Asymmetric Diels-Alder reactions with 5-menthylxylo-2(5H)-furanones
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
CHAPTER IV

THE SYNTHESIS OF ENANTIOMERICALLY PURE DECALINES AND HEXAHYDROINDANES

4.1 Introduction

The Diels-Alder reactions of 5-menthyl-2(5H)-furanone (2.16a) with a number of simple dienes, like substituted butadienes and cyclopentadiene, were described in Chapter II. We have shown that enantiomerically pure substituted cyclohexenes and norbornenes, with up to four new stereogenic centers, are readily obtained in this way. This chapter deals with the synthesis of substituted decalines and hexahydroindanes. Furthermore, the Diels-Alder additions of 5-menthyl-2(5H)-furanone to activated dienes to produce enantiomerically pure substituted cyclohexanones, will be discussed. The fact that these ring systems are found in numerous bioactive substances formed our main reason to develop efficient methodology for the preparation of optically active substituted 5,6- and 6,6-acyclic compounds. The drimanes, for example, form an important class of natural decalines. Two examples, poligodial (4.1) and warburganal (4.2) are shown in Figure 4.1.

Several sesquiterpenes of the drimane class have recently attracted interest because of their important biological activity including insect antifeedant, plant growth regulation, cytotoxic, antifungal, molluscicidal, and anticomplemental properties. Optically pure decalines and hexahydroindanes may also form interesting building blocks for the construction of the AB or CD rings of a steroid, for example progesterone (4.3).
The diterpenoids of the labdane class form another interesting group of decaline type natural products. Two examples of this class of compounds are grindelic acid (4.4) and forskolin (4.5) (see Figure 4.2).

The latter compound has been the subject of intense medical and chemical interest because of its considerable therapeutic potential, e.g. a pronounced antihypertensive (blood pressure lowering) activity is observed. Also compactin (4.6) has been the subject of an increasing number of synthetic efforts, as it has been shown to lower the serum cholesterol levels. Therefore this compound may serve as an important tool in the prevention and treatment of coronary artery diseases.

4.2 The synthesis of hydroindanes and decalines

Among the many approaches to synthesize optically active hydroindane and decaline systems, the proline-catalyzed asymmetric aldol cyclization (Hajos-Parrish reaction) has been highly successful. It was found that the triketone 4.9 could be converted, with a catalytic amount (3% molar equiv.) of (S)-(-)-proline, to optically active bicyclic diketone (+)-4.10 in 100% chemical and 93.4% optical yield.

\[ \text{Scheme 4.1} \]
For the corresponding decaline system the chemical yield was 71%, and the optical yield was 70%. Other attractive routes to the decalines are the intramolecular Diels-Alder reaction or the intermolecular Diels-Alder reaction.

Our approach to these decaline and hydrindane skeletons is based on intermolecular Diels-Alder reactions of (5R)-5-(l-menthyloxy)- or (5S)-5-(d-menthyloxy)-2(5H)-furanone with 1-ethenylcyclohexenes and 1-ethenylcyclopentenes. These reactions have the possibility to furnish in a single operation enantiomerically pure decalines and indanes (See Figure 4.3) with up to four new stereogenic centers.

![Figure 4.3](image)

4.3 Reactions of (5R)-5-(l-menthyloxy)-2(5H)-furanone with 1-ethenylcyclohexene, 1-ethenylcyclopentene and 1,2-bis(methylene)cyclohexane

4.3.1 The synthesis of the dienes

For the synthesis of 1,2-substituted decalines and hexahydroindanes, 1-ethenylcyclopentene (4.17) and 1-ethenylcyclohexene (4.18) were required. These compounds were prepared in high yields in a two step procedure by reaction of vinylmagnesium bromide with cyclopentanone (4.13) or cyclohexanone (4.14), respectively, followed by dehydration of the alcohols and hydroquinone. The elimination of water was effected by distillation from KHSO₄ at 180 °C. Dienes 4.17 and 4.18 were isomerically pure as determined by ¹H NMR.

![Scheme 4.2](image)
By employing 1,2-bis(methylene)cyclohexane (4.23) as a diene in the Diels-Alder reactions 2,3-disubstituted-9,10-dehydrodecalines can be formed. The synthesis of 1,2-bis(methylene)cyclohexane (4.23)\textsuperscript{17} starts from commercially available cis-cyclohexane-1,2-dicarboxylic acid (4.19).

![Scheme 4.3]

Hexamethylphosphorous triamide was used for the one step conversion of the cis-diacid 4.19 to the diamide 4.20 in 91% yield. Product 4.20 could be used in the next reaction step without purification. The advantage of this method is that no anhydride is formed, which is a potential side reaction in an alternative route via the corresponding diacid chloride of 4.19 and dimethylamine. Reduction of diamide 4.20 with lithium aluminum hydride afforded amine 4.21 in 80% yield. Subsequent treatment of amine 4.21 with hydrogen peroxide yielded the amine oxide 4.22, which was pyrolyzed to produce the desired diene 4.23.\textsuperscript{18} Unfortunately, the yield in this last reaction step was only 10%. The reason for this low yield might be an incomplete oxidation of diamine 4.21 or insufficient cooling of the pyrolysate during the pyrolysis of 4.22. Furthermore, a part of diene 4.23 polymerizes during the synthesis.

