CHAPTER II

THE ASYMMETRIC SYNTHESIS OF 5-MENTHYLOXY-2(5H)-FURANONE AND THE APPLICATION IN DIELS-ALDER REACTIONS

2.1 Introduction

2.1.1 Chiral butenolides and pyranosides

There is considerable interest in using chiral butenolides\(^1\) and pyranosides\(^2\) as chiral synthons\(^3\) in the preparation of various natural products.\(^4\) Several of these compounds are readily available in enantiomerically pure form, show high stereocontrol in addition reactions and are multifunctional. The chiral butenolide \((S)-5-(hydroxy-methyl)-2(5H)-furanone (2.4)\) (Scheme 2.1), which has most frequently been used, can be derived from \((S)-\text{glutamic acid}, (2.1)\), \(\text{D-ribonolactone (2.2)}\), or \(\text{D-mannitol (2.3)}\).

\[ \text{Scheme 2.1} \]

Very recently another efficient method for the synthesis of optically pure \(2.4 (R = H)\), starting from levoglucosenone, was described by Koseki et al.\(^8\).

\(\gamma\)-Alkyl butenolides \(2.4\) have been explored by Koga et al. in the synthesis of several
lignan-type lactones like (+)-trans-burseran, (-)-isostegane and (+)-steganacin.\textsuperscript{9} Furanone 2.4 was also used by Hanessian and co-workers in the synthesis of the C\textsubscript{14}-C\textsubscript{20} and C\textsubscript{32}-C\textsubscript{38} segments of amphotericin B.\textsuperscript{10} Related \(\alpha,\beta\)-unsaturated cyclic compounds, which possess a stereogenic center \(\gamma\) to the carbonyl as well as \(\alpha\) to an oxygen atom, are the 2,3-dideoxy-hex-2-eno-pyranosiduloses 2.5 (Figure 2.1).\textsuperscript{11} A related system, containing the same enone moiety, has the general structure 2.6.\textsuperscript{12}

\[ \text{Figure 2.1} \]

These compounds can be prepared enantiomerically pure and in high yields by using simple procedures starting from cheap readily available materials, for example D-glucose and methyl \(\alpha\)-D-glucopyranoside.\textsuperscript{13} The chemistry of the \(\alpha,\beta\)-unsaturated sugar derivatives 2.5 and 2.6 has been explored very nicely in the total synthesis of several natural products and analogues thereof, such as annulated pyranosides,\textsuperscript{14} actinobolin,\textsuperscript{15} grandisol\textsuperscript{16} and crysanthenic acids.\textsuperscript{17} Compounds 2.4-2.6 are derivatives of natural products and consequently the absolute stereochemistry at the stereogenic centers is already defined by the starting materials. As a result only one enantiomer is available in most cases. Another consequence is that pyranosides 2.5 and 2.6 are often substituted at the C2, C4 and C5 positions with alkyl or alkoxy substituents. All reactions with these butenolides and pyranosiduloses are therefore substrate controlled. Because of these disadvantages we have been searching for a comparable system which would overcome these problems, and which would make use of a chiral auxiliary for the stereocontrol. At the start of our research no butenolides were known in which the absolute configuration is controlled by a chiral auxiliary.

Compounds with the general structure 2.7 seemed very attractive, due to the presence of an acetal moiety, which is a useful functionality for the introduction of a variety of chiral auxiliaries. The advantage of using an enantiomerically pure alcohol for the introduction of the chirality in this system is that it allows more flexibility in synthetic applications as compared to compounds like 2.4 and 2.5. By using both enantiomers of the chiral auxiliary alcohol, both enantiomers of the alkoxyfuranones are accessible.
Furthermore compounds 2.4, 2.5 and 2.6 are of the type C5 and C6 chiral building blocks, while our aim was to develop a new C4 chiral building block and to use this in diastereoselective Diels-Alder reactions. The advantage of using a 5-membered ring system over a 6-membered ring system is that the former is more rigid and therefore has less conformational flexibility. Consequently, with the furanone system higher selectivities can be expected.

2.1.2 The use of chiral butenolides and pyranosides in stereoselective cycloaddition reactions

An essential structural feature of the chiral butenolides 2.4 and 2.7 is the α,β-unsaturated ester moiety, while the pyranosiduloses 2.5 and 2.6 contain an enone system. Because both groups of compounds have an activated C,C double bond, they can be used as dienophiles in cycloaddition reactions.

Butenolides 2.4 and 2.7 and pyranosiduloses 2.5 and 2.6 have a directing group (at C5 and C6 respectively), which shields one of the π-faces of the molecule from being attacked. As shown in Figure 2.3 a re-face addition is expected with the S-butenolide.
In this sense, the stereogenic center at respectively C5 and C6 is responsible for the
diastereoselectivity induced at C3 and C4 of the butenolides, or at C4 and C5 in the
case of the chiral pyranosiduloses, in the cycloaddition reaction.
Examples of asymmetric Diels-Alder reactions\textsuperscript{18} of chiral butenolides and pyranosi-
duloses have been reported together with other interesting reactions such as 1,3-
dipolar cycloadditions.\textsuperscript{19} A directing effect of the y-substituent was indeed found in
several cases, e.g. the reaction of butadiene (2.8) with several chiral alkoxyethyl-
butenolides 2.4, prepared from D-ribonolactone, affords enantiomerically pure bicyclic
adducts 2.9 with a diastereomeric excess >99%.\textsuperscript{20}

\[
\text{Scheme 2.2}
\]

Also in the case of the 6-membered unsaturated ketone 2.5, the addition takes place
from the less hindered side of the molecule with complete stereocontrol.\textsuperscript{21}
One example of a 1,3-dipolar cycloaddition is the selective trans addition of diazo-
propane to butenolide 2.4, although both possible regioisomers were obtained.\textsuperscript{22}
Also in the case of pyranosides such as 2.5 (R = Ac), the addition of diazomethane
takes place stereoselectively from the less hindered side of the molecule.\textsuperscript{23} Furthermore, the 1,3-dipolar cycloadditions of nitrones 2.11 to racemic 2.10, proceed with
complete regio- and diastereocontrol to produce compounds 2.12a and 2.12b.\textsuperscript{24} See
Scheme 2.3

\[
\text{Scheme 2.3}
\]
2.2 The synthesis of enantiomerically pure 5-methoxy-2(5H)-furanone

