Asymmetric 1,3-Dipolar Cycloadditions to 5-(R)-Menthyloxy-2(5H)-Furanone

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Abstract: Various diazo compounds, nitrile oxides, nitrones and azomethine ylides were examined in 1,3-dipolar cycloadditions to enantiomerically pure 5-(R)-menthyloxy-2(5H)-furanone 1a. Pyrazoline 9 was obtained in 100% c.y. as a mixture of 2 diastereoisomers in ratios up to 72 : 28, whereas pyrazoline 16 was obtained in 100 % c.y. as a single enantiomer. Photochemically pyrazolines 9 and 10 have been converted to cyclopropanes 11 and 13. Under thermal conditions pyrazoline 9 is converted to 4-methyl-5-menthyloxy-2(5H)-furanone. Isoxazoles 21a-24a were obtained enantiomerically pure via nitrile oxide addition to 1a in 64-67% yield. Nitro addition afforded isoxazolines 27, 28 and 34 with complete anti-facial- and regiochemistry, but with endo-exo selectivities up to 76%. Enantiomerically pure isoxazolines were obtained in 25-75% yield. Pyrrolidine 36 was obtained diastereomerically pure in 81% c.y. Pyrrolidines 42 and 45, however, were obtained as diastereomeric mixtures in 37% resp. 6% yield.

Introduction

Cycloadditions are undoubtedly a cornerstone in synthetic methodology. In order to control the absolute stereochemistry of the ring systems which are formed, regio-, facial-, and endo/exo-selectivity are decisive factors. Therefore it is not surprising that a variety of asymmetric Diels-Alder reactions and 1,3-dipolar cycloadditions have been developed in the last decade.1,2 The 1,3-dipolar cycloaddition reactions of nitrones and nitrile oxides to alkenes have been extensively used for the preparation of isoxazolidines and isoxazoles.3 Further transformations offer access to a variety of functional intermediates for synthesis, in many cases with multiple stereogenic centers introduced during the cycloaddition process. Cycloadditions to α,β-unsaturated carboxylic acid derivatives are particularly useful because high regioselectivity is often observed.3b To introduce asymmetry in the 1,3-dipolar cycloaddition a number of approaches has been used, including reaction of the 1,3-dipole and the dipolarophile in an intramolecular fashion. A number of complex natural products has been synthesized this way.3c,d The use of chiral 1,3-dipoles3 and chiral dipolarophiles has been reported. Diazo compounds5, nitrile oxides5, nitrones5 and azomethine ylides9 have been added to activated chiral olefins. In several cases high diastereoselectivity was found. We have demonstrated that γalkoxy butenolides are particularly useful for asymmetric cycloaddition reactions, as was shown for Diels-Alder reactions to 5-(R)-menthyloxy-2(5H)-furanone 1a and 5-methoxy-2(5H)-furanone 2 (figure 1).10 These butenolides also proved to be excellent chiral 1,3-dipolarophiles (scheme 1).11

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As part of our program to investigate the scope and stereoselectivity of cycloaddition reactions of γ-alkoxy butenolides\textsuperscript{12} additions of diazo compounds, nitrile oxides and nitrones to 5-(R)-menthylxy-2(5H)-furanone 1\texttextit{a} were conducted. Furthermore several azomethine ylide additions to 1\texttextit{a} were examined. An important aspect of this study is the elucidation of the stereoselectivity in 1,3-dipolar cycloadditions to γ-alkoxy butenolides.

The starting material, 5-menthylxy-2(5H)-furanone 1, is readily prepared via methylene blue sensitized photooxidation of furfural\textsuperscript{13}, followed by acetalization with \textit{l}-menthol (scheme 2). A mixture of diastereomeric 5-menthylxy-2(5H)-furanones 1\texttextit{a} and 1\texttextit{b} in a 6 : 4 ratio is formed. Enantiomerically pure 5-(R)-menthylxy-2(5H)-furanone 1\texttextit{a} is obtained via a crystallization-epimerization procedure.\textsuperscript{9a} The major diastereoisomer 1\texttextit{a} readily crystallizes at -20 °C from petroleum ether 140-160. The crystallization is accompanied by a remarkable second order asymmetric transformation of 1 in solution. The slow "crystallization induced epimerization" of 1\texttextit{b} is driven by the continuous removal of the major crystalline isomer 1\texttextit{a} from the solution. The epimerization rate can be increased thermally or by acid catalysis. This epimerization-crystallization process allows the isolation of pure 1\texttextit{a} up to 80% yield (scheme 2).\textsuperscript{14}
Diazokane additions

