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Asymmetric Diels-Alder Reactions with 5-Menthyloxy-2(5H)-furanone

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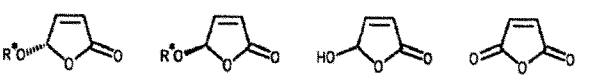
Abstract: A new class of chiral dienophiles, 5-alkoxy-2(5H)-furanones, has been developed. Both enantiomers of 5-menthyloxy-2(5H)-furanone are readily available in enantiomerically pure form, starting from furfural and *d*- or *l*-menthol. Excellent diastereoselectivities (d.e. ≥99%) are obtained in thermal Diels-Alder reactions with several cyclic and acyclic dienes. The use of silyl dienol ethers has resulted in new routes to enantiomerically pure cyclohexanones in a highly regioselective manner.

Since its discovery in 1928 the Diels-Alder reaction has become one of the most powerful tools in organic synthesis. Its great importance is based on the broad scope in the generation of six membered ring systems and the ability to create up to four contiguously stereogenic centers in a single synthetic operation. High asymmetric induction has been achieved in diastereoselective and enantioselective Diels-Alder reactions.[1] Methodology includes the use of various chiral auxiliaries attached to the diene[2] or dienophile[3] or the employment of chiral Lewis acid catalysts.[4]

Using chiral dienophiles excellent diastereofacial selectivity has been reached when one of the π-faces of the dienophile is effectively shielded,[5] as is the case in 8-phenylmenthyl acrylates.[6] Thermal Diels-Alder reactions with chiral dienophiles in general need further improvement as in most cases complete diastereoselectivity is not obtained. The inherent problem of many chiral dienophiles used so far is their conformational flexibility leading to lower selectivities. A very successful way to circumvent this problem has been the use of Lewis acid catalysts in combination with various chiral auxiliaries.[7] A major disadvantage of Lewis acids is that they often catalyze the polymerization of the dienes employed extensively. Furthermore, various chiral auxiliaries used so far are rather expensive or require multistep synthesis.

Our aim, therefore, was to develop a new chiral dienophile to be reactive in thermal Diels-Alder reactions, without the need for Lewis acid catalysis. In addition it should show complete diastereoselectivity to furnish enantiomerically pure products after removal of the auxiliary. It appeared to us that enantiomerically pure furanones 1, with an alkoxy substituent at C_5, would be very suitable as conformational restriction is intrinsic to the chiral butenolide moiety.[8]



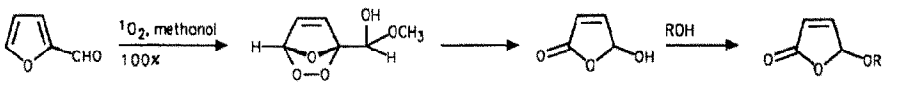
(5S)-1 (5R)-1 2 3

We considered the asymmetric acetalization of 5-hydroxybutenolide 2, with an enantiomerically pure auxiliary alcohol, an attractive way to obtain 5-alkoxy-2(5H)-furanones 1. A requirement is that

high diastereoselection takes place in the formation of the acetal stereogenic center or that the diastereoisomers formed can be separated easily. In principle this would provide a facile route to enantiomerically pure 5-alkoxy-2(5H)-furanones 1 which can be considered chiral analogs of maleic anhydride 3 although with slightly reduced dienophilicity.[9]

Synthesis of enantiomerically pure 5-menthyloxy-2(5H)-furanone

The synthesis of enantiomerically pure 5-alkoxy-2(5H)-furanones starts from 5-hydroxy-2(5H)-furanone. In the literature several procedures are described to prepare racemic 5-hydroxy- and 5-alkoxy-2(5H)-furanones.[10] For a large scale synthesis of 5-hydroxy-2(5H)-furanone (2) the photo-oxidation of furfural (4) is probably most suitable (Scheme 1).[11]



Scheme 1 4 2 5 (R = CH_3, 74%)

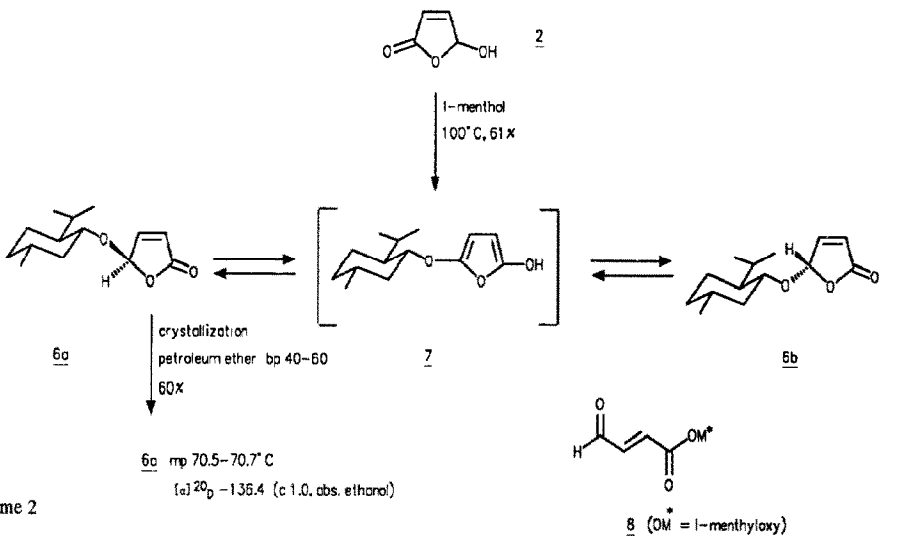
We have performed several of these experiments on a 100 g scale without any difficulties, providing the desired butenolide 2 in quantitative yield. Racemic 5-methoxy-2(5H)-furanone (5) was obtained by refluxing 5-hydroxy-2(5H)-furanone (2) for 3 days in dry methanol. After distillation of the product, pure 5 was obtained as a colorless oil in 74% yield.

In preliminary experiments for the synthesis of enantiomerically pure 5-alkoxy-2(5H)-furanones 1, the asymmetric acetalization of 2 was executed using the chiral alcohols *l*-borneol, racemic isoborneol, fenchyl alcohol and α-methylbenzyl alcohol. In all these cases a mixture of two diastereoisomers of 1 was obtained. In the cases of *l*-borneol, isoborneol and fenchyl alcohol the ratio of diastereoisomers was approximately 50:50. In the case of α-methylbenzyl alcohol a mixture of isomers was obtained in a ratio of 60:40. As we have not observed high diastereoselectivities in the asymmetric acetalization of 2, a separation step appeared to be inevitable. Unfortunately, it was not possible to separate the diastereoisomers by means of crystallization.

In order to be synthetically useful the chiral auxiliary alcohol has to meet the following criteria:

1. The 5-alkoxy-2(5H)-furanone, which results upon reaction of the proper chiral alcohol with 2, should be a crystalline compound making it, in principle, possible to separate both diastereoisomers by means of crystallization.
2. Both enantiomers of the chiral alcohol have to be available giving the possibility to prepare both enantiomers of the corresponding 5-alkoxy-2(5H)-furanone 1.
3. The auxiliary alcohol has to be relatively inexpensive in order to prepare 5-alkoxy-2(5H)-furanones in larger quantities.

The alcohol of choice, which meets all these criteria, is menthol. Heating of hydroxyfuranone 2 with 1.1 to 1.5 equivalents of *l*-menthol at 100 °C for 20 h without solvent afforded 6 in 61% yield as a mixture of diastereoisomers 6a and 6b (ratio 60:40) after removal of the excess menthol by distillation (Scheme 2).



