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Diastereoselectivity in the Formation of Bicyclic Cyclopropane Carboxylic Acid Lactones

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Abstract: The intramolecular cyclization of malonic acid allylic esters yields bicyclic cyclopropane carboxylic acid lactones in a phase transfer catalysed reaction. The substituents of the allylic moiety and the reaction temperature influence the diastereomeric composition of the products.

Keywords: cyclopropanes; diastereoselectivity; ^{1}H-NMR; conformational analysis

Cyclopropane carboxylic acid derivatives are useful intermediates for the preparation of natural and unnatural biologically active compounds,[1-4] such as the pyrethroid type insecticides. Most of the biologically active cyclopropane derivatives have one or more chiral centers and their biological activity significantly depends on the configuration of the stereoisomers; e.g. the relative toxicity data of the stereoisomers of the pyrethroid insecticide Allethrin (Fig. 1) for housefly differ by about two orders of magnitude.[5]

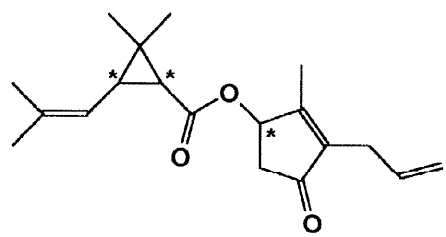

Fig. 1

Recently we have developed a new convenient phase transfer catalytic method for the preparation of cyclopropane carboxylic acid derivatives[6] from non-activated olefins and CH-acids, e.g. malonic esters in the presence of solid potassium carbonate, iodine and a lipophilic quaternary ammonium salt, usually tricaprylmethyl ammonium chloride (Aliquat®, TCMC). If the

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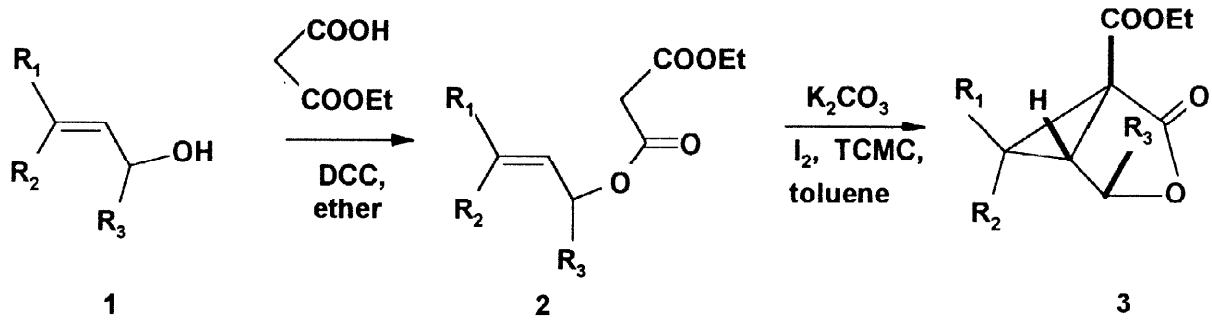
CH-acid moiety is incorporated into the side chain of an olefin at a favourable position, such as in the malonic acid allylic esters **2**, an intramolecular reaction occurs, resulting in the formation of derivatives of type **3** having the lactone ring and the ester group on the opposite side of the cyclopropane ring (Scheme 1).



1 **2** **3**

1 and 2		**3**	
a, E	**R_1=Me, R_2=R_3=H**	**a, exo**	**R_1=Me, R_2=R_3=H**
a, Z	**R_1=H, R_2=Me, R_3=H**	**a, endo**	**R_1=H, R_2=Me, R_3=H**
b	**R_1=Ph, R_2=R_3=H**	**b, exo**	**R_1=Ph, R_2=R_3=H**
		b, endo	**R_1=H, R_2=Ph, R_3=H**
c	**R_1=Ph, R_2=H, R_3=Me**	**c, exo**	**R_1=Ph, R_2=H, R_3=Me**
		c, endo	**R_1=H, R_2=Ph, R_3=Me**
d	**R_1=Ph, R_2=H, R_3=Ph**	**d, exo**	**R_1=Ph, R_2=H, R_3=Ph**
		d, endo	**R_1=H, R_2=Ph, R_3=Ph**
e	**R_1=Ph, R_2=H, R_3=$PhCH_2$**	**e, exo**	**R_1=Ph, R_2=H, R_3=$PhCH_2$**
		e, endo	**R_1=H, R_2=Ph, R_3=$PhCH_2$**