### 4.3.2 The Diels-Alder reactions

When 1-ethenylcyclopentene (4.17) and 1-ethenylcyclohexene (4.18) were allowed to react with 5-menthyloxy-2(5H)-furanone (4.24) at 120 °C, pure Diels-Alder adducts 4.25 and 4.26 were obtained in 77% and 70% yield, respectively, as crystalline compounds. Again singlets were observed for the acetal hydrogens in the $^1$H NMR spectra of 4.25 and 4.26. This means that also in these cases the addition of the dienes 4.17 and 4.18 has taken place from the less hindered side of furanone 4.24, i.e. trans
relative to the menthyloxy substituent.

Scheme 4.4

The regioselectivity of the cycloaddition was established by 2D COSY $^1$H NMR analysis of the racemic methoxy compound 4.27, prepared from racemic 5-methoxy-2(5H)-furanone and 1-ethenylcyclohexene (4.18). From the COSY spectrum it was deduced that the cycloadduct possesses the configuration as depicted in Figure 4.4.

Figure 4.4: COSY spectrum of compound 4.27
For compound 4.26 the same regioselectivity is expected on basis of identical behaviour of 4.24 and 5-methoxy-2(5H)-furanone. The assignment was made on the basis of the 1,4 relationship established between the vinylic hydrogen (H₄) and the acetal hydrogen (H₁). The high regioselectivity of the cycloaddition is mainly attributed to steric effects as the polarization of the diene is expected to be small. The steric interactions between the menthyloxy substituent of 4.24 and the cyclohexene ring of 4.18 are minimal in the case of situation A leading to 4.26, whereas in the case of situation B the steric interactions are less favorable for the cycloaddition reaction (see Figure 4.5).

![Figure 4.5](image)

The absence of proton-proton coupling (J < 1 Hz) for the acetal hydrogen (H₁) and the coupling constants for the hydrogen atom next to the carbonyl functionality confirms the all-cis relationship of the hydrogen atoms and the menthyloxy substituent at the stereogenic centers of compounds 4.25 and 4.26. This is in complete agreement with a trans and endo-selective cycloaddition of 1-ethenylcyclohexene (4.18) and 1-ethenylcyclopentene (4.17) relative to the menthyloxy substituent of 4.24, as was expected on the basis of the results we had obtained so far. Such all-cis relationship at the newly created stereogenic centers in 2,3-disubstituted decalines, as the result of an endo selective cycloaddition, was also observed by Cook and Lawrence in the reaction of maleic anhydride with 1-ethenylcyclohexene (4.18). Furthermore, the coupling constants of cycloadduct 4.26 were in agreement with those of the maleic anhydride and N-phenylmaleimide adducts of 4.18. (For comparable results see also Section 4.7, Figure 4.7).

1,2-Bis(methylene)cyclohexane (4.23), dissolved in benzene, was allowed to react with (5R)-5-(1-menthylxy)-2(5H)-furanone (4.24) for 42 h in a sealed tube at 100 °C. The 2,3-disubstituted-9,10-dehydrodecane 4.28 was isolated in 51% yield as a single enantiomer, since we have started with enantiomerically pure furanone 4.24 and no epimerization was observed by ¹H NMR during the reaction. The addition of diene 4.23 to (5R)-5-(1-menthylxy)-2(5H)-furanone (4.24) results in the formation of two new stereogenic centers and takes place trans to the menthyloxy substituent as was
deduced from the singlet observed for the acetal hydrogen in the 300 MHz $^1$H NMR spectrum of 4.28.

![Diagram](image)

*Scheme 4.5*

### 4.4 Reactions of 5-menthyl-2(5H)-furanone with activated dienes

The Diels-Alder reactions of (5R)-5(l-menthyl)-2(5H)-furanone with more activated dienes, in this case silyl dienol ethers, were next examined. In a normal Diels-Alder reaction the addition of an electron-donating substituent will raise the HOMO of the diene, and thus results in a diminished energy gap with the LUMO of the dienophile, in our case furanone 4.24. Apart from an acceleration of the reaction, a further advantage of alkoxy substituted dienes is the high regioselectivity obtained in Diels-Alder reactions. We were interested in these silyloxy substituted dienes as they open the possibilities for synthesizing enantiomerically pure polycycles with four new stereogenic centers, which can be introduced in a one pot reaction sequence (see Section 4.6).

"Danishefsky's diene", 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (4.32)\(^20\) (Scheme 4.6), which has been used with great success in the synthesis of numerous natural products\(^21\) is known to combine high reactivity with high regioselectivity. The cycloaddition reaction with 4.32 furnishes highly functionalized products, which open the possibility of introducing additional stereogenic centers and functional groups. The advantage of using silyl dienol ethers is the fact that the Diels-Alder adduct can be hydrolyzed under extremely mild conditions. With 2-alkoxy-1,3-butadienes, such as 2-ethoxy-1,3-butadiene\(^22\) more drastic conditions, like strong acids, have to be used to hydrolyze the enol ether of the cycloadduct, and this may result in undesired side reactions.