The chemistry of racemic 5-alkoxy-2(5H)-furanones 2.7 has been explored to some extent by Farina and co-workers, for example in the synthesis of trans-3-cyanoacrolein,\textsuperscript{25} 5-hydroxy- and 5-methoxy-3-pyrrolin-2-ones,\textsuperscript{26} and DL-erythrose and DL-threose\textsuperscript{27}. The 1,4-additions of amines and thiols to 5-alkoxy butenolides have been described by De Lange and Feringa.\textsuperscript{28} Racemic 5-alkoxy-2(5H)-furanones 2.7 have also received attention as starting materials in the total synthesis of natural products. De Graw succeeded in synthesizing pilocarpine by a selective trans addition of ethyl diethylmalonate to 5-ethoxy-2(5H)-furanone (2.7b, \( R = \text{Et} \)).\textsuperscript{29} Other total syntheses in which 5-hydroxy- or 5-alkoxy-2(5H)-furanones play a pivotal role are those of camptothecine,\textsuperscript{30} strigol,\textsuperscript{31} and verrucarine J.\textsuperscript{32} In all these cases only racemic products were obtained. It would therefore be of great interest if 5-alkoxy-2(5H)-furanones 2.7 were available as pure enantiomers, since this opens possibilities for stereoselective C,C bond forming reactions.

There are several pathways conceivable to obtain the 5-alkoxyfuranones 2.7 in enantiomerically pure form. One is the separation of both enantiomers by resolution. For 5-alkoxyfuranones 2.7 this will be a difficult case because there is, for example, no way to form diastereomeric salts, which could be separated by crystallization. Separation via chromatography may be possible but probably is not appropriate for synthetic purposes.

Another possibility would be the resolution via diastereoisomers using a covalently bound chiral auxiliary compound. A serious drawback, however, is that in this case 50\% of the compound is lost as the unwanted isomer, unless a recycling step is available, e.g. through epimerization or racemization.

The most effective method would be asymmetric synthesis which, in principle, allows complete conversion of an appropriate achiral starting material into a single enantiomer of the chiral butenolide. As far as we know, no asymmetric synthesis of 5-alkoxy-2(5H)-furanones 2.7 had been reported at the start of this investigation.

\[ \text{Scheme 2.4} \]
We considered the asymmetric acetalization of 5-hydroxybutenolid 2.13 with an enantiomerically pure auxiliary alcohol an attractive way to obtain 5-alkoxy-2(5H)-furanones 2.7 (Scheme 2.4). 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.

2.2.1 The synthesis of 5-hydroxy-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 synthesize racemic 5-hydroxy- and 5-alkoxy-2(5H)-furanones. These products can be prepared by photooxidation,\textsuperscript{33,34} \text{CrO}_3/H_2SO_4\textsuperscript{35} or PCC oxidation\textsuperscript{36} of several furan derivatives. For a large scale synthesis of 5-hydroxy-2(5H)-furanone (2.13) the photooxidation of furfural (2.14) is probably most suitable.\textsuperscript{37} Photolysis of furfural, using methylene blue or rose bengal as sensitizer, in methanol at room temperature with oxygen continuously bubbling through the solution, provided 5-hydroxy-2(5H)-furanone (2.13) as a solid material. We have performed several of these experiments on a 100 gram scale without any difficulties. The advantages of this reaction are that the starting materials (furfural, methanol, and oxygen) are inexpensive and the reaction provides the desired product in quantitative yield. No side products are formed except methyl formate, which can easily be removed by distillation. In large scale preparation, with extended reaction times (up to 3 days), some 5-methoxy-2(5H)-furanone (2.7a) may be formed already. The proposed mechanism of the photooxidation is shown in Scheme 2.5.\textsuperscript{37}

![Scheme 2.5]

The [4+2] cycloaddition of singlet oxygen to furfural yields an endoperoxide. Next, an addition of methanol to the aldehyde group takes place providing compound 2.15.
This is followed by fragmentation, resulting in endoperoxide cleavage and elimination of methyl formate. Instead of furfural, 2-furancarboxylic acid can also be used.\textsuperscript{38} Racemic 5-methoxy-2(5H)-furanone (2.7a) was obtained by refluxing 5-hydroxy-2(5H)-furanone (2.13) for 3 days in dry methanol. After distillation of the product, pure 2.7a was obtained as a colorless oil in 74\% yield. Racemic 5-alkoxy-2(5H)-furanones can also be obtained directly by the irradiation of 2-furfural (2.14) or 2-furancarboxylic acid in e.g. methanol or ethanol.\textsuperscript{39}

2.2.2 The synthesis of enantiomerically pure 5-alkoxy-2(5H)-furanones

In preliminary experiments for the synthesis of enantiomerically pure 5-alkoxy-2(5H)-furanones 2.7, the asymmetric acetalization of 2.13 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 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 2.13, a separation step appeared to be inevitable. Unfortunately, it was not possible to separate the diastereoisomers by means of crystallization because these products were either oils, or the difference in solubility between both diastereoisomers was not large enough. For synthetic use therefore 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 5-hydroxy-2(5H)-furanone (2.13), 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 which means they can either be bought or they are readily accessible through synthesis, opening the possibility of synthesizing both enantiomers of the corresponding 5-alkoxy-2(5H)-furanone.

3. The alcohol of choice 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. For the synthesis of enantiomerically pure 5-menthyloxy-2(5H)-furanone (2.16) two procedures were developed. The simplest route is to heat the hydroxyfuranone 2.13 with 1.1 to 1.5
equivalents of l-menthol at 100 °C for 20 hours, without solvent. After removal of the excess menthol by distillation, the menthylxyfuranone 2.16 was obtained in 61% yield (Scheme 2.6).

\[
\text{HO-} \xrightarrow{1-\text{menthol \ 100°C \ 61\%}} \text{menthylxyfuranone} \ 2.16
\]

Scheme 2.6

As was readily deduced from the \(^1\text{H}\) NMR spectrum the product consisted of a mixture of 2 diastereoisomers (2.16\(a\) + 2.16\(b\)) in a 60:40 ratio (Figure 2.4). The ratio was determined by integration of the signals of the acetal hydrogen of 2.16\(a\) and 2.16\(b\) around 6 ppm. Structure 2.16\(a\) was assigned to the major diastereoisomer (vide infra).

