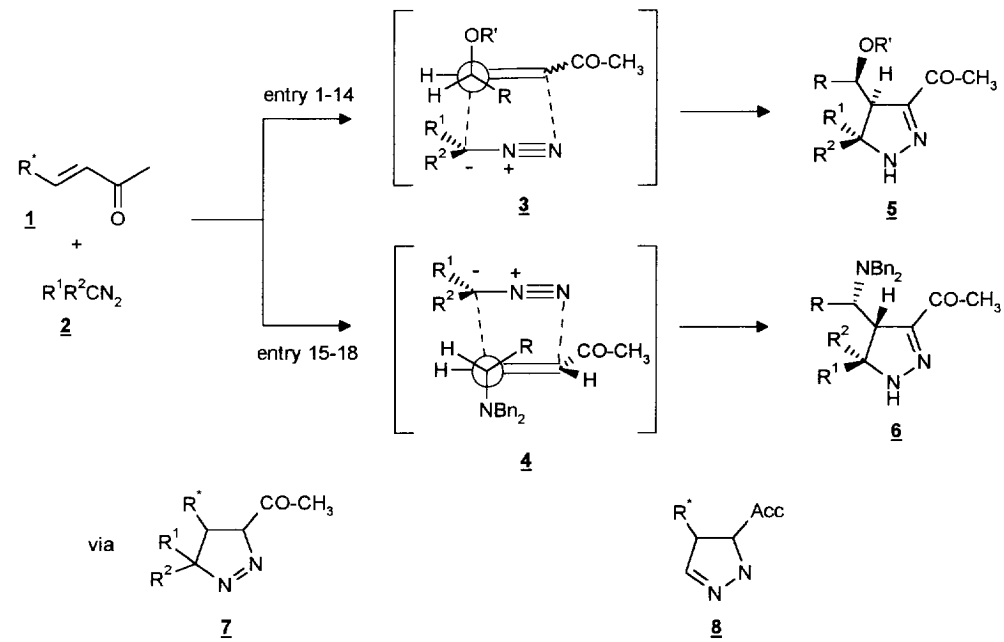
To the best of our knowledge there are only a few examples of the cycloaddition of diazo derivatives to open chain α,β-unsaturated carbonyl compounds bearing a chiral amino- or alkoxy-substituent in γ-position. [2] Mancera et al. report on the addition of diazomethane and -ethane to α,β-unsaturated esters and ketones with a sugar residue. [3] The cycloaddition leads to one single diastereomer, generally as a mixture of tautomers, which were converted to pyrazole derivatives. The formation of non-conjugated Δ^2-pyrazolines **8** was assumed for the stereoselective addition of diazomethane to γ-amino enones. [4] Similar compounds e.g. γ-amino-α,β-didehydroamino acid esters, which naturally cannot isomerize, give Δ^1-pyrazolines in reactions with diazomethane. Only in this case the absolute stereochemistry of the cycloadducts was established by X-ray analysis. [5]

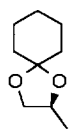
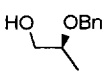
Results and Discussion

We originally intended to investigate the stereoselectivity of the addition of diazo compounds to γ-alkoxy-substituted enones **1a-c** (Tab.1, entry 1 - 14) . It turned out that the reaction proceeds with good yields and high diastereofacial selectivity at room temperature. In some cases only one diastereomer was observed according to NMR spectroscopy. Because of the instability of the products **5**, attempts to separate the diastereomers by chromatographic methods failed. It is noteworthy that a decrease of the reaction

temperature to -78 °C generally causes somewhat higher stereoselectivity (e.g. entry 1 and 2). In a few exceptions no temperature effect was observed. The bulky diphenyldiazomethane reacted stereospecifically even at 40°C. In general (Z)-enones react with slightly higher diastereoselectivity.

Scheme 1



1	a	b	c	d	e
R*					

2	R^1	R^2
a	H	H
b	Me	H
c	Ph	Ph

The tautomeric form of the products was determined with the help of DEPT ^{13}C NMR techniques. Apart from substituent signals, three signals are left for the pyrazoline ring, which belong to a secondary, a tertiary and a quarternary carbon atom. This finding clearly demonstrates that the primarily formed Δ^1-pyrazolines **7** must have undergone a 1,3-H-shift to the expected thermodynamically more stable Δ^2-pyrazolines **5**. [6]

These results are not in accord with the assumptions previously made in the γ-amino-enone series; [4] we therefore decided to include γ-amino substituted enones **1d-e** (Tab.1, entry 15 - 18) in our work. Practical investigations confirmed the analogous reaction behavior of **1d-e**, i. e. the formation of conjugated Δ^2-pyrazolines **6** rather than the non-conjugated derivatives **8**.