Scheme 1

The cyclization reaction is very fast, and the colour of the iodine disappears in a few minutes at the boiling point of the toluene resulting in the intermediate iodomalonic ester derivatives, which also transform rapidly to the desired bicyclic products. The structure of these compounds was satisfactorily determined by spectroscopic methods.[6] The two rings are *cis*-fused and the R_3 group is exclusively in the exo position.

The fact that these compounds are potential intermediates in the synthesis of some biologically active compounds possessing additional chiral centers prompted us to examine whether their stereochemistry could be influenced by the substituents of the starting material and the reaction temperature.

As we reported earlier,[6] the synthesis of the simplest member of this family of compounds, **3a** (**exo** and **endo**) started from crotyl alcohol and gave a mixture of products, **3a, exo** and **3a, endo** which were independent of the configuration of the alcohol (**1a, E** or **1a, Z**). We have now determined the exo/endo ratio and found this to be dependent on the reaction temperature (Table 1).

For the preparation of **3b** *trans*-cinnamyl alcohol **1b** was used and after its esterification by malonic acid monoethyl ester followed by treatment of the resultant diester **2b** according to the

protocol described in the Experimental at three different temperatures an exo/endo mixture of the product **3b** was prepared in satisfactory yield. The two isomers could be separated by column chromatography using silica gel as adsorbent. The differentiation of the exo- and endo-isomers was based on the ^3J(H-5,H-6) coupling constants. For the endo isomer, J=8.2-8.5 Hz; for the exo form, J=5.0-5.5 Hz, which is in accordance with the known[7] relationship that ^3J(H-5,H_{cis}-6) > ^3J(H-5,H_{trans}-6) in cyclopropane derivatives. In the case of **3b** the signal of the methyl groups of the carboxyethyl moiety was also useful for the differentiation of the two isomers because this gave two triplets due to the effect of the phenyl group at the C(6) position (see Table 2). The result was confirmed by DPFGNOE (Double Pulse Filtered Gradient Nuclear Overhauser Effect) experiments. By the selective irradiation of the signal of the proton at C(6) position at 2.90 (d) positive effects were found for the signals at 3.29 (t), 4.36 (d), and 7.30 (m) ppm. Irradiation of the signal at 3.59 (d) gave positive effects for the signals at 3.02 (dd) and 7.30 (m), but there was no NOE transfer at 4.09 ppm.

The exo isomer of **3b** could be obtained cleanly and its recrystallization from ether/hexane yielded crystals with melting point 82-83 °C suitable for X-ray diffraction study. The ORTEP drawing of **3b, exo** is shown in Fig. 2.