![Figure 2.4: Part of the \(^1\text{H}\) NMR spectrum of a) a 1:1 mixture of 2.16\(a\) and 2.16\(b\), b) diastereomerically pure 2.16\(a\), showing the signals of the acetal hydrogen and the olefinic hydrogens.](image-url)
An alternative procedure to synthesize 2.16 is by heating a mixture of l-menthol, 5-hydroxy-2(5H)-furanone (2.13) and a catalytic amount of p-TsOH in refluxing benzene or toluene under azeotropic removal of water. This procedure proved to be very successful in the synthesis of 3-methyl-5-menthyloxy-2(5H)-furanone as is described in Chapter III. The major side product formed during the acetalization of 5-hydroxy-2(5H)-furanone (2.13) with menthol is an α,β-unsaturated aldehyde, which is most likely the menthyl ester of B-formylacrylic acid (2.19). Based on 1H NMR this product is formed in less than 10% yield. In the 300 MHz 1H NMR spectrum of the crude reaction product the following signals are found, which support the structure 2.19, as proposed in Scheme 2.7; at 6.68 ppm a doublet with J = 15.8 Hz, which indicates a trans C=C bond, at 6.90 ppm a double doublet with J = 7.5 and 15.8 Hz, and at 9.62 ppm a doublet with J = 7.5 Hz, which indicates an aldehyde next to a CH. These three signals all have the same integration, which is in accordance with structure 2.19. This compound can be formed as a result of a thermal cis-trans isomerization of 2.17 to the B-formylacrylic acid 2.18 followed by an esterification with menthol to compound 2.19.

Scheme 2.7

This α,β-unsaturated aldehyde 2.19 is easily removed from the reaction mixture by stirring an ethereal solution of the crude 5-menthyloxy-2(5H)-furanone (2.16) with a saturated sodium hydrogen sulfite solution, after which the 5-menthyloxy-2(5H)-furanone (2.16) is obtained as an oil or a low melting solid. Fortunately, the major diastereoisomer 2.16a crystallizes readily at -23 °C from an n-hexane or petroleum ether (40-60) solution of the mixture 2.16a + 2.16b. After two crystallizations from petroleum ether (40-60) or n-hexane, enantiomerically pure 2.16a was obtained as a white crystalline compound in 60% yield. Diastereomerically pure (5R)-5-(l-menthyl-ox)-2(5H)-furanone 2.16a is now commercially available and is sold by Fluka Chemie as (R)-5-[(1R)-menthylxyl]-2(5H)-furanone. In a similar way as described above the enantiomer of lactone 2.16a, with the opposite configuration at the acetal center, was obtained by starting with d-menthol as the chiral auxiliary. The absolute configuration at the acetal center of compound 2.16a was proven by an X-ray investigation of the
Diels-Alder adduct of 2.16a and 2,3-dimethyl-1,3-butadiene (*vide infra*).
The crystallization process is accompanied by a remarkable second order asymmetric
transformation⁴¹ of 2.16 in solution, providing again a 60:40 ratio of diastereoisomers
(2.16a + 2.16b) after removal of a part of 2.16a during crystallization. The slow
epimerization of 2.16b into 2.16a was deduced from ¹H NMR analysis of the solution
of 2.16 (60:40 ratio) prior to crystallization and the mother liquor just after
crystallization of 2.16a. This "crystallization induced epimerization" is essentially driven
by the continuous removal of the major crystalline isomer 2.16a from the solution.
The epimerization probably takes place via enolization⁴² of 2.16b (and 2.16a) to the
unstable 5-(l-menthyl)oxy)-2-hydroxyfuran intermediate 2.20, which has lost its
stereogenic center at C-5. This process can be catalyzed by traces of acid present
during the crystallization of 2.16a.

![Scheme 2.8](image)

In contrast, when enantiomerically pure 2.16a is heated for several hours at reflux in
toluene or petroleum ether (40-60) with careful exclusion of acid, it is not in equili-
brium with 2.16b. This property of 2.16a is essential for successful use in enantiose-
lective thermal Diels-Alder reactions. Support for this presumed enolization can be
found in the dimerization of 2-mercaptothiophene to 2.23.⁴³ The dimerization of 2.22
may be rationalized in term of a tautomerization of 2.22 to 2,5-dihydro-2H-2-thioxo-
thiophene (2.21) followed by a Michael addition of 2-mercaptothiophene (2.22) onto
acceptor 2.21 although intermediate 2.21 was not detected by ¹H NMR spectroscopy.

![Scheme 2.9](image)
A number of "crystallization-induced asymmetric transformations" have recently been published. Fukumoto et al. synthesized the menthyl half-ester of ethylmalonic acid as a mixture of two diastereoisomers (ratio 11:9), starting from ethylmalonic acid and l-menthol. When the product was set aside for several days at room temperature, the compound was nearly a single stereoisomer (>99% diastereoisomeric excess). One example in which two stereogenic centers were simultaneously inverted was recently reported by Clark et al.

![Scheme 2.10](image)

When racemic 3-cyanoethyl-hexahydrobenzo[a]quinoliniz-one (2.24) was treated with 1.05 equivalents of (+)-10-camphorsulfonic acid ((+)-CSA) in hot ethyl acetate, the (+)-CSA salt of (+)-2.24 was obtained in 90% yield. The (+)-2.24 obtained from this salt had an enantiomeric excess >98%.

![Scheme 2.25](image)
Another surprising example of crystallization induced asymmetric transformation was found by Reider et al.\(^{46}\) (Scheme 2.11). Racemic 3-aminobenzodiazepinone (2.25) was converted into optically pure 3-(S)-2.25b in greater than 90% yield. In the presence of CSA the crystalline 3-(S)-amine-CSA salt is essentially removed from the system by virtue of its insolubility, driving the equilibrium.

Another way to obtain enantiomerically pure 5-alkoxy-2(5H)-furanones may be a separation of both enantiomers via a kinetic resolution process. A kinetic resolution of 5-methoxy-2(5H)-furanone (2.7a) by cinchonidine catalyzed thiophenol addition has afforded enantiomerically enriched (R)-2.7a with an enantiomeric excess of 13%.\(^{47}\) Further optimizations by Faber have resulted in an increase of the enantiomeric excess up to 91%.\(^{48}\)

### 2.3 Diastereoselective Diels-Alder reactions

As has already been mentioned in Section 2.1.2 the thermal Diels-Alder reaction of dienes with chiral butenolides and pyranosides are expected to proceed with a high endo selectivity and diastereoselectivity. When 2.16a was heated at 110 °C in dry toluene for 4.5 h with a twofold excess of cyclopentadiene (2.27) it was converted into the adduct 2.28 in 99% isolated yield. Analytically pure product was obtained in 65% yield by crystallization from petroleum ether (40-60) at -40 °C.

\[
\begin{align*}
\text{H}_2\text{O} & \quad \text{O} \\
\text{H-1} & \quad \text{H-2} \\
2.16a & \quad 2.27 & \quad 2.28
\end{align*}
\]

Scheme 2.12

Based on \(^1\)H NMR and \(^13\)C NMR adduct 2.28 was obtained as a single isomer, which indicates a diastereoselectivity (d.e.) >97%. When a 60:40 mixture of diastereoisomers 2.16a and 2.16b was used, adduct 2.28 was obtained with a diastereoselectivity of 20%.

