Asymmetric Diels-Alder reactions with 5-menthyloxy-2(5H)-furanones
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CHAPTER V

ATTEMPTED SYNTHESIS OF WARBURGANAL

5.1 Introduction

In the previous chapter the stereoselective synthesis of substituted hydridanes and decalines by reaction of 5-menthylxylo-2(5H)-furanone with 1-ethenylcycloalkenes was described. The addition products were obtained as single enantiomers and the absolute configuration of the new stereogenic centers was confirmed by X-ray analysis. These ring systems are very common in Nature. Some examples were already given in Chapter IV (Figure 4.1 and 4.2). It seemed to us that the asymmetric Diels-Alder reaction with 5-menthylxylo-2(5H)-furanone might open the possibility to synthesize in an enantioselective manner a variety of naturally occurring compounds. The two main questions of interest for us are: first, is it possible to prepare optically active decalines via an intermolecular instead of the commonly employed intramolecular cycloaddition reaction, and second, does our approach also work for decalines (and hydridanes) with an angular alkyl substituent?

We have focused our attention on the synthesis of enantiomerically pure warburganal, an insect antifeedant, and other closely related compounds (see Chapter IV, Figure 4.1). Among a number of different synthetic strategies leading to these molecules, the application of the Diels-Alder reaction to construct the appropriately functionalized decalines has proven to be especially attractive. There have been several reports on the synthesis of drimane sesquiterpenes, but until now only a limited number of enantioselective routes are known.\(^1\) This was the main reason for us to focus our attention on the asymmetric synthesis of this class of compounds. Another important reason for the development of an asymmetric synthesis of drimanes is the phytotoxicity associated with the racemates in some cases.\(^2\)

5.2 The synthesis of warburganal and related compounds

For the synthesis of the carbon skeleton of warburganal (Figure 4.1) and related sesquiterpenes several methods have been developed. In most cases reactions between
1,3,3-trimethyl-2-ethenyl-1-cyclohexene (5.1) and dimethyl acetylenedicarboxylate\(^3\) or acetylene dicarboxylate\(^4\) were used for this purpose. The addition products have been applied in the synthesis of several drimanes. They formed the starting materials for: cinnamolide, polygodial, isodrimeninol, drimenin, warburganal,\(^5\) cinnamodial\(^6\) and winterin.\(^4\)

For the Diels-Alder reactions with 1,3,3-trimethyl-2-ethenyl-1-cyclohexene (5.1) mentioned above highly reactive dienophiles like acetylenedicarboxylates are needed. In the reaction of 5.1 with maleic anhydride (5.2), the expected adduct 5.3 is not formed. Instead diene 5.1 first undergoes isomerization to compound 5.4, which then reacts with 5.2, to give the Diels-Alder adduct 5.5.\(^{3a}\)

\[
\text{Scheme 5.1}
\]

The reactivity of diene 5.1 can be improved by the introduction of electron-donating substituents. Snowden has described the synthesis of pyrrolidine substituted 1,3,3-trimethyl-2-ethenyl-1-cyclohexene 5.6. It was found that this dienamine\(^7\) reacted with dimethyl fumarate (5.7) in refluxing xylene to provide the cycloadduct 5.8 exclusively.\(^8\) To our knowledge this is the only reported example of an intermolecular Diels-Alder between a non-acetylenic dienophile and a derivative of diene 5.1.

\[
\text{Scheme 5.2}
\]
Elimination of pyrrolidine by heating 5.8 with acetic anhydride afforded 5.9, which is a key intermediate in the synthesis of several drimane related sesquiterpens.

All the routes described above give racemic products. The number of enantioselective syntheses of drimane related compounds is still very limited. The asymmetric construction of the decaline system via a diastereoselective and regioselective intramolecular Diels-Alder reaction has only been reported in one case. Cyclization of 5.11, formed by combination of 5.10 and the halfester of maleic acid and menthol, afforded substituted decalines as a mixture of diastereoisomers 5.12 and 5.13. The ratio of 5.12 and 5.13 was only 1.75:1.

Both isomers could readily be separated by crystallization, to provide pure isomer 5.12 with the required terpene stereochemistry. This compound formed the key intermediate in the synthesis of enantiomerically pure drimenin, cinnamolide and polygodial.

Considering the lack of efficient asymmetric syntheses of drimane related sesquiterpenes, and because of the excellent results we had obtained in the asymmetric synthesis of decaline systems (as described in Chapter IV), we assumed that the asymmetric Diels-Alder reaction of 5-menthylxyloxy-2(5H)-furanone (5.18) with a proper diene would be an attractive approach for the construction of drimane sesquiterpene precursors.