Scheme 2

Structure 6a was assigned to the major diastereoisomer (*vide infra*). The diastereomeric ratio is readily determined from the ^{1}H NMR spectrum of the product by integration of the signals of the acetal hydrogen atoms of 6a and 6b. A slight amount of 8 (<10%) is formed as byproduct during the acetalization of 5-hydroxy-2(5H)-furanone with menthol. It is readily removed from the reaction mixture by stirring an ethereal solution of the crude 5-menthyloxy-2(5H)-furanone (6a/6b) with a saturated sodium hydrogen sulfite solution, after which 6 is obtained as an oil or a low melting solid. The major diastereoisomer 6a crystallizes readily at -23 °C from *n*-hexane or petroleum ether (bp 40-60) solutions of the mixture of 6a and 6b. After two crystallizations enantiomerically pure 6a was obtained as a white crystalline compound in 60% yield. The crystallization process is accompanied by a remarkable *second order asymmetric transformation*[12] of 6 in solution, providing again a 60:40 ratio of diastereoisomers (6a and 6b) after removal of part of 6a during crystallization. The slow epimerization of 6b into 6a was deduced from ^{1}H NMR analysis of the solution of 6 (60:40 ratio) prior to crystallization and the mother liquor just after crystallization. This "crystallization induced epimerization" is essentially driven by the continuous removal of the major crystalline isomer 6a from the solution. The epimerization probably takes place via enolization[13] of 6b (and 6a) to the unstable 5-(*l*-menthyloxy)-2-hydroxyfuran intermediate 7, which has lost its stereogenic center at C_5. This epimerization-crystallization process allows the isolation of enantiomerically pure menthyloxy-2(5H)-butenolides in high yields (up to 80%). The epimerization process is very likely catalyzed by traces of acid present during the crystallization of 6a and the addition of small amounts of *p*-toluenesulphonic acid facilitates the 2nd order asymmetric transformation.[14] In contrast, when enantiomerically pure 6a is heated for several hours at reflux in toluene or petroleum ether (bp 40-60) with careful exclusion of acid, it is not in equilibrium with 6b. This property of 6a is essential for successful use in enantioselective thermal Diels-Alder reactions.

By a similar sequence, using *d*-menthol as chiral auxiliary alcohol, (5S)-5-(*d*-menthyloxy)-2(5H)-furanone is obtained.

Diastereoselective Diels-Alder reactions

An essential feature of chiral butenolide 6a is the directing group at C_5 which shields one of the π-faces of the molecule from being attacked. As shown in Figure 1 a re-face addition is expected with the S-butenolide. In this sense, the stereogenic center at C_5 is responsible for the diastereoselectivity exerted during the cycloaddition reaction at the α,β-unsaturated ester moiety of the butenolide 6.

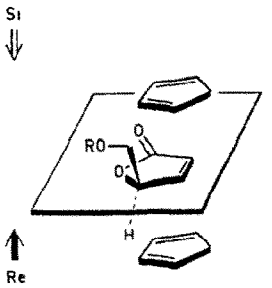
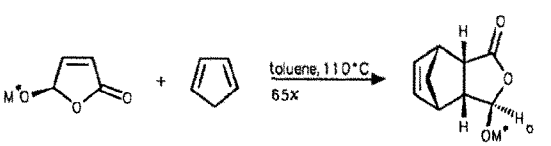


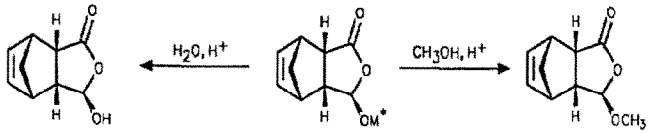
Figure 1 π-Face selective addition of 6a.

The thermal Diels-Alder reaction of dienes with chiral butenolide 6a is expected to proceed with a high endo selectivity and diastereoselectivity. When 6a was heated at 110 °C in dry toluene for 4.5 h with a twofold excess of cyclopentadiene (9) it was converted into the adduct 10 in 99% isolated yield. Based on ^{1}H NMR and ^{13}C NMR analysis of 10 it was shown to be a single isomer indicating a diastereoselectivity (d.e.) >96%. Analytically pure product was obtained in 65% yield by crystallization from petroleum ether (bp 40-60) at -40 °C. When a 60:40 mixture of diastereoisomers 6a and 6b was used, adduct 10 was obtained with a diastereoselectivity of 20%. *These results show that a complete π-face selective addition takes place and that no epimerization of 6a occurs during the cycloaddition reaction.* Based on the very small coupling constant (J < 1 Hz) of the acetal proton (H_a) of adduct 10, it is concluded that the addition of cyclopentadiene has taken place from the less hindered side of 6a.



Scheme 3 6a 9 10

The endo-addition was confirmed by extensive 2D NMR studies (COSY, NOESY) of 10. The diastereoselectivity can be rationalized by the model depicted in Figure 2. In the case of 6a the large menthyloxy group at C_5 protects one side of the molecule from being attacked by cyclopentadiene.
The chiral auxiliary *l*-menthol is readily removed by hydrolysis (H_2O/SiO_2 or H_2O/H_3CCOCH_3/-CH_3COOH) or methanolysis (CH_3OH/p-TsOH) of 10 leading to enantiomerically pure hydroxy- or methoxy-substituted lactones 11 and 12, respectively (Scheme 4). Compound 11 has been used as a key intermediate in the synthesis of dehydro-aspidospermidine.[15]



11 10 12

Scheme 4

Table 1 shows the results of the asymmetric Diels-Alder reactions of several dienes with 6a. All reported yields are after purification by means of crystallization, except in the case of the Diels-Alder reaction with butadiene sulfone (21). Excellent stereochemical control is exerted in all cases except two. In fact only one diastereoisomer of the Diels-Alder product was found when enantiomerically pure 6a was used as dienophile. Any optical enrichment during work-up was carefully excluded. However, at 190 °C, needed for the Diels-Alder reaction between 6a and anthracene (19), epimerization of the dienophile was observed. Two cycloaddition products were isolated with an approximate ratio of 60:40. Diastereomerically pure product 20 was, however, obtained through a single crystallization from *n*-butyl ether. One other exception was found in the case of butadiene sulfone (21) (entry 6). The released SO_2 probably forms sulfurous acid with traces of water, which catalyses partial epimerization of 6a resulting in a mixture of (5R)- and (5S)-5-(*l*-menthyloxy)-2(5H)-furanone (6a + 6b). Reaction of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) with 2-methyl-1,3-butadiene (13) resulted in a mixture of two regioisomers with a ratio of 50:50, as was determined by ^{1}H NMR and ^{13}C NMR. The low yield in some cases is due to the fact that the cycloadducts are very soluble in most organic solvents, which makes crystallization difficult. Even in apolar solvents, like *n*-hexane or petroleum-ether (bp 40-60), the products are fairly soluble.

