Tetrahedron Letters,Vol.26,No.13,pp 1631-1634,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

UNCATALYZED ASYMMETRIC DIELS-ALDER ADDITION OF CYCLOPENTADIENE TO (E)- AND (Z)-(R)-4,5-DI-O-ISOPROPYLIDENE-PENT-2-ENONATES

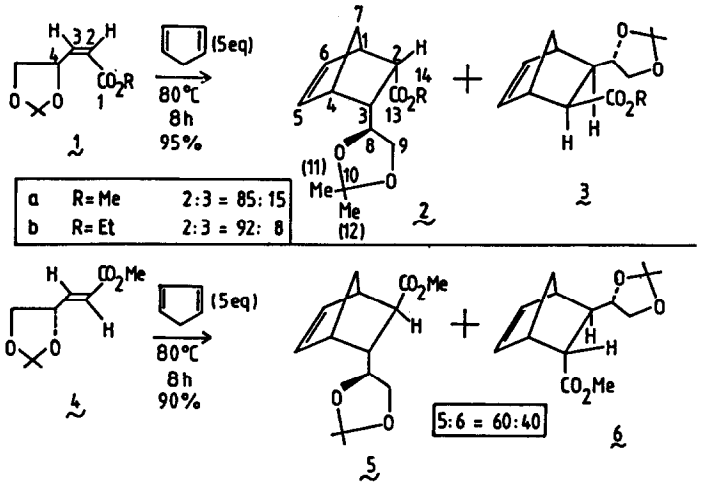
Johann Mulzer[+] and Michael Kappert
Institut für Organische Chemie der Freien Universität Berlin,
Takustr. 3, D-1000 Berlin 33
Gottfried Huttner and Ibrahim Jibril
Lehrstuhl für Synthetische Anorganische Chemie, Fakultät für Chemie,
Universität Konstanz, Postfach 5560, D-7700 Konstanz, FRG.

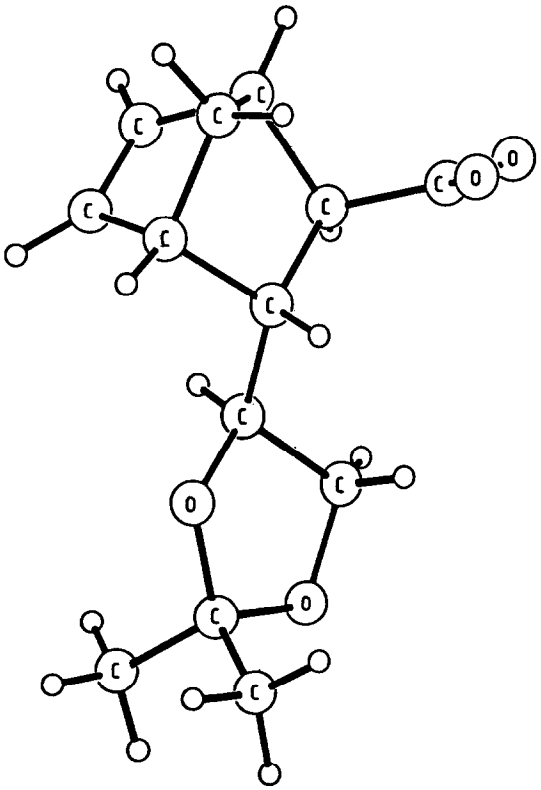
Summary: The uncatalyzed Diels-Alder addition of cyclopentadiene to the acrylic ester derivatives 1 proceeds with high diastereo- and enantioface selectivity.

Diastereoface-selective Lewis acid catalyzed Diels-Alder addition to chiral acrylic acid derivatives are under intensive investigations by several groups[1]. In connection with our studies on stereocontrolled additions of (R)-2,3-isopropylidene glyceraldehyde derivatives[2] we reacted cyclopentadiene with the acrylic esters 1 and 4[2b] under purely thermal conditions. Mixtures of 2/3 and 5/6, respectively, were obtained in high yields, and readily separated by gravity column chromatography (silicagel, hexane/ether 6:1)[3]. Basic hydrolysis of 2 with concomitant epimerization at C-2 furnished the crystalline acid 12, whose configuration was determined by X-ray analysis[4] (Fig. 1). 12 is also available by saponification of 5, so that the structures of 2 and 5 are certain. In 3 and 6 the relative configurations of C-2/3 with respect to the 8-(R)-centre have not been determined yet. However, the exo-exo- and endo-exo-arrangements of the side chains clearly follow from the ^1H-^1H-coupling constants $J_{1,2}$ and $J_{3,4}$, which throughout all adducts (2,5,3, and 6) show a value of 3.8-4.0 Hz for exo-H and 1.7-1.8 Hz for endo-H.

