Kurzmitteilung / Short Communication

Diels-Alder Reaction of Racemic β-Isopropyl-α-methylene-β-lactone with Enantiomerically Pure 5,6,7,7a-Tetrahydro-7a-methyl-1-phenyl-4*H*-indene and Retro Cleavage of the Resulting Spiro-β-lactones: The First Case of a Perfect Topological Resolution

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The racemic β-isopropyl-α-methylene-β-lactone **1** undergoes a configuration-dependent, highly selective [4 + 2] cycloaddition to the enantiomerically pure cyclopentadiene **2**; chromatographic separation of the adducts and subsequent thermal retro cleavage provide the pure enantiomers (*S*)-**1** and (*R*)-**1** in 99% e.e.

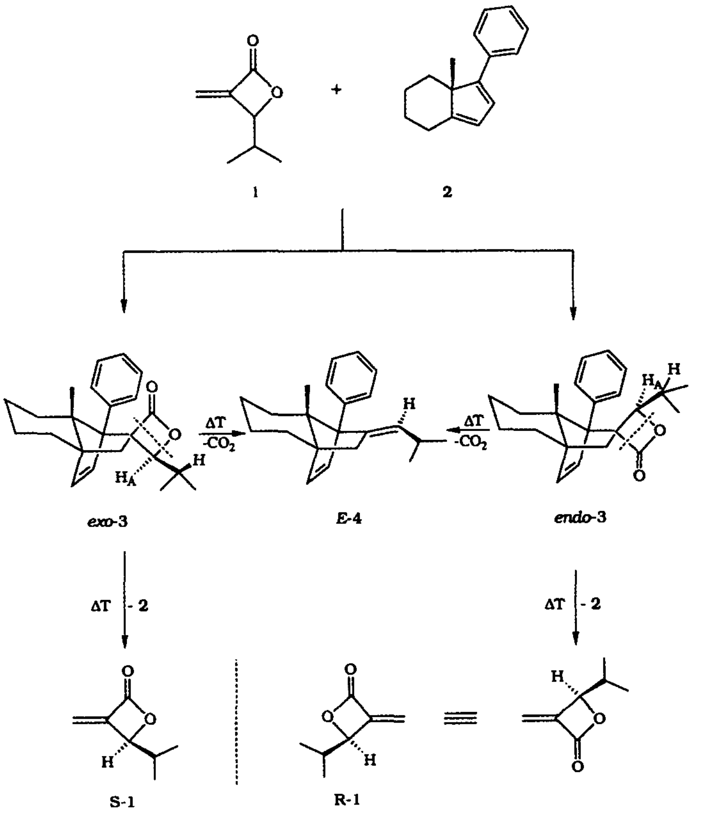
Recent selectivity tests with the enantiomerically pure cyclopentadiene **2** disclosed the fact that α-substituted dienophiles like itaconic and citraconic anhydride provide, in contrast to unsubstituted ones, *exo* adducts nearly exclusively[1]. If one chooses a chiral α-substituted dienophile such as the α-methylene-β-lactone **1**, *exo* addition should only operate for the (*S*) enantiomer to form the *exo*-**3** adduct (Scheme 1). The (*R*) isomer may not cycloadd at all, as we have recently demonstrated for butenolides[1b], or undergo *endo* addition to form *endo*-**3**, in which steric interactions are minimized as well. The first case entails the well-established phenomenon of kinetic resolution, the second case constitutes a stereoselective process based on topological resolution. Applied to Diels-Alder cycloadditions, in a topological resolution the reacting molecules are configurated in such a way that their approach is obliged to occur only from one face of each of the two diastereofacial partners.