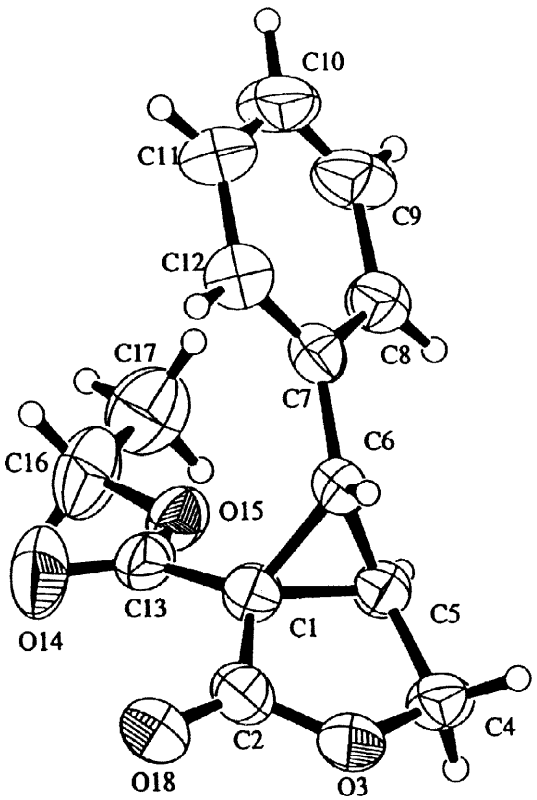
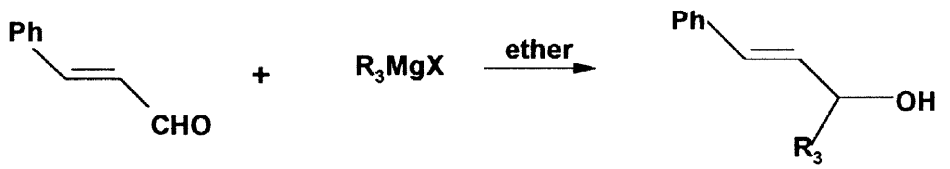


Fig. 2

To check the effect of the R_3-substituent on the exo/endo isomer ratio, compounds **3c-e** were also prepared; cinnamaldehyde was reacted with Grignard reagents using the usual reaction conditions and the alcohols **1c-e**[8,9] thus obtained were esterified with monoethyl malonate to give **2c-e** (Scheme 2).



1c-e

R_3 = Me, Ph, $PhCH_2$

Scheme 2

Transformation of these esters into the mixture of isomers **3c-e** was conducted at different temperatures (see Table 1) using the usual method described in the Experimental, and the crude reaction mixture was purified by column chromatography. NMR data used for the identification of these products are collected in Table 2.

Table 1
The percentage of exo isomer in the cyclization products **3a-e**

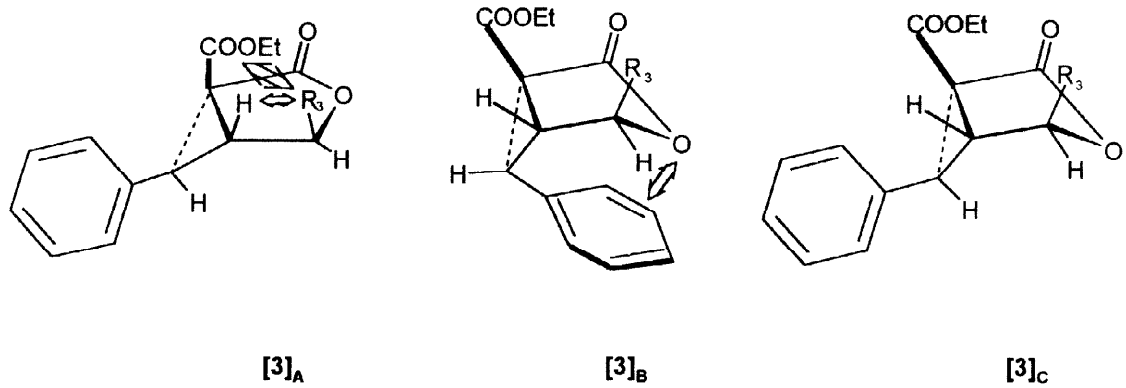
exo isomer %	**3a**	**3b**	**3c**	**3d**	**3e**
110 °C	60	60	62	65	30
60 °C	65	74	-	-	-
20 °C	65	77	45	*	40

*Cyclization product was not observed.

The percentage of the exo isomer in the products **3a-e** as a function of the reaction temperature are shown in Table 1. Data show that the exo isomer is dominant in each case except **3e**, and its proportion is slightly increased by increasing bulkiness of the R_3 substituent.