Our first attempt in the asymmetric construction of the drimane skeleton was the Diels-Alder reaction between (5R)-5-(l-menthylxyloxy)-2(5H)-furanone (5.18) and 1,3,3-trimethyl-2-ethenyl-1-cyclohexene (5.1).

Scheme 5.3
5.3 The reaction of \((SR)\)-\((1\text{-menthylary})\)-2(5H)-furanone with 1,3,3-trimethyl-2-ethenyl-1-cyclohexene

5.3.1 The synthesis of 1,3,3-trimethyl-2-ethenyl-1-cyclohexene

The synthetic route to 1,3,3-trimethyl-2-ethenyl-1-cyclohexene (5.1) is depicted in Scheme 5.4. The bottleneck in the synthesis of this diene is the availability of cyclocitral (5.16). This aldehyde can either be synthesized from citral (5.14) by means of cyclization of the corresponding imine in concentrated sulfuric acid,\(^9\) or through ozonolysis of \(\beta\)-ionone (5.15).\(^3\) The cyclization of citralanil (prepared from citral and aniline) gave aldehyde 5.16 in only 25% yield (lit.\(^{10}\) 41%). As this reaction is performed in concentrated sulfuric acid at low temperature the solution becomes very viscous. Therefore in a large scale preparation, (i.e. 50 g of citral), effective mixing of the reagents is no longer possible. This results in considerable formation of tarry black insoluble side products. Aldehyde 5.16 was also prepared in 79% yield (lit.\(^{3}\) 50%) by the ozonolysis of \(\beta\)-ionone (5.15). For a large scale preparation of 5.16 by means of ozonolysis the reaction time for complete conversion is too long to be of practical use. Another disadvantage is that during this reaction the temperature has to be maintained constantly at -40 °C. Following the procedure of Ley et al.,\(^5\) aldehyde 5.16 was allowed to react with trimethylsilylmethylmagnesium chloride to provide the intermediate \(\beta\)-hydroxysilane 5.17, which on stirring in THF with \(p\)-toluenesulfonic acid gave diene 5.1 in 80% yield.

\[
\text{CHO} \quad \xrightarrow{\text{a}} \quad \text{5.16} \quad \xrightarrow{\text{b}} \quad \text{5.17} \quad \xrightarrow{\text{p-TsOH \quad THF \quad 80\% \quad 16h}} \quad \text{5.1}
\]

\(a\) 1. \(\text{C}_6\text{H}_5\text{NH}_2\) 2. conc. \(\text{H}_2\text{SO}_4\), -20°C
3. \(\text{KOH, CH}_3\text{OH, } 0^\circ\text{C}\)

\(b\) 1. \(\text{O}_3, \text{CH}_3\text{OH, } -60^\circ\text{C}\)
2. \(\text{Zn, 50\% aqueous CH}_3\text{CO}_2\text{H, RT, 1h, 79%}\)

Scheme 5.4
5.3.2 Attempted Diels-Alder reactions

Refluxing diene 5.1 with (5R)-5-(l-menthylxy)-2(5H)-furanone (5.18) in xylene at 138 °C for 24 hours did not yield cyclization product 5.19. Compounds 5.1 and 5.18 were recovered unchanged. Even at higher temperatures (refluxing decaline) no product could be isolated.

![Scheme 5.5](image)

These results were not completely unexpected on consideration of literature reports on Diels-Alder reactions of 5.1 and maleic anhydride. Robins and Walker\(^{11}\) observed that at room temperature 1-ethenyl-2-methyl-1-cyclohexene (5.20) did not react with \(p\)-benzoquinone (5.21).

![Scheme 5.6](image)

When the same reaction was performed in benzene at 100 °C only dark brown tarry products were formed and adduct 5.22 could not be isolated. Comparable results were reported by Stork \textit{et al.}\(^{12}\) who found that 1,3-dimethyl-2-ethenyl-1-cyclohexene (5.23) did not react with maleic anhydride (5.2).

5.4 The reaction of (5R)-5-(l-menthylxy)-2(5H)-furanone with 1-[(2-(2,6,6-trimethyl-1-cyclohexen-1-yl)-ethenyl]pyrrolidine

Based on the results with 5.1 and the reports by Snowden (\textit{vide supra}) it can be expected that dienamine 5.6 might be a better candidate in the cycloaddition reaction.
with 5-menthlyoxy-2(5H)-furanone (5.18).