Table 1: Synthesis of pyrazolines **5** and **6** from enones **1** and diazo compounds **2**

entry	1	2	product	conditions	yield	ratio of diastereomers
1	**(E)-a**	**a**	**5a**	r.t., 2 h	90 %	85 : 15
2	**(E)-a**	**a**	**5a**	-78°C, 1 d	92 %	> 95 : 5
3	**(E)-a**	**a**	**5a**	r.t., 2 d, 10 kbar	97 %	77 : 23
4	**(Z)-a**	**a**	**5a**	r.t., 2 h	93 %	91 : 9
5	**(Z)-a**	**a**	**5a**	-78°C, 1d	90 %	> 95 : 5
6	**(E)-a**	**b**	**5b**	-78°C, 1d	97 %	85 : 15
7	**(Z)-a**	**b**	**5b**	0°C, 4h	91 %	95 : 5
8	**(Z)-a**	**b**	**5b**	-78°C, 1d	92 %	95 : 5
9	**(E)-a**	**c**	**5c**	40°C, 5d	90 %	> 95 : 5
10	**(Z)-a**	**c**	**5c**	40°C, 5d	91 %	> 95 : 5
11	**(E)-b**	**a**	**5d**	-78°C, 1d	90 %	83 : 17
12	**(E)-b**	**b**	**5e**	-78°C, 1d	93 %	87 : 13
13	**(E)-b**	**c**	**5f**	40°C, 5d	88 %	> 95 : 5
14	**(E)-c**	**a**	**5g**	-78°C, 1 d	85 %	70 : 30
15	**(E)-d**	**a**	**6a**	0°C, 4h	95 %	95 : 5
16	**(E)-d**	**a**	**6a**	-78°C, 1d	95 %	> 95 : 5
17	**(E)-d**	**a**	**6a**	r.t., 2 d, 10 kbar	97 %	92 : 8
18	**(E)-e**	**a**	**6b**	-78°C, 1d	94 %	95 : 5

Another goal of our investigations was to carry out 1,3-dipolar cycloadditions under high pressure conditions. [7] Some results are included in Tab. 1 and 2 (entry 3, 17, 22). However no significant change of stereoselectivity (sometimes even a slightly worse ratio of diastereomers) was found. However we succeeded in adding ethyl diazoacetate **2** (R^1 = H, R^2 = COOEt) to enones **1** under these conditions as well as in refluxing dioxane. In both cases a 50 : 50 diastereomeric mixture was formed.

The stereochemical outcome of the above reaction was determined by X-ray analyses of the major isomer of **6a** (shown in Fig. 1) and of a racemic mixture of **5b** (Fig. 2). [8] They allow us to establish the relative stereochemistry. Considering the products in the conformation as shown in scheme 1, the relative orientation at C4 and C-α of substituent in position 4 (C2/C6 in Fig. 1; C2/C4 in Fig. 2) is *syn* for both representatives of the γ-amino- and the γ-alkoxy-substituted series.

This is quite surprising for γ-alkoxy-substituted derivatives. Although it is known that the stereochemical outcome of addition reactions to such compounds depends on the reagent employed [9, 10] , in 1,3-dipolar cycloadditions *anti*-selectivity was always observed. [11,12]

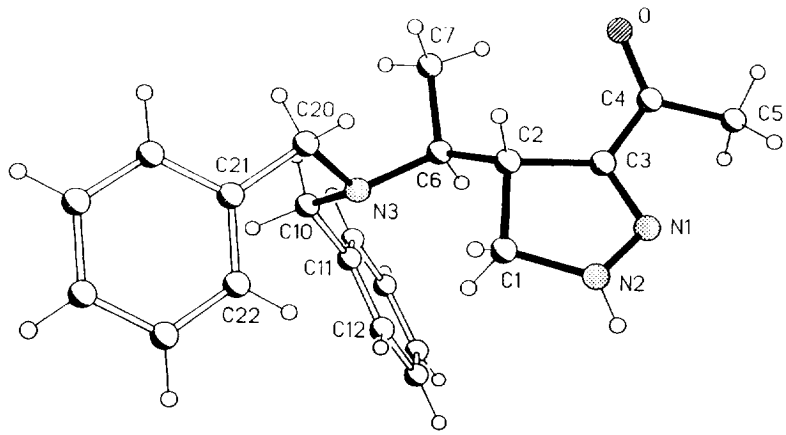


Fig. 1: X-ray structural analysis of compound **6a**

In contrast, additions to the C=C double bond of (E)-α,β-unsaturated γ-N,N-dibenzylamino-carbonyl compounds are reported to proceed via a Houk-model-like transition state [13] leading to *syn* isomers. [4,5,14] The stereochemical results of additions to the C=C bond of enones **1** are governed by the allylic moiety. Some transition state models have been applied for those reactions to allylic systems. [9, 10]