Taking into account the possible elemental steps in the cyclopropane ring formation (Scheme 3) (as well as the shape of the products **3**) the effect of the R_3 substituent on the exo/endo ratio might be partially explained by a steric interaction between the R_3 group and the hydrogen atom at the anellation point and/or the carboxyethyl group in the radical type transition state (Fig. 3, $[\mathbf{3}]_A$, see also Scheme 3) which is diminished if the lactone moiety is in an envelope-like conformation. As a consequence, the repulsive force between the lactone-oxygen and the phenyl group in the endo position (Fig. 3, $[\mathbf{3}]_B$) would be increased, making the formation of the endo-product energetically more demanding and the exo isomer (Fig. 3, $[\mathbf{3}]_C$) more favourable.

In one instance, where R_3 = $PhCH_2$ (**3e**), this explanation does not work because in this case the endo isomer is more favourable.



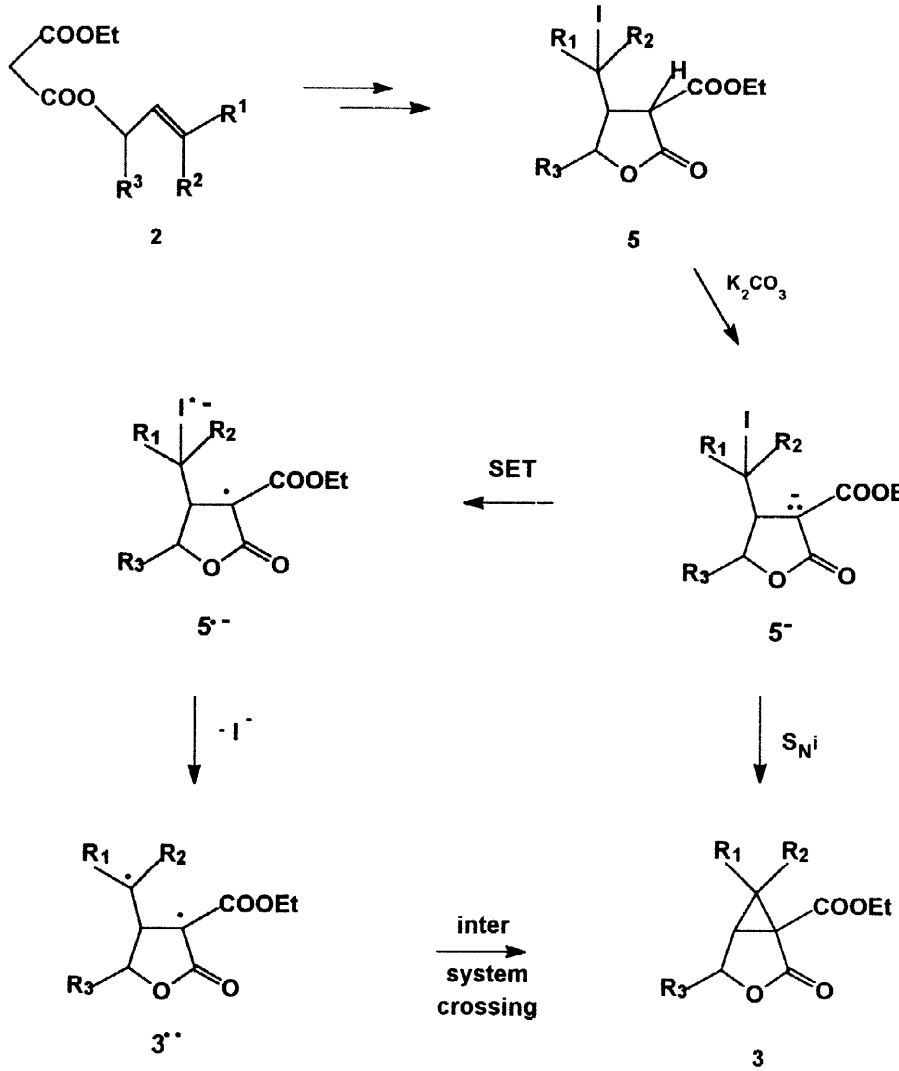
$[3]_A$ $[3]_B$ $[3]_C$

Fig. 3

Table 2
^{1}H-NMR data for compounds **3a-e**

	δ($CDCl_3$, 400 MHz)
3a	**exo**: 1.31 (m, 6H), 1.71 (m, 1H), 2.55 (t, 1H, *J* 5.0 Hz), 4.19 (d, 1H, *J* 9.3 Hz), 4.29 (m, 3H) **endo**: 1.22 (d, 3H, *J* 6.5 Hz), 1.33 (t, 3H, *J* 7.1 Hz), 2.35 (m, 1H), 2.74 (dd, 1H, J_1 5.4 Hz, J_2 8.2 Hz), 4.13 (d, 1H, *J* 10.0 Hz), 4.25 (m, 2H), 4.44 (dd, 1H, J_1 5.4 Hz, J_2 10.0 Hz)