5.4.1 Improved synthesis of 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde

Dienamine 5.6 is prepared by reaction of aldehyde 5.26 with pyrrolidine. In most cases this aldehyde is synthesized by addition of acetylene to 2,2,6-trimethyl-cyclohexanone (5.24),\textsuperscript{5,13} followed by a rearrangement of the adduct with (Ph\textsubscript{3}SiO)\textsubscript{3}VO.

\begin{equation}
\text{NH}_3, \text{NaNH}_2, \text{HC} = \text{CH} \quad \text{98%} \\
\text{5.24} \quad \text{5.25} \quad \text{140°C, 6h} \quad \text{81%} \\
\text{5.26}
\end{equation}

Scheme 5.7

As part of our enantioselective Diels-Alder approach to optically active drimane sesquiterpenes, we looked for a more efficient route to 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde (5.26), mainly because the starting material 5.24 has to be prepared in a multistep synthesis. We have developed two new routes to aldehyde 5.26; the first one via a one carbon chain extension of aldehyde 5.16 and the second using a one carbon chain shortening starting from carboxylic acid 5.28.

Our first synthesis of aldehyde 5.26 starts from cyclocitral (5.16) (Scheme 5.8). Via a Peterson olefination of 5.16 with methoxy(trimethylsilyl)methyl lithium\textsuperscript{14,15} the carbon chain was extended with one carbon atom to \(\beta\)-hydroxysilane 5.27.\textsuperscript{16} The product was obtained as a mixture of diastereoisomers with a ratio of 2:1. Treatment of the adduct with 90% aqueous formic acid for 10 minutes afforded aldehyde 5.26 in 75% yield.

\begin{equation}
\text{5.16} \quad \text{5.27} \quad \text{5.26}
\end{equation}

Scheme 5.8

The second synthesis of 5.26 starts from \(\beta\)-ionone (5.15). This compound was oxidized via a haloform reaction, according to the procedure of He and Wu\textsuperscript{1} with sodium
hypobromite to carboxylic acid 5.28 in 95% yield (lit.1 90%). In most cases the carboxylic acid was used in the next reaction step without purification. Treatment of 5.28 with one equivalent of diphenyl phosphoryl azide (DPPA),17 according to the methodology developed by Van Leusen and Wildeman,18 afforded the corresponding acyl azide 5.29, which was converted without isolation and purification into the desired aldehyde via a Curtius rearrangement19 in a refluxing 0.5 N HCl/dioxane solution. After purification by distillation 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde (5.26) was obtained in 71% yield. This compound was in all respects identical with an independently prepared sample.

Reaction between aldehyde 5.26 and pyrrolidine gave, according to the procedure of Snowden,8 dienamine 5.6 in 88% yield (lit.8 96%).

\[ \text{Scheme 5.9} \]

The first route to aldehyde 5.26 has a number of serious disadvantages, which may form a limitation for a large scale preparation of 5.26. Firstly, the starting material 5.16 is not readily available on large scale (see Section 5.3.1), and secondly, another serious draw-back of this reaction sequence is the use of s-butyl lithium at low temperatures (-70 °C). Also because of the low overall yield of this multistep synthesis mentioned above, we searched for an alternative route which can be carried out on a large scale and in which starting materials are used that are more easily available. Especially the second route to aldehyde 5.26, which consists of two operatively simple reaction steps, is a considerable improvement as compared to current syntheses of aldehyde 5.26.

Another activated diene, which could serve as a precursor in the synthesis of enantiomerically pure dimanes is 2-(2-methoxyethenyl)-1,3,3-trimethyl-1-cyclohexene
We have synthesized 5.31 in two different ways. The first route follows the procedure of Lallemand et al.\textsuperscript{3a}

\begin{align*}
\text{2,6,6-Trimethyl-1-cyclohexene-1-acetaldehyde} & \xrightarrow{\text{CH}_3\text{OH, } p\text{-TsOH}} \text{corresponding dimethoxy acetal} 5.30 \xrightarrow{\text{reflux in benzene, } p\text{-TsOH}} 5.31 \\
\text{is first converted into the} & \text{yielding} 5.31 \text{as a mixture of } E \text{ and } Z \text{ isomers (ratio 60:40).} \\
\text{corresponding dimethoxy acetal} 5.30 & \text{Subsequently, methanol is eliminated by refluxing in benzene with a catalytic amount of } p\text{-TsOH,} \\
\text{yielding} 5.31 & \text{ratio 60:40). The} \\
\text{overall yield of} 5.31 & \text{was 87\% (lit.}\textsuperscript{3a} \text{62\%).} \\
\text{Our second approach is based on silyl compound} 5.27 & \text{In contrast to the acid work-up} \\
\text{yielded the} 5.31 & \text{shown in Scheme 5.8, a basic work-up procedure with potassium hydride in THF,} \\
\text{enol ether} 5.31 & \text{yields the enol ether} 5.31 \text{in 40\% yield via a syn-elimination of } -\text{OSiMe}_3.\textsuperscript{16}
\end{align*}

