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Kinetic Resolution in Diels-Alder Processes

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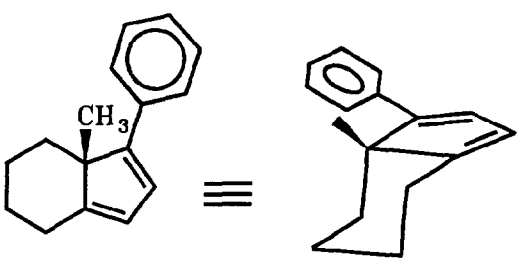
This paper is dedicated to the memory of Günther Snatzke

Abstract: Examples of highly efficient kinetic resolutions with the bicyclic chiral cyclopentadiene **1** and several selected cyclic dienophiles are reported. In combination with a thermal retro-Diels-Alder process this procedure provides easy access to both enantiomers of these dienophiles.

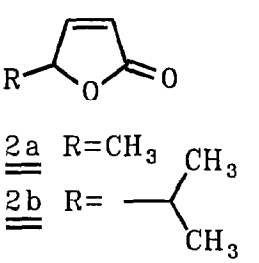
Chiral cyclopentadienes with very clear cut topological preferences have been shown to give rise to cycloadducts with a high degree of selectivity.[1,2,3]

If they are treated with chiral racemic, cyclic dienophiles, stereogenic centres in the close neighbourhood of the 2π-system are expected to influence strongly cycloaddition rates of the corresponding enantiomers. This type of chiral recognition may in selected cases lead to kinetic resolution. Having cyclopentadiene **1** available we choose as a simple, and from the synthetic view point, useful example[4] butenolide **2** as a promising candidate to check this possibility.

Since very reliable face selectivity (β-approach) and endo-selectivity have been shown to go along with predictable regioselectivity one can, on the basis of the endo-transition state **3**, safely argue in favour of the S-enantiomer as the acceptable candidate for the Diels-Alder addition, while the R-enantiomer should suffer form a strong methyl group - diene interaction in the transition state. To ensure the mildest possible reaction conditions we decided on a high pressure process with mild Lewis acid catalysis ($ZnCl_2$) and were very pleased to note excellent recognition in the case of the butenolides **2a** and **2b**.