Two stereoproblems are involved in the addition step: 1) diastereoface selectivity with respect to the attack at C-3 in 1/4. 2) enantioface selectivity with respect to the cyclopentadiene moiety (endo-exo-selectivity).

1) The diastereoface problem is regularly interpreted in terms of the Felkin-Anh transition states 7/8, in which the double bond is attacked along a trajec-





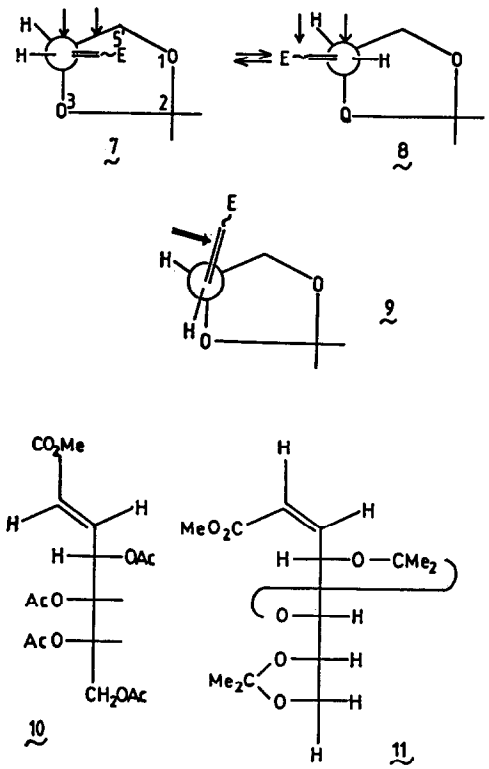


Figure 1: Crystal Structure of 12
(m.p. 66-67°C)

jectory anti to the neighbouring oxygen atom (antiperiplanar effect of electronegative substituents)[5]. This argument would leave 7 as the reactive conformation in the formation of the major products 2 and 5, a conclusion which appears unlikely in view of the severe steric congestion between the diene, C-5 and the ester group. We therefore prefer a partically eclipsed conformation like 9 which avoids unfavorable interactions and offers an open face to the attacking diene. Obviously the steric factors override the antiperiplanar effect.

2) The endo-directing effects of the ester group and the dioxolane ring are significant and cooperate in the case of 1, whereas they roughly balance each other off in the case of 4.

For an uncatalyzed Diels-Alder addition the overall stereoselection is unusually high. Under the plausible assumption that 2/3 and 5/6 merely differ with respect to the exo/endo-position of the substituents it may be concluded that in 1/4 the ul[6]-diastereoface selection is quantitative and independent of the C-1-C-2-fragment, which in turn has a clear influence on the endo-exo-ratio ranging from 60:40 (5:6) to 92:8 (2b:3b). These results are in contradiction to those reported by Horton and Machinani[7], who found complete lk[6]-diastereoface selectivity in the addition of cyclopentadiene to the acrylic ester derivatives 10/11. The reason for this discrepancy must be due to the presence of the two additional (S)-centres in the stereocontrolling appendage, which outweigh the effect of the 4-(R)-centre.

The synthetic utility of 2a,b lies in the fact that these compounds are readily available in gram quantities and, after elaboration of the appendages and/or oxidative cleavage of the 5,6-double bond may be converted into a variety of mono- and bicyclic cyclopentanoids. Via 5 the 2,3-trans-series is accessible as well. Applications of these concepts to natural product syntheses (e.g. santalene and prostaglandins) are under intensive investigation in our laboratory.

Acknowledgement. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

References and Notes

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2a) J. Mulzer, A. Angermann, Tetrahedron Lett. 24, 2843 (1983); b) J. Mulzer, M. Kappert, Angew. Chem. 95, 60 (1983); 96, 726 (1984); Int. Ed. Engl. 22, 63 (1983); 23, 704 (1984).

3) As an illustration, some analytical data are given for 2a and 3a.

2a: ^{1}H NMR ([D_6]-Benzene): δ=0.98 (d, J=9.0 Hz, 1H, 7-H); 1.29 (s, 3H, CH_3); 1.34 (d, J=9.0 Hz, 1H, 7-H); 1.49 (s, 3H, CH_3); 2.34 (ddd, J=10.0, 10.0 and 3.8 Hz, 1H, 3-H); 2.69 (dd, J=10.0 and 3.8 Hz, 1H,2-H); 2.91 and 3.20 (2 br. s,