\begin{align*}
\text{Scheme 5.10}
\end{align*}

\begin{align*}
\text{2,6,6-Trimethyl-1-cyclohexene-1-acetaldehyde} (5.26) & \text{is first converted into the} \\
\text{corresponding dimethoxy acetal} 5.30 & \text{by reflux in methanol with a catalytic amount of} \\
\text{p-TsOH. Subsequently, methanol is eliminated by refluxing in benzene with a catalytic} \\
\text{amount of} p\text{-TsOH,} & \text{yielding} 5.31 \text{as a mixture of} E \text{ and } Z \text{ isomers (ratio 60:40).} \\
\text{The overall yield of} 5.31 & \text{was 87\% (lit.}\textsuperscript{3a} \text{62\%).} \\
\text{Our second approach is based on silyl compound} 5.27 & \text{In contrast to the acid work-up} \\
\text{yielded the} 5.31 & \text{shown in Scheme 5.8, a basic work-up procedure with potassium hydride in THF,} \\
\text{enol ether} 5.31 & \text{yields the enol ether} 5.31 \text{in 40\% yield via a syn-elimination of } -\text{OSiMe}_3.\textsuperscript{16}
\end{align*}

\begin{align*}
\text{Scheme 5.10}
\end{align*}

\begin{align*}
\text{5.5 Attempted Diels-Alder reactions with activated dienes}
\end{align*}

Because Snowden\textsuperscript{8} had only reported the Diels-Alder reaction of dienamine 5.6 with dimethyl fumarate (5.7) and no cyclic dienophiles had been used, we started our investigations with the Diels-Alder reaction of maleic anhydride (5.2) and N-phenylmaleimide (5.32). When dienamine 5.6 was heated with one equivalent of maleic anhydride (5.2) in refluxing toluene the solution immediately turned black. Even when diene 5.6 was added very slowly to a solution of maleic anhydride (5.2) in toluene at 0 °C, and under careful exclusion of moisture, the solution became brown. After stirring for one hour at room temperature and evaporation of the solvent no product could be isolated. Furthermore, no maleic anhydride (5.2) could be detected
by means of $^1$H NMR spectroscopy, but on the other hand aldehyde 5.26 had been formed, meaning that enamine 5.6 must have been hydrolyzed during the reaction. However, when N-phenylmaleimide (5.32) was used instead of maleic anhydride (5.2) no rapid decomposition was observed. Reaction of 5.32 with dienamine 5.6 in refluxing xylene at 140 °C afforded the drimane precursor 5.34 in 32% yield. The product was characterized by $^1$H and $^{13}$C NMR spectroscopy. By means of $^1$H COSY and NOESY it was established that product 5.34 was the result of an endo-addition of N-phenylmaleimide to diene 5.6.

![Reaction scheme](image)

**Scheme 5.12**

In our case the pyrrolidine ring is eliminated during the reaction, whereas Snowden reported that in the reaction of 5.6 with dimethyl fumarate (5.7) the pyrrolidine ring is still present in the Diels-Alder adduct. In the latter case the pyrrolidine ring was eliminated by heating the adduct with 1.5 equivalent of acetic anhydride in refluxing xylene for 24 hours. As we have used the same reaction conditions (refluxing xylene), the faster elimination of the pyrrolidine from the initial adduct 5.33 may be explained by steric interactions. As the adduct is the result of an endo-attack, the pyrrolidine ring and the amide part of 5.23 are in a cis-relationship. However, in the case of adduct 5.8, obtained by Snowden, the pyrrolidine ring and the neighboring ester substituent are in a trans-position. Consequently, the steric interactions with the pyrrolidine ring may be higher in the case of compound 5.23 and therefore the
elimination may be facilitated compared to 5.8.

When \((5R)-5-(\text{-menthyl oxy})-2(5H)\)-furanone \(5.18\) was used as the dienophile in the cycloaddition reaction with \(5.6\) no cycloaddition product could be isolated. When the same reaction was performed at elevated temperature (refluxing toluene or xylene) only a brown reaction mixture was obtained in which the starting materials had disappeared but from which no product could be isolated, whereas at room temperature no reaction took place. The reason for these disappointing results may be the instability of the dienamine \(5.6\). When this diene is stored at room temperature it turns brown and considerable decomposition occurs. Furthermore, the pyrrolidine which is eliminated during the reaction can give a 1,4-addition to the 5-menthyl oxy-2(5H)-furanone. In this way the dienophile is no longer available for the Diels-Alder reaction with \(5.6\).