These results show that a complete π-face selective addition takes place and that no epimerization of 2.16a occurs during the cycloaddition reaction. Based on the very small coupling constant (\(J < 1 \text{ Hz}\)) of the acetal proton of adduct 2.28, indicating a trans arrangement of H-1 and H-2, it is concluded that the addition of cyclopentadiene has taken place from the less hindered side of the molecule. The diastereoselectivity can
be rationalized by the model depicted in Figure 2.3. In the case of 2.16a the large menthyloxy group at C₃ protects one side of the molecule from being attacked by cyclopentadiene. The endo-attack of cyclopentadiene was further established by extensive 2D NMR studies (COSY, NOESY).

In the NOESY-spectrum there was a clear cross-peak between one of the "bridge-head" hydrogens H-8 and H-2, whereas no cross-peak was observed between the "bridge-head" hydrogen H-8 and the acetal hydrogen H-1, which might be possible if the exo-adduct had been formed. If an exo-attack of cyclopentadiene (2.27) had taken place the cross peak between H-2 and H-8 would certainly not have been observed.
Also the cross-peak between H-1 and H-4 clearly indicates that an endo-attack of cyclopentadiene has occurred. In the case of an exo-attack this cross signal would not be possible concerning the orientation of these two hydrogen atoms, as is shown by molecular models. All these results are in complete agreement with the structure 2.28 proposed in Figure 2.5.

The chiral auxiliary menthol is readily removed by hydrolysis (H₂O/SiO₂ or H₂O/H₃CCOCH₃/CH₃COOH) or methanolysis (CH₃OH/p-TsOH) leading to enantio-merically pure hydroxy or methoxy substituted lactones 2.29 and 2.39, respectively (Scheme 2.13). Compound 2.29 has been used in racemic form by Magnus and co-workers as the key intermediate in the synthesis of d,l-dehydroaspidospermidine systems. In that case 2.29 was prepared by the Diels-Alder reaction between hydroxyfuranone 2.13 and cyclopentadiene 2.27. The recovered menthol (> 90%), which was purified by a single bulb-to-bulb distillation (130 °C, 30 mm Hg), had an optical purity of 97%.

Scheme 2.13

Table 2.1 shows the results of the asymmetric Diels-Alder reactions of several dienes with 2.16a. All reported yields are after purification by means of crystallization, except in the case of the Diels-Alder reaction with butadiene sulfone (2.37). Excellent stereochemical control is exerted in all cases except two (vide infra). In fact only one diastereoisomer of the Diels-Alder product was found when enantiomerically pure 2.16a was used as dienophile. However, at 190 °C, needed for the Diels-Alder reaction between 2.16a and anthracene (2.35), epimerization of the dienophile was observed. Two cycloaddition products were isolated with an approximate ratio of 60:40. Diastereomerically pure product 2.36 was obtained through a single crystallization from n-butyl ether. One other exception was found in the case of butadiene sulfone (2.37) (entry 6). The released SO₂ probably forms sulfurous acid with traces of water, which catalyses the epimerization of (5R)-5-(l-menthylxy)-2(5H)-furanone (2.16a) resulting in a mixture of (5R)- and (5S)-5-(l-menthylxy)-2(5H)-furanone (2.16a + 2.16b). ¹H NMR also indicated that at the same time an α,β-unsaturated aldehyde
was formed. It is most likely that this product is formed by ring opening of the furanone 2.16a, eventually followed by a cis-trans isomerization of the C-C double bond.

Table 2.1: Asymmetric Diels-Alder Reactions of (5R)-5-(l-menthylxylo)-2(5H)-furanone (2.16)

<table>
<thead>
<tr>
<th>entry</th>
<th>diene</th>
<th>product</th>
<th>temp</th>
<th>%yield</th>
<th>%de</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cyclopentadiene (2.27)</td>
<td>2.28</td>
<td>110 °C</td>
<td>65</td>
<td>&gt;96</td>
<td>d</td>
</tr>
<tr>
<td>2</td>
<td>2-methylbutadiene (2.29)</td>
<td>2.30</td>
<td>120 °C</td>
<td>56</td>
<td>&gt;96c</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>2,3-dimethylbutadiene (2.31)</td>
<td>2.32</td>
<td>120 °C</td>
<td>44</td>
<td>96e</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>1,3-cyclohexadiene (2.33)</td>
<td>2.34</td>
<td>120 °C</td>
<td>47</td>
<td>&gt;96</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>anthracene (2.35)</td>
<td>2.36</td>
<td>190 °C</td>
<td>63</td>
<td>20</td>
<td>d</td>
</tr>
<tr>
<td>6</td>
<td>butadiene sulfone (2.37)</td>
<td>2.38</td>
<td>120 °C</td>
<td>77</td>
<td>73</td>
<td>72</td>
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<td>2.38</td>
<td>120 °C</td>
<td>45</td>
<td>&gt;96</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
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<td>2.28</td>
<td>110 °C</td>
<td>60</td>
<td>20f</td>
<td>d</td>
</tr>
</tbody>
</table>

*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 menthylxylo derivative of the product. The enantiomeric excess (e.e.) was determined on the basis of GC analysis of the methoxy derivative (see Section 2.5). *c*Mixture of two regioisomers (50:50 ratio). *d*Not determined. *e*Starting material 2.16a + 2.16b (98:2 ratio). *f*Starting material 2.16a + 2.16b (60:40 ratio).

Reaction of (5R)-5-(l-menthylxylo)-2(5H)-furanone (2.16a) with 2-methyl-1,3-butadiene (2.29) resulted in a mixture of two regioisomers with a ratio of 50:50, as was determined by $^1$H NMR and $^{13}$C NMR. Two well separated signals for the acetal hydrogen were observed at 5.27 ppm and 5.28 ppm (300 MHz), both having a coupling constant of <1 Hz, demonstrating that in both cases a trans attack relative to the menthylxylo group had occurred. 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 (40-60), the products are fairly soluble.