3b	**exo**: 0.94 (t, 3H, *J* 7.1 Hz), 2.90 (d, 1H, *J* 5.5 Hz), 3.29 (m, 1H), 3.96 (m, 2H), 4.36 (d, 1H, *J* 9.3 Hz), 4.50 (dd, 1H, J_1 4.8 Hz, J_2 9.3 Hz), 7.30 (m, 5H) **endo**: 1.37 (t, 3H, *J* 7.1 Hz), 3.02 (ddd, 1H, J_1 1.0 Hz, J_2 5.2 Hz, J_3 8.5 Hz), 3.59 (d, 1H, *J* 8.5 Hz), 4.09 (dt, 1H, J_1 1.0 Hz, J_2 10.0 Hz), 4.33 (m, 2H), 4.38 (dd, 1H, J_1 5.2 Hz, J_2 10.0 Hz)
3c	**exo**: 0.92 (t, 3H, *J* 7.1 Hz), 1.53 (d, 3H, *J* 6.4 Hz), 2.88 (d, 1H, *J* 5.4 Hz), 3.06 (d, 1H *J* 5.4 Hz), 3.96 (m, 2H), 4.60 (q, 1H, *J* 6.4 Hz), 7.30 (m, 5H) **endo**: 1.37 (t, 3H *J* 7.1 Hz), 1.46 (d, 3H, *J* 6.4 Hz), 2.78 (d, 1H, *J* 8.5 Hz), 3.55 (d, 1H, *J* 8.5 Hz), 4.33 (m, 3H), 7.30 (m, 5H)
3d	**exo**: 0.87 (t, 3H, *J* 7.1 Hz), 3.02 (d, 1H, *J* 5.4 Hz), 3.31 (d, 1H, *J* 5.4 Hz), 3.93 (m, 2H), 5.42 (s, 1H), 7.25 (m, 5H), 7.40 (m, 5H) **endo**: 1.33 (t, 3H *J* 7.1 Hz), 2.96 (d, 1H *J* 8.5 Hz), 3.64 (d, 1H, *J* 8.5 Hz), 4.32 (m, 2H), 5.13 (s, 1H), 7.25 (m, 5H), 7.40 (m, 5H)
3e	**exo**: 0.88 (t, 3H, *J* 7.1 Hz), 2.86 (d, 1H, *J* 5.6 Hz), 3.03 (dd, 1H, J_1 1.3 Hz, J_2 5.6 Hz), 3.10 (m, 2H), 4.16 (m, 2H), 4.72 (t, 1H, *J* 5.6 Hz) 7.26 (m, 5H), 7.31 (m, 5H) **endo**: 1.28 (t, 3H *J* 7.1 Hz), 2.81 (dd, 1H, J_1 0.6 Hz, J_2 8.5 Hz), 3.10 (m, 2H), 3.48 (d, 2H, *J* 8.5 Hz) 3.86 (m, 2H), 4.47 (t, 1H, *J* 5.5 Hz), 7.26 (m, 5H), 7.31 (m, 5H)