Table 1: Asymmetric Diels-Alder Reactions of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a)

entry	diene	temp	product	%yield[a]	%de[b]	%ee[b]
1	cyclopentadiene (9)	110 °C	10a (10b)	65 (90)	>96	[d]
2	2-methylbutadiene (13)	120 °C	14a (14b)	56 (69)	>96[c]	>99
3	2,3-dimethylbutadiene (15)	120 °C	16a (16b)	44 (82)	96[e]	96
4	1,3-cyclohexadiene (17)	120 °C	18a (18b)	47 (56)	>96	>99
5	anthracene (19)	190 °C	20a (20b)	63 (52)	20	[d]
6	butadiene sulfone (21)	120 °C	23a	77	73	72
7	butadiene (22)	120 °C	23a	45	>96	>99
8	cyclopentadiene (9)	110 °C	10a	60	20[f]	[d]

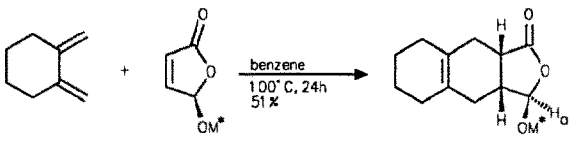
[a]Yields (not optimized) for isolated products. [b]Diastereomeric excess (d.e.) was determined on the basis of ^{1}H NMR and ^{13}C NMR of the menthyloxy derivative of the product. The enantiomeric excess (e.e.) was determined on the basis of GC analysis of the methoxy derivative. [c]Mixture of two regioisomers (50:50 ratio). [d]Not determined. [e]Starting material 6a and b (98:2 ratio). [f]Starting material 6a and 6b (60:40 ratio).

It should be noted that under various conditions no reaction was observed between butenolides 5 and 6 and furan.

The menthyloxy-substituted cycloadducts 10b-20b were solvolysed in methanol to provide the

enantiomerically pure substituted products (*vide infra*). The racemic methoxy-substituted adducts 10b-23b were independently prepared by Diels-Alder reaction of the dienes 9-22 with racemic (5R,S)-5-methoxy-2(5H)-furanone (5). The yields of racemic cycloadducts 10a-23a are shown in Table 1 in parenthesis.

In an effort to prepare optically active decalines by extending the asymmetric Diels-Alder reactions to exocyclic dienes, 1,2-bis(methylene)cyclohexane (24) was investigated. Diene 24 was prepared in a 4 step sequence from cis-cyclohexane-1,2-dicarboxylic acid.[16] 1,2-Bis(methylene)cyclohexane (24), dissolved in benzene, was allowed to react with (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) for 42 h in a sealed tube at 100 °C, to afford cis-2,3-disubstituted-9,10-dehydrodecaline 25 in 51% isolated yield as a single enantiomer (Scheme 5).

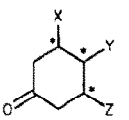


Scheme 5

24 6a 25

The addition of diene 24 to (5R)-5-(*l*-menthyloxy)-2(5H)-furanone results in the formation of two new stereogenic centers and again takes place *trans* to the menthyloxy substituent. The stereochemical assignment is based on NMR studies and the singlet observed for H_a in the 300 MHz ^{1}H NMR spectrum of 25 is characteristic for the trans relationship between the acetal- and the bridgehead-hydrogen atoms.

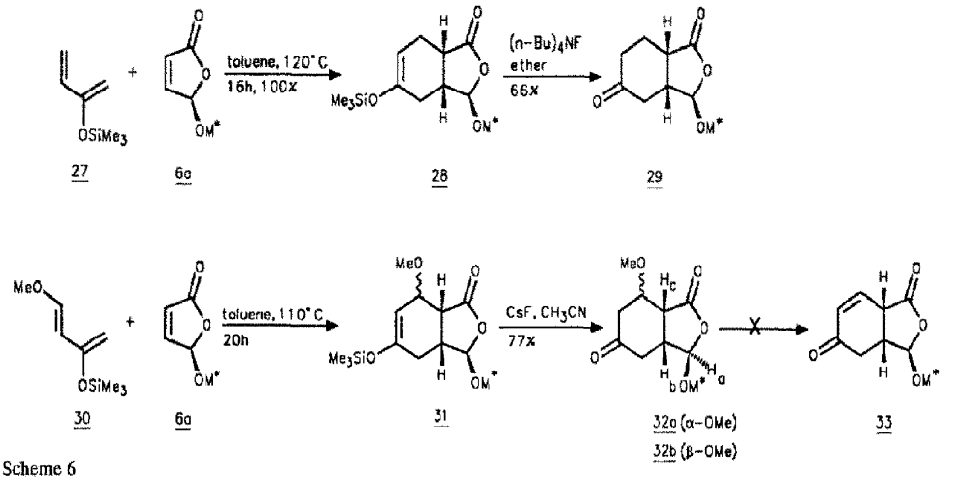
The Diels-Alder reactions of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone with more activated dienes, in particular silyl dienol ethers, were next examined. Apart from an acceleration of the reaction an advantage of alkoxy substituted dienes is the high regioselectivity obtained in Diels-Alder reactions. For example Danishefsky's diene, 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (30) has been used with great success in the synthesis of numerous natural products and is known to combine high reactivity with high regioselectivity.[17] Our main interest in silyloxy-substituted dienes stems from the possibility of synthesizing enantiomerically pure 3,4- and 3,4,5-substituted cyclohexanones 26.



26

(5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) and 2-trimethylsilyloxy-1,3-butadiene (27) were allowed to react at 120 °C in dry toluene. After treating the resulting silyl enol ether 28 with tetrabutyl-ammonium fluoride in diethyl ether, the 3,4-disubstituted cyclohexanone 29 was obtained as a single isomer in 66% yield (Scheme 6). Again the addition of the diene has taken place with complete π-face selectivity *trans* to the menthyloxy substituent of furanone 6a, as was deduced from the singlet observed for the acetal hydrogen.

Although the Diels-Alder reaction of 27 provided a single diastereoisomer, two diastereomeric adducts were obtained in 77% yield and a 2:1 ratio (^{1}H NMR) with Danishefsky's diene 30.



27 6a 28 29

30 6a 31 32a (α-OMe) 32b (β-OMe) 33

Scheme 6

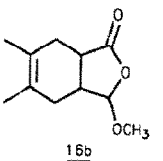
As 30 possesses the same polarization as 2-trimethylsilyloxy-1,3-butadiene it is expected that in this reaction again only one regioisomer would be formed. After hydrolysis of the silyl enol ether 31 with tetrabutylammonium fluoride 32 was isolated as a mixture of two diastereoisomers. Extensive ^{1}H NMR analysis showed that only a *trans*-addition of diene 30 relative to the menthyloxy substituent of furanone 6a had taken place, as was deduced from the coupling constant of the acetal hydrogens. Therefore, the only conclusion can be that both diastereoisomers of 32 are epimeric at the carbon bearing the MeO-substituent. The two diastereoisomers 32a and 32b are, therefore, most likely the result of a concurrent endo and exo addition of 30 to 5-menthyloxy-2(5H)-furanone. Both isomers were easily separated by means of flash chromatography, yielding the major isomer as an oil and the minor isomer as a crystalline compound. The assignment of the absolute stereochemistry of 32a was based on the X-ray analysis (*vide infra*).

Various attempts to eliminate the MeO-substituent of 32 were undertaken as this would yield disubstituted α,β-unsaturated cyclohexanone 33 in enantiomerically pure form. This compound is of particular interest as a chiral building block as it opens the possibility of preparing tetrasubstituted cyclohexanones *via* tandem additions to the enone moiety. However, treatment of Diels-Alder adduct 32 with 0.05 N HCl in THF, or trifuoroacetic acid in CH_2Cl_2, or heating for 2 h at 150 °C did not yield 33. Comparable results were found by Danishefsky *et al.*[18] in the reaction of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene with maleic anhydride.