We began with the Diels-Alder reaction of 5-menthyl-2(5H)-furanone (4.24) with 2-trimethylsilyloxy-1,3-butadiene\(^23\) (4.29). Both compounds were allowed to react at 120 °C in dry toluene. After treating the resulting silyl enol ether 4.30 with tetra-
butylammonium fluoride in diethyl ether, the 3,4-disubstituted cyclohexanone 4.31 was obtained as a single isomer in 66% yield. Only one signal was observed for the acetal hydrogen in the 300 MHz $^1$H NMR spectrum of 4.31 meaning that the cycloaddition reaction had taken place with complete $\pi$-face- and regioselectivity. Again the addition of the diene has taken place trans to the menthyloxy substituent of furanone 4.24, as was deduced from the singlet observed for the acetal hydrogen of 4.31. The high regioselectivity observed for this reaction is not unexpected considering the HOMO of the diene.

![Diagram of the reaction]

Scheme 4.6

Although the Diels-Alder reaction of 4.29 provided a single diastereoisomer, two diastereomeric adducts were obtained in 77% yield and a 2:1 ratio ($^1$H NMR) with Danishefsky's diene 4.32. As diene 4.32 possesses the same polarization as 2-trimethylsilyloxy-1,3-butadiene (4.29) it is expected that in this reaction again only one regioisomer is formed. After hydrolysis of silyl enol ether 4.33 with tetrabutylammonium fluoride product 4.34 was isolated as a mixture of two diastereoisomers. The $^1$H NMR spectrum of 4.34 showed that only a trans-addition of diene 4.32 relative to the menthyloxy substituent of the furanone ring 4.24 had taken place, as
was deduced from the coupling constants of the acetal hydrogens \((J = 0 \text{ Hz and } 4.0 \text{ Hz})\). Thus, the hydrogen atoms \(H_b\) and \(H_c\) possess a \textit{trans} relationship towards \(H_a\) at the acetal center. Therefore, the only conclusion can be that both diastereoisomers of \(4.34\) are epimeric at the carbon atom bearing the MeO-substituent. The two diastereoisomers are, therefore, most likely the result of a combined endo and exo addition of \(4.32\) on to 5-methyloxy-2(5H)-furanone \((4.24)\). Both epimers 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 was based on the X-ray structure of \(4.34\) (see Section 4.5).

Various attempts to eliminate the MeO-substituent of \(4.34\) were undertaken as this would yield disubstituted \(\alpha,\beta\)-unsaturated cyclohexenone \(4.35\) in enantiomerically pure form. This compound is of particular interest as a chiral building block, for it opens a variety of synthetic possibilities like 1,2- or 1,4-additions and alkylation at the \(\alpha\)-position relative to the ketone. However, treatment of Diels-Alder adduct \(4.34\) with 0.05 N HCl in THF, or trifluoroacetic acid in \(\text{CH}_2\text{Cl}_2\), did not yield product \(4.35\). Heating compound \(4.34\) for 2 h at 150 °C gave the equally negative result.

Comparable results were found by Danishefsky \textit{et al.}\textsuperscript{25} in reactions of \textit{trans}-1-methoxy-3-trimethylsilyloxy-1,3-butadiene \((4.32)\) with maleic anhydride \((4.36)\) (Scheme 4.7) and \textit{trans}-methylcrotonate \((4.39)\) (Scheme 4.8). The addition product \(4.37\) gave after work-up (THF/0.005 N HCl 4:1) only the starting material as there was no indication of the formation of enone \(4.38\).

The Diels-Alder reaction of \(4.32\) with \textit{trans}-methyl crotonate \((4.39)\) afforded upon chromatography a 2:1 mixture of the epimeric adducts \(4.40\) and \(4.41\). Only in the case of \(4.41\), with the methoxy group in an axial position, methanol could be eliminated by treating the Diels-Alder adduct with 0.005 N HCl, yielding the enone \(4.43\). Under these conditions the equatorial methoxy group in \(4.40\) and \(4.42\) was not eliminated. (Scheme 4.8).

Danishefsky has shown that the \(\beta\)-methoxy ketones generally are not converted to
enones under acidic hydrolysis conditions. He also noted that the hydrolytic fate of the adducts was influenced by the nature of the substituents of the cycloadduct and their stereochemical relationship to the methoxy substituent.

The problem of hydrolysis was very recently circumvented by Vorndam, by employing a catalytic amount of trimethylsilyl triflate (TMSOTf) instead of acid hydrolysis. Treating the Diels–Alder adduct of Danishefsky’s diene (4.32) and maleic anhydride (4.36) with TMSOTf afforded the enone 4.38 in 98% yield. The use of TMSOTf might offer resolution of the problem of conversion of 4.33 to 4.35. However, we have not examined this point.

\[
\begin{align*}
\text{Scheme 4.8}
\end{align*}
\]

**4.5 The X-ray structure of 4.34**

To distinguish which isomer of 4.34 was the result of an *endo*-attack of (5R)-5-(l-menthyl oxy)-2(5H)-furanone (4.24) to Danishefsky’s diene 4.32, an X-ray structure was determined of one of the two isomers. The minor isomer of 4.34 could be crystallized from *n*-hexane to yield crystals suitable for an X-ray analysis. Compound 4.34 crystallized in the monoclinic space group *P*2\(_1\) with unit cell dimensions *a* = 5.663(1) Å, *b* = 11.235(1) Å, *c* = 15.193(1) Å, \(\beta = 91.660(1)^\circ\) and two molecules in each unit cell. The data collection was performed at 293 K. The crystal structure of compound 4.34 is depicted in Figure 4.6. The X-ray structure was based on the absolute configuration of *l*-menthol. Bond distances and bond angles are listed in Tables 4.1 and 4.2 (the hydrogen atoms are omitted for clarity). The structure shows that this isomer is the result of an *endo*-attack of Danishefsky’s diene 4.32 to 5-menthyl oxy-
2(5H)-furanone (4.24), since the methoxy substituent of 4.34 is in an endo-position, and the hydrogen atoms at C1, C5 and C9 are in a cis relationship to each other.