5-(R)-Menthyloxy-2(5H)-furanone 1a was treated with 1.5 eq. of diazomethane as an ethereal solution at different temperatures (scheme 3; table 1). The reaction proceeded in all cases quantitatively to yield 1-pyrazoline 9 in a regioselective manner. However, the reaction is not diastereoselective, both anti-9a and syn-adducts 9b (with respect to the 5-menthyloxy substituent) are formed. The maximum diastereomeric excess of 44% was achieved at -40 °C. Based upon the Karplus relationship the coupling constant between H₆ and H₅a in the anti-isomer 9a is smaller than 1.0 Hz, whereas the coupling constant between H₆ and H₅a in the syn-isomer 9b is between 8.5 and 13.5 Hz. The spectrum shows a singlet for H₆(trans) whereas H₆(cis) has a coupling constant J₆,₅ₐ of 6 Hz. Both diastereoisomers can be separated via crystallization.

![Scheme 3](image)

Table 1: Influence of the temperature on the diastereomeric ratio of the 1-pyrazolines.

<table>
<thead>
<tr>
<th>entry</th>
<th>temperature</th>
<th>ratio</th>
<th>9a</th>
<th>9b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 °C</td>
<td></td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>-10 °C</td>
<td></td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>-20 °C</td>
<td></td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>-40 °C</td>
<td></td>
<td>72</td>
<td>28</td>
</tr>
</tbody>
</table>

1-Pyrazoline 9 is a precursor for 4-methyl-2(5H)-furanones and cyclopropane derivatives. We have previously shown that thermal conditions led to 5-(R)-menthyloxy-4-methyl-2(5H)-furanone 14 in quantitative yield.10a

Compound 9a is considered an attractive precursor for optically active 1,2-disubstituted cyclopropanes. To study the optimum conditions, photochemical experiments were conducted with racemic 3,4-diaza-6-methoxy-1-oxa-2-oxo-bicyclo[3.3.0]octene 10 (scheme 4). Irradiation of 10 (mixture of diastereomers) at 180-300 nm under various conditions resulted in D₅-elimination. Besides cyclopropane 11, 4-methyl furanone 12 and cycloreversion product 2 are formed. These results show a strong resemblance to those found by Neumann et al.15 for a diazopropane adduct. As is seen in table 2, solvent and sensitizer are of great influence on the amount of cyclopropane 11 formed. Upon addition of benzophenone, cycloreversion is suppressed as well as the formation of the 4-methylated product 12 (entry 1,4,5). The results compare favourably with results found by Fariña et al.16 for the corresponding pyrrolypyrazolines, e.g. 66% cyclopropane, 19% methyl compound and 15% cycloreversion.

![Scheme 4](image)
Table 2: Influence of solvent and sensitizer on the photochemical formation of cyclopropane 11.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>benzophenone (eq.)</th>
<th>11</th>
<th>12</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>50</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>acetone</td>
<td></td>
<td>50</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>benzene</td>
<td>1</td>
<td>70</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>1</td>
<td>70</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>2</td>
<td>95</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

With this results in mind we subjected enantiomerically pure product 9a to the same procedure. When 9a was irradiated in CH₂Cl₂ in the presence of 2 eq. of benzophenone 71% of cyclopropane 13 and 29% of methylated product 14 were found (scheme 5). Attempts to optimize the ratio are under current investigation.

![Scheme 5](image)

In contrast to the diazomethane addition the addition of ethyl diazoacetate 15 to 5-(R)-menthylxy-2(5H)-furanone 1a (scheme 6), however, proceeds with complete diastereofacial- and regio-selectivity to yield enantiomerically pure 16. Note that tautomerization of the 1-pyrazoline to the thermodynamically more stable 2-pyrazoline has taken place, due to the acidic nature of the proton α to the ester moiety.