Enantiomeric excess and absolute configuration determination

The enantiomeric excess of the methoxy derivatives obtained by methanolysis of the Diels-Alder adducts was determined on basis of GC analysis. The chiral capillary GC column used was a XE-60 (S)-valine-(S)-α-phenylethylamide (50 m x 0.25 mm, Chrompack). The racemic methoxy adducts gave two well separated peaks for both enantiomers, whereas a single peak was observed for the products obtained *via* methanolysis of the adducts obtained by the asymmetric Diels-Alder reactions with (5R)-

5-(*l*-menthyloxy)-2(5H)-furanone (See Table 1). This is illustrated in Figure 2 which shows the GC chromatograms of a: racemic 16b, obtained by the cycloaddition of racemic 5-methoxy-2(5H)-furanone (5) and 2,3-dimethyl-1,3-butadiene (15), and b: of enantiomerically pure 16b obtained *via* methanolysis of 16a.



16b

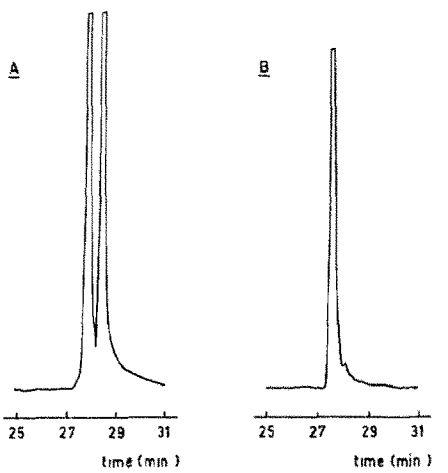


Figure 2 GC chromatogram of a) racemic 16b and b) enantiomerically pure 16a

In the case of the racemic 2-methyl-1,3-butadiene adduct 14b, four well separated peaks with ratio 1:1:1:1 were observed (two for both regioisomers), while for the enantiomerically pure compound only two signals were observed (ratio 1:1) for the two regioisomers. These results confirm, that after methanolysis, the products are obtained with an e.e. ≥ 99.9%.

Despite various attempts, no suitable crystals for an X-ray analysis could be obtained of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a), and the absolute configuration at the acetal center was therefore not unequivocally established. Also, no significant differences between the energy levels of both diastereoisomers of 6a and 6b were found by MM-2 calculations.

To establish the actual configuration of the acetal stereogenic center of 5-menthyloxy-2(5H)-furanone (6a) and the Diels-Alder adducts, an X-ray analysis of the 2,3-dimethyl-1,3-butadiene adduct 16a was performed. Single crystals, suitable for X-ray analysis, were obtained by crystallization from petroleum ether (bp 40-60) under condition of solvent evaporation.

The crystal structure of compound 16a[19] is depicted in Figure 3a and was based on the absolute configuration of (1R,2S,5R)-(-)-menthol.[20] The absolute configuration at the acetal stereogenic center can be assigned on the basis of this structure analysis to be R. As no epimerization is observed under Diels-Alder conditions and complete stereocontrol is found it also prove that the acetal stereogenic center of 5-(*l*-menthyloxy)-2(5H)-furanone (6a) has the R-configuration. Furthermore, this X-ray analysis confirms the trans relationship between the acetal hydrogen and the hydrogen at C_5, and therefore confirms that the addition of 2,3-dimethyl-1,3-butadiene indeed has occurred from the less hindered side of butenolide 6a. The torsion angle of 77° between H_4 and H_5 is in agreement with the very small coupling constant ($J < 1$ Hz) found for H_4 in the ^1H NMR, which also is indicative of a trans addition of 2,3-dimethyl-1,3-butadiene relative to the menthyloxy group of

6a. The calculated coupling constant according to the Karplus relation[21] is equal to 0.1 Hz. In general the small coupling constant for the acetal hydrogen is a good indication for a trans addition of dienes, relative to the menthyloxy group of 6a.

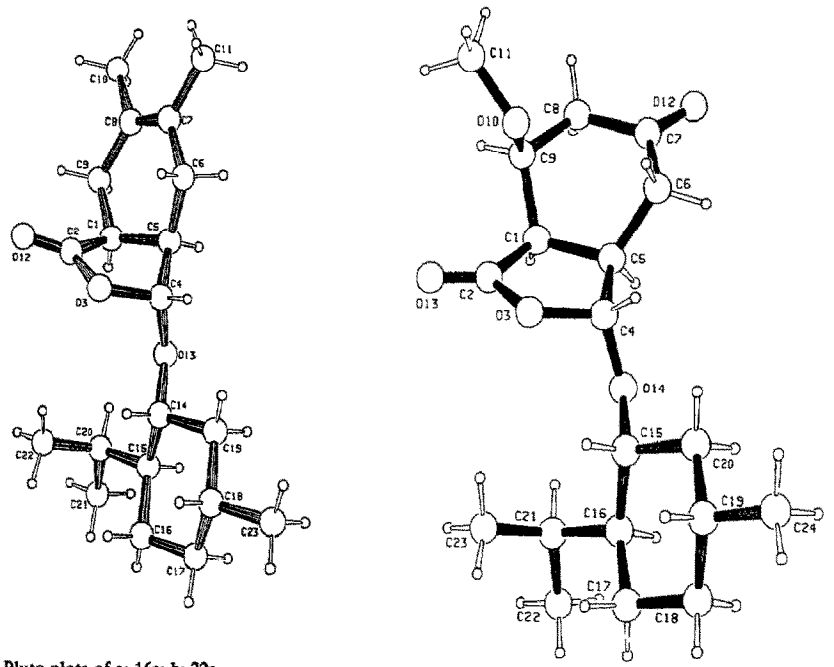


Figure 3: Pluto plots of a: 16a; b: 32a

To distinguish which isomer of 32 was the result of an *endo*-attack of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) to Danishefsky's diene 30 an X-ray structure was determined on one of the two isomers. The minor isomer of 32 could be crystallized from *n*-hexane to yield suitable crystals for an X-ray analysis.[19] The crystal structure of compound 32a is depicted in Figure 3b. The structure shows that this isomer is the result of an *endo*-attack of Danishefsky's diene to 5-menthyloxy-2(5H)-furanone since the methoxy substituent of 32a is in an *endo*-position, and the hydrogen atoms at C_1, C_5 and C_9 are in a *cis* relationship to each other. Furthermore, the structure of 32a shows that diene 30 added *trans* to the menthyloxy substituent of furanone 6a as the hydrogen atoms at C_1 and C_5 are in a *trans* position relative to the hydrogen at C_4, the acetal center. The observed regioselectivity of the addition of diene 30 to 6a is in accordance with what is expected on basis of the HOMO-LUMO interaction between the diene and the furanone dienophile.

Conclusions

We may conclude that a very versatile new class of chiral dienophiles, the γ-alkoxy butenolides, has been developed. Both enantiomers of 5-menthyloxy-2(5H)-furanone are readily available in enantiomerically pure form, starting from furfural and *d*- and *l*-menthol. Advantages of 5-menthyloxy-2(5H)-furanones compared to auxiliary based dienophiles are; i. the short synthetic route, ii. both

enantiomers are readily available in good yields, iii. a cheap chiral auxiliary is used. Furthermore, no Lewis acid catalysis is needed in asymmetric Diels-Alder reactions with 6. Excellent stereochemical results were obtained in the thermal Diels-Alder reactions with several cyclic and acyclic dienes. The diastereoselectivities (≥ 96%) are comparable with the selectivities obtained with chiral butenolides derived from D-ribonolactone. The chiral auxiliary menthol can easily be recovered by hydrolysis or alcoholysis. Finally, the use of silyl dienol ethers results in new routes to enantiomerically pure cyclohexanones in highly regioselective manner.