Because of the side reactions which occurred with dienamine \(5.6\), probably due to its instability under the given reaction conditions, we switched to diene \(5.31\) which bears a methoxy substituent as activating group instead of an amine. Unfortunately this diene showed no reaction at all with \((5R)-5-(\text{-menthyl oxy})-2(5H)\)-furanone \(5.18\). Under various reaction conditions, for example refluxing for four days in xylene at 140 °C, both the diene \(5.31\) and \((5R)-5-(\text{-menthyl oxy})-2(5H)\)-furanone \(5.18\) were recovered unchanged.

One explanation for the low reactivity of dienes \(5.6\) and \(5.31\) may be the polarization of the dienes. Considering the HOMO of \(5.6\) and \(5.31\) and LUMO of \((5R)-5-(\text{-menthyl oxy})-2(5H)\)-furanone \(5.18\), the most favorable attack is the one as depicted in Figure 5.1. However, this attack is highly unfavorable due to the steric interactions between the menthyl oxy group of the dienophile and the tetrasubstituted cyclohexene ring of \(5.31\) and \(5.6\).

![Figure 5.1](image_url)
5.6 Conclusions

In conclusion we have developed a new synthesis of aldehyde 5.26 and therefore of the activated dienes 5.6 and 5.31, which are important intermediates in the synthesis of drimane related sesquiterpenes. However, despite the activation compared to diene 5.1, neither of the dienes 5.6 and 5.31 gave the desired Diels-Alder reactions with 5-menthylxyloxy-2(5H)-furanone (5.18) producing the drimane skeleton.

5.7 Experimental section

For general remarks see Section 2.5.

β-Cyclocitral (5.16)

a) Via cyclization of citral
To a stirred solution of citral (5.14) (50.26 g, 0.33 mol) in ether was added aniline (30.75 g, 0.31 mol) which had been dissolved in ether (30 mL). After standing for ½ h at room temperature the water which had been formed was separated. After evaporation of the solvent, the crude reaction product was used in the next reaction step without further purification. At -20 °C and under an inert atmosphere of nitrogen the crude citralanil, dissolved in ether (50 mL), was added to a vigorously stirred 95% H₂SO₄ solution (330 mL). After stirring for 45 minutes at -25 °C, the black reaction mixture was poured onto 1 kg of crushed ice and extracted with ether. The combined organic layers were dried over MgSO₄. After evaporation of the solvent under reduced pressure the product was purified by distillation yielding α-cyclocitral (17.57 g, 35%) as a slightly yellow oil. The isomerization into β-cyclocitral (5.16) was effected by stirring a solution of α-cyclocitral for a few minutes in methanolic KOH (5%) (100 mL) at 0 °C.10 After the addition of brine (250 mL) the solution was extracted with ether. The combined organic layers were dried over Na₂SO₄, filtered and the solvent evaporated under reduced pressure yielding product 5.16 as a colorless liquid.

The 1H NMR data were in complete accordance with those reported in the literature.α 1H NMR (CDCl₃, 60 MHz): δ 1.17 (s, 6H), 1.4-1.8 (m, 4H), 2.15 (s, 3H), 2.08 (m, 2H), 10.1 (s, 1H).

b) Via ozonolysis of 6-ionone
A solution of 6-ionone (5.15) (25.0 g, 0.13 mmol) in methanol (300 mL) was cooled to -40 °C and ozone was bubbled through the solution for 5-6 h. After zinc powder (13 g) and 50% acetic acid (105 mL) were added, the solution was allowed to reach room temperature, and stirring was continued for 1 h. After work up according to the literature procedureα and bulb-to-bulb distillation (120 °C, 12 mm Hg) the product 5.16 (15.55 g, 79%) was obtained as a colorless oil.

2-Ethenyl-1,3,3-trimethyl cyclohexene (5.1)

This compound was synthesized according to the procedure of Ley et al.α Reaction of trimethylsilylmethylmagnesium chloride with aldehyde 5.16 (10.0 g, 65.8 mmol) in diethyl ether gave the intermediate β-hydroxysilane 5.17, which on stirring with
p-toluenesulfonic acid in THF for 18 h gave the diene 5.1 in 80% yield (lit.\(^5\) 95%). The diene was purified by column chromatography (SiO\(_2\), petroleum ether 40-60) and obtained as a colorless oil. \(^1\)H NMR (CDCl\(_3\), 60 MHz): \(\delta\) 1.00 (s, 6H), 1.4-1.8 (m, 4H), 1.67 (s, 3H), 1.98 (m, 2H), 4.93 (dd, \(J = 3, 18\) Hz, 1H), 5.22 (dd, \(J = 3, 12\) Hz, 1H), 6.22 (ddm, \(J = 12, 18\) Hz, 1H).