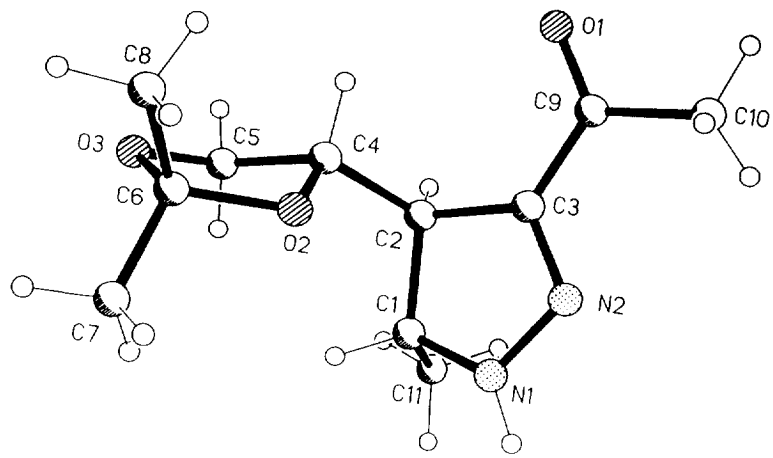


Fig. 2: X-ray structural analysis of compound **rac-5b**

Our findings can nicely be explained on the basis of the "antiperiplanar effect". [9,15,16] According to this model the substituents at the chiral center with the highest repulsion effect (in our case the heteroatoms O or N) occupy an antiperiplanar position with respect to the dipole attack. Utilizing this model for each case (amino- and alkoxy series), two reactive conformations are to be taken into account. From the stereochemistry found in the products **5** and **6**, those geometries are apparently preferred in which the hydrogen at the chiral center points to the outside region. This places the substituent R in the "inside"

position. Applying these models **3** and **4** it can be easily understood that stereoselectivity decreases as R increases in size (entry 2 and 11 or 16 and 18).[5]

Mulzer [16] and Reetz [5, 14a] proposed a modified model for similar reactions. A transition state geometry is discussed wherein the allylic H-atom points to the incoming dipole. In this way steric and torsional congestions will be minimized. These assumption leads to the same stereochemical results.

The application of Houk`s model of the "inside alkoxy effect" [17] for the γ-alkoxy-substituted series does not explain the formation of the major products **5**.

Interestingly, identical pyrazolines **5** were formed using (E)- or (Z)-isomers of enones **1.** Obviously the reaction of the Z-derivatives also proceeds via **3** [5] and is not ruled by the principle of 1,3-allylic strain. [18]

Another problem arises if diazoethane **2b** is used as the dipole. This creates further stereocenter in position 5. In this case the formation of four diastereomers is conceivable. Because only two diastereomers were found we assume that the formation of the chiral C5 atom is stereoselective. The X-ray analysis of **rac-5b** shows the position of the methyl group is *anti* with respect of the chiral substituent R*. Apparently in the transition state model **3** the substituent R^1 (R^1 = Me) turns to the less shielded side of the double bond.

In previous works the diastereoselectivity of the cycloaddition of various 1,3-dipoles to the α,β-unsaturated ester **9** was investigated [11a-c] and recently rationalized by quantum chemical methods. [11c] Data about the stereoselection of the diazomethane addition to **9** were not included because this reaction had not been investigated. However, based on theoretical calculations, it was predicted that this reaction should be "almost stereorandom". [11c] In our hands an 81 : 19 mixture was formed at 0 °C. In view of the above results, and because of similar NMR data, we assume that the main stereoisomer is again the *syn*-derivative **10**.

Scheme 2

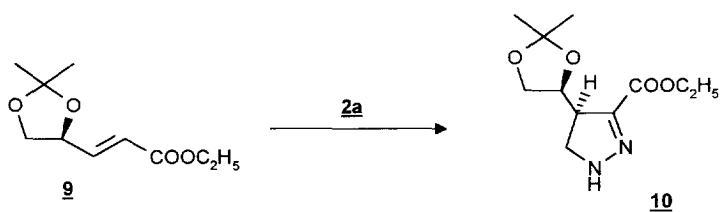


Table 2: Synthesis of pyrazoline **10** from (E)-enoate **9** and diazomethane **2a**

entry	conditions	yield	ratio of diastereomers
19	r.t., 2h	95 %	74 : 26
20	0°C, 4h	92 %	81 : 19
21	-78°C, 1d	94 %	81 : 19
22	r.t., 2 d, 10 kbar	96 %	74 : 26

Acknowledgement - G. Galley thanks the Fonds der Chemischen Industrie for a Promotionsstipendium. The continuous encouragement and support of our work by Prof. J. Liebscher, Humboldt-Universität Berlin, is thankfully acknowledged. We thank Prof. J. Mulzer, Freie Universität Berlin and Prof. J. Liebscher for a critical review of this manuscript and Prof. M. T. Reetz, Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr for the loan of a Thesis of D. Röhrig (ref. 4). Finally, experimental contributions of Mrs. K. Brosche are noted with gratitude.

Experimental Part

The ^{1}H NMR spectra were recorded on a Bruker AC-300 (300 MHz) spectrometer, the ^{13}C NMR spectra on a Bruker AC-300 (75 MHz) spectrometer. 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 in 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).

For compounds **5b**, **5d**, **5e**, **5g**, **6b** the NMR data of the major diastereomer are given. Enones **1** were synthesized according to literature procedures (**1a** [19], **1d-e** [4]) or an analogous way. The enoate **9** was purchased from Merck Co.

General procedure for the synthesis of enones 1.

To a solution of 19 mmol of the enantiomerically pure aldehyde [20] in benzene/petrolether (1/1, 150 ml) was added 20 mmol of acetylmethylene triphenylphosphorane (6.37 g). The mixture was stirred for 24 h at room temperature, then concentrated, and 150 ml of ether was added. The solid triphenylphosphine oxide was filtered off and washed several times with small amounts of ether. The combined solutions were concentrated to yield a syrup that was purified by column chromatography over silica gel (eluent: ethyl acetate/hexanes) .