Experimental section

General remarks

Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. Infrared spectra were recorded on a Perkin Elmer 257 Grating Spectrophotometer or on a Mattson Instruments 4020 GALAXY Series FT-IR equipped with a Hewlett-Packard 7550 Graphics Plotter. ^{1}H NMR spectra were recorded on a Hitachi Perkin Elmer R-24B High Resolution NMR spectrometer (at 60 MHz), or on a Varian VXR-300 spectrometer (at 300 MHz). Chemical shifts are for 60 MHz spectra denoted in δ-units (ppm) relative to tetramethylsilane (TMS) as an internal standard at δ = 0 ppm. For 300 MHz spectra the ^{1}H NMR chemical shifts are determined relative to the solvent and converted to the TMS scale using δ ($CHCl_3$) = 7.26 ppm. ^{13}C NMR spectra were recorded on a Varian XL-100 (at 25.16 MHz), a Nicolet NT 200 (at 50.32 MHz), or a Varian VXR-300S (at 75.48 MHz) spectrometer. Chemical shifts are denoted in δ-units (ppm) relative to the solvent and converted to the TMS scale using δ ($CDCl_3$) = 76.91 ppm. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Mass spectra were recorded on an AEI-MS-902 mass spectrometer by EI (acc. voltage 8 kV, voltage 70 eV). Elemental analyses were performed in the Microanalytical Department of this laboratory. The X-ray data collection was performed on a Nonius CAD4F-diffractometer equipped with a graphite monochromator and interfaced to a PDP11/23. All reagents and solvents were purified and dried if necessary, according to standard procedures. Diene 24 was prepared according to the literature procedures.[16] *l*- And *d*-menthol were purchased from Janssen Chimica, Fluka and Aldrich, and were used without further purification.

5-Hydroxy-2(5H)-furanone (2)

Freshly distilled furfural (4) (100 g, 1.04 mol), dissolved in methanol (600 mL), was photooxygenated using a 700W high pressure Hg-lamp[22] and a few milligrams of methylene blue as sensitizer. A stream of oxygen was introduced through a glass filter (P_2) into the reaction vessel. Kaptan 500 H was used as U.V. filter and a Hanau Q 700 lamp served as the source of light. The reaction was followed by ^{1}H NMR, taking samples from the solution at regular intervals, until all the furfural was consumed. After evaporation of the solvent under reduced pressure 5-hydroxy-2(5H)-furanone (2) (104 g, 100%) was obtained as an oil, which solidified upon standing. The product 2 was pure enough to be used in the next reaction step without further purification. The product can be crystallized from carbon tetrachloride, yielding pure 2 as a white crystalline compound. Mp 57.3-59.2 °C (lit.[23] 58.0-60.0 °C); ^{1}H NMR ($CDCl_3$, 60 MHz): δ 5.41 (br.s, 1H), 5.83 (s, 1H), 6.13 (d, J = 7 Hz, 1H), 7.31 (d, J = 7 Hz, 1H).

5-Methoxy-2(5H)-furanone (5)

5-Hydroxy-2(5H)-furanone (2) (50 g, 0.5 mol) was dissolved in dry methanol (200 mL) and refluxed for 3 days. After evaporation of the solvent under reduced pressure and distillation of the residue (70-72 °C, 2 mm Hg) the product (42 g, 74%) was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 3.50 (s, 3H), 5.83 (s,1H), 6.18 (d, J = 6 Hz, 1H), 7.22 (d, J = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.31 (q), 103.92 (d), 124.40 (d), 150.62 (d), 170.21 (s).

(5R)-5-(l-Menthyloxy)-2(5H)-furanone (6a)

5-Hydroxy-2(5H)-furanone (2) (50 g, 0.5 mol) and *l*-menthol (100 g, 0.64 mol) were heated for 20 h at 100 °C. The unreacted *l*-menthol was removed by distillation (bp 80-90 °C, 0.1 mm Hg). Distillation of the residue (bp 120-123 °C, 0.01 mm Hg) gave the product 6 (72.5 g, 61%) as a yellow oil consisting of two diastereoisomers (ratio 60:40). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.69-1.08 (m, 12H), 1.12 (m, 1H), 1.36 (m, 1H), 1.62 (m, 2H), 2.00-2.24 (m, 2H), 3.36 + 3.60 (2 x dt, J = 4.2, 10.6 Hz, 1H), 5.92 + 6.04 (2 x s, 1H), 6.15 (m, 1H), 7.14 (m, 1H). The product solidified upon standing at room temperature. After two crystallizations from petroleum ether (bp 40-60) diastereomerically pure 6a was obtained, as determined by the ^{1}H NMR and ^{13}C NMR spectra of 6a. The mother liquors were combined and gave a second crop of diastereomerically pure 6a. Total yield 42.5g, 60%. Mp 70.5-70.7 °C; $[\alpha]_D$ -136.4 (c 1.0, abs. ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.80 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 7.2 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.80-1.10 (m, 2H), 1.25 (m, 1H), 1.41 (m, 1H), 1.66 (m, 3H), 2.12 (m, 2H), 3.66 (dt, J = 4.2, 10.6 Hz, 1H), 6.08 (s, 1H), 6.20 (dd, J = 1.2, 5.6 Hz, 1H), 7.16 (dd, J = 1.2, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 15.51 (q), 20.57 (q), 21.93 (q), 22.87 (t), 25.04 (d), 31.17 (d), 33.93 (t), 40.05 (t), 47.46 (d), 78.79 (d), 100.26 (d), 124.36 (d), 150.79 (d), 170.56 (s); HRMS calcd 238.155, found 238.157; Analysis calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.49; H, 9.18.

(5S)-5-(d-Menthyloxy)-2(5H)-furanone

This compound was prepared from 5-hydroxy-2(5H)-furanone (2) and *d*-menthol in the same way as described for (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) (*vide supra*). Mp 74.2-74.4 °C; $[\alpha]^{20}_D$ +139.7 (c 1.0, $CHCl_3$).

[3R-[3α(1R,2S*,5R*),3aα,4α,7α,7aα]]-3a,4,7,7a-Tetrahydro-3-[[5-methyl-2-(1-methyl-ethyl)-cyclohexyl]-oxy]-4,7-methanoisobenzofuran-1(3H)-one (10a)*

(5R)-5-(*l*-Menthyloxy)-2(5H)-furanone (6a) (10.0 g, 42.0 mmol) and cyclopentadiene (9) (8.32 g, 126 mmol) were dissolved in dry benzene and refluxed for 18 h. After evaporation of the solvent under reduced pressure and bulb-to-bulb distillation of the residue, 12.8 g (99%) of the product was obtained as a viscous oil. Analytically pure product was obtained by crystallization from petroleum ether (bp 40-60) at -40 °C. Yield after crystallization 8.30 g (65%). Mp 73.0-75.0 °C; $[\alpha]_D$ -130.9 (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.70 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.75-1.00 (m, 3H), 1.15 (m, 1H), 1.28 (m, 1H), 1.37 (d, J = 8.8 Hz, 1H), 1.58 (m, 2H and d, J = 8.8 Hz, 1H), 2.00 (m, 2H), 2.84 (m, 1H), 3.12 (m, 1H), 3.28 (m, 2H), 3.40 (dt, J = 4.4, 11.0 Hz, 1H), 5.00 (s, 1H), 6.17 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 15.56 (q), 20.68 (q), 22.08 (q), 22.99 (t), 25.24 (d), 31.16 (d), 34.13 (t), 39.67 (t), 44.48 (d), 45.50 (d), 47.54 (2 x d), 48.10 (d), 51.62 (t), 76.43 (d), 101.80 (d), 134.06 (d), 136.12 (d), 177.17 (s); HRMS calcd 304.204, found 304.203; Analysis calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.26; H, 9.43.