![Scheme 6](image)

**Nitrile Oxide Additions**

The nitrile oxides 17-20 were prepared in situ, by dehydrohalogenation of the corresponding hydroximic acid chlorides, using triethylamine as the base. The hydroximic acid chlorides were prepared using literature procedures, starting from the corresponding aldehydes. Condensation of the aldehydes with hydroxylamine-hydrochloride provided the oximes. Subsequent chlorination using N-chlorosuccinimide gave the acids in high yield. ¹⁸

The reactions with 5-(R)-menthylxy-2(5H)-furanone 1a were performed at room temperature in diethyl ether as the solvent with reaction times of 16 hours using 1.5 equivalents of nitrile oxide, to ensure that all the 5-(R)-menthylxy-2(5H)-furanone 1a had reacted. Triethylamine was added very slowly to maintain a continuous low concentration of 1,3-dipolar reagent.

The reaction of each nitrile oxide 17-20 afforded two of the four possible diastereoisomers (scheme 7). These products were the two anti-cycloadducts. Isoxazoles 21a-24a were formed as the major adduct, whereas only minor amounts of regioisomeric cycloadducts 21b-24b were observed (<15 %). The high regioselectivity and complete diastereoselectivity allowed the isolation of the pure major isoxazoles 21a-24a in good yields (table 3). This is concluded from the 1H NMR spectrum of the crude reaction mixture of each cycloaddition reaction.
Table 3: Chemical yield of isoxazoles 21a-24a.

<table>
<thead>
<tr>
<th>Nitrile oxide</th>
<th>R</th>
<th>Products</th>
<th>ratio a:b</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Ph</td>
<td>21a,b</td>
<td>n.d.</td>
<td>67</td>
</tr>
<tr>
<td>18</td>
<td>p-CIC₆H₄</td>
<td>22a,b</td>
<td>90:10</td>
<td>64</td>
</tr>
<tr>
<td>19</td>
<td>p-MeOC₆H₄</td>
<td>23a,b</td>
<td>91:9</td>
<td>67</td>
</tr>
<tr>
<td>20</td>
<td>i-Pr</td>
<td>24a,b</td>
<td>92:8</td>
<td>65</td>
</tr>
</tbody>
</table>

*Chemical yield of isolated pure adducts 21a-24a.

The regiochemistry was deduced from ¹H NMR, NOESY experiments, and by the molecular structure of 22a as determined by X-ray analysis (figure 2). The major products were assigned structures 21a-24a. The ¹H NMR absorptions of H₃₃ of 21a-24a are shifted upfield compared to the absorptions for H₆₆ of 21b-24b and furthermore the ¹H NMR absorptions of H₆ and H₆₆ of 21a-24a are shifted downfield compared to the absorptions of H₆ and H₃₃ of 21b-24b (note the difference in numbering of the different atoms in both regioisomers!). The upfield shift for H₃₃ of 21a-24a compared to the ¹H NMR absorption for H₆₆ of 21b-24b can be explained by the fact that for 21a-24a, H₃₃ is located on the carbon next to the isoxazole imine, whereas H₆₆ of 21b-24b is located on the carbon next to the isoxazole oxygen. This gives rise to a ¹H NMR absorption at lower field. Also the downfield shift for H₆₆ of 21a-24a compared to H₆₆ of 21b-24b is a clear indication for the reverse regiochemistry. This difference in neighboring atoms is also the reason for the downfield shift for the absorption of H₆ of 21a-24a compared to that of H₆ of 21b-24b. It should be noted that the coupling patterns for both isomers are the same, which is further proof for the fact that they are regioisomers. Furthermore a NOE enhancement is observed between H₃₃ and the ortho-aryl hydrogens in 21a-23a. A similar enhancement for H₆₆ is absent in the NOESY-spectra of 21b-23b.
Excellent diastereofacial selectivity is observed in all nitrile oxide additions described here. This is clearly shown by the appearance of a singlet for the acetal proton H₆ for 21a-24a (H₄ for 21b-24b), which implies a trans relationship between H₆a and H₆b (H₄a and H₄b, respectively) and an anti-facial approach of the 1,3-dipolar reagent with respect to the alkoxy-substituent. The 1,3-dipolar reagent approaches from the Si face, as the Re face is shielded by the bulky alkoxy group (figure 3). This steric congestion inhibits attack so that the reagents approach from the sterically less encumbered direction exclusively. This is in accordance with the complete p-face selective Diels-Alder reactions, amine, and thiol additions and tandem 1,4-addition-alkylations to 1a, 8,9,10 and the preferred anti-selectivity in nitrone and nitrile oxide additions to 5-substituted butenolides.19