As it was shown earlier,[6] the radical type reaction leading to products of type **3** proceeds via the intermediate **5**, which can give the end product theoretically in two ways: 1. an intramolecular nucleophilic substitution reaction in the anion 5^-; or, 2. since the iodine leaving group is attached to a tertiary carbon atom, the stereoelectronic condition of the S_{Ni} reaction cannot be easily fulfilled, and as a consequence the anion can give one electron to the iodine resulting in the formation of a $5^{\bullet -}$ intermediate (SET reaction) which transforms itself into the biradical $3^{\bullet\bullet}$ of parallel spins and subsequently to the end product.[10,11]



Scheme 3

A plausible interpretation of the endo preference for **3e** could be achieved using conformational analysis of **3c** and **3e**, which was performed by the particularly efficient low mode conformational (LMOD)[12] search implemented by the MacroModel package.[13] The low mode search developed by Kolossváry et al.[12] is based on the fact that the potential energy surface is a network of interconnected minima and saddle points. Starting from any local minima this LMOD forces[14] the molecule through a barrier by a single leap along one of the low-

frequency eigenvectors from the starting conformation. This allows the molecule to cross barriers most of the time and represents a powerful technique to explore the available conformational space. Furthermore there is no need for special treatment of cyclic molecules, which makes LMOD suitable for the conformational analysis of systems having both acyclic and cyclic substructures.

Since the formation of bicyclic cyclopropane carboxylic acid lactones **3** is expected to run under thermodynamic control[15] the diastereoselectivity can be rationalised by the calculation of relative stabilities of endo and exo products. Although the chemical stability can always be formulated in terms of conformational free energy differences it is usual to calculate only the energy difference between the lowest energy conformers. This approach, however, eliminates entropic effects which might have a characteristic effect on relative stabilities. We therefore calculate conformational free energies for endo and exo isomers of **3c** and **3e** using a recently developed algorithm called MINTA[16,17]. This method calculates the molecular configuration integral in all degrees of freedom, which allows the direct calculation of conformational free energies from the results of a previously performed conformational analysis. The LMOD-MINTA method was successfully applied for prediction of the anomeric free energy of monosaccharides,[17] the calculation of binding free energies in the enantioselective binding of amino acid derivatives by synthetic hosts,[16] and the quantification of the chiral recognition of organic ammonium salts by chiral crown ethers.[18] Rationalisation of the diastereoselectivity observed in the formation of bicyclic cyclopropane lactones represents an interesting challenge for this methodology. All calculations were performed on an SGI Indy workstation using the AMBER* force field in the MacroModel package. Electrostatic treatment of systems involved a distance dependent dielectric constant ($\varepsilon = 1$) and atomic charges obtained from the force field. 1000 LMOD steps were applied for each conformational search. Low energy conformers were obtained using the TNCG algorithm and an energy window of 35 kJ/mol for the selection of chemically significant conformer populations. Total energy of conformations corresponding to global minima were calculated to be 77.03 kJ/mol and 79.51 kJ/mol for the exo and endo isomers of **3c**, respectively. Global minima of the exo and endo isomers of **3e** were located at 70.06 kJ/mol and 67.85 kJ/mol, respectively. Conformational free energy differences between exo and endo conformers of **3c** and **3e** were found to be 2.50 kJ/mol and -2.93 kJ/mol. Calculated diastereoselectivities are 67 % of **3c, exo** and 76 % of **3e, endo** which are in fair agreement with experimental data (62 % and 70 %, respectively). Successful prediction of diastereoselectivities in the formation of bicyclic cyclopropane lactones demonstrates the capability of the LMOD/MINTA approach to calculate conformational free energy differences with high accuracy.