The diene was purified by column chromatography (SiO\(_2\), petroleum ether 40-60) and obtained as a colorless oil. \(^1\)H NMR (CDCl\(_3\), 60 MHz): S 1.00 (s, 6H), 1.4-1.8 (m, 4H), 1.67 (s, 3H), 1.98 (m, 2H), 4.93 (dd, \(J = 3, 18\) Hz, 1H), 5.22 (dd, \(J = 3, 12\) Hz, 1H), 6.22 (ddm, \(J = 12, 18\) Hz, 1H).

\(\alpha\)-[Methoxy(trimethylsilyl)methyl]-2,6,6-trimethyl-1-cyclohexenemethanol (5.27)

Under an inert atmosphere of \(\text{N}_2\), a solution of \(\text{methoxymethyltrimethylsilane}\) (6.80 g, 57.6 mmol) in dry THF (50 mL) was treated with a 1.3 M solution of \(\text{s-butyllithium}\) in hexane (45 mL) at -70 °C, followed by warming to -25 °C. After stirring for an additional 15 min, cyclocitral (8.00 g, 52.6 mmol) was added and stirring was continued at -25 °C for 0.5 h. Water (100 mL) was added and the resulting mixture was extracted with ether (3 x 50 mL). The combined organic layers were washed with brine and dried on \(\text{MgSO}_4\). After filtration and evaporation of the solvent the product was purified by bulb-to-bulb distillation (110 °C, 0.1 mm Hg) to afford 5.27 (12.8 g, 90%) as a slightly yellow oil. The \(^1\)H NMR and \(^13\)C NMR spectra showed that the product consisted of a mixture of two diastereoisomers with a ratio of 2:1.

Major isomer: \(^1\)H NMR (CDCl\(_3\), 300 MHz): S 0.10 (s, 9H), 1.02 (s, 3H), 1.09 (s, 1H), 1.42 (m, 2H), 1.58 (m, 2H), 1.90 (s, 3H), 1.96 (m, 2H), 3.17 (d, \(J = 7.0\) Hz, 1H), 4.33 (m, 1H); \(^13\)C NMR (CDCl\(_3\)): S -2.25 (q), 19.15 (t), 21.93 (q), 28.58 (q), 28.98 (q), 34.32 (t), 34.81 (s), 40.02 (t), 61.97 (q), 72.96 (d), 81.53 (d), 132.50 (s), 137.02 (s).

Minor isomer: \(^1\)H NMR (CDCl\(_3\), 300 MHz): S 0.13 (s, 9H), 1.03 (s, 3H), 1.10 (s, 3H), 1.42 (m, 2H), 1.58 (m, 2H), 1.85 (s, 3H), 1.96 (m, 2H), 3.24 (d, \(J = 7.0\) Hz, 1H), 3.39 (s, 3H), 3.40 (d, \(J = 7.2\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)): S -2.67 (q), 19.30 (t), 21.93 (q), 28.58 (q), 29.10 (q), 33.95 (s), 34.10 (t), 40.09 (t), 60.57 (q), 71.28 (d), 78.91 (d), 131.80 (s), 141.87 (s).

2,6,6-Trimethyl-1-cyclohexene-1-acetaldehyde (5.26)

Compound 5.27 (5.00 g, 18.52 mmol) (mixture of isomers), dissolved in 90% aqueous formic acid (25 mL), was stirred at room temperature for 10 min. This solution was then poured very carefully in saturated \(\text{NaHCO}_3\) (250 mL) and extracted with ether (2 x 100 mL). The combined organic layers were washed with saturated \(\text{NaHCO}_3\), dried over \(\text{Na}_2\text{SO}_4\) and evaporated under reduced pressure yielding a yellow oil. After bulb-to-bulb distillation (140 °C, 12 mm Hg) (lit.\(^5\) 48-50 °C, 0.4 mm Hg) the pure product 5.26 (2.29 g, 75%) was obtained as a colorless oil. Spectroscopic data were in complete agreement with those reported in the literature.\(^5\) \(^1\)H NMR (CDCl\(_3\), 300 MHz): S 0.92 (s, 6H), 1.44 (m, 2H), 1.53 (s, 3H), 1.59 (m, 2H), 1.96 (m, 2H), 3.05 (br.s, 2H), 9.48 (t, \(J = 2.2\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\)): 19.22 (t), 20.05 (q), 27.92 (q), 32.75 (t), 39.06 (t), 43.64 (t), 128.40 (s), 132.37 (s), 201.13 (s).