Since we used the optically pure chiral auxiliary based 1,3-dipolarophile, 5-(R)-menthyloxy-2(5H)-furanone, optically pure isoxazoles were obtained in good yields. These chiral heterocycles can be used as precursors for natural product synthesis.

**Nitrone additions**

C-phenyl-N-phenyl nitrone 25, C-phenyl-N-methyl nitrone 26, and a cyclic nitrone 33 were tested in the 1,3-dipolar cycloaddition reaction to 5-(R)-menthyloxy-2(5H)-furanone (1a). Nitrones 25 and 26 were prepared using literature procedures.20 The reaction between 1a and nitrones 25 and 26 were performed in toluene at reflux with reaction times of 12 hours (scheme 8). The cycloadditions afforded in each case two of the eight possible isoxazolidines 27a and 27b, or 28a and 28b, respectively, in excellent yields.

![Scheme 8](image)

The NMR chemical shifts and coupling patterns of the protons at the bridgehead (H₆, H₃a) support the regiochemistry as indicated for all four compounds. In particular the upfield H₆ proton relative to the downfield H₃a excludes the alternative isoxazolidine structure. The appearance of either a singlet or a doublet with a very small coupling constant implies a trans-relationship between H₆ and H₃a. This can be explained by an anti-facial approach of the nitrone with respect to the 5-alkoxy substituent located on the 1,3-dipolarophile. Again only approach from the Si face is observed (figure 4).

The addition of C-phenyl-N-phenyl nitrone (R=Ph) 25 to 5-(R)-menthyloxy-2(5H)-furanone 1a results in a mixture of diastereoisomers 27a and 27b in a 65:35 ratio (isolated yield 27a: 55%; 27b: 25%). These results can be rationalized by an exo approach of the nitrone for the major cycloadduct (i.e. 27a), which has the Z-configuration (transition state 29, Figure 4). The minor adduct (i.e. 27b) is formed by the endo approach of Z-nitrone (32). However these results can also be explained by an endo approach of the nitrone in an E-configuration (31) for the major adduct and the exo approach of this isomer for the minor adduct (30).
Asymmetric 1,3-dipolar cycloadditions

Very surprisingly the C-phenyl-N-methyl nitrone (R=Me) 26 gives a completely different ratio of diastereoisomers. Unfortunately this ratio could not be determined by NMR spectroscopy as the major adduct showed very broad signals in the $^1$H NMR spectrum of the crude reaction mixture. (After separating both isomers by column chromatography the adduct showed a large temperature dependency in the NMR spectra. When the temperature was raised, normal absorptions were observed in both $^1$H and $^{13}$C-NMR spectra.). However, from the isolated yields and $^1$H NMR data of both cycloadducts (i.e. 28a: 27%; 28b: 60%) it could be concluded that the major cycloadduct 28b had the same stereochemistry as the minor adduct of biphenyl nitrene, i.e. 27b. Therefore this product was either formed by an endo approach of the Z-nitrene (32) or by the exo approach of the E-nitrene (30). The minor adduct 28a with nitrene 25 was formed either by an exo approach of the Z-nitrene (29) or an endo approach of the E-nitrene (31).