As regards the temperature dependence of the exo ratio, at present we cannot give a coherent explanation which may be connected with the complicated elemental steps of the cyclopropane ring formation. One can imagine that in certain compounds the reaction goes through the ionic intermediate $\mathbf{5}^-$ only while in another case it chooses the radical type ring formation via the intermediate $\mathbf{3}^{\bullet\bullet}$.

Conclusion

The stereochemistry of the intramolecular cyclization reaction of malonic acid allylic esters depends on the substituents of the allylic moiety. The exo product is more favourable but in one case the endo derivative was the dominant isomer. The reaction temperature can also slightly influence the diastereomeric composition of the product.

Experimental

All commercially available chemicals were purchased from Merck Ltd., Hungary and they were used without any further purification. ^{1}H-NMR spectra were recorded on VARIAN INOVA UNITY plus 400 spectrometer operating at 399.96 MHz. Chemical shifts are given on the δ scale, δ(TMS) = 0 ppm in $CDCl_3$. The free induction decays (FID) were acquired using a spectral width of 6 kHz and 65 K data points. 4-16 scans were collected using 39.1° excitation pulse and 5.4 s acquisition time without pulse delay. IR spectra were recorded on a Perkin-Elmer Model 1600 instrument. TLC plates were developed on Merck Kieselgel 60 F plates with an eluent hexane-acetone 4:1. Column chromatography was carried out on Merck Kieselgel 60 to 200 mesh with the same eluent. All new compounds gave satisfactory elemental analysis.

Preparation of the esters ***2***

To a solution of 0.01 mol of the appropriate alcohol **1** and 1.32 g (0.01 mol) of monoethyl-malonate in 50 ml of diethyl ether 2.06 g (0.01 mol) of dicyclohexyl-carbodiimide was added portionwise at 0 °C. After the addition the mixture was stirred for a further 5 hours allowing the temperature to reach room temperature. The precipitate was then filtered, washed with diethyl ether and the solvent was evaporated. The residue was purified by column chromatography.

2a[6] yellowish liquid, all physical properties were identical with those described in ref. 6.

2b yellow liquid, IR(neat): 1754, 1734, 1679 cm^{-1}, NMR: 1.27 (t, 3H, *J* 7.1 Hz), 3.1 (s, 2H), 4.24 (m, 4H), 6.35 (dd, 1H, J_1 5 Hz, J_2 12 Hz), 7.3 (m, 6H). Anal. calcd. for $C_{14}H_{16}O_4$: C 67.74, H 6.45, found C 67.56, H 6.41.

2c colorless liquid, IR(neat): 1740, 1732, 1666 cm^{-1}, NMR: 1.29 (t, 3H, *J* 7.1 Hz), 2.64 (d, 2H *J* 8.4 Hz), 3.5 (s, 2H), 4.21 (m, 3H), 6.35 (dd, 1H, J_1 5 Hz, J_2 12 Hz), 7.3 (m, 6H). Anal. calcd. for $C_{15}H_{18}O_4$: C 68.67, H 6.92, found C 68.59, H 6.82.

2d yellow liquid, IR(neat): 1740, 1732, 1665 cm^{-1}, NMR: 1.28 (t, 3H, *J* 7.1 Hz), 3.5 (s, 2H), 4.21 (m, 3H), 6.35 (dd, 1H, J_1 5 Hz, J_2 12 Hz), 7.3 (m, 11H). Anal. calcd. for $C_{20}H_{20}O_4$: C 74.04, H 6.22, found C 73.88, H 6.08.

2e yellow liquid, IR(neat): 1741, 1732, 1677 cm^{-1}, NMR: 1.28 (t, 3H, *J* 7.1 Hz), 3.1 (m, 2H), 3.5 (s, 1H), 4.21 (m, 3H), 6.15 (dd, 1H, J_1 5 Hz, J_2 12 Hz), 7.3 (m, 11H). Anal. calcd. for $C_{21}H_{22}O_4$: C 74.52, H 6.56, found C 74.56, H 6.61.