3-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-propenoic acid (5.28)

In a 1L erlenmeyer \(\text{NaOH}\) (51.0 g, 1.28 mol) was dissolved in water (200 mL). After cooling the solution with an ice-bath, bromine (51.0 g, 0.32 mol) was added. After stirring for 1 h, \(\beta\)-ionone (13.5 g, 70.2 mmol), dissolved in dioxane (30 mL), was added and the ice bath was subsequently removed. Stirring was continued for 4 h at room temperature, followed by the addition of a 10% aqueous sodium bisulfite
solution (300 mL). The resulting solution was extracted with ether (3 x 100 mL). After acidification of the aqueous layer with concentrated HCl the precipitated acid 5.28 was removed by filtration, washed with cold water, and dried in vacuo yielding 3-(2,6,6-trimethyl-1-cyclohexene-1-yl)-2-propenoic acid (5.28) (12.5 g, 92%) as a white solid. This product was used in the next reaction step without purification, but can be crystallized from water/ethanol yielding the product as white needles. Mp 106.5-107.0 °C (lit.1 mp 105-107 °C). 

\[ \text{H NMR (CDCl}_3, 300 \text{ MHz): } \delta \text{ 1.07 (s, 6H), 1.47 (m, 2H), 1.62 (m, 2H), 1.78 (s, 3H), 2.07 (m, 2H), 5.85 (d, J = 16.1 Hz, 1H), 7.56 (d, J = 16.1 Hz, 1H)} \]

\[ \text{13C NMR (CDCl}_3, 300 \text{ MHz): } \delta \text{ 18.78 (t), 21.61 (q), 28.63 (q), 33.58 (t), 33.94 (s), 39.71 (t), 120.59 (d), 135.64 (s), 136.98 (s), 146.57 (d), 172.66 (s).} \]

2,6,6-Trimethyl-1-cyclohexene-1-acetaldehyde (5.26)

To a cooled solution (5 °C) of 3-(2,6,6-trimethyl-1-cyclohexene-1-yl)-2-propenoic acid (5.28) (1.94 g, 10.0 mmol) and triethylamine (1.10 g, 11.0 mmol) in dioxane (7 mL) was added in 5 min diphenyl phosphoryl azide (3.00 g, 11.0 mmol). After stirring for 1 h at room temperature under N, the mixture was diluted with brine (50 mL) and extracted three times with ether (20, 15 and 10 mL). To the concentrated organic extracts was added dioxane (15 mL) and 0.5 N aqueous hydrogen chloride (10 mL). The mixture was then refluxed in a preheated oil bath (120 °C) under N, until the carbon dioxide and nitrogen evolution ceased (12-15 min). The resulting reaction mixture was immediately cooled in an ice bath, diluted with brine (50 mL), extracted with pentane (2 x 25 mL), concentrated and purified by bulb-to-bulb distillation (80 °C, 0.5 mm Hg), providing pure 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde (5.26) (1.22 g, 71%) as a pale yellow liquid. A nearly colorless oil was obtained by rapid chromatography over a short column of Al₂O₃ (II-III) with CHCl₃/pentane (1:2) as eluent. Spectroscopic data were in agreement with those from an independently prepared sample (vide supra). The scale of this reaction was raised without any difficulties to the tenfold.

1-[(2,6,6-Trimethyl-1-cyclohexen-1-yl)-ethenyl]pyrrolidine (5.6)

In a round bottom flask fitted with a reflux condenser 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde (5.26) (2.90 g, 17.5 mmol) and pyrrolidine (1.37 g, 19.2 mmol) were dissolved in toluene (50 mL) and heated at 60 °C for 1 h. After evaporation of the solvent and bulb-to-bulb distillation (80 °C, 0.7 mm Hg) the product (3.37 g, 88%) was obtained as a colorless oil. 

\[ \text{H NMR (CDCl}_3, 300 \text{ MHz): } \delta \text{ 0.98 (s, 6H), 1.43 (m, 2H), 1.55 (m, 2H), 1.72 (s, 3H), 1.85 (m, 4H), 1.96 (m, 2H), 3.03 (m, 4H), 4.52 (d, J = 14.0 Hz, 1H), 6.14 (d, J = 14.0 Hz, 1H)} \]

\[ \text{13C NMR (CDCl}_3, 300 \text{ MHz): } \delta \text{ 19.37 (t), 21.93 (q), 24.71 (t), 28.89 (q), 32.98 (t), 34.20 (s), 39.61 (t), 48.98 (t), 95.76 (d), 124.64 (s), 137.06 (s), 138.80 (d).} \]