The endo/exo selectivity of acyclic nitrones in 1,3-dipolar cycloadditions has been a point of discussion over the last decade. Although several dipolarophiles show a definite endo selectivity, also reactions in which the exo transition state is preferred are known. Chmielewski and Panfil concluded that the 1,3-dipolar cycloaddition of biphenyl nitrones to butenolides preferably proceeds in an exo manner. It therefore is reasonable to assume that the major adduct in the 1,3-dipolar cycloaddition of the C-phenyl-N-methyl nitrene (25) and 5-methyloxy-2(5H)-furanone (1a) was formed through the exo-transition state of the nitrene in the Z-configuration (29), whereas the minor adduct was either formed by the exo attack of the E-nitrene (31), or by the endo attack of the Z-nitrene (32).

There is a significant barrier for rotation in nitrones, but it is not sufficient to prohibit E-Z interconversion of C-phenyl-N-methyl nitrene (scheme 9) under the reaction conditions (i.e. boiling toluene). Furthermore, it is well known that the E-nitrene is more reactive than the Z form. So the E=Z interconversion is in competition with the cycloaddition. Assuming that addition of the C-phenyl-N-methyl nitrene (26) also takes place preferentially in the exo manner, this reaction should involve the E isomer of the nitrene (30), which apparently predominates. The minor adduct is either formed by the exo attack of the Z isomer (29) or by the endo attack of the E isomer (31).

![Scheme 9](image-url)
The isomeric isoxazolidines 27a and 27b (as well as 28a and 28b) were separated by column chromatography and obtained in analytically pure form. The endo/exo stereochemistry, mentioned above, is based on extensive NMR investigations. Most relevant are the coupling constants $J_{H3,H3a}$ of the diastereoisomers. For 27a (28a, 120°C) this coupling constant is 9.0 Hz (8.1 Hz), implying a cis-relationship between $H_3$ and $H_{3a}$, whereas 27b (28b, RT) has a $J_{H3,H3a}$ of 2.6 Hz (3.9 Hz) which implies a trans-relationship between $H_3$ and $H_{3a}$.

The 1,3-dipolar cycloaddition between 3-dihydro-2H-pyrrole-1-oxide (33) and 1a was performed in toluene at reflux (scheme 10). Cycloadducts 34a and 34b were obtained in 85% yield and a 7:1 ratio. NMR analysis, as described above, showed that no regioisomers are formed. Again only Si facial attack has occurred. The major diastereoisomer 34a was isolated by column chromatography. The relative configurations of 34a and 34b were established via the magnitude of $J_{H8a,H8b}$. For 34a, $J_{H8a,H8b}$ = 0 Hz indicating a trans relationship between $H_{8a}$ and $H_{8b}$. Cyclic nitrones are incapable of E/Z isomerization, therefore only two of the transition states (Figure 4) are responsible for the products formed in the cycloaddition. The nitrone has the E conformation, therefore the major cycloadduct was formed by an exo approach of the nitrone, whereas the minor adduct was formed by an endo attack of the 1,3-dipole.

Scheme 10

This exo selectivity has also been observed in several other additions of cyclic nitrones to butenolides.24 When the 1,3-dipolar cycloaddition of nitrone 25 to 1a was performed in chloroform at room temperature a ratio of 89:11 for 27a and 27b was found. However, this reaction proceeded very slowly. After 16 days only 33% of the 1,3-dipolarophile was converted. But since the ratio of cycloadducts was the same as for nitrone 33 the E/Z interchange apparently does not take place at room temperature and the products were only formed by the attack of the Z-nitrone.

These optical active heterocycles are attractive chiral multifunctional building blocks. As an example the reductive ring cleavage of isoxazolidine 34a with lithium aluminium hydride is given (scheme 11). This reaction provides aminotriol 35 in 77% yield as a single enantiomer. Isoxazolidines 27a,b, 28a,b, and 34a are starting materials for optically pure amino triols, whereas a range of subsequent reactions are possible with these compounds.

Scheme 11

All nitrone additions to optically pure 5-(R)-menthylxylo-2(5H)-furanone (1a) show the same regio- and stereoselectivities as observed for achiral 5-(R,S)-methoxy-2(5H)-furanone. The extra steric bulk of the menthol moiety does not influence the reactions but in this way optically pure isoxazolidines are formed.
Azomethine ylide additions

If azomethine ylides could be added to 5-(R)-menthyl-2(5H)-furanone 1a, 3,4-cis-bis-functionalized pyrrolidines are accessible (scheme 12).