In the literature it had been reported that, when furan was used as a dienophile, no reaction was observed in the Diels-Alder reaction with 5-ethoxy-2(5H)-furanone 2.7b. Under various conditions no reaction was observed between butenolide 2.4 (R = H, Ac) and furan. Probably because of the aromatic character of the furan ring, the cycloaddition reaction is energetically less favorable.
2.4 Absolute configuration determination by means of X-ray analysis

Despite various attempts, no suitable crystals for an X-ray analysis could be obtained of (5R)-5-(l-menthxyloxy)-2(5H)-furanone (2.16a), and the absolute configuration at the acetal center was therefore unknown. Also, no significant differences were found by MM-2 calculations of 2.16a and 2.16b between the energy levels of both diastereoisomers.

To obtain information about the actual configuration of the acetal stereogenic center of the 5-menthylxloxy-2(5H)-furanones (2.16), an X-ray analysis of the 2,3-dimethyl-1,3-butadiene adduct 2.32 was performed. Single crystals, suitable for X-ray analysis, were obtained by crystallization from petroleum ether (40-60) under condition of solvent evaporation. Compound 2.32 crystallized in the monoclinic space group P2₁ with unit cell dimensions a = 7.365(1) Å, b = 10.592(2) Å, c = 12.256(1) Å, α = 90.00°, β = 97.78(1)°, γ = 90.00° and two molecules in each unit cell. The approximate dimensions of the crystal were 0.15 x 0.32 x 0.50 mm. The data collection was performed at low temperature (130 K).

![PLUTO plot of 2.32](image_url)
The crystal structure of compound 2.32 is depicted in Figure 2.6 and was based on the absolute configuration of (1R,2S,5R)-(-)-menthol.\textsuperscript{51} Bond distances and bond angles are listed in Tables 2.2 and 2.3 (the hydrogen atoms have been omitted). The absolute configuration at the acetal stereogenic center can be assigned on the basis of the structure analysis of compound 2.32 and was proven to be R. As no epimerization is observed under Diels-Alder conditions and complete stereocontrol is observed it also proofs that the acetal stereogenic center of 5-((\textit{I}-menthoxy)-2(5H)-furanone (2.16a) has the R-configuration. Furthermore this X-ray analysis confirms the trans relation-
ship between the acetal hydrogen and the hydrogen at C-5, and therefore confirms that the addition of 2,3-dimethyl-1,3-butadiene (2.31) indeed has occurred from the less hindered side of butenolide 2.16a. 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 $^1$H NMR, which also is indicative of a trans addition of 2,3-dimethyl-1,3-butadiene (2.31) relative to the menthyloxy group of 2.16a. The calculated coupling constant according to the Karplus relation 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 the diene, relative to the menthyloxy group of 2.16a.

2.5 Determination of the enantiomeric excess

As mentioned already, the chiral auxiliary can be recovered by methanolysis of the Diels-Alder products yielding the corresponding methoxylactones. These lactones were also synthesized as racemates by reaction of the proper diene with racemic 5-methoxy-2(5H)-furanone (2.7a). All reactions were performed in dry toluene (110 °C) or decaline (190 °C). The yields of the cycloaddition reactions varied in these cases between 52% for anthracene and 82% for 2,3-dimethyl-1,3-butadiene. These reactions were not optimized as the main goal was to obtain material for the e.e. determination of the compounds obtained via methanolysis of the corresponding menthyloxy compounds (vide infra).

The enantiomeric excess of the methoxy derivatives obtained by methanolysis was determined on basis of GC analysis. The chiral capillary GC column used was a XE-60 (S)-valine-(S)-α-phenylethylamine (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 products obtained by the asymmetric cycloaddition with (5R)-5-(l-menthyl)-2(5H)-furanone (2.16a) (Table 2.1). This is illustrated in Figure 2.7 which shows a: the GC chromatogram of racemic 2.40, obtained by the cycloaddition of racemic 5-methoxy-2(5H)-furanone (2.7) and 2,3-dimethyl-1,3-butadiene (2.31), and b: of enantiomerically pure 2.40 obtained via methanolysis of 2.32. This means that after the methanolysis, the products are obtained with an e.e. ≥ 99.9%.

In the case of the racemic 2-methyl-1,3-butadiene adduct 2.30, 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 after methanolysis.

Figure 2.7: GC chromatogram of a) racemic 2.40 and of b) enantiomerically pure 2.40

2.6 Conclusions

We may conclude that both enantiomers of 5-menthylxyloxy-2(5H)-furanone are readily available in enantiomerically pure form, starting from furfural and d- or l-menthol. The advantage of 5-menthylxyloxy-2(5H)-furanone over systems like 2.4 or 2.5 is that the synthetic route is much shorter, but most important that both enantiomers are readily available in good yields and a cheap chiral auxiliary is used. 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 2.4, derived from D-ribonolactone. The yields of these reactions can probably be improved by isolating the cycloaddition products by column chromatography instead of crystallization, because they are in most cases very soluble in all organic solvents. The chiral auxiliary menthol can easily be recovered by hydrolysis or alcoholysis.

2.7 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. 1H 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 1H NMR chemical shifts are determined relative to the solvent and converted to the TMS scale using δ (CDCl₃) = 7.26 ppm. 13C 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 (CDCl₃) = 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) by Mr. A. Kiewiet. Elemental analyses were performed in the Microanalytical Department of this laboratory by Mr. H. Draayer, J. Ebels, A.F. Hamminga, J. Hommes and J.E. Vos. The X-ray data collection was performed by Mr. F. van Bolhuis with Mo Kα radiation on a Nonius CAD4F-diffractometer equipped with a graphite monochromator and interfaced to a PDP11/23. All reagents and solvents were purified and dried where necessary, according to standard procedures. 1-And d-menthol were purchased from Janssen Chimica, Fluka and Aldrich, and were used without further purification.

5-Hydroxy-2(5H)-furanone (2.13)
Freshly distilled furfural (2.14) (100 g, 1.04 mol), dissolved in methanol (600 mL), was photooxygenated in the apparatus described by J.C. Hummelen using a few milligrams of methylene blue as the sensitizer. A stream of oxygen was introduced through a glass filter (P₂o) into the reaction vessel. Kaptan 500 H was used as U.V. and blue filter and a Hanau Q 700 lamp served as the lightsource. The reaction was followed by 1H 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 (2.13) (104 g, 100%) was obtained as an oil, which solidified upon standing. The product 2.13 was pure enough to be used in the next reaction step without further purification. The product can be crystallized from carbon tetrachloride, yielding pure 2.13 as a white crystalline compound. Mp 57.3-59.2 °C (lit. 58.0-60.0 °C); 1H NMR (CDCl₃, 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 (2.7g)
5-Hydroxy-2(5H)-furanone (2.13) (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. 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃): δ 56.31 (q), 103.92 (d), 124.40 (d), 150.62 (d), 170.21 (s).