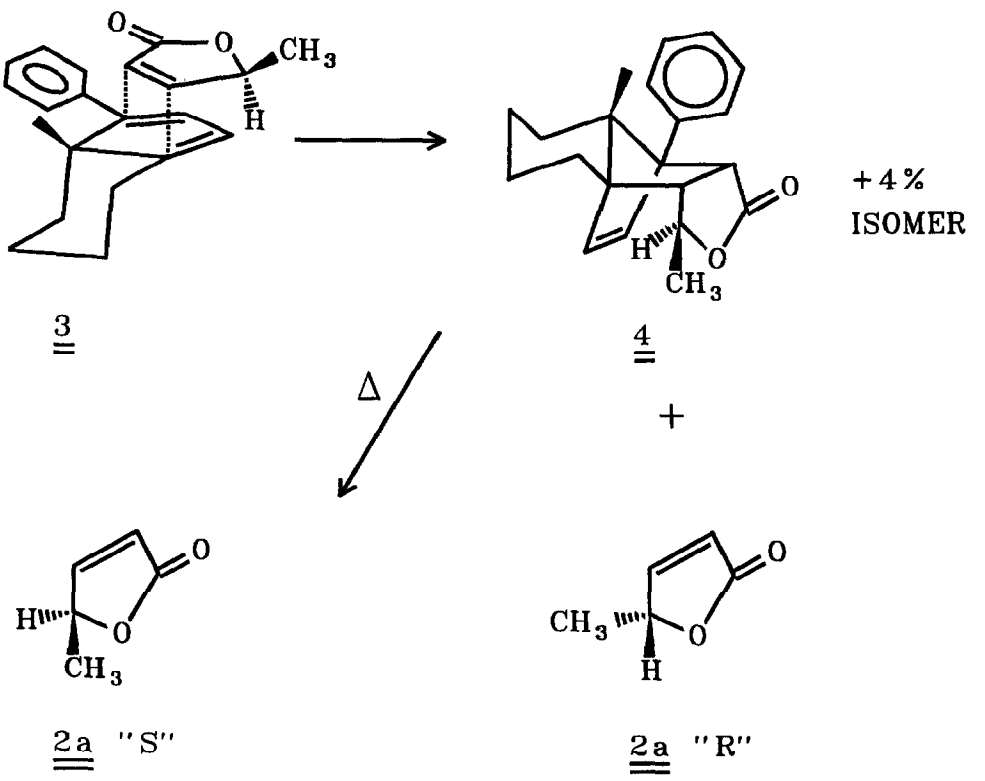


1



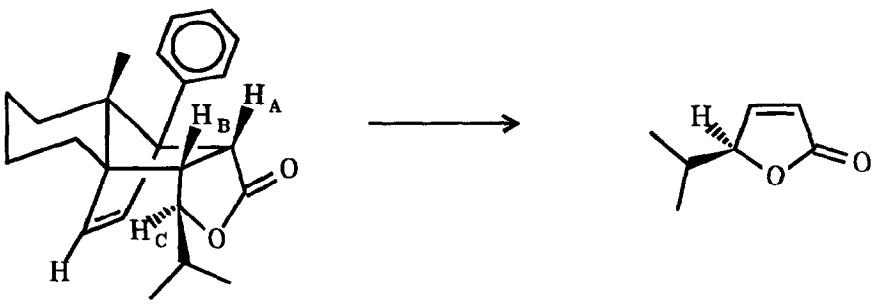
2a R=CH_3

2b R=



3 4 2a "S" 2a "R"

While the first formed adduct **4**, was accompanied by 4% of the regio and the stereoisomer (1 : 1) which could, however, be separated by flash chromatography, the reaction with the more bulky isopropyl group gave rise to cycloadduct **5** exclusively. In both cases NMR-data indicated very clearly that they represented the adduct of the "S"-enantiomer. Of particular help for this assignment are the resonances for H_A, H_B, H_C which leave no doubt as far as the purity and the absolute configuration of **5** is concerned. (For relevant NOE-measurements see Table 1.)



5 2b "R"

Table 1

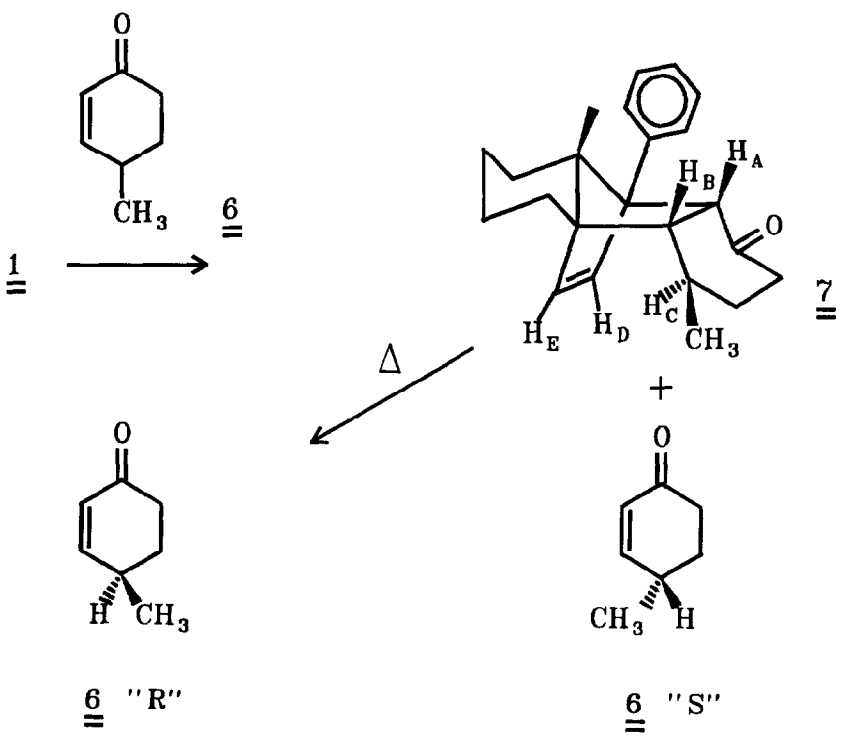
Irradiation		NOE observed
6.17	(H_E)	H_C (7%)
4.02	(H_A)	H_B, CH_3, C_6H_5
3.71	(H_C)	H_E, H_B, H_D
0.80	(CH_3)	H_A, H_B, C_6H_5

Table 2

Irradiation		NOE observed
5.93	(H_E)	H_D (6 %)
3.66	(H_A)	H_B, CH_3 (S)
0.78	(CH_3, S)	H_A, H_B, C_6H_5

Both adducts **4** and **5** underwent thermal retro-Diels-Alder processes to give rise to enantiomerically pure[5] butenolides in very high chemical yield.