[3R-[3α(1R,2S*,5R*),3aα,7aα]]-3a,4,7,7a-Tetrahydro-5-methyl-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]-oxy]-1(3H)-isobenzofuranone and [3R-[3α(1R*,2S*,5R*)-3aα,7aα]]-3a,4,7,7a-tetrahydro-6-methyl-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-1(3H)-isobenzofuranone (14a)*

(5R)-5-(*l*-Menthyloxy)-2(5H)-furanone (6a) (3.14 g, 13.2 mmol) and 2-methyl-1,3-butadiene (13) (2.71 g, 39.8 mmol) were dissolved in dry toluene (5 mL) and heated for 24 h in a sealed stainless steel tube (volume 10 mL) at 110 °C. After evaporation of the solvent, the residue was crystallized from petroleum ether (bp 40-60) at -20 °C, to provide pure 14a (0.39 g, 56%) as a white crystalline compound. Based on ^{1}H NMR the product consisted of a mixture of two diastereoisomers (ratio 1:1). Mp 68.3-73.5 °C; $[\alpha]_D$ 200.7 (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.73-1.06 (m, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 1.21 (m, 1H), 1.36 (m, 1H), 1.67 (m, 2H and 2 x s, 3H), 1.80 (m, 1H), 2.15-2.55 (m, 6H), 3.05 (m, 1H), 3.50 (2 x dt, J = 4.2, 10.6 Hz, 1H), 5.26 (2 x s, 1H), 5.39 (2 x m, 1H); ^{13}C NMR ($CDCl_3$): δ 15.37 (q), 20.73 (q), 21.95 (t), 22.05 (q), 22.90 (t), 23.18 (q), 23.54 (q), 23.64 (t), 25.37 (d), 26.22 (t), 28.06 (t), 31.17 (d), 34.15 (t), 35.24 (d), 36.38 (d), 37.66 (d), 38.62 (d), 39.61 (t), 47.65 (d), 76.25 (d), 103.44 (d), 118.01 (d), 119.05 (d), 131.22 (s), 132.69 (s), 178.46 (s); HRMS calcd 306.219, found 306.218; Analysis calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.18; H, 9.74.

[3R-[3α(1R*,2S*,5R*),3aα,7aα]]-3a,4,7,7a-Tetrahydro-5,6-dimethyl-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]-oxy]-1(3H)-isobenzofuranone (16a)

A solution of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) (1.23 g, 5.16 mmol) and 2,3-dimethyl-1,3-butadiene (15) (0.85 g, 10.32 mmol) in dry toluene is refluxed for 24 h. After evaporation of the solvent under reduced pressure a colorless oil (1.74 g, 105%) was obtained. Analytically pure product (0.73 g, 44%) was obtained by crystallization from petroleum ether (bp 40-60) at -18 °C. Mp 72.2-72.3 °C; $[\alpha]_D$ -214.1 (c 1.0, *n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.70-1.04 (m, 12H), 1.18 (m, 1H), 1.33 (m, 1H), 1.59 (m, 2H + 2 x s, 6H), 1.76 (br dd J = 8.8, 17.6 Hz, 1H), 1.96-2.14 (m, 3H), 2.20 (br dd, J = 8.8, 17.6 Hz, 1H), 2.46 (br d, J = 9.8 Hz, 1H), 2.43 (q, J = 7.8 Hz, 1H), 2.99 (dt, J = 2.6, 7.7 Hz, 1H), 3.46 (dt, J = 4.2, 11.1 Hz, 1H), 5.22 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.46 (q), 18.74 (q), 19.19 (q), 20.75 (q), 22.08 (q), 22.98 (t), 25.41 (d), 28.27 (t), 30.18 (t), 31.22 (d), 34.21 (t), 36.70 (d), 38.97 (d), 39.68 (t), 47.70 (d), 76.31 (d), 103.60 (d), 123.25 (s), 124.56 (s), 178.61 (s); HRMS calcd 320.235, found 320.237; Analysis calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.82; H, 10.06.

Crystal structure determination of 16a

The single X-ray structure determination was performed at low temperature (130 K) with Mo Kα radiation (λ = 0.71073 Å) on a Nonius CAD4F-diffractometer equipped with a graphite monochromator and interfaced to a PDP11/23. A suitable crystal of the title compound, having approximate dimensions of 0.15 x 0.32 x 0.50 mm, was obtained by crystallization from petroleum ether (bp 40-60) *via* slow evaporation of the solvent. It crystallized in the monoclinic space group $P2_1$. The monoclinic cell parameters and volume are: a = 7.365(1) Å, b = 10.529(2) Å, c = 12.256(2) Å, β = 97.78(1)° and V = 941.7(5) Å^3. For Z = 2 and FW = 320.48 the calculated density is 1.130 g/cm^3. By using the Θ - 2Θ scan mode for 1°≤ Θ ≤ 30°, 2873 unique reflections were obtained, a number of 2269 reflections with I ≥ 3.0σ(I) were used in the refinements. 25 Reflections in the range 8.2° ≤ Θ ≤ 18.5° were used to define the unit cell parameters. The structure was solved by direct methods and based on the absolute configuration of the *l*-menthol part.[20] The positions of all the H-atoms could be revealed from a single final difference map based on all the non H-atoms. Block-diagonal least squares of F, with unit weights, converged to a final R = 0.051 and Rw = 0.064 respectively., using anisotropic temperature factors for the non H-atoms and fixed isotropic temperature factors (B = 5.0 Å^3) for the H-atoms. In the final refinements the H-atoms were constrained to their corresponding C-atom at a distance of 0.95 Å.

[3R-[3α(1R*,2S*,5R*),3aα,4α,7α,7aα]]-3a,4,7,7a-Tetrahydro-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-4,7-ethanoisobenzofuran-1(3H)-one (18a)

In a small stainless steel tube (contents 10 mL) a solution of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) (1.00 g, 4.20 mmol) and 1,3-cyclohexadiene (17) (2.20 g, 27.5 mmol) in dry toluene (5 mL) was heated at 110 °C for 24 h. After evaporation of the solvent and addition of dry acetone to the residue, the white material which precipitated was removed by filtration. Evaporation of the solvent *in vacuo* and crystallization of the residue from *n*-hexane yielded product 18a (0.63 g, 47%) as a white crystalline compound. Bp 150 °C (0.07 mm Hg); $[\alpha]_D$ -131.8 (c 1.0, *n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.72 (d, J = 7.3 Hz, 3H), 0.84 (d, J = 7.3 Hz, 3H), 0.91 (d, J = 5.9 Hz, 3H), 0.79-1.03 (m, 3H), 1.16 (m, 1H), 1.27 (m, 3H), 1.50 (m, 2H), 1.61 (m, 2H), 2.03 (m, 2H), 2.44 (dt, J = 2.2, 9.5 Hz, 1H), 2.78 (m, 1H), 2.88 (dd, J = 3.7, 9.5 Hz, 1H), 3.04 (m, 1H), 3.41 (dt, J = 3.7, 10.3 Hz, 1H), 5.13 (d, J = 1.5 Hz, 1H), 6.23 (m, 2H); ^{13}C NMR ($CDCl_3$) 15.94 (q), 21.06 (q), 22.45 (q), 23.33 (t), 23.36 (t), 23.83 (t), 25.61 (d), 31.53 (d), 31.74 (d), 31.94 (d), 34.49 (t), 40.06 (t), 45.63 (d), 46.32 (d), 47.91 (d), 77.01 (d), 104.27 (d), 132.63 (d), 134.14 (d), 178.31 (s); HRMS calcd 318.219, found 318.218; Analysis calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.74; H, 9.79.