5(*S*)-E-5,6-O-Cyclohexylidene-hex-3-en-2-one (1b): Bulb to bulb distillation ($Kp._{0.1mbar}$ 215°C) and following column chromatography (SiO_2, hexane : ethyl acetate = 7 : 3), yield: 77% (additional isolable compound: 4% Z-Isomer), colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 6.66 (dd, 1H, 15.9/5.8, =C<u>H</u>-CH-O), 6.27 (dd, 1H, 15.9/1.2, =CH-CO), 4.64 (qd , 1H, 6.9/1.0, CH-O), 4.15 (ABX, 1H, 6.6/8.2,CH_2O), 3.64 (ABX, 1H, 7.0/8.2, CH_2O), 1.36-1.65 (m, 10H, CH_2), 2.24 (s, 3H, CH_3-CO); ^{13}C NMR (δ/ppm): 197.9 (C=O), 143.6 (=<u>C</u>H-CH-O), 130.9 (=<u>C</u>H-CO), 110.8 (OCO), 74.6 (CH-O), 68.4 (CH_2O), 36.0, 35.1, 24.9, 23.8, 23.7 (CH_2-cyclohex.), 27.2 (<u>C</u>H_3-CO), $[\alpha]_{546}^{20}$ = +36.0°; Anal. Calcd. for $C_{12}H_{18}O_3$ (210.27): C: 68.55%, H: 8.63%, Found: C: 68.87%, H: 8.53%.

5(*S*)-E-5-Benzyloxy-6-hydroxy-hex-3-en-2-one (1c): Column chromatography (SiO_2, hexane:ethyl acetate = 1:1), yield: 82%, colourless oil; ^{1}H NMR (δ/ppm, J/Hz): 7.30-7.38 (m, 5H, arom.), 6.68 (dd, 1H, 16.2/6.2, =C<u>H</u>-CH-O), 6.31 (dd, 1H, 16.2/1.0, =CH-CO), 4.63 (AB, 1H, 11.7, CH_2-ar.), 4.47 (AB, 1H, 11.7, CH_2-ar.), 4.15 (m, 1H, CH-O), 3.59-3.71 (m, 2H, CH_2O), 3.00 (b, 1H, OH), 2.26 (s, 3H, CH_3-CO); ^{13}C NMR (δ/ppm): 198.2 (C=O), 143.3 (=<u>C</u>H-CH-O), 137.6 (ar. C), 132.5 (=<u>C</u>H-CO), 128.5, 128.0,

127.9 (ar. CH), 79.1 (CH-O), 71.5 (CH_2-ph), 64.4 (CH_2OH), 27.1 ($\underline{C}H_3$-CO), $[\alpha]_{546}^{20}$ = +54.5°; Anal. Calcd. for $C_{13}H_{16}O_3$ (220.27): C: 70.89%, H: 7.32%, Found: C: 70.47%, H: 7.20%.

Reaction of enones 1 and enoate 9 with diazo compounds 2.

Reactions with diazomethane **2a**

Diazomethane was prepared from N-methyl-N-nitroso-p-toluenesulphonamide (Diazald®, Aldrich Company) as an ether solution by using the Diazald-Kit for destillation. [21]
0.5 mmol of the enone **1** or (E)-enoate **9** was dissolved in 1 ml of diethyl ether and brought to the required temperature (see Table). Then a freshly prepared solution containing about 2 mmol of diazomethane was added. The mixture was stirred until T.L.C. showed completion of the cycloaddition. The solution was concentrated by rotary evaporation to yield pale yellow oily compounds.

Reactions with diazoethane **2b**

Diazoethane **2b** was prepared by treatment of an ether solution of N-ethyl-N'-nitro-N-nitrosoguanidine (purchased by Aldrich Company) with an aquaeous solution of potassium hydroxide.
The procedure used in the reactions with diazomethane was followed.

Reactions with diphenyldiazomethane **2c**

Diphenyldiazomethane was prepared by dehydrogenation of benzophenone hydrazone with mercuric oxide in petrolether. [22]
To 0.5 mmol of the enone dissolved in 4 ml of dichloromethane was added 0.5 mmol (97 mg) of diphenyldiazomethane. The solution was heated to reflux until T.L.C. showed completion of the reaction (about 5 days). To compensate evaporation new solvens was added from time to time. Then the mixture was concentrated to yield crystalline compounds.The compounds were recrystallized from hexane-ethyl acetate.

General Procedure for High Pressure-Induced Cycloadditions.

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.

Compound **1** or **9** (0.5 mmol) was dissolved in 1 ml of diethyl ether and the mixture was cooled to - 78°C. Then a freshly prepared solution of the diazo compound (2 mmol) was added. This mixture was rapidly introduced into a Teflon tube (diameter: 5mm, length: 20 cm). After sealing the tubes were immediately immersed into the transmitter liquid of the high pressure apparatus. The piston was inserted and the pressure is raised to 10 kbar. The reaction mixture was kept under these conditions for 2 days. After decompression the tubes were opened carefully (pressure inside), the solvent was removed and the residue analyzed using NMR techniques.