1-H and 4-H); 3.20 (s, 3H, $CO_2C\underline{H}_3$); 3.72 (dd, J=8.0 and 6.0 Hz, 1H, acetonide-O-$C\underline{H}_2$); 3.98 (ddd, J=10.0, 6.0 and 6.0 Hz, 1H, acetonide-O-C$\underline{H}$); 4.10 (dd, J= 8.0 and 6.0 Hz, 1H, acetonide-O-$C\underline{H}_2$); 6.32 (t, J= 2.0 Hz, 2H, 2-H + 2-H.) - ^{13}C-NMR ($CDCl_3$): δ=25.10 and 27.19 (q, C-11 and C-12); 45.97,46.22, 48.43 and 49.21 (d, C-1, C-4, C-3, C-2); 46.91 (t, C-7); 51.15 (q, C-14); 69.27 (t, C-9); 77.11 (d, C-8); 107.95 (s, C-10); 135.27 and 135.54 (d, C-5, C-6); 173.40 (s, C-13). The NMR spectra were recorded at 80 MHz with TMS as internal standard. - IR(neat): 3060 m, 2980 s, 2940 s, 2865 s (CH), 1730 s (C=O), 1571 w (C=C), 1450 m, 1430 s (CH def.), 1380 s, 1370 s (gem. CH_3), 1335 s, 1245 s, 1202 s, 1184 s, 1147 s, 1068 s (C-O), 1052 s, 967 m, 935 m, 910 m, 860 s, 847 s, 725 s cm^{-1}. $[\alpha]_D^{22}$=20.4° (c=6.66, $CHCl_3$). - MS (70 eV, 60°C): m/e=252 (2.8%, M^+); 237 (20.9%, M^+-CH_3); 221 (20.9%, M^+-OCH_3); 194 (27.9% M^+-$(CH_3)CO$); 186 (6.3%, M^+-C_5H_6); 177 (4.9%); 162 (18.2%); 152 (13.9%); 129 (33.5%); 117 (31.4%); 111 (63.6%); 101 (16.1%, -acetonide); 97 (36.4%); 91 (16.7%); 72 (33.6%); 66(100%, -C_5H_6); 59 (16.8%, -CO_2CH_3).

3a: ^{1}H-NMR ($[D]_6$-Benzene): δ=1.25 (s, 3H, $C\underline{H}_3$), 1.35 (d, J=9.0 Hz, 1H, 7-H); 1.38 (s, 2H, $C\underline{H}_3$); 1.72 (ddd, J=8.0, 8.0 and 1.8 Hz, 1H, 3-H); 2.15 (dd, J=8.0 and 1.8 Hz, 1H, 2-H); 2.20 (d, J=9.0 Hz, 1H, 7-H); 2.70 and 3.16 (2 br. s, 1-H and 4-H); 3.24 (s, 3H, $CO_2C\underline{H}_3$); 3.53 (dd, J=8.0 and 6.0 Hz, 1H, acetonide-O-$C\underline{H}_2$); 3.89 (dd, J=8.0 and 6.0 Hz, 1H, acetonide-O-$C\underline{H}_2$); 4.20 (ddd, J=8.0, 6.0 and 6.0 Hz, 1H, acetonide-O-C$\underline{H}$); 5.84 (dd, J=5.5 and 3.0 Hz, 1H, 2-H or 3-H); 6.02 (dd, J=5.5 and 3.0 Hz, 1H, 2-H or 3-H). - ^{13}C-NMR ($CDCl_3$): δ=25.29 and 26.98 (q, C-11, C-12); 43.88 (t, C-7); 44.04, 44.79, 47.06 and 47.76 (d, C-1, C-4, C-3, C-2); 51.58 (q, C-14); 68.84 (t, C-9); 77.08 (d, C-8); 108.37 (s, C-10); 136.63 and 139.14 (d, C-5, C-6); 175.22 (s, C-13). The NMR spectra were recorded at 80 MHz with TMS as internal standard. - IR(neat): 3060 m, 2992 s, 2948 s, 2880 s (CH), 1730 s (C=O), 1570 w (C=C), 1455 m, 1432 s (CH def.), 1380 s, 1370 s (gem. CH_3), 1352 s, 1325 m, 1252 s, 1238 s, 1210 s, 1180 s, 1150 s, 1060 s (C-O), 1032 s, 938 m, 897 m, 860 s, 790 m, 720 s cm^{-1}. $[\alpha]_D^{22}$=65.9° (c=6.66, $CHCl_3$).

4) Structural data: $C_{13}H_{18}O_4$ (238.28), orthorhombic, $P2_12_12_11$, a=10.18(1), b= 12.297(8), c=19.50(3) Å, V=2441 Å^3, Z=8, ρ_{calc}=1.30 gcm^{-3}, $\mu_{Mo\text{-}K\alpha}$=1.0 cm^{-1}, λ=0.71069 Å, 2°< 2θ <45°, total reflections =1841, of which 1547 reflections with I>2σ, R_1=0.074. R_2=0.076. ω-scan with 1.8< $\dot{\omega}$ <29.3 min^{-1}.[8]

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8) The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication.

(Received in Germany 2 November 1984)