![Figure 4.6: Pluto plot of 4.34](image)

Table 4.1: Bond distances for 4.34 in Ångströms.

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* Numbers in parentheses are estimated standard deviations in the last significant digits.
Table 4.2: Bond angles for 4,34 in degrees.*

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* Numbers in parentheses are estimated standard deviations in the last significant digits.

Furthermore, the structure of 4,34 shows that diene 4,32 added _trans_ to the menthylxy substituent of furanone 4,24 as the hydrogens 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 4,32 to 4,24 is in accordance with what is expected on basis of the HOMO-LUMO interaction between the diene and the furanone dienophile.²⁷

### 4.6 Diels-Alder reactions with 1-(1-trimethylsilyloxyethenyl)cycloalkenes

Next, we extended the cycloaddition to 1-(1-trimethylsilyloxyethenyl)cycloalkenes 4,44 and 4,47 (Scheme 4.9). The silyloxydienes 4,44 and 4,47 were readily obtained from the corresponding enones²³b using LDA and trimethylsilyl chloride in THF.²⁸ Reaction of these dienes with (5R)-5-(1-menthylxy)-2(5H)-furanone afforded the expected tricyclic adducts. In situ hydrolysis of the resulting silyl enol ethers 4,45 and 4,48 at -80 °C with CsF in wet acetonitrile or tetrabutylammonium fluoride in THF gave enantiomerically pure 4,46 and 4,49 (80% and 70% overall yield, respectively) (Scheme 4.9).

As judged from ^1_H NMR and ^13_C NMR only one isomer had been formed in both cases. This means that four new stereogenic centers can be introduced in a one pot operation in a completely controlled way. The ^1_H NMR spectrum indicated the _trans_
relationship between H₄ and the acetal hydrogen (J = 0.9 Hz for 4.46 and J = 4.5 Hz for 4.49), which is in accordance with an *endo*-selective addition.

Fukumoto *et al.* also reported complete *endo*-selectivity with a related system, which concerned the cycloaddition reaction between 1-(1-t-butyldimethylsilyloxyethenyl)cyclohexene and maleic anhydride. However, from the ¹H NMR spectra of 4.46 and 4.49 it was not clear at which π-face of the enol moiety the protonation of 4.45 and 4.48 had taken place. This means that the hydroindanone 4.46 and the decalinone 4.49 could have a *cis*- or a *trans* ring fusion. For 1-decalone it is known that the *trans* fused isomer is more stable than the corresponding *cis* isomer as the first compound possesses no gauche interactions. Also the *trans*-syn-*trans*-perhydro-9-phenantrone ringsystem is more stable than the *cis*-syn-*cis* isomer.²⁹

### 4.7 The X-ray structure of 4.49

The absolute configuration of 4.46 and 4.49 was established by means of a single crystal X-ray analysis. Proper crystals of 4.46 and 4.49, suitable for an X-ray analysis, were obtained by crystallizing both compounds from petroleum ether 40-60 by slow evaporation of the solvent. Compound 4.49 crystallized in the monoclinic space group P2₁ (Z=2), with unit cell dimensions a = 5.817(2) Å, b = 11.784(2) Å, c = 15.034(2) Å and β = 96.78(1)°. The position of the hydrogen atoms was revealed from succeeding Fourier difference maps. The crystal structure of 4.49 is depicted in Figure 4.7. Bond distances and bond angles are listed in Table 4.3 and 4.4. The indicated
absolute configuration in the X-ray structure is based on the known absolute configuration of the l-menthol segment.

![Figure 4.7: PLUTO plot of 4.49](image)