The related cyclohexenones and cyclopentenones are considered to be valuable intermediates and so we also addressed the problem of kinetic resolution for two compounds from this area. A very efficient separation of enantiomers was noticed with 4-methyl-cyclohexenone **6**. Again one cycloadduct was generated exclusively and NMR-data were completely in line with constitution and configuration **7** for this adduct (see NOE data in Table 2); particularly relevant information being the lack of any Overhauser effect at the methyl doublet (1.09 δ) on irradiation at H_E.

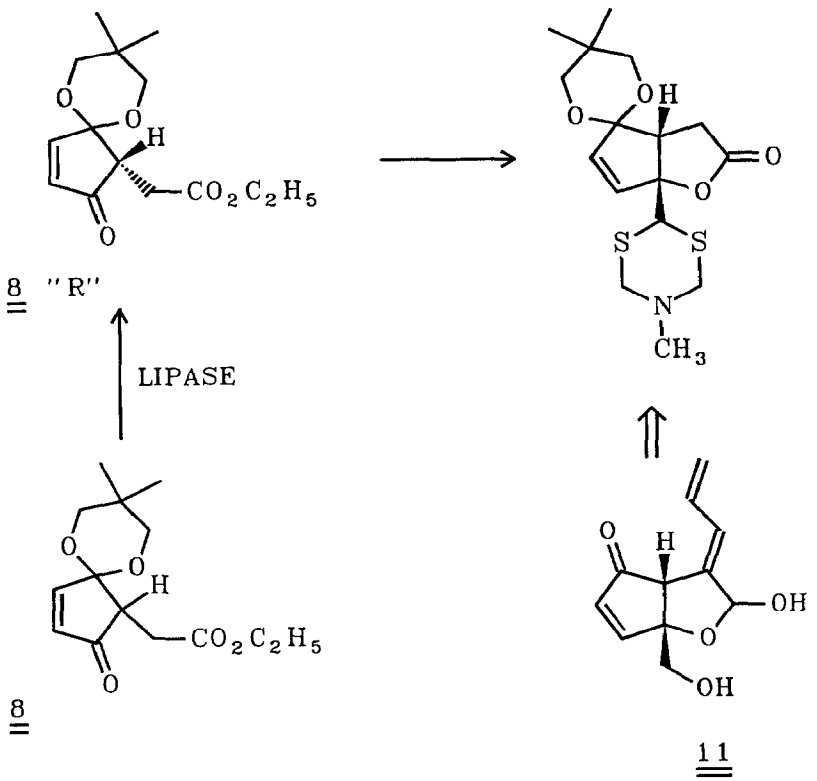


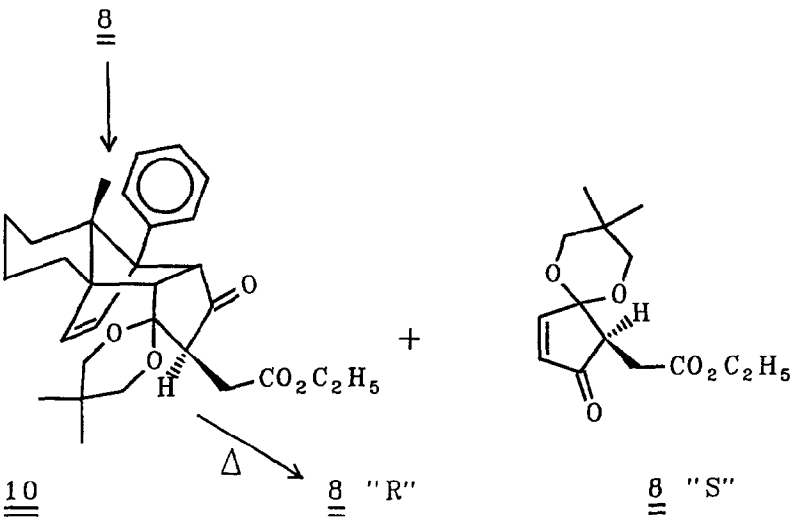
The 6"S"-enantiomer remained untouched in the reaction mixture and can be purified by chromatography.