Methoxydienolefination (5.31)

a) Via Peterson olefination

A stirred solution of trimethylsilylmethoxymethane (10.0 g, 84.6 mmol) in dry THF (10 mL) was cooled to -70 °C. After the addition of s-butyllithium (65 mL, 1.3 M) the solution was warmed to -25 °C. The mixture was subsequently cooled to -30 °C and 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde (5.26) (12.16 g, 79.9 mmol), dissolved in dry THF (25 mL), was added slowly. Stirring was continued for 1 h at -30 °C, followed by stirring for 1½ h at room
temperature. After the addition of water (100 mL) the solution was extracted with ether. The combined organic layers were dried over MgSO₄, filtered and the ether was evaporated under reduced pressure. The residue was dissolved in dry THF (150 mL). After the addition of potassium hydride (16.0 g, 0.40 mol) the resulting mixture was heated for 1 h at 60 °C. Water was added and the reaction mixture was extracted with ether. The combined organic layers were dried over MgSO₄ and the ether was removed by evaporation under reduced pressure. The crude product was purified by bulb-to-bulb distillation (115 °C, 12 mm Hg) yielding 5.31 (5.80 g, 40%) as a colorless oil. Spectroscopic data were in complete agreement with those reported in the literature.

b) Via acetal formation
A mixture of methanol (2.5 mL) and trimethylorthoformate (3.8 g, 35.8 mmol) was cooled to -30 °C. Aldehyde 5.16 (2.87 g, 18.9 mmol) was added followed by the addition of p-toluenesulfonylic acid (4.7 mg) dissolved in methanol (0.3 mL). The reaction mixture was stirred for 24 h followed by work up as described in the literature. Acetal 5.30 was dissolved in dry benzene (50 mL). After the addition of a catalytic amount of p-toluenesulfonylic acid and quinoline the solution was refluxed for 21 h in a Dean-Stark apparatus. At set times solvent was removed and replaces by a same amount of dry benzene. After a work up procedure as described in the literature diene 5.31 (2.90 g, 87%) was obtained as a colorless oil. ¹H NMR showed that product 5.31 consisted of a mixture of E and Z isomers with ratio 60:40. Spectroscopic data were in complete agreement with those described in the previous experiment.

Attempted reaction of dienolether 5.31 with racemic 5-methoxy-2(5H)-furanone
A mixture of diene 5.31 (360 mg, 2.0 mmol) and 5-methoxy-2(5H)-furanone (342 mg, 3.0 mmol) was dissolved in dry xylene (25 mL) and heated for 4 days at 140 °C. After evaporation of the solvent ¹H NMR indicated that no reaction had occurred. Both starting materials were recovered unchanged. When the temperature was raised to 190 °C the same negative results were obtained. Identical results were also obtained with enantiomERICally pure (5R)-5-(l-menthylaoxy)-2(5H)-furanone as the dienophile.

Attempted reaction of dienamine 5.6 with (5R)-5-(l-menthylaoxy)-2(5H)-furanone (5.18)
A mixture of (5R)-5-(l-menthylaoxy)-2(5H)-furanone (5.18) (0.24 g, 1.01 mmol) and dienamine 5.6 (0.22 g, 1.00 mmol), dissolved in dry toluene (5 mL), was heated in a sealed tube, for 2 days, at 130 °C. After evaporation of the solvent a dark brown oil was obtained in which no product could be detected.

Reaction of dienamine 5.6 with N-phenylmaleimide (5.32)
A solution of dienamine 5.6 (418 mg, 1.91 mmol) and N-phenylmaleimide (5.32) (220 mg, 1.27 mmol) in dry toluene (25 mL) was refluxed for 20 h. After evaporation of the solvent under reduced pressure the product 5.34 was crystallized from n-butylether yielding yellow/brown crystals (131 mg, 32%). ¹H NMR (CDCl₃, 300 MHz): δ 1.01 (s, 3H), 1.16 (s, 3H), 1.19 (s, 3H), 1.36-1.76 (m, 5H), 2.60 (br.d, J = 11.1 Hz, 1H), 3.28 (s, 1H), 6.20 (d, J = 5.6 Hz, 1H), 7.02 (dd, J = 2.8, 5.6 Hz, 1H), 7.28-7.47 (m, 5H); ¹³C NMR (CDCl₃): δ 17.55 (q), 17.76 (t), 31.62 (q), 31.77 (q), 36.44 (s), 38.06 (s), 39.83 (t), 40.07 (t), 51.61 (d), 118.14 (d), 122.66 (s), 126.39 (2 x d), 128.31 (d), 128.83 (d), 131.94 (s), 163.90 (s), 173.91 (s).
5.8 References and notes

   For the preparation of other dienamines see:
15. For the preparation of methoxytrimethylsilylane it is more facile to use iodomethyltrimethylsilane instead of chloromethyltrimethylsilane. For the preparation of iodomethyltrimethylsilane see: Ambasht, S.; Chiu, S.K.; Peterson, P.E.; Queen, J. Synthesis 1980, 318.
b) Magnus, P.; Roy, G. Organometallics 1982, 1, 553.
18. a) Wildeman, J.; van Leusen, A.M. to be published.