Table 4.3: Bond distances for 4.49 in Ångströms.*

<table>
<thead>
<tr>
<th>Atom1</th>
<th>Atom2</th>
<th>Distance</th>
<th>Atom1</th>
<th>Atom2</th>
<th>Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>O3</td>
<td>C2</td>
<td>1.360(4)</td>
<td>C8</td>
<td>C13</td>
<td>1.534(6)</td>
</tr>
<tr>
<td>O3</td>
<td>C4</td>
<td>1.457(4)</td>
<td>C9</td>
<td>C10</td>
<td>1.539(7)</td>
</tr>
<tr>
<td>O14</td>
<td>C2</td>
<td>1.190(5)</td>
<td>C10</td>
<td>C11</td>
<td>1.528(7)</td>
</tr>
<tr>
<td>O15</td>
<td>C7</td>
<td>1.207(6)</td>
<td>C11</td>
<td>C12</td>
<td>1.527(7)</td>
</tr>
<tr>
<td>O16</td>
<td>C4</td>
<td>1.392(5)</td>
<td>C12</td>
<td>C13</td>
<td>1.536(6)</td>
</tr>
<tr>
<td>O16</td>
<td>C17</td>
<td>1.450(5)</td>
<td>C17</td>
<td>C18</td>
<td>1.518(6)</td>
</tr>
<tr>
<td>C1</td>
<td>C2</td>
<td>1.530(5)</td>
<td>C17</td>
<td>C22</td>
<td>1.519(6)</td>
</tr>
<tr>
<td>C1</td>
<td>C5</td>
<td>1.531(5)</td>
<td>C18</td>
<td>C19</td>
<td>1.546(6)</td>
</tr>
<tr>
<td>C1</td>
<td>C13</td>
<td>1.523(6)</td>
<td>C18</td>
<td>C24</td>
<td>1.550(6)</td>
</tr>
<tr>
<td>C4</td>
<td>C5</td>
<td>1.527(5)</td>
<td>C19</td>
<td>C20</td>
<td>1.528(6)</td>
</tr>
<tr>
<td>C5</td>
<td>C6</td>
<td>1.536(6)</td>
<td>C20</td>
<td>C21</td>
<td>1.517(6)</td>
</tr>
<tr>
<td>C6</td>
<td>C7</td>
<td>1.512(6)</td>
<td>C21</td>
<td>C22</td>
<td>1.538(6)</td>
</tr>
<tr>
<td>C7</td>
<td>C8</td>
<td>1.541(6)</td>
<td>C21</td>
<td>C23</td>
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<td>C9</td>
<td>1.557(6)</td>
<td>C24</td>
<td>C25</td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td>C24</td>
<td>C26</td>
<td>1.519(6)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are estimated standard deviations in the least significant digits.

As we have started with diastereomerically pure (5R)-5-(l-menthyl)oxy)-2(5H)-furanone (4.24) and no epimerization took place during the addition reaction, the absolute configuration at the acetal center is still R.
As expected the addition of the diene had occurred trans relative to the menthylxy substituent of 4.24 as can be concluded from the trans relationship between the hydrogen atoms at C4 and C5. It was deduced from this X-ray structure that the regioselective addition of silyl enol ether 4.47 is in accordance with expectations based on the HOMO-LUMO interactions between 1-(1-trimethylsilyloxyethyl)cyclohexene 26 (4.47) and furanone 4.24. Furthermore, as the hydrogen atoms at C1, C3 and C13 are in an all-cis relationship it means that the addition of the diene has also taken place in an endo selective manner. The hydrolysis of the silyl enol ether resulted in the formation of the trans fused decalone 4.49 as the hydrogens at C8 and C13 possess a trans relationship. For compound 4.46, the molecular structure determined by X-ray analysis showed the same absolute configuration of the new created stereogenic centers as for 4.49. No refinements of the X-ray structure were performed in this case. Again, a regioselective endo attack of diene 4.44 had taken place, and after hydrolysis of the enol ether 4.45 with CsF a trans fused 5,6-ring system was formed. It is remarkable that under kinetically controlled conditions the trans fused products are formed. Perhaps this is a results of the annulated lactone moiety, but at this moment the reason for these results are still unclear.
4.8 Conclusions

In this Chapter we have shown that disubstituted decalines and hydrindanes are readily available in good to high yields via intermolecular Diels-Alder reactions with 5-menthylxy-2(5H)-furanone. These reactions proceed with complete trans diastereoselectivity, regioselectivity and endoselectivity. By using silyl dienol ethers, like Danishefsky's diene, enantiomerically pure di- and trisubstituted cyclohexanones were synthesized in good yields and with complete regioselectivity and diastereoselectivity. Furthermore, our results show that in a 'one pot' procedure enantiomerically pure substituted decalones and hydrindanones with four consecutive new stereogenic centers can be generated in high yield.

4.9 Experimental section

For general remarks, see Chapter 2, Section 2.4. Dienes 4.17 and 4.18 were synthesized according to literature procedures.\[3R-[3a(1R*,2S*,5R*),3aa,8aa,8ba)]-3a,4,6,7,8,8a,8b-Octahydro-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-1H-indeno[4,5-c]furan-1-one (4.25)

A mixture of (5R)-5-(1-menthylxy)-2(5H)-furanone (4.24) (4.00 g, 16.8 mmol), 1-ethenylcyclopentene (4.17) (4.46 g, 48.5 mmol) and a few milligrams of hydroquinone was heated at 120 °C for 2 days. After cooling to room temperature dry acetone was added and some polymeric material was removed by filtration. The product was purified by precipitation from acetone at -80 °C yielding a colorless oil (4.28 g, 77%) which solidified upon standing at room temperature. Mp 82.2-83.6 °C; \([\alpha]^{20}_D -129.0°\) (c 1.000, CH₂Cl₂); \(^1\)H NMR (CDCl₃, 300 MHz): \(\delta \) 0.67-1.00 (m, 12H), 1.13 (m, 1H), 1.28 (m, 1H), 1.52 (m, 3H), 1.72 (m, 1H), 1.85 (m, 1H), 2.02 (m, 3H), 2.18 (m, 4H), 2.36 (m, 1H), 2.56 (m, 1H), 3.11 (t, \(J = 8 \) Hz, 1H), 3.40 (m, 1H), 5.12 (s, 1H), 5.43 (m, 1H); \(^1\)C NMR (CDCl₃): \(\delta \) 15.30 (q), 20.67 (q), 21.98 (q), 22.78 (t), 24.82 (t), 25.13 (d), 27.54 (t), 30.84 (t), 31.05 (d), 34.04 (t), 38.10 (d), 39.59 (d), 40.75 (d), 40.91 (d), 47.47 (d), 76.16 (d), 104.39 (d), 114.31 (d), 146.42 (s), 176.39 (s); HRMS calcd 332.235, found 332.236; Anal. Calcd for C₂₁H₃₂O₃: C, 75.86; H, 9.70. Found: C, 75.75; H, 9.61.