For an example from the cyclopentenone field we decided in favour of ketal **8** which had already served very well in our recent enantioselective preparation of the didemnenones **11**.[6] The desired pure enantiomer **8**"R" had for this synthesis been obtained by a lipase hydrolysis of the racemic mixture, which left configuration **8**"R" untouched. But as the enantiomer **8**"S" was under these conditions converted into an acid its safe isolation and purification posed serious problems. Kinetic resolution of the ester was therefore considered the method of choice to lay hands on both enantiomers of this ketoester.

Although the cycloaddition was in this case comparatively slow the cycloadduct obtained could easily be proven again by NMR-data to have an absolute configuration as portrayed in **10**. Subsequent heating of this material produced enantiomerically pure **8**"R" which turned out to be of the same absolute configuration as the non hydrolyzed ester of the lipomod-PC-treatment. Although the absolute configuration of the lipase product had been determined by an X-ray structure analysis of lactone **11**, which results from nucleophilic attack of a 1,3-dithiane anion, the computations were not completely unambiguous.

The completely predictable kinetic resolution experiment thus serves very well as a final proof for the configuration assignment of this important intermediate. In conclusion one may state that cyclic racemic 2π-systems with a stereogenic centre at the α- or β-position to the double bond are extremely promising candidates for a highly predictable and quite efficient kinetic resolution in a high pressure Diels-Alder process. Further applications are actively investigated.





Experimental

IR spectra were taken in chloroform with a Perkin-Elmer 580. For 1H- and 13C-NMR spectra Bruker WH-90, WP-200, AM-300 and WM-400 were used with solvents indicated. Mass spectra were recorded with a Finnigan MAT-312 at an ionization potential of 70 eV, and elemental analyses were done with a Heraeus CHN rapid analyzer. For TLC separation Merck plates 60 F/254 were used and for flash chromatography Baker silica gel 30-60 υm. The high pressure experiments were run in a commercial Nova Swiss apparatus.

General procedure for cycloadditions: 9 mmol of diene **1** and 5 mmol of the dienophile are mixed with 4.5 ml of a 2.2M solution of $ZnCl_2$. This mixture was sealed in a teflon hose and pressurized as indicated. For work up 10 ml of sat.aq. NH_4Cl was added and this was followed by extraction with dichloromethane. The solution was dried with $MgSO_4$, filtered, and concentrated. The separation of adduct and non reacted enantiomer was achieved by flash chromatography on silica (petrolether/ether 5 : 1).

Cycloadduct **4**: 6.5 kbar, 70 h, RT. Yield: 48%; $[\alpha]_D$: -82.6 (C = 1.03, CHCl3); IR (CHCl3): 2932, 2864, 1756, 1600, 1444, 1384, 1180 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.19-7.43 (m, 5H), 6.29 (d, J = 6, 1H), 6.17 (d, J = 6, 1H), 4.15 (d,q, J = 3, J = 7, 1H), 4.11 (d, J = 9, 1H), 2.58 (dd, J = 3, J = 9, 1H), 1.82-2.07 (m, 2H), 1.01-1.78 (m, 5H), 1.38 (d, J = 7, 3H), 0.78 (s, 3H), 0.69 (d, J = 13, 1H) ppm ; MS (50°C): m/z (%) = 308 (M^+,18), 307 (59), 250 (15), 237 (62), 221 (70), 210 (100), 195 (26), 181 (42), 167 (55), 152 (17), 141 (12), 105 (39), 91 (45), 77 (26). HRMS: m/z calcd. for $C_{21}H_{24}O_2$ 308.1776; found 308.1775.