[3R-[3α(1R*,2S*,5R*),3aα,4α,11α,11aα]]-3a,4,11,11a-Tetrahydro-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-4,11-ethanoanthra[2,3-c]furan-1(3H)-one (20a)

A solution of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) (2.00 g, 8.43 mmol) and anthracene (19) (1.50 g, 8.43 mmol) in decaline (25 mL) was refluxed at 190 °C for 18 h under a nitrogen atmosphere. After evaporation of the solvent *in vacuo*, *n*-butyl ether was added to the residue, yielding enantiomerically

pure 20a (2.19 g, 63%) as a white crystalline compound. Mp 170.5-172.0 °C; $[\alpha]_D$ -65.4 (c 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.62-1.00 (m, 12H), 1.12 (m, 1H), 1.29 (m, 1H), 1.60 (m, 2H), 1.99 (m, 2H), 2.80 (m, 1H), 3.20-3.38 (m, 2H), 4.45 (d, J = 2.8 Hz, 1H), 4.68 (d, J = 3.5 Hz, 1H), 5.03 (d, J = 1.7 Hz, 1H), 7.10 (m, 4H), 7.28 (m, 4H); ^{13}C NMR ($CDCl_3$) 15.66 (q), 20.53 (q), 21.99 (q), 23.15 (t), 25.35 (d), 31.06 (d), 34.11 (t), 39.64 (t), 45.51 (d), 45.67 (d), 47.46 (d), 47.54 (d), 48.19 (d), 76.57 (d), 101.84 (d), 123.53 (d), 123.81 (d), 124.47 (d), 125.05 (d), 126.25 (d), 126.74 (d), 138.87 (s), 139.76 (s), 141.30 (s), 141.95 (s), 174.89 (s); HRMS calcd 416.235, found 416.236.

[3R-[3α(1R*,2S*,5R*),3aα,7aα]]-3a,4,7,7a-Tetrahydro-3-[[5-methyl-2-(1-methylethyl)-cyclohexyl]oxy]-1(3H)-isobenzofuranone (23a)

(5R)-5-(*l*-Menthyloxy)-2(5H)-furanone (6a) (1.00 g, 4.20 mmol) and 1,3-butadiene (22) (0.59 g, 21.0 mmol) were dissolved in dry toluene (8 mL) and heated for 24 h at 110 °C in a sealed stainless steel tube (volume 10 mL). After evaporation of the solvent and addition of dry acetone the polymeric material was removed by filtration over a small pad of Celite. After evaporation of the acetone the product was obtained as a colorless oil. Based on ^1H NMR and ^{13}C NMR spectra only one diastereoisomer had been formed. The product was crystallized from petroleum ether (bp 40-60) at -20 °C yielding analytically pure 23a (0.55 g, 45%) as white crystals. Mp 81.6-83.4 °C; $[\alpha]_D$ -205.7 (c 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.71-1.04 (m, 12H), 1.19 (m, 1H), 1.32 (m, 1H), 1.62 (m, 2H), 1.82 (m, 1H), 2.03 (m, 2H), 2.18 (m, 2H), 2.44 (m, 2H), 3.04 (m, 1H), 3.48 (dt, J = 4.4, 11.0 Hz, 1H), 5.26 (s, 1H), 5.66 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 15.37 (q), 20.75 (q), 21.43 (t), 22.08 (q), 22.88 (t), 22.97 (t), 25.36 (d), 31.18 (d), 34.15 (t), 35.56 (d), 37.73 (d), 39.61 (t), 47.65 (d), 76.24 (d), 103.44 (d), 123.98 (d), 125.31 (d), 178.48 (s); HRMS calcd 292.204, found 292.203; Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found C, 73.96; H, 9.52.

Reaction of (5R)-5-(l-menthyloxy)-2(5H)-furanone with butadiene sulfone (21)

A solution of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) (2.01 g, 8.43 mmol) and butadiene sulfone (21) (2.00 g, 16.95 mmol) in dry toluene (10 mL) was heated at 110 °C for 24 h in a sealed stainless steel tube. After evaporation of the solvent, ether was added and the precipitate was removed by filtration. The solvent was evaporated under reduced pressure and the residue was purified by bulb-to-bulb distillation yielding a slightly yellow oil (1.90 g, 77%). The ^1H NMR spectrum indicated that a mixture of products had been formed. These products were the results of a Diels-Alder reaction between butadiene and furanone 6a and its epimer 6b. Furthermore, part of these cycloadducts had been hydrolyzed to the corresponding aldehydes.

General procedure for the methanolysis of the cycloadducts

Compound 16a (366 mg, 1.14 mmol) was dissolved in dry methanol (50 mL). After the addition of a catalytic amount of *p*-toluenesulfonic acid the solution was refluxed for 2 h. This reaction mixture was used for e.e. determination (*vide infra*). The ^1H NMR spectrum of 16a was identical to the one obtained for racemic 16a, synthesized by means of the Diels-Alder reaction of 15 with racemic 5-methoxy-2(5H)-furanone (5).

Enantiomeric excess determination

The enantiomeric excess (e.e.) of the products obtained from the methanolysis of the Diels-Alder products 14a, 16a, 18a and 23a was determined on basis of GC analysis. The capillary column used was a XE-60 (S)-valine-(S)-α-phenylethylamide (50 m x 0.25 mm, Chrompack no. 7490). The conditions for racemic 16b were as following: injection temperature 200 °C, detector temperature 200 °C and column temperature 125 °C. Total flow of He gas 99.1 mL/min. Headpressure 30 psi. Two baseline separated signals were observed with retention times of 41.32 and 42.36 minutes respectively and a ratio of 49.9:50.1. When the product 16b, obtained from the methanolysis of 16a, was injected only the first signal was observed. Integration indicated an e.e. >99.9%.

[3R-[3α(1R*,2S*,5R*),3aα,9aα]]-3a,4,6,7,8,9,9a-Octahydro-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-naphto[2,3-c]furan-1(3H)-one (25)

In a sealed tube were heated a mixture of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) (0.51 g, 2.14 mmol) and 1,2-bis(methylene)cyclohexane (24) (0.26 g, 2.40 mmol) in dry benzene (10 mL) at 80 °C for 18 h. Because no complete conversion had occurred, a second amount of diene 24 (0.90 g, 8.33 mmol) was added and heating was continued for another 24 h at 100 °C. After the solvent had been removed *in vacuo* the volatile material was removed by heating in a kugelrohr apparatus (140 °C, 0.15 mm Hg). The brown residue was dissolved in *n*-hexane and the insoluble material was removed by filtration. After evaporation of the solvent the product was purified by crystallization from pentane yielding 25 (0.38 g, 51%) as a white solid. Mp 112.4-113.8 °C; $[\alpha]^{20}_D$ -218.0 (c 0.986, diethyl ether); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.72-1.20 (m, 12H), 1.36 (m, 1H), 1.45-1.93 (m, 12H), 1.96-2.38 (m,4H), 2.45 (q, J = 8.0 Hz, 1H), 3.03 (dd, J = 1.9, 8.0 Hz, 1H), 3.48 (dt, J = 4.1, 10.5 Hz, 1H), 5.13 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.43 (q), 20.83 (q), 22.14 (q), 22.81 (2 x t), 22.94 (t), 25.41 (d), 26.87 (t), 28.89 (t), 29.80 (t), 30.29 (t), 31.24 (d), 34.20 (t), 36.36 (d), 38.62 (d), 39.66 (t), 47.69 (d), 76.29 (d), 103.57 (d), 125.33 (s), 126.68 (s), 178.90 (s); HRMS calcd 346.251, found 346.250; Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.42; H, 9.85.