A mixture of (5R)-5-(l-menthylxy)-2(5H)-furanone (4.24) (0.50 g, 2.10 mmol) and 1-ethenylcyclohexene (4.18) (0.34 g, 3.15 mmol) was heated at 120 °C for 3 days. After the reaction mixture was cooled to room temperature, acetone was added and the insoluble material was removed by filtration. After evaporation of the solvent in vacuo the product was crystallized from petroleum-ether 40-60 yielding 4.26 (0.51 g, 70%) as a white solid. Mp 126.5-127.5 °C; \([\alpha]^{20}_D -175.7°\) (c 1.000, CH₂Cl₂); \(^1\)H NMR (CDCl₃, 300 MHz): \(\delta \) 0.73-1.05 (m, 12H), 1.15-1.41 (m, 4H), 1.56-1.78 (m, 2H), 1.78-2.19 (m, 6H), 2.22 (m, 2H), 2.38 (m, 2H), 3.04 (t, \(J = 8 \) Hz, 1H), 3.47 (dt, \(J = 4.3, 10.7 \) Hz, 1H), 5.18 (d, \(J = 2.7 \) Hz, 1H), 5.28 (m, 1H); \(^1\)C NMR (CDCl₃): \(\delta \) 15.22 (q), 20.60...
cis-N,N,N',N'-Tetramethyl-1,2-cyclohexanedicarboxamide (4.20)
Starting from cis-1,2-cyclohexanedicarboxylic acid (4.19) (20.36 g, 0.12 mol) the corresponding amide 4.20 was synthesized according to the literature procedure. Yield: 24.18 g (91%) (lit.17 88%). Mp 76.0-77.6 °C (lit? 74-75 °C).

cis-N,N,N',N'-Tetramethyl-1,2-cyclohexanedimethanamine (4.21)
A solution of diamide 4.20 (26.6 g, 0.118 mol) in dry THF (140 mL) was stirred under a nitrogen atmosphere. Lithium aluminum hydride (5.90 g, 0.16 mol) was added in portions and the solution was refluxed for 1 h. After the addition of water (6 mL), 15% NaOH (6 mL) and again water (18 mL) the resulting slurry was filtered by suction over a sintered glass filter. After evaporation of the solvent the product 4.21 (18.79 g, 80%) was obtained as a slightly yellow oil. The spectroscopic data were in complete agreement with those reported in the literature.17

1,2-Bis(methylene)cyclohexane (4.23)
Diamine 4.21 (18.7 g, 94.3 mmol) was dissolved in methanol (32 mL) and cooled to 0 °C. Hydrogen peroxide (21 mL of 30% aqueous solution) was added. The same amount of H₂O₂ was added after 3h and 5h successively. After stirring for 36 h at room temperature the solution was worked up according to the literature procedure, yielding 4.22 as a highly viscous oil. Diene 4.23 was generated by pyrolysis of bis(amine-N-oxide) 4.22 using an oil bath at 150-170 °C (100 mm Hg). Diene 4.23 was passed through a water-cooled condenser and then collected in a liquid nitrogen cooled vacuum trap. Water was added to the pyrolysat and the two layers were separated. The upper layer of the diene was washed with water and dried over anhydrous K₂CO₃ followed by 4Å sieves. The yield of 4.23 was 10% based on bisamine 4.21 (lit.17 73%).

[3R-[3α(1R*,2S*,5R*),3aa,9αa]-3α,4,6,7,8,9,9a-Octahydro-3-[[5-methyl-2-(1-methylethyl)cyclohexyl]oxyl]naphta[2,3-c]furan-1(3H)-one (4.28)
In a sealed tube at 80 °C were heated a mixture of (5R)-5-(1-methyloxy)-2(5H)-furanone (4.24) (0.51 g, 2.14 mmol) and 1,2-bis(methylene)cyclohexane (4.23) (0.26 g, 2.40 mmol) in dry benzene (10 mL) for 18 h. Because no complete conversion had occurred a second amount of diene 4.23 (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 4.28 (0.38 g, 51%) as a white solid. Mp 112.4-113.8 °C; [α]D²⁰ -218.0° (c 0.986, diethyl ether); ¹H NMR (CDCl₃, 300 MHz): δ 0.72-1.20 (m, 12H), 1.20 (m, 1H), 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); ¹³C NMR (CDCl₃): 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 C₂₆H₃₄O₃: C, 76.26; H, 9.89. Found: C, 76.42; H, 9.85.
[3R-[3α(1R*,2S*,5R*),3αα,7αα]-Tetrahydro-3-[[5-methyl-2-(1-methylethyl)-cyclohexyloxy]-1,5(3H,4H)-isobenzofurandione (4.31)]