4(*R*)-3-Acetyl-4-(4(*S*)-2,2-dimethyl-[1,3]-dioxolane-4-yl)-4,5-dihydro-1H-pyrazole (5a): ^{1}H NMR (δ/ppm, J/Hz): 6.55 (b, 1H, NH), 4.38 (q, 1H, 6.3, CH-O), 4.02 (ABX, 1H, 6.3/8.6, CH_2O), 3.87 (ABX, 1H, 6.8/10.4, CH_2O), 3.67-3.75 (m, 2H, CH_2N), 3.41 (dt, 1H, 5.0/6.2, $\underline{C}H$-CH-O), 2.38 (s, 3H, CH_3-CO), 1.39 (s, 3H, CH_3C), 1.31 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 194.3 (C=O), 148.9 (C=N), 108.9 (OCO), 74.0 (CH-O), 68.6 (CH_2O), 51.2 (CH_2N), 45.4 ($\underline{C}H$-CN), 26.4 ($\underline{C}H_3$-CO), 25.7, 25.2 (CH_3C); $[\alpha]_{546}^{20}$ = +52.5°; Anal. Calcd. for $C_{10}H_{16}N_2O_3$ (212.25): C: 56.59%, H: 7.60%, N: 13.20%, Found: C: 56.21%, H: 7.62%, N: 13.07%.

4(*R*)5(*R*)-3-Acetyl-4-(4(*S*)-2,2-dimethyl-[1,3]-dioxolane-4-yl)-5-methyl-4,5-dihydro-1H-pyrazole (5b) ^{1}H NMR (δ/ppm, J/Hz): 6.81 (b, 1H, NH), 4.25 (q, 1H, 6.5, CH-N), 4.15-4.20 (m, 1H, CH-O), 4.01 (ABX, 1H, 6.2/8.7, CH_2O), 3.81 (ABX, 1H, 7.0/8.7, CH_2O), 2.99 (dd, 1H, 4.8/6.4, CH-CH-O), 2.39 (s, 3H, CH_3-CO), 1.41 (s, 3H, CH_3C), 1.32 (s, 3H, CH_3C), 1.19 (d, 3H, 6.5, CH_3CH); ^{13}C NMR (δ/ppm): 194.4 (C=O), 147.1 (C=N), 108.7 (OCO), 74.3 (CH-O), 68.1 (CH_2O), 59.5 (CHN), 52.6 (CH-CN), 26.4, 25.2 (CH_3C), 25.5 (CH_3-CO), 21.3 (CH_3CH); $[\alpha]_{546}^{20}$ = -107.2°; Anal. Calcd. for $C_{11}H_{18}N_2O_3$ (226.27): C: 58.41%, H: 7.96%, N: 12.39%, Found: C: 58.59%, H: 8.09%, N: 12.51%.

Crystal data for **rac-5b** at 173 K: $C_{11}H_{18}N_2O_3$, monoclinic, $P2_1/c$, a = 874.8 (3), b = 1343.8 (3), c = 1088.1 (3) Å, ß = 105.57 (2)° , Z = 4, Mo - $K\alpha$ radiation, Siemens R3 diffractometer, $2\Theta_{max}$ 50 °. The structure was refined on F^2 (programm SHELXL-93, G. M. Sheldrick, Univ. of Göttingen) to $wR(F^2)$ 0.155 for all 2190 reflections (conventional $R(F)$ 0.050). Other details as for **6a**.

4(*R*)-3-Acetyl-4-(4(*S*)-2,2-dimethyl-[1,3]-dioxolane-4-yl)-5,5-diphenyl-4,5-dihydro-1H-pyrazole (5c): ^{1}H NMR (δ/ppm, J/Hz): 7.12-7.34 (m, 10H, ar. CH), 6.60 (b, 1H, NH), 4.56 (d, 1H, 4.9, CH-CH-O), 3.52 (ABX, 1H, 5.9/8.6, CH_2O), 3.41-3.53 (m, 1H, CH-O), 3.45 (ABX, 1H, 6.8/8.3, CH_2O), 2.44 (s, 3H, CH_3-CO), 1.22 (s, 3H, CH_3C), 1.03 (s, 3H, CH_3C); ^{13}C NMR (δ/ppm): 193.7 (C=O), 152.1 (C=N), 145.1, 140.0, 128.7, 128.3, 127.9, 127.8, 127.7, 125.9, 107.7 (OCO), 78.9 (C-N), 74.3 (CH-O), 66.2 (CH_2O), 49.8 (CH-CN), 26.0 (CH_3-CO), 26.0, 24.5 (CH_3C); mp. 234°C; $[\alpha]_{546}^{20}$ = +8.0°; Anal. Calcd. for $C_{22}H_{24}N_2O_3$ (364.44): C: 72.50%, H: 6.64%, N: 7.69%, Found: C: 73.00%, H: 6.58%, N: 7.70%.