The α-methylene-β-lactone **1** is readily available[2], and since its cycloaddition to cyclopentadiene has been described already[3], we were confident that the Diels-Alder reaction would take place. However, the retro cleavage was expected to constitute a problem since with the unsubstituted cyclopentadienes *exo* as well as *endo* adducts did not regenerate the α-methyl-β-lactone on pyrolysis at 400°C, but instead decarboxylation to form a semicyclic double bond[4] occurred (see dotted lines in *exo-* and *endo*-**3**). For the phenyl-substituted diene **2**, nonetheless, generally much lower retro cleavage temperatures (250–300°C) are necessary[1] and, therefore, retro cleavage to yield (*S*)-**1** and (*R*)-**1** instead of decarboxylation to (*E*)-**4** was in principle feasible.

Under high pressure (6.5 kbar) and at room temperature the racemic mixture of lactones underwent smooth cycloaddition to form a 1:1 mixture of the two isomeric Diels-Alder adducts *exo*- and *endo*-**3** in 98% yield. These were conveniently separated by flash chromatography, and each was isolated in 48% yield (total 96%). MS and NMR data (see Experimental) left no doubt that these were the expected [4 + 2] cycloadducts.

Their configuration was assigned by NMR spectroscopy. The *exo*-configurated cycloadduct **3** is characterized by carbonyl deshielding of the angular methyl group, whose signal is located at $\delta = 1.32$. The same is true for the *ortho*-protons of the phenyl ring, whose signals appear as a separate multiplet centered at $\delta = 7.52$. As one should expect for *exo*-**3**, irradiation of the lactone proton H_A gives rise to an NOE with the two neighboring olefinic protons.

Scheme 1



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This establishes the *exo* orientation in *exo*-**3** as well as the absolute configuration at the lactone center.

For the second isomer, which was formed in exactly the same amount, the *endo* configuration was indicated by the normal proton resonances (no carbonyl deshielding) for both the methyl group and the aromatic ring. Again, NOE for H_A established the configuration portrayed in *endo*-**3**, as evidenced by appreciable enhancements with the protons of the angular methyl group and the aromatic ring.

One quite characteristic, but not predicted difference between *exo*- and *endo*-**3** was seen in the coupling constants for the doublet of H_A, i.e. 8.0 Hz for *exo*-**3** and only 1.5 Hz for *endo*-**3**. Inspection of molecular models left no doubt that only in *exo*-**3** the coupling protons (H_A and the isopropyl methinyl proton) possess an antiperiplanar arrangement, while in *endo*-**3** the low-energy conformation of the coupling protons are nearly 90° to one another. Again, these coupling-constant data are well in line with the assigned configurations of *exo*- and *endo*-**3**.

As expected, vacuum flash pyrolysis led to retro cleavage already at 300°C, and decarboxylation to the olefin (*E*)-**4** proved to be only a minor product (ca. 5%). As had been noticed already[4] for the parent cyclopentadiene adduct, only the (*E*)-configurated olefin **4** was formed and thus retention obtained. Since NOE measurements established the (*E*) configuration for the parent cyclopentadiene case[4] and given the fact that only one exocyclic olefin product was formed on decarboxylation, we relied on the very close similarity in the chemical shifts for configurational assignment.

The separate lactones (*S*)-**1** (71%) and (*R*)-**1** (74%) and the regained diene **2** (92%) were isolated from the pyrolysate by flash chromatography. NMR measurement with (+)-HFC (Aldrich) as chemical shift reagent established an e.e. value of >98%. More accurate HPLC data, provided by Professor Mosandl (Frankfurt), proved the e.e. to be 99% in both cases.

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Experimental

High-pressure experiments were conducted at 6.5 kbar in a NOVA-SWISS instrument. – TLC sheets were Alugram SIL G/UV_{245} (Merck).