Scheme 12

A suitable precursor for the 1,3-dipole in this reaction is N-methoxymethyl-N-(trimethylsilyl)benzylamine 36, which was synthesized according to a literature procedure. The reaction proceeds with lithium fluoride under ultrasonic conditions. These conditions are necessary due to the presence of a heterogeneous system, since lithium fluoride is hardly soluble in acetonitrile. Within 30 minutes 1a is converted to diastereomerically pure 37 in 81% yield. The trans-configuration of 37 was established by $^1$H NMR. The coupling constant $J_{6,5a} = 0$ Hz, which is in agreement with a trans-configuration between H$_6$ and H$_{5a}$, according to the Karplus relationship. The lithium cation is essential for the reaction, because when instead of lithium cesium was used no identifiable products were detected.

A cycloaddition of the corresponding N-butoxymethyl-N-(trimethylsilylmethyl) benzylamine to N-phenyl maleimide, which is a more reactive substrate, was reported to yield the cycloadduct in 80%.

A second azomethine ylide 42 was generated in situ from ethyl pyruvate 38 and alanine 39 (scheme 13). After formation of the iminium ion 40 spontaneous decarboxylation takes place yielding the ylide 42. The ylide 42 was subsequently reacted with 5-(R)-menthyl-2(5H)-furanone 1a to give 43 as a diastereomeric mixture in a ratio of 23 : 2. The two isomers appear to be epimeric at C$_6$. The pyrrolidines are formed by an anti-facial approach, as is evident from the coupling constant $J_{H6,H5a}$, which is 2.7 Hz, indicating a trans-relationship. The stereochemistry on C$_3$ has been determined by the value of the coupling constant $J_{H3,H2a}$, which is 8.42 Hz, indicating a cis-relationship. The configuration on C$_6$ could not be determined but by comparison to the N-methylmaleimide adduct, we presume that the endo-ester is formed as the major product.
A third azomethine ylide, N-benzyl-\(\alpha\)-ethoxycarbonyl substituted ylide 45, was generated *in situ* by reaction from N-(benzyl)-ethylglycine 44 and paraformaldehyde. Reaction of 45 with dimethylfumarate, an activated dipolarophile, gave 3,4-di(methoxycarbonyl)-2-ethoxycarbonyl-N-phenylpyrrolidine in 87% yield as a mixture of 2 diastereoisomers on \(C_2\) in a ratio of 2 : 1.\(^{28}\) Reaction of 45 with racemic 5-methoxy-2(5H)-furanone 2 yielded N-phenyl-1-oxa-2-oxo-3-methoxycarbonyl-4-aza-6-methoxy-[3.3.0]bicyclooctane and N-phenyl-1-oxa-2-oxo-5-methoxycarbonyl-4-aza-6-methoxy-[3.3.0]bicyclooctane in 55% yield as a mixture of 8 isomers.\(^{10}\) Reaction with the less reactive 5-(R)-menthyl-2(5H)-furanone 1a yielded only 6% of N-phenyl-1-oxa-2-oxo-3-ethoxycarbonyl-4-aza-6-(R)-menthyl-2(5H)-furanone 46a and N-phenyl-1-oxa-2-oxo-5-ethoxycarbonyl-4-aza-6-(R)-menthyl-2(5H)-furanone 46b in the ratio 1 : 2 (scheme 13). The coupling constant \(J_{H_6,H_5a}\) for the diastereoisomers was found to be 2.20 and 2.56 Hz, indicating a *trans*-relationship for \(H_5a\) and \(H_6\) in both 46a and 46b. Coupling constants \(J_{H_2a,H_3}\) and \(J_{H_5a,H_5}\) were found to be 13.18 and 9.80 Hz, showing that in both cases cycloaddition has taken place *via endo*-approach of the azomethine ylide 45. On basis of the \(^1\)H NMR analysis it appeared that 46a and 46b are two regioisomers as indicated in scheme 14.