4(*R*)-3-Acetyl-4-(1(*S*)-1,2-O-cyclohexylidene-ethyl)-4,5-dihydro-1H-pyrazole (5d) : ^{1}H NMR (δ/ppm, J/Hz): 6.66 (b, 1H, NH), 4.26-4.16 (q, 1H, 4.5, CH-O), 3.95 (ABX, 1H, 6.2/8.6, CH_2O), 3.85 (ABX, 1H, 6.2/8.6, CH_2O), 3.60-3.75 (m, 2H, CH_2N), 3.35 (dt, 1H, 4.5/5.3, CH-CH-O), 2.31 (s, 3H, CH_3-CO), 1.32-1.53 (m, 10H, CH_2); ^{13}C NMR (δ/ppm): 194.1 (C=O), 148.6 (C=N), 109.2 (OCO), 73.6 (CH-O), 68.2 (CH_2O), 51.4 (CH_2N), 45.4 (CH-CN), 36.0, 34.6, 24.9, 23.8, 23.5 (CH_2-cyclohex.), 25.5 (CH_3-CO); $[\alpha]_{546}^{20}$ = -92.0°; Anal. Calcd. for $C_{13}H_{20}N_2O_3$ (252.31): C: 61.88%, H: 7.99%, N: 11.10%, Found: C: 61.66%, H: 7.97%, N: 10.78%.

4(*R*)5(*R*)-3-Acetyl-4-(1(*S*)-1,2-O-cyclohexylidene-ethyl)-5-methyl-4,5-dihydro-1H-pyrazole (5e): ^{1}H NMR (δ/ppm, J/Hz): 6.57 (b, 1H, NH), 4.09-4.16 (m, 1H, CH-O), 3.92 (ABX, 1H, 6.1/8.6, CH_2O), 3.75 (ABX, 1H, 6.9/8.7, CH_2O), 3.41 (q, 1H, 7.0, CH-N), 2.90 (dd, 1H, 5.0/6.8, CH-CH-O), 2.31 (s, 3H, CH_3-CO), 1.39-1.53 (m, 10H, CH_2), 1.12 (d, 3H, 6.5, CH_3CH); ^{13}C NMR (δ/ppm): 194.4 (C=O), 147.2 (C=N), 109.2 (OCO), 74.0 (CH-O), 67.9 (CH_2O), 59.8 (CHN), 52.8 (CH-CN), 36.1, 34.7, 25.0, 23.8, 23.7 (CH_2-cyclohex.), 25.5 (CH_3-CO), 21.2 (CH_3CH); $[\alpha]_{546}^{20}$ = +25.4°; Anal. Calcd. for $C_{14}H_{22}N_2O_3$ (266.34): C: 63.14%, H: 8.33%, N: 10.52%, Found: C: 63.59%, H: 8.19%, N: 10.31%.

4(*R*)-3-Acetyl-4-(1(*S*)-1,2-O-cyclohexylidene-ethyl)-5,5-diphenyl-4,5-dihydro-1H-pyrazole (5f) : ^{1}H NMR (δ/ppm, J/Hz): 7.12-7.49 (m, 10H, ar. CH), 6.61 (b, 1H, NH), 4.52 (d, 1H, 5.5, CH-CH-O), 3.69-3.81 (m, 1H, CH-O), 3.52 (ABX, 1H, 5.8/8.6, CH_2O), 3.46 (ABX, 1H, 6.8/8.4, CH_2O), 2.41 (s, 3H, CH_3-CO), 1.24-1.58 (m, 10H, CH_2); ^{13}C NMR (δ/ppm): 193.7 (C=O), 152.0 (C=N), 145.1, 140.8 (ar. C), 128.6, 128.5, 128.2, 128.1, 127.9, 127.7, 126.0 (ar. CH), 108.4 (OCO), 79.0 (C-N), 73.7 (CH-O), 66.2 (CH_2O), 50.1 (CH-CN), 35.8, 34.2, 25.0, 23.7, 23.4 (CH_2-cyclohex.), 26.0 (CH_3-CO); mp. 192°C; $[\alpha]_{546}^{20}$ = +288.0°; Anal. Calcd. for $C_{25}H_{28}N_2O_3$ (404.51): C: 74.23%, H: 6.98%, N: 6.92%, Found: C: 74.57%, H: 6.77%, N: 7.04%.

4(*R*)-3-Acetyl-4-(1(*S*)-1-benzyloxy-2-hydroxy-ethyl)-4,5-dihydro-1H-pyrazole (5g) : ^{1}H NMR (δ/ppm, J/Hz): 7.14-7.27 (m, 5H, ar. CH), 6.72 (b, 1H, NH), 3.25-4.55 (m, 9H), 2.28 (s, 3H, CH_3-CO); ^{13}C NMR (δ/ppm): 193.8 (C=O), 148.2 (C=N), 137.1 (ar. C), 127.5, 126.9, 126.8 (ar. CH), 77.7 (CH-O), 71.0 (CH_2-ph), 60.8 (CH_2OH), 50.8 (CH_2N), 41.9 (CH-CN), 24.6 (CH_3-CO).