3α,3α,7α-3α,4,7,7α-Tetrahydro-5-methyl-3-methoxy-1(3H)-isobenzofuranone and 3α,3α,7α-3α,4,7,7α-Tetrahydro-6-methyl-3-methoxy-1(3H)-isobenzofuranone
A solution of 5-methoxy-2(5H)-furanone (2.7g) (3.00 g, 26.3 mmol) and isoprene (2.29) (7.16 g, 0.11 mol) in dry toluene (10 mL) was heated for 24 h at 110 °C in a sealed stainless steel tube. After evaporation of the solvent under reduced pressure the crude product was purified by bulb-to-bulb distillation (150 °C, 14 mm Hg) yielding the pure cycloadduct (3.29 g, 69%) as a colorless oil. From the 13C NMR spectrum was deduced that the product consisted of a mixture of two regioisomers in a ratio of 1:1. 1H NMR (CDCl₃, 300 MHz): δ 1.65 (s, 1.5H), 1.67 (s, 1.5H), 2.06-2.66
(m, 5H), 2.98 (dt, J = 2.56, 8.06 Hz, 0.5H), 3.06 (dt, J = 1.84, 8.42 Hz, 0.5H), 3.46 (2 x s, 3H), 4.98 (s, 1H), 5.38 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta 21.27 (t), 22.41 (q), 22.75 (q), 23.00 (t), 25.56 (t), 27.36 (t), 34.27 (d), 35.42 (d), 36.73 (d), 37.65 (d), 55.53 (q), 107.72 (d), 117.61 (d), 118.37 (d), 130.90 (s), 132.10 (s), 177.56 (s).

3α,3αa,7αa-3αa,4,7,7αa-3α,4,7,7αa-Tetrahydro-5,6-dimethyl-3-methoxy-1(3H)-isobenzofuranone
A solution of 5-methoxy-2(5H)-furanone (2.7a) (1.50 g, 13.16 mmol) and 2,3-dimethyl-1,3-butadiene (2.31) (2.16 g, 26.34 mmol) in dry toluene (10 mL) was heated for 24 h at 110 °C in a sealed tube. After evaporation of the solvent under reduced pressure and distillation (100 °C, 0.01 mm Hg) of the residue, the product (2.12 g, 82%) was obtained as a colorless oil. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 1.59 (s, 6H), 1.78 (m, 1H), 2.14 (m, 2H), 2.33 (m, 1H), 2.48 (m, 1H), 2.96 (m, 1H), 3.42 (s, 3H), 4.92 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta 18.30 (q), 18.73 (q), 27.92 (t), 29.82 (t), 36.12 (d), 38.36 (d), 55.90 (q), 108.21 (d), 123.12 (s), 124.31 (s), 178.22 (s); HRMS calcd 196.110, found 196.110.

3α,3αa,4α,7αa,7aα-3α,4,7,7αa-Tetrahydro-3-methoxy-4,7-ethanoisobenzofuran-1(3H)-one
5-Methoxy-2(5H)-furanone (a) (1.50 g, 13.2 mmol) and anthracene (2.34 g, 13.2 mmol) were dissolved in decaline (25 mL) and heated for 24 h at 190 °C. After evaporation of the solvent the product (1.99 g, 52%) was obtained as a slightly brown powder which was pure according to \(^1\)H NMR. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 2.84 (dd, J = 1.8, 3.3, 9.9 Hz, 1H), 3.28 (dd, J = 3.7, 9.9 Hz, 1H), 3.38 (s, 3H), 4.46 (d, J = 3.3 Hz, 1H), 4.69 (d, J = 3.7 Hz, 1H), 4.80 (d, J = 1.8 Hz, 1H), 7.16 (m, 4H), 7.33 (m, 4H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta 45.44 (d), 45.69 (d), 47.30 (d), 47.88 (d), 54.68 (q), 106.65 (d), 123.66 (d), 123.93 (d), 124.63 (d), 125.00 (d), 126.33 (d), 126.37 (d), 126.77 (d), 126.89 (d), 138.66 (s), 139.62 (s), 141.18 (s), 141.83 (s), 175.13 (s).

Reaction of 5-hydroxy-2(5H)-furanone with l-borneol
A mixture of 5-hydroxy-2(5H)-furanone (2.13) (1.24 g, 12.4 mmol) and l-borneol (2.00 g, 13.0 mmol) were heated at 110 °C for 24 h. Because part of the l-borneol had sublimated out of the reaction mixture, a second amount of l-borneol (0.50 g, 3.24 mmol) was added and heating was continued for another 4 h. After bulb-to-bulb distillation (150 °C, 0.15 mm Hg) the product (1.97 g, 71%) was obtained as a slightly yellow oil. Based on the \(^1\)H and \(^{13}\)C NMR spectrum, it was concluded that the product consisted of a mixture of two diastereoisomers in a ratio of 1:1. Attempts to crystallize the product from pentane at room temperature failed. Only at low
temperatures (-20 or -70 °C) a crystalline compound could be obtained, but in this way no enrichment of the diastereoisomers could be accomplished. ¹H NMR (CDCl₃, 300 MHz): δ 0.81-0.85 (4 x s, 9H), 1.04-1.24 (m, 3H), 1.65 (m, 2H), 1.85 (m, 1H), 2.21 (m, 1H), 3.92 (ddd, J = 1.46, 3.30, 9.89 Hz, 0.5H), 4.07 (ddd, J = 1.46, 3.30, 9.52 Hz, 0.5H), 5.92 (m, 1H), 6.17 (m, 1H), 7.19 (m, 1H); ¹³C NMR (CDCl₃): δ 13.13 (q), 13.51 (q), 18.59 (2 x q), 19.46 (q), 19.51 (q), 26.13 (t), 26.35 (t), 27.81 (t), 27.98 (t), 35.82 (t), 36.88 (t), 44.67 (d), 44.73 (d), 47.42 (s), 47.73 (s), 48.93 (s), 49.25 (s), 84.62 (d), 87.19 (d), 102.32 (d), 104.48 (d), 124.53 (2 x d), 150.47 (d), 150.70 (d), 170.50 (2 x s).