A solution of (5R)-5-(l-methoxy)-2(5H)-furanone (4.24) (2.60 g, 10.9 mmol) and silyloxydienes 4.25 (3.78 g, 26.7 mmol) in dry toluene (2 mL) was heated in sealed tube for 16 h at 120 °C. After evaporation of the solvent under reduced pressure, the crude product 4.30 was obtained as an oil in 100% yield. IR: neat, cm⁻¹: 1780 (C=O), 1260 (C-O), 1195, 1105 (Si-O); ¹H NMR (CDCl₃, 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 (brs, 1H), 5.25 (s, 1H); ¹³C NMR (CDCl₃): δ 28.15 (t), 31.15 (d), 34.11 (t), 35.25 (d), 39.53 (d), 39.57 (t), 47.61 (d), 76.28 (d), 1.8, 7.1 Hz, 1H), 3.4 Hz, 1H), 4.70 (brs, 1H), 5.25 (s, 1H); ¹³C NMR (CDCl₃): δ 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 C₁₈H₂₈O₂: C, 70.07; H, 9.15. Found C, 69.84; H, 9.13.

[3R-[3α(1R*,2S*,5R*),3αα,7αα]-Tetrahydro-7-methoxy-3-[[5-methyl-2-(1-methylethyl)cyclohexyloxy]-1,5(3H,4H)-isobenzofurandione and [3R-[3α(1R*,2S*,5R*),3αα,7αα]-Tetrahydro-7-methoxy-3-[[5-methyl-2-(1-methylethyl)cyclohexyloxy]-1,5(3H,4H)-isobenzofurandione (4.34)]

A solution of (5R)-5-(l-methoxy)-2(5H)-furanone (4.24) (3.00 g, 12.6 mmol) and trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (4.32) (4.44 g, 25.8 mmol) was refluxed for 20 h in dry toluene (10 mL) under a nitrogen atmosphere. The residue was dissolved in acetonitrile (25 mL) and treated with cesium fluoride (3.00 g, 13.2 mmol) yielding product 4.34 as a mixture of two diastereoisomers (ratio 2:1). Both isomers were separated by flash chromatography (SiO₂, diethyl ether). The total yield after evaporation of the solvent was 77%.

Minor diastereoisomer (7α-4.34) was obtained as a white crystalline compound after crystallization from n-hexane. Mp 93.1-93.4 °C; [α]²⁰ D -124.5° (c 1.084, CH₂Cl₂); ¹H NMR (CDCl₃, 300 MHz): δ 0.68-1.05 (m, 14H), 1.10-1.21 (m, 1H), 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); ¹³C NMR (CDCl₃): 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 308.200; found 308.200; Anal. Calcd for C₁₈H₂₈O₂: C, 70.07; H, 9.15. Found C, 69.84; H, 9.13.

Major diastereoisomer (7β-4.34) was obtained as an oil. Bp 200 °C (0.001 mm); [α]²⁰ D -124.5° (c 1.084, CH₂Cl₂); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃): 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 C₁₈H₂₈O₂: C, 70.43; H, 8.93. Found: C, 70.63; H, 8.96.

Minor diastereoisomer (7α-4.34) was obtained as a white crystalline compound after crystallization from n-hexane. Mp 96.9-97.2 °C; [α]²⁰ D -199.9° (c 1.000, CH₂Cl₂); ¹H NMR (CDCl₃, 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, 1H, J = 2.2, 16.9 Hz), 2.54 (m, 2H), 2.80
Crystal structure determination of 4.34

The single crystal X-ray determination was performed at 293 K with CuKα 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 title compound, having approximate dimensions 0.40 x 0.20 x 0.15 mm, crystallized from n-hexane in the monoclinic space group P2₁ with a = 5.663(1) Å, b = 11.235(1) Å, c = 15.193(1) Å, β = 91.660(1)° and V = 966.2 Å³. For Z = 2 and FW = 338.45 the calculated density is 1.163 g cm⁻³. By using the θ - 2θ scan mode for 1° ≤ θ ≤ 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 synthesis. 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 Å²) for the H-atoms. In the final refinements the H-atoms were riding on their corresponding atoms at a distance of 0.96 Å.

[3R-[3α(R*,2S*,5R*),3aa,5ab,8aa,8ba]]-Octahydro-3-[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-1H-indeno[4,5-c]furan-1,5(3H)-dione (4.46)