4(*R*)-3-Acetyl-4-(1(*R*)-1-dibenzylamino-ethyl)-4,5-dihydro-1H-pyrazole (6a): ^{1}H NMR (δ/ppm, J/Hz): 7.08-7.27 (m, 10H, ar. CH), 6.51 (b, 1H, NH), 6.04 (b, 1H, NH), 3.85 (dd, 1H, 9.8/1.7), 3.70 (AB, 2H, 13.7, NCH_2-ph), 3.47-3.59 (m, 1H, CH_2N), 3.28-3.42 (m, 1H, CH_2N), 3.23 (AB, 2H, 13.7, NCH_2-ph), 2.65-2.74 (m, 1H, CH-N), 2.23 (s, 3H, CH_3-CO), 0.89 (d, 3H, 6.7, CH_3); ^{13}C NMR (δ/ppm): 194.0 (C=O), 152.5 (C=N), 139.8 (ar. C), 128.8, 128.0, 126.7 (ar. CH), 55.1 (CH_2NH), 53.5 (NCH_2-ph), 52.9 (CH-N), 44.9 (CH-CN), 10.6 (CH_3-C), 25.6 (CH_3-CO); $[\alpha]_{546}^{20}$ = +64.5°; Anal. Calcd. for $C_{21}H_{25}N_3O$ (335.45): C: 75.19%, H: 7.51%, N: 12.53%, Found: C: 74.61%, H: 7.76%, N: 12.34%.

Crystal data for **6a** at 173 K: $C_{21}H_{25}N_3O$, orthorhombic, $P2_12_12_1$, a = 722.31 (9), b = 1474.9 (2), c = 1782.1 (2) Å, ß = 105.57 (2)° , Z = 4, Mo - $K\alpha$ radiation, Siemens P4 diffractometer, $2\Theta_{max}$ 55 °, $wR(F^2)$ 0.108 for all 2533 reflections, (conventional $R(F)$ 0.040). The absolute configuration could not be determined directly but was based on the known configuration of the starting material. [23]

4(*R*)-3-Acetyl-4-(1(*R*)-1-dibenzylamino-2-phenyl-ethyl)-4,5-dihydro-1H-pyrazole (6b) : ^{1}H NMR (δ/ppm, J/Hz): 6.92-7.28 (m, 15H, ar. CH), 6.03 (b, 1H, NH), 3.81 (AB, 2H, 13.6, NCH_2-ph), 3.75-3.79 (m, 1H), 3.63 (q, 1H, 7.1, CH_2N), 3.32-3.50 (m, 1H, CH_2N), 3.32-3.50 (m, 2H, NCH_2-ph), 3.32-3.50 (m, 1H, CH-N), 3.08 + 2.65 (ABX, 2H, 3.8/14.1, CCH_2-ph), 1.98 (s, 3H, CH_3-CO); ^{13}C NMR (δ/ppm): 193.9 (C=O), 152.9 (C=N), 139.8, 139.7 (ar. C), 129.0, 128.3, 128.1, 127.9, 126.9, 125.8 (ar. CH), 58.2 (CH-N), 54.9 (CH_2NH), 54.4 (NCH_2-ph), 44.0 (CH-CN), 32.7 (CH_2-ph), 25.2 (CH_3-CO); $[\alpha]_{546}^{20}$ = -30.0°; Anal. Calcd. for $C_{27}H_{29}N_3O$ (411.55): C: 61.29%, H: 7.10%, N: 10.21%, Found: C: 61.57%, H: 7.10%, N: 10.10%.

Ethyl 4(*R*)-4-(4(*S*)-2,2-dimethyl-[1,3]-dioxolane-4-yl)-4,5-dihydro-1H-pyrazole-3-carboxylate (10) : ^{1}H NMR (δ/ppm, J/Hz): 6.46 (b, 1H, NH), 4.27 (q, 1H, 3.5, CH-O), 4.01 (ABX, 1H, 6.2/8.6, CH_2O), 3.83 (ABX, 1H, 6.6/8.0, CH_2O), 3.56-3.65 (m, 2H, CH_2N), 3.63 (q, 2H, 3.40, CH_3-CH_2), 3.27-3.31 (m, 1H, CH-CH-O), 1.28 (s, 3H, CH_3C), 1.22 (s, 3H, CH_3C), 1.21 (t, 3H, 3.40, CH_3-CH_2); ^{13}C NMR (δ/ppm): 162.7 (C=O), 140.8 (C=N), 108.9 (OCO), 74.0 (CH-O), 68.4 (CH_2O), 60.9 (CH_3-CH_2O), 51.2 (CH_2N), 46.7 (CH-CN), 26.4, 25.2 (CH_3C), 14.2 (CH_3-CH_2); $[\alpha]_{546}^{20}$ = +18.2°; Anal. Calcd. for $C_{10}H_{16}N_2O_3$ (212.25): C: 56.59%, H: 7.60%, N: 13.20%, Found: C: 56.21%, H: 7.62%, N: 13.07%.