**Reaction of 5-hydroxy-2(5H)-furanone with racemic isoborneol**

A mixture of 5-hydroxy-2(5H)-furanone (2.13) (0.88 g, 8.82 mmol) and isoborneol (1.49 g, 9.66 mmol) was heated for 24 h at 120 °C. After bulb-to-bulb distillation the product (1.54 g, 74%) was obtained as a yellow oil. The ¹H NMR and ¹³C NMR spectra showed that the product consisted of a mixture of diastereoisomers in a ratio of 1:1. ¹H NMR (CDCl₃, 300 MHz): δ 0.79 (s, 1.5H), 0.80 (s, 1.5H), 0.85 (s, 1.5H), 0.90 (s, 3H), 0.92 (s, 1.5H), 1.01 (m, 2H), 1.45-1.98 (m, 5H), 3.63 (dd, J = 3.48, 7.88 Hz, 0.5H), 3.74 (dd, J = 3.48, 7.51 Hz, 0.5H), 5.90 (s, 0.5H), 5.94 (s, 0.5H), 6.18 (m, 1H), 7.13 (dd, J = 1.10, 5.49 Hz, 0.5H), 7.17 (dd, J = 1.10, 5.49 Hz, 0.5H); ¹³C NMR (CDCl₃): δ 11.45 (q), 19.72 (q), 19.78 (q), 26.75 (t), 33.79 (t), 38.38 (t), 39.31 (t), 44.70 (d), 44.80 (d), 46.27 (s), 46.38 (s), 48.69 (s), 49.03 (s), 86.13 (d), 88.92 (d), 101.43 (d), 104.45 (d), 124.28 (d), 124.38 (d), 150.39 (d), 150.81 (d), 170.38 (s).

**Reaction of 5-hydroxy-2(5H)-furanone with α-methylbenzyl alcohol**

5-Hydroxy-2(5H)-furanone (2.13) (1.10 g, 11.0 mmol) and racemic α-methylbenzyl alcohol (2.70 g, 21.1 mmol) were heated for 24 h at 120 °C. After bulb-to-bulb distillation (170 °C, 0.15 mm Hg) and flash chromatography (SiO₂/CH₂Cl₂) the product (1.42 g, 63%) was obtained as a colorless oil. The product consisted of a mixture of diastereoisomers, ratio 60:40, as was deduced from ¹H and ¹³C NMR spectra. ¹H NMR (CDCl₃, 300 MHz): δ 1.52 (d, J = 6.2 Hz, 1.8H), 1.55 (d, J = 6.6 Hz, 1.2H), 4.89 (q, J = 6.6 Hz, 0.4H), 4.98 (q, J = 6.6 Hz, 0.6H), 5.71 (t, J = 1.3 Hz, 0.6H), 6.10 (t, J = 1.3 Hz, 0.4H), 6.13 (dd, J = 1.3, 5.7 Hz, 0.4H), 6.16 (dd, J = 1.3, 5.7 Hz, 0.6H), 7.10 (dd, J = 1.3, 5.7 Hz, 0.4H), 7.13 (dd, J = 1.3, 5.7 Hz, 0.6H), 7.34 (m, 5H); ¹³C NMR (CDCl₃): δ 22.15 (q), 23.37 (q), 76.54 (d), 77.73 (d), 100.43 (d), 101.32 (d), 124.24 (d), 125.95 (d), 126.44 (d), 127.66 (d), 128.15 (d), 128.54 (d), 140.87 (s), 141.82 (s), 150.55 (d), 150.79 (d), 170.02 (s), 170.39 (s).

**Reaction of 5-hydroxy-2(5H)-furanone with fenchyl alcohol**

5-Hydroxy-2(5H)-furanone (2.13) (2.00 g, 20.0 mmol) and racemic fenchyl alcohol (5.00 g, 32.4 mmol) were dissolved in dry toluene (15 mL) and refluxed for 24 h. After bulb-to-bulb distillation (120 °C, 0.001 mm Hg) the product (2.53 g, 54%) was obtained as a colorless oil which solidified upon standing at room temperature. On the basis of ¹H NMR and ¹³C NMR the diastereomeric excess of the product was determined to be 0%. The product could be crystallized from n-hexane at -23 °C but no improvement in the d.e. was observed. ¹H NMR (CDCl₃, 300 MHz): δ 0.78 (s, 1.5H), 0.89 (s, 1.5H), 0.95-1.14 (m, 2H), 1.02 (s, 1.5H), 1.06 (s, 1.5H), 1.08 (s, 1.5H), 1.11 (s, 1.5H), 1.28-1.48 (m, 2H), 1.54-1.68 (m, 3H), 3.26 (d, J = 1.5 Hz, 0.5H), 3.36 (d, J = 1.5 Hz, 0.5H), 5.83 (s, 0.5H), 5.90 (s, 0.5H), 6.18 (m, 1H), 7.15 (dd, J = 1.1, 5.5 Hz,0.5H), 7.19 (dd, J = 1.1, 5.5 Hz, 0.5H); ¹³C NMR (CDCl₃): δ 19.20 (q), 19.41 (q), 20.98 (q), 21.15 (q), 25.56 (t), 25.59 (t), 25.74 (t), 25.79 (t), 29.79 (t), 29.80 (q), 31.09 (q), 38.94 (s), 39.23 (s), 40.85 (t), 41.08 (t), 47.93 (d), 48.25 (d), 48.63 (s), 49.03 (s), 92.15 (d), 94.92 (d), 103.45 (d), 104.91 (d), 124.66 (d), 124.87 (d), 150.34 (d), 170.38 (s).
(5R)-5-(I-Menthylxy)-2(5H)-furanone (2.16a)

5-Hydroxy-2(5H)-furanone (2.13) (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 (b.p. 80-90 °C, 0.1 mm Hg). Distillation of the residue (bp 120-123 °C, 0.01 mm Hg) gave the product 2.16 (72.5 g, 61%) as a yellow oil consisting of two diastereoisomers (ratio 60:40).

1H NMR (CDCl₃, 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 (40-60) diastereomerically pure 2.16a was obtained, as was determined by the 1H NMR and 13C NMR spectra of 2.16a. The mother liquids were combined and gave a second crop of diastereomerically pure 2.16a. Total yield 42.5 g, 60%. Mp 70.5-70.7 °C; [α]D -136.4° (c 1.0, abs. ethanol); 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃): 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), 170.56 (s); HRMS calcd 238.155, found 238.157; Analysis calcd for C₉H₁₆O₂: C, 70.56; H, 9.30. Found: C, 70.49; H, 9.18.