(R)Angelica lactone was purified by distillation to yield 30% **2a** which proved to be identical to a sample as described earlier.[5]

Cycloadduct **5**: 6.5 kbar, 3 d, RT. Yield: 38%, m.p. 125°C (ether); $[\alpha]_D$: -88.3 (C = 1.035, $CHCl_3$); IR (KBr): 3057, 2955, 1757, 1604, 1176, 1019, 762 cm^{-1}; ^{1}H-NMR (200 MHz, CDCl3): δ = 7.21-7.42 (m, 5H), 6.29 (d, J = 6, 1H), 6.17 (d, J = 6, 1H), 4.02 (d, J = 9, 1H), 3.71 (dd, J = 3.5, J = 6.5, 1H), 2.67 (dd, J = 3.5, J = 9, 1H), 1.03-2.06 (m, 8H), 0.97 (d, J = 7, 3H), 0.93 (d, J = 7, 3H), 0.80 (s, 3H), 0.63-0.76 (m, 1H) ppm; MS (20°C): m/z (%) = 336 (M^+,10), 237 (24), 221 (21), 210 (100), 196 (11), 181 (11.7), 167 (21), 165 (11), 121 (24), 91 (10); HMRS: m/z calcd. for $C_{23}H_{28}O_2$ 336.2098; found 336.2089; anal. found C 81.77, H 8.58; $C_{23}H_{28}O_2$ requires C 82.10, H 8.39.

(S)-Isopropyl butenolide was purified by distillation to yield 36% of the S-enantiomer identical to a sample as described earlier.[5]

Cycloadduct **7**: 6.5 kbar, 3 d, RT. Yield: 41%, m.p. 128°C; $[\alpha]_D$: +15.2 (C = 1.025, $CHCl_3$); IR (KBr): 3028, 2921, 1703, 1604, 1497, 1460, 1446, 760, 703 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.15-7.36 (m, 5H), 6.23 (d, J = 6, 1H), 3.66 (d, J = 10, 1H), 2.25-2.41 (m, 2H), 1.77-2.13 (m, 3H), 1.52-1.72 (m, 3H), 1.15-1.46 (m, 5H), 1.09 (d, J = 6, 3H), 0.78 (d, J = 1, 3H), 0.44-0.56 (m, 1H) ppm; MS (120°C): m/z (%) = 320 (M^+,2), 212 (19), 210 (100), 196 (11), 167 (15); HRMS: m/z calcd. for $C_{23}H_{28}O$ 1320.21401; found 320.21403.

Cycloadduct **10**: 9 kbar, 4 weeks, RT. Yield: 49%, colourless oil; $[\alpha]_D$: -14.7 (C = 1.0, $CHCl_3$); IR ($CHCl_3$): 1732, 1132, 1104 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.17- 7.44 (m, 5H), 6.32 (d, J = 6, 1H), 6.08 (d, J = 6, 1H), 4.10 (q, J = 7, 2H), 3.2-3.9 (m, 6H), 2.57 (dd, J = 6, J = 17, 1H), 2.48 (dd, J = 7, J = 17, 1H), 2.26 (d, J = 11, 1H), 2.04 (d,tr, J = 4, J = 14, 1H), 1.34-1.79 (m, 5H), 1.21 (tr, J = 7, 3H), 1.12 (s, 3H), 0.82 (s, 3H), 0.78 (s, 3H), 0.67 (d, J = 13, 1H) ppm; MS (120°C): m/z (%) = 478 (M+,33) 433 (4), 392 (8), 264 (17), 236 (13), 210 (100), 195 (11), 167 (23), 141 (53); HRMS: m/z calcd. for $C_{30}H_{38}O_5$ 478.271925; found 478.27176.

Ketalester 8 "S" was purified by chromatography to provide a 40% yield of a colourless oil, $[\alpha]_D$: -29.1 (C = 1.12, $CHCl_3$). The spectroscopic data proved this compound to be identical to the material described earlier.[6]

General procedure for retro-diene reactions: 0.5 mmol of the corresponding adduct was pyrolyzed at 300°C. The material obtained this way was separated to yield the diene **1** in the early non polar fractions and provided ketalester 8 "R" with petrolether/ether 1 : 1. $[\alpha]_D$: +34.1 (C = 0.64, $CHCl_3$).

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