References and Notes

1. Pätzel, M., Galley, G., Jones, P. G., Chrapkowsky, A. *Tetrahedron Lett.* **1993**, *36*, 5707.
2. For cycloaddition to achiral enones see a) Regitz, M., Heydt, H. in *1,3-Dipolar Cycloaddition* Vol.1 (Ed. Padwa), Wiley, 1984, 394-558 b) *The Chemistry of Enones* Ed. S. Patai and Z. Rapoport, Wiley, New York, 1989 c) For cycloaddition of diazo compounds to enantiomerically pure butenolides see Rispens, M. T., Keller, E., de Lange, B., Zijlstra, R.W.J., Feringa, B.L, *Tetrahedron Asymmetry* **1994**, *5*, 607.
3. Mancera, M., Rodrigez, E., Roffe, I., Galbis, J. *Carbohydrate Res.* **1991**, *210*, 167.
4. Thesis, Röhrig, U., Universität Marburg 1991.
5. Reetz, M. T., Kayser, F., Harms, K. *Tetrahedron Lett.* **1992**, *33*, 3453.
6. a) This tautomerism of pyrazolines is well known and depends on the substitution pattern. Carruthers, W., *Cycloaddition Reactions in Organic Chemistry*, Pergamon Press, 1990; b) Further prove comes from the ^{13}C NMR spectra. Due to the conjugation effect the signal of the carbonyl carbon is high field shifted.
7. In contrast to the Diels-Alder reaction nothing is known about the influence of high pressure conditions on the stereoselectivity of 1,3-dipolar cycloadditions. Matsumoto, K., Acheson, R.M, in *Organic Synthesis at High Pressures*, Wiley-Interscience, 1991.

8. A racemic mixture of **5b** was obtained by treatment of enone **1a** with KOH and subsequent cycloaddition with diazoethane. This racemic sample **rac 5b** was used for X-ray crystal analysis, because enantiomerically pure **5b** did not crystallize properly.
9. Mulzer, J., Altenbach, H.-J, Braun, M., Krohn, K., Reissig, H.-U. *Organic Synthesis Highlights*, Verlag Chemie, Weinheim 1991 and literature cited therein.
10. Patrocinio, V.L., Costa, P.R.R, Correia, C. R.D *Synthesis*, **1994**, 474 and literature cited therein.
11. a) for cycloaddition of azomethine ylides see Annunziata, R., Cinquini, M., Cozzi, F., Raimondi, L., Pilati, T, *Tetrahedron: Asymmetry,* **1991**, *2,* 1329, b) for cycloaddition of nitrile oxides see Jäger, V., Müller, I., Schohe, R., Frey, M., Ehrler, R., Häfele, B., Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8,* 79, c) for cycloaddition of nitrones and a rationale for the observed selectivities see Annunziata, R., Benaglia, M., Cinquini, M., Raimondi, L., *Tetrahedron* **1993**, *38*, 8629.
12. The cycloaddition with silylnitronates affords also *syn*-adducts. Galley, G., Pätzel, M., *unpublished results.*
13. Paddon, M.N., Rondan, N.G., Houk, K. N. *J. Am. Chem. Soc.* **1982,** *104,* 7182.
14. a) Reetz, M. T. *Angew. Chemie* **1991**, *103*, 1559, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531 b) Reetz, M.T., Röhrig, D. *Angew. Chemie* **1989**, *101*, 1732, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1706.
15. Caramella, P., Ronda, N.G., Paddon-Row, M.N., Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103,* 2438.
16. Mulzer, J., Kappert, M., Huttner, G., Jibril, I. *Tetrahedron Lett.* **1985**, *26,* 1631.
17. a) Houk, K. N., Wu, Y.-D., Duh, H.-Y., Moses, S.R. *J. Am. Chem. Soc.* **1986,** *108,* 2754; b) Houk, K. N., Paddon-Row, M. N., Rondan, N.G., Wu, Y.-D., Brown, F.K., Spellmeyer, D.C., Metz, J. T., Li, Y., Loncharich, R. J. *Science* **1986,** *231,* 1108; c) Houk, K. N., Moses, S.R., Wu, Y.-D., Rondan, N. G., Jäger, V., Schohe, R., Fronczek, F. R. *J. Am. Chem. Soc.* **1984,** *106,* 3880.
18. Hoffmann, R.W. *Chem. Rev.* **1989**, *89*, 1841 b) Hoffmann, R.W., Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113,* 5006.
19. Ronnenberg, H., Borch, G., Buchecker, R., Arpin, N., Liaaen-Jensen, S. *Phytochemistry,* **1982**, *21,* 2087.
20. a) Dumont, R., Pfander, H. *Helv. Chim. Acta* **1983**, *66,* 814; Häfele, B., Jäger, V. *Liebigs Ann. Chem.* **1987**, 85; see also ref. 10 page 248 b) Schrötter, E., Luong, T.T., Schick, H. *J. Prakt. Chem.* **1990**, *332*, 191 c) Jäger, V., Wehner, V. *Angew. Chem.* **1989**, *101*, 512; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 469. d) Reetz, M.T., Drewes, M. W., Schmitz, A. *Angew. Chem.* **1987**, *99*, 1186; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141.
21. deBoer, T. J., Backer, H. J. *Org. Synthesis, Coll. Vol. 4* **1963**, 250.
22. Miller, J. B. *J. Org. Chem.* **1959**, *24*, 560.
23. Full details of the structure determination have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen 2, Germany. Any request for material should quote a full literature citation and the reference number CSD 401196 **(rac-5b)** and 401197 **(6a)**.

(*Received in Germany* 27 *October* 1994; *revised* 23 *November* 1994; *accepted* 26 *November* 1994)