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

This compound was prepared from 5-hydroxy-2(5H)-furanone (2.13) and d-menthol in the same way as described for (5R)-5-(l-menthoxy)-2(5H)-furanone (2.16a) (vide supra). Mp 74.2-74.4 °C; [α]D -139.7 °C; [α]D -130.9° (c 1.0, CHCl₃). 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃): 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 q), 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 C₉H₁₆O₂: C, 74.96; H, 9.27. Found: C, 75.26; H, 9.43.

(3R)-5-(l-Menthoxy)-2(5H)-furanone (2.16a) (10.0 g, 42.0 mmol) and cyclopentadiene (2.27) (8.52 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 (40-60) at -40 °C. Yield after crystallization 8.30 g (65%). Mp 73.0-75.0 °C; [α]D -130.9° (c 1.0, CH₂Cl₂); 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃): 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 q), 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 C₉H₁₆O₂: C, 74.96; H, 9.27. Found: C, 75.26; H, 9.43.
of the solvent, the residue was crystallized from petroleum ether (40-60) at -20 °C. To provide pure 2,30 (0.39 g, 56%) as a white crystalline compound. Based on 1H NMR the product consisted of a mixture of two diastereoisomers (ratio 1:1). Mp 68.3-73.5 °C; [a]D 200.7° (c 1.0, CH2Cl2); 1H NMR (CDCl3, 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); 13C NMR (CDCl3): 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 320.235, found 320.237; Analysis calcd for C19H30O3; C, 74.47; H, 9.87. Found: C, 74.18; H, 9.74.

[3R-[(3α(1R*,2S*,5R*),3αα,7αα)]-3α,4,7α-Tetrahydro-5,6-dimethyl-3-[[5-methyl-2-(1-methyl-ethyl)cylohexyl]oxy]-1(3H)-isobenzofuranone (2.32)

A solution of (5R)-5-(l-methyloxy)-2(5H)-furanone (2.16a) (1.23 g, 5.16 mmol) and 2,3-dimethyl-1,3-butenadiene (2.31) (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, 2.30) was obtained. Analytically pure product (0.73 g, 44%) was obtained by crystallization from petroleum ether (40-60) at -18 °C. Mp 72.2-72.3 °C; [a]D -214.1° (c 1.0, n-hexane); 1H NMR (CDCl3, 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); 13C NMR (CDCl3): 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 C20H22O3; C, 74.96; H, 10.06. Found: C, 74.82; H, 10.06.

Crystal structure determination of 2.32

The single X-ray structure determination was performed at low temperature (130 K) with Mo Kα radiation (lambda = 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 (40-60) via slow evaporation of the solvent. It crystallized in the monoclinic space group P21. 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) Å3. For Z = 2 and FW = 320.48 the calculated density is 1.130 g/cm3. 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. 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 Å2) for the H-atoms. In the final refinement the H-atoms were constrained to their corresponding C-atom at a distance of 0.95 Å.

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[3R-3α(1R*,2S*,5R*),3aa,4α,7α]3a,4,7,7a-Tetrahydro-3-[[5-methyl-2-(1-methyl-ethyl)cyclohexyl]oxy]-4,7-ethanoisobenzofuran-1(3H)-one (2.34)

In a small stainless steel tube (contents 10 mL) a solution of (5R)-5-(l-menthylxlo)-2(5H)-furanone (2.16a) (1.00 g, 4.20 mmol) and 1,3-cyclohexadiene (2.33) (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 2.34 (0.63 g, 47%) as a white crystalline compound. Bp 150 °C (0.07 mm Hg); [α]D -131.8° (c 1.0, n-hexane);

1H NMR (CDCl3, 300 MHz): 8 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); 13C NMR (CDCl3) 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 C18H26O3: C, 75.43; H, 9.49. Found: C, 75.74; H, 9.79.

[3R-3α(1R*,2S*,5R*),3aa,4α,7α]3a,4,7,7a-Tetrahydro-3-[[5-methyl-2-(1-methyl-ethyl)cyclohexyl]oxy]-4,11-ethanoanthracene(2,3-c)-furan-1(3H)-one (2.36)

A solution of (5R)-5-(l-menthylxlo)-2(5H)-furanone (2.16a) (2.00 g, 8.43 mmol) and anthracene (2.35) (1.50 g, 8.43 mmol) in 25 mL of decalin 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 product 2.36 (2.19 g, 63%) as a white crystalline compound. Mp 170.5-172.0 °C; [α]D -65.4° (c 1.0, CH2Cl2); 1H NMR (CDCl3, 300 MHz): 8 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); 13C NMR (CDCl3) 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*),3aa,7aa]3a,4,7,7a-Tetrahydro-3-[[5-methyl-2-(1-methyl-ethyl)cyclohexyl]oxy]-1(3H)-isobenzofuranone (2.38)

(5R)-5-(l-Menthylxlo)-2(5H)-furanone (2.16a) (1.00 g, 4.20 mmol) and 1,3-butadiene (2.8) (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 13C NMR spectra only one diastereoisomer had been formed. The product could be crystallized from petroleum ether (40-60) at -20 °C yielding analytically pure 2.38 (0.55 g, 45%) as white crystals. Mp 81.6-83.4 °C; [α]D -205.7° (c 1.0, CH2Cl2); 1H NMR (CDCl3, 300 MHz): 8 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); 13C NMR (CDCl3): 8 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; Analysis calcd for C18H26O3: C, 73.93; H, 9.65. Found C, 73.96; H, 9.52.
Reaction of (SR)-5-(l-methyl)-2(5H)-furanone with butadiene sulfone (2.37)

A solution of (5R)-5-(l-methyl)-2(5H)-furanone (2.16a) (2.01 g, 8.43 mmol) and butadiene sulfone (2.37) (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 2.16a and its epimer 2.16b. Furthermore, part of these cycloadducts had been hydrolyzed to the corresponding aldehydes.

General procedure for the methanolysis of the cycloadducts

Compound 2.32 (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 the e.e. determination (vide infra). The 1H NMR spectrum was identical to the one obtained from the racemic compound, synthesized by means of the Diels-Alder reaction with racemic 5-methoxy-2(5H)-furanone.

Enantiomeric excess determination

The enantiomeric excess (e.e.) of the products obtained from the methanolysis of the Diels-Alder products 2.30, 2.32, 2.34 and 2.38 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 2.40 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 2.40. obtained from the methanolysis of 2.32. was injected only the first signal was observed. Integration indicated an e.e. >99.9%.

2.8 References

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