A mixture of (5R)-5-(l-menthyl)-2(5H)-furanone (4.24) (4.01 g, 16.8 mmol), diene 4.44 (4.59 g, 25.2 mmol) and a few milligrams of hydroquinone was heated at 100 °C for 3 days. After evaporation of the solvent in vacuo and removal of the volatile compounds (130 °C, 0.002 mm Hg) the crude product 4.45 (6.50 g, 92%) was obtained as an oil. This product was used in the next reaction step without further purification. Crude product (650 mg, 1.55 mmol) was dissolved in THF (20 mL) and cooled to -80 °C. Tetrabutylammonium fluoride (732 mg, 2.32 mmol), dissolved in a few milliliters of THF, was added. After stirring for 30 minutes at -80 °C, water was added and the resulting solution was extracted 3 x with diethyl ether. The combined organic layers were dried over Na₂SO₄. After evaporation of the solvent in vacuo the residue was purified by chromatography using a chromatotron (SiO₂, n-hexane, isopropyl ether 1:1) yielding product 4.46 (432 mg, 80%) as a white solid. Analytically pure product was obtained by crystallization from n-hexane. Mp 137.2-139.5 °C; [α]D° 159.6° (c 0.228, CH₂Cl₂); 1H NMR (CDCl₃, 300 MHz): δ 0.73-1.05 (m, 12H), 1.19 (m, 1H), 1.35 (m, 2H), 1.50 (m, 1H), 1.61 (m, 2H), 1.74 (m, 2H), 2.04 (m, 4H), 2.32 (dd, J = 8, 15 Hz, 1H), 2.56 (dd, J = 7, 15 Hz, 1H), 2.65 (m, 1H), 2.72 (m, 1H), 2.93 (m, 1H), 3.24 (t, J = 8 Hz, 1H), 3.74 (m, 1H), 5.28 (d, J = 0.9 Hz, 1H); 13C NMR (CDCl₃): δ 15.32 (q), 20.60 (q), 21.88 (q), 22.28 (t), 22.74 (t), 25.09 (d), 26.15 (t), 28.53 (t), 31.01 (d), 33.91 (t), 37.35 (t), 38.73 (d), 39.55 (t), 40.36 (d), 42.67 (d), 47.37 (d), 50.78 (d), 77.25 (d), 103.37 (d), 175.34 (s), 210.20 (s); Anal. Calcd for C₂₁H₃₂O₄: C, 72.38; H, 9.26. Found C, 72.43; H, 9.31.

[3R-[3α(R*,2S*,5R*),3aa,5ab,9aa,9ba]]-Octahydro-3-[5-methyl-2-(1-methylethyl)cyclohexyl]oxy]-naphthal[1,2-c]furan-1,5(3H,4H)-dione (4.49)

Compound 4.49 was prepared in the same way as described for 4.46. After reaction of
(5R)-5-(1-menthy1oxy)-2(5H)-furanone (4.24) (2.00 g, 8.40 mmol) with 1-(1-trimethylsilyloxy-etheny1)cyclohexene (4.47) (2.48 g, 12.65 mmol), treatment of the crude product 4.48 with tetrabutylammonium fluoride (4.00 g, 12.68 mmol) and purification by crystallization from n-hexane 4.49 (2.12 g, 70%) was obtained as a white solid. Mp 134.9-136.9 °C (n-heptane); [α]D 20 155.8° (c 1.520, CH2Cl2); 1H NMR (CDCl3, 300 MHz): δ 0.74-1.06 (m, 12H), 1.15-1.40 (m, 5H), 1.50 (m, 1H), 1.63 (m, 2H), 1.74 (m, 1H), 1.90-2.15 (m, 3H), 2.32 (m + dd, J = 9, 18 Hz, 2H), 2.50 (m, 2H), 2.61 (dd, J = 8, 18 Hz, 1H), 2.78 (m, 1H), 3.30 (dd, J = 7, 10 Hz, 1H), 3.49 (dt, J = 5, 11 Hz, 1H), 5.32 (d, J = 4.5 Hz, 1H); 13C NMR (CDCl3): δ 15.56 (q), 20.75 (q), 21.48 (t), 22.06 (q), 22.92 (t), 25.24 (t), 25.51 (d), 25.85 (t), 27.19 (d), 31.19 (d), 34.06 (t), 35.87 (d), 37.75 (t), 39.77 (t), 39.98 (d), 42.82 (d), 47.55 (d), 47.64 (d), 77.64 (d), 104.47 (d), 174.98 (s), 209.31 (s); HRMS calcd 362.246, found 362.245.

Crystal structure determination of 4.49
The single crystal X-ray determination was performed at low temperature (130 K) with MoKα 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 0.40 x 0.25 x 0.20 mm, crystallized from petroleum ether 40-60, by slow evaporation of the solvent, in the monoclinic space group P21. The monoclinic cell parameters and volume are: a = 5.817(2) Å, b = 11.782(2) Å, c = 15.034(2) Å, β = 96.78(1)° and V = 1023.3 Å3. For Z = 2 and FW = 362.51 the calculated density is 1.176 g/cm3. By using the Θ - 2Θ scan mode for Θ = 1° to Θ = 30°, 3109 unique reflections were obtained, a number of 2740 reflections with I > 0.00(I) were used in the refinements. 25 Reflections in the range 7.6° ≤ Θ ≤ 21.4° were used to define the unit cell parameters. The structure was solved by direct methods and based on the absolute configuration of l-menthol part. The position of the H-atoms could be revealed from succeeding Fourier difference maps. Block-diagonal least-squares of F, with unit weights, converged to a final R = 0.066 and wR = 0.074, respectively, using anisotropic temperature factors (B = 4.0 Å2) for the H-atoms. In the final refinements the positions of the H-atoms were constrained to their corresponding C-atoms at a distance of 0.95 Å.

4.10 References and notes


23. This enolether was prepared in 15% according to: a) Jung, M.E.; McCombs, C.A. *Tetrahedron Lett.* 1976, 2935.