Cyclization reaction of ***2a-e*** *to* ***3a-e***

To a suspension of 3.3 g of potassium carbonate, 3 g of iodine and one drop of TCMC in 10 ml of toluene 0.005 mol of **2a-e** ester was added and the mixture was stirred vigourously at the desired temperature. After 3 hours the solid was filtered off. The filtrate was washed with 20% aqueous sodium-thiosulphate solution and with water, dried over magnesium sulphate and

the toluene was evaporated. The residue was purified by column chromatography and used as sample for the NMR-investigation (see Table 2).
3a[6] yellow oil, IR(neat): 1778, 1734 cm^{-1}.
3b[18] yellow oil, IR(neat): 1778, 1724 cm^{-1}. The **exo** isomer is white crystal, m.p. 82-83 °C (from diethyl ether/hexane).
3c yellow oil, IR(neat): 1779, 1732 cm^{-1}. Anal. calcd. for $C_{15}H_{16}O_4$: C 69.20, H 6.22, found C 69.04, H 5.99.
3d yellow oil, IR(neat): 1779, 1727 cm^{-1}. Anal. calcd. for $C_{20}H_{18}O_4$: C 74.50, H 5.63, found C 74.36, H 5.50.
3e yellow oil, IR(neat): 1779, 1728 cm^{-1}. Anal. calcd. for $C_{21}H_{20}O_4$: C 74.97, H 5.99, found C 74.89, H 5.87.

Grignard reactions of cinnamaldehyde

A solution of 0.075 mol of alkyl halogenide (methyl iodide, iodobenzene or benzyl chloride) in 30 ml of diethyl ether was added dropwise to a suspension of 1.8 g (0.075 mol) of magnesium turnings in 15 ml of dry diethyl ether under nitrogen atmosphere. After the complete dissolution of the magnesium, 8 g (0.06 mol) of cinnamaldehyde **4** in 15 ml of diethyl ether was added dropwise. The suspension was boiled until the aldehyde was completely consumed (checked by TLC). 7.5 g of ice was added to the reaction mixture, then concd. HCl was added dropwise until the complete dissolution of the precipitate. The ethereal layer was separated and the aqueous layer washed twice with diethyl ether. The combined organic extracts were dried over magnesium sulphate and the solvent was evaporated. Column chromatography of the crude product yielded the alcohol **1c-e** in 55-80%.
1c colorless liquid, b.p. 70 °C/0.2 mmHg (lit.: 118 °C/12 mmHg[8]), IR(neat): 3410, 1670 cm^{-1}.
1d colorless liquid, b.p. 115 °C/ 0.2 mmHg (lit.: 158-160 °C/4 mmHg[8]), IR(neat): 3360, 1664 cm^{-1}.
1e white crystals, m.p. 59-60 °C (lit.: 65-66 °C[9]), IR(neat): 3404, 1674 cm^{-1}.
Spectroscopic and other data of these compounds are identical with those described in the literature.

X-ray diffraction studies

Data were collected on an R-AXIS IIc imaging plate mounted on a Rigaku RU-H2R rotating anode generator using Mo-K_α radiation. **3b, exo** gave only very small crystals resulting in a data set of limited accuracy. However, the data allowed for an unequivocal determination of the relative configuration in the molecules of **3b, exo**. Crystal data for the compound, $C_{14}H_{14}O_4$, M= 246.25, triclinic, P-1, a = 7.937(10), b = 13.667(10), c = 6.248(10) Å, α = 93.52(10), β = 100.32(10)° γ = 80.24(10), Z = 2; total data collected = 1845, independent reflections = 1574. The initial model obtained by direct methods (SHELXS-86[20]), was refined against 1574 observations to convergence [final R indices for $I > 2\sigma(I)$: R_1 = 0.1201, wR_2 = 0.3569, for all data R_1 = 0.1757, wR_2 = 0.4469] (SHELXL-93[21]). Atomic coordinates, bond lengths and angles, and thermal motion parameters have been deposited at the Cambridge Crystallographic Data Centre.

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