[3R-[3α(1R*,2S*,5R*),3aα,7aα]]-Tetrahydro-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-1,5(3H,4H)-isobenzofurandione (29)

A solution of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) (2.60 g, 10.9 mmol) and silyloxydiene 27 (3.78 g, 26.7 mmol) in dry toluene (2 mL) was heated in a sealed for 16 h at 120 °C. After evaporation of the solvent under reduced pressure, the crude product 28 was obtained as an oil in 100% yield. IR: neat, cm^{-1}: 1780 (C=O), 1260 (C-O), 1195, 1105 (Si-O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.05 (s, 9H), 0.71 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.60-1.05 (m, 3H), 1.09-1.20 (m, 1H), 1.32-1.40 (m, 1H), 1.67 (m, 2H), 1.73-2.65 (m, 7H), 2.95 (dt, J = 1.8, 7.1 Hz, 1H), 3.45 (dt, J = 4.4, 10.6 Hz, 1H), 4.70 (br.s, 1H), 5.25 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 0.01 (q), 15.33 (q), 20.72 (q), 21.07 (t), 22.04 (q), 22.85 (t), 25.34 (d), 28.15 (t), 31.15 (d), 34.11 (t), 35.25 (d), 39.53 (d), 39.57 (t), 47.61 (d), 76.28 (d), 101.20 (d), 103.11 (d), 147.36 (s), 177.98 (s).

The crude cycloaddition product 28 (300 mg, 0.79 mmol) was dissolved in diethyl ether (2 mL). After the addition of tetrabutylammonium fluoride, the solution was stirred for 30 minutes at room temperature. Two drops of water were added and the resulting solution was dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, product 29 (160 mg, 66%) was obtained as a white solid. Analytically pure product was obtained by crystallization from *n*-hexane. Mp 93.1-93.4 °C. IR: neat, cm^{-1}: 1790, 1710 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.68-1.05 (m, 14H), 1.10-1.21 (m, 2H), 1.27-1.45 (m, 2H), 1.58-1.73 (m, 2H), 1.90-2.90 (m, 5H), 3.10-3.60 (m, 3H), 5.30 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.38 (q), 19.57 (t), 20.73 (q), 22.05 (q), 22.85 (t), 23.89 (t), 25.40 (d), 31.17 (d), 34.05 (t), 36.88 (d), 37.22 (t), 39.42 (t), 42.01 (d), 47.52 (d), 76.73 (d), 102.52 (d), 176.99 (s), 208.31 (s); HRMS calcd 308.199, found 308.200; Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.07; H, 9.15. Found 69.84; H, 9.13.

[3R-[3α(1R*,2S*,5R*),3aα,7α,7aα]]-Tetrahydro-7-methoxy-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-1,5(3H,4H)-isobenzofurandione and [3R-[3α(1R*,2S*,5R*),3aα,7B,7aα]]-Tetrahydro-7-methoxy-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-1,5(3H,4H)-isobenzofurandione (32)

A solution of (5R)-5-(*l*-menthyloxy)-2(5H)-furanone (6a) (3.00 g, 12.6 mmol) and *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (30) (4.44 g, 25.8 mmol) was refluxed for 20 h in dry toluene (10 mL) under a nitrogen atmosphere. After evaporation of the solvent *in vacuo* all volatile compounds were removed with a kugelrohr apparatus at reduced pressure (100 °C, 0.1 mm Hg). The residue was dissolved in acetonitrile (25 mL) and treated with cesium fluoride (3.00 g, 13.2 mmol) yielding product 32 as a mixture of two diastereoisomers (ratio 2:1). Both isomers were separated by flash chromatography (SiO_2, diethyl ether). The total yield of 32 after evaporation of the solvent was 77%.

Major diastereoisomer (7B-32) was obtained as an oil. Bp 200 °C (0.001 mm Hg); $[\alpha]^{20}_D$ -124.5 (c 1.084, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.71-1.04 (m, 12H), 1.19 (m, 1H), 1.32 (m, 1H), 1.62 (m, 2H), 2.00 (m, 2H), 2.16 (dd, J = 9.0, 15.5 Hz, 1H), 2.38 (dd, J = 2.9, 15.8 Hz, 1H), 2.65 (m, 2H), 2.92 (m, 1H), 3.35 (m, 1H + s, 3H), 3.48 (m, 1H), 4.18 (q, J = 3.4 Hz, 1H), 5.28 (s, 1H); ^{13}C NMR

($CDCl_3$): δ 15.43 (q), 20.81 (q), 22.09 (q), 22.91 (t), 25.45 (d), 31.24 (d), 34.11 (t), 39.30 (t), 39.55 (t), 40.86 (d), 41.93 (t), 42.17 (d), 47.57 (d), 56.45 (q), 76.54 (d), 76.97 (d), 103.49 (d), 174.97 (s), 205.64 (s); HRMS calcd 338.209, found 338.208; Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.63; H, 8.96.

Minor diastereoisomer (7α-32) was obtained as a white crystalline compound after crystallization from *n*-hexane. Mp 96.9-97.2 °C; $[\alpha]^{20}_D$ -199.9 (c 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.75-1.06 (m, 12H), 1.18 (m, 1H), 1.34 (m, 1H), 1.62 (m, 2H), 2.01 (m, 1H), 2.12 (m, 1H), 2.30 (dd, J = 2.2, 16.9 Hz, 1H), 2.54 (m, 2H), 2.80 (m, 2H), 3.08 (dd, J = 4.0, 10.3 Hz, 1H), 3.31 (s, 3H), 3.48 (m, 1H), 4.15 (m, 1H), 5.41 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 15.58 (q), 20.74 (q), 22.02 (q), 22.87 (t), 25.16 (d), 31.17 (d), 34.04 (t), 37.77 (t), 39.29 (d), 39.93 (t), 41.22 (t), 45.15 (d), 47.50 (d), 57.15 (q), 75.92 (d), 78.21 (d), 106.04 (d), 173.71 (s), 206.26 (s); HRMS calcd 338.208, found 338.209; Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.21; H, 8.88.

Crystal structure determination of 7α-32

The single crystal X-ray determination was performed at 293 K with CuK radiation (λ = 1.5406 Å) on a Nonius CAD4F computer controlled kappa axis diffractometer equipped with a graphite monochromator and interfaced to a PDP11/23. A suitable crystal of the titel compound, having approximate dimensions 0.40 x 0.20 x 0.15 mm, crystallized from *n*-hexane in the monoclinic space group $P2_1$ with a = 5.663(1) Å, b = 11.235(1) Å, c = 15.193(1) Å, β = 91.660(1) and V = 966.2 Å^3. For Z = 2 and FW = 338.45 the calculated density is 1.163 gcm^{-1}. By using the Θ - 2Θ scan mode for $1° \leq \Theta \leq 72°$, 2171 unique reflections were obtained, a number of 1874 reflections with intensities $I \geq 3.0\sigma(I)$ were used in the refinement. 25 Reflections in the range of $36.1° \leq \Theta \leq 54.2°$ were used to define the unit cell parameters. The structure was partly solved by direct methods. The remaining atoms could be revealed from succeeding difference Fourier syntheses. Block-diagonal least-squares of F, with unit weights, converged to a final R = 0.069 and wR = 0.076, respectively, using anisotropic temperature factors for the non-H atoms and isotropic thermal parameters (5.0 Å^2) for the H-atoms. In the final refinements the H-atoms were riding on their corresponding atoms at a distance of 0.96 Å.

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