Adduct Formation: A mixture of lactone **1** (169 mg, 1.34 mmol), diene **2** (470 mg, 2.24 mol) and CH_2Cl_2 (0.1 ml) was transferred to a teflon tube and stored at room temp. and 6.5 kbar for 11 d. Subsequent flash chromatography on silica gel [petroleum ether/ether (25:1)] afforded the adducts as colorless solids each in 48% yield.

exo-**3**: M.p. 90–91°C. – IR ($CHCl_3$): $\tilde{\nu}$ = 2929 cm^{-1}, 1801, 1603. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.57 (br. d, *J* = 12 Hz, 1H), 0.84 (d, *J* = 7 Hz, 3H), 0.93 (d, *J* = 7 Hz, 3H), 1.32 (s, 3H), 1.79 (d, *J* = 13 Hz, 1H), 1.19–1.90 (m, 8H), 2.24 (d, *J* = 13 Hz, 1H), 3.74 (d, *J* = 8 Hz, 1H), 6.15 (d, *J* = 6 Hz, 1H), 6.21 (d, *J* = 6 Hz, 1H), 7.23–7.43 (m, 3H), 7.47–7.58 (m, 2H). – MS: *m/z* (%) = 336 (4.5) [M^+], 292 (6.0), 210 (100), 195 (13), 181 (19), 167 (42). – $C_{23}H_{28}O_2$: calcd. 336.2089; found 336.2057 (MS).

endo-**3**: M.p. 133–134°C. – IR ($CHCl_3$): $\tilde{\nu}$ = 2934 cm^{-1}, 1806, 1605, 1126. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.93 (d, *J* = 7 Hz, 3H), 0.95 (d, *J* = 7 Hz, 3H), 1.09 (s, 3H), 1.18–1.59 (m, 5H), 1.59–1.72 (m, 1H), 1.79 (s, 2H), 1.82–1.97 (m, 2H), 2.08 (dsept, *J* = 7/1.5 Hz, 1H), 3.81 (d, *J* = 1.5 Hz, 1H), 6.16 (d, *J* = 6 Hz, 1H), 6.29 (d, *J* = 6 Hz, 1H), 7.24–7.45 (m, 5H). – MS: *m/z* (%) = 336 (1) [M^+], 292 (2), 210 (100). – $C_{23}H_{28}O_2$: calcd. 336.2089; found 336.2057 (MS).

Retro Cleavage: 169 mg (0.50 mmol) of the corresponding Diels-Alder adduct was pyrolyzed at ca. 300°C/0.8 Torr and the pyrolysate separated by flash chromatography on silica gel [petroleum ether/ether (10:1)] to yield diene **2** (92%), 5% of olefin (*E*)-**4** and the corresponding lactones.

(R)-4-(1-Methyletyhl)-3-methylene-1-oxetane-2-one [(*R*)-**1**]: Yield 45 mg (71%). – $[\alpha]_D$ = –59 (*c* = 0.765; $CHCl_3$). – Data see ref.[2b].

(S)-4-(1-Methylethyl)-3-methylene-1-oxetane-2-one [(*S*)-**1**]: Yield 47 mg (74%). – $[\alpha]_D$ = +62 (*c* = 0.695; $CHCl_3$). – Data see ref.[2b].

The olefin (*E*)-**4** was shown to be the same material in both pyrolyses, and its structure assignment rests on the following spectral data of the combined material. – IR ($CHCl_3$): $\tilde{\nu}$ = 2952 cm^{-1}, 2924, 2860, 1600, 1132, 1100. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.43 (br. d, *J* = 13 Hz, 1H), 0.81 (s, 3H), 0.83 (d, *J* = 7 Hz, 3H), 1.03 (d, *J* = 7 Hz, 3H), 1.11–1.97 (m, 8H), 2.18 (dd, *J* = 14/2 Hz, 1H), 2.34 (dsept, *J* = 10/7 Hz, 1H), 5.14 (td, *J* = 10/2 Hz, 1H), 5.88 (d, *J* = 6 Hz, 1H), 6.05 (d, *J* = 6 Hz, 1H), 7.18–7.45 (m, 5H). – MS: *m/z* (%) = 292 (8.8) [M^+], 277 (3), 249 (6), 210 (40), 167 (100).

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