![Scheme 14](image-url)

**AM1 calculations**

In order to rationalize the contrary modes of addition of the ylides to the 5-(R)-menthyl-2(5H)-furanone 1a, we have performed AM1 calculations.\(^{29}\) This allows us to perform a FMO analysis on the AM1 calculated frontier orbitals to determine the HOMO-LUMO control of the 1,3 dipolar reactions. All HOMO-LUMO orbital energies were obtained from AM1 optimized geometries. From the according eigenvectors, atomic contributions to the molecular orbitals of interest were substracted to predict the preferred regiochemistry, based on the assumption that atoms with the larger HOMO contribution are expected to react with atoms with the larger LUMO coefficient in the 1,3 dipolar reactions. Calculational results are summarized in tables 4 and 5.

From the analysis of the HOMO-LUMO energies (table 5) of both the furanone and the 1,3-dipolarophiles, it can be seen that the smallest HOMO-LUMO gap exists for the LUMO of the furanone and the HOMO of the 1,3-dipole. Furthermore, the observed regioselectivity can be explained by the magnitude of the atomic components in the frontier orbitals of interest. In all cases, the atom with the calculated larger HOMO coefficient on the 1,3-dipole reacts with the atom with the larger LUMO coefficient on the furanone.

In the case of diazomethane derivatives the 1,3-dipole carbon is expected to react with the \(\beta\)-enone carbon atom. For the nitrile oxides\(^{30}\) this atom is expected to react with the 1,3-dipole oxygen. Furthermore, in the case of ethoxy carbonyl azomethine ylide the \(\alpha\)-ester carbon atom is supposed to react with the \(\beta\)-enone carbon atom of the dipolarophile. This means that the AM1 calculations are in perfect agreement with the experimentally obtained results, except for the nitrones. In this case AM1 does not
show any preference in regioselectivity based on the atomic frontier orbital contributions of these 1,3-dipoles. The factors governing the regioselectivity of the nitrone additions are under current investigation. However, in most cases AM1 calculations provide a useful tool for the prediction of the preferred regioselectivity in these type of reactions (when kinetically controlled).

Table 4: AM1 calculated FMO energies and atomic contributions.

<table>
<thead>
<tr>
<th>compound</th>
<th>ΔE HOMO (eV)</th>
<th>ΔE LUMO (eV)</th>
<th>HOMO x</th>
<th>HOMO y</th>
<th>LUMO x</th>
<th>LUMO y</th>
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<td>0.233</td>
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<td>H\textsubscript{2}C=N=N</td>
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<td>1.074</td>
<td>0.761</td>
<td>-0.629</td>
<td>0.560</td>
<td>0.518</td>
</tr>
<tr>
<td>EtO\textsubscript{2}C</td>
<td>-9.495</td>
<td>-0.120</td>
<td>-0.764</td>
<td>0.555</td>
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<td>-0.539</td>
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<td>Ph\textsuperscript{N}=\textsuperscript{O}</td>
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<td>0.746</td>
<td>-0.592</td>
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</tr>
<tr>
<td>iPr\textsuperscript{N}=\textsuperscript{O}</td>
<td>-10.074</td>
<td>1.097</td>
<td>0.468</td>
<td>-0.573</td>
<td>-0.484</td>
<td>-0.256</td>
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<tr>
<td>Ph\textsuperscript{N}=\textsuperscript{O}</td>
<td>-9.380</td>
<td>-0.503</td>
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<td>-0.491</td>
<td>-0.234</td>
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<td>Ph\textsuperscript{N}=\textsuperscript{O}</td>
<td>-8.907</td>
<td>0.548</td>
<td>-0.662</td>
<td>0.636</td>
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<tr>
<td>Ph\textsuperscript{N}=\textsuperscript{O}</td>
<td>-8.403</td>
<td>-0.728</td>
<td>0.482</td>
<td>-0.502</td>
<td>-0.360</td>
<td>-0.266</td>
</tr>
<tr>
<td>Ph\textsuperscript{N}=\textsuperscript{O}</td>
<td>-8.452</td>
<td>-0.302</td>
<td>0.479</td>
<td>-0.514</td>
<td>0.390</td>
<td>0.345</td>
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Table 5: AM1 calculated HOMO-LUMO and LUMO-HOMO energy gaps of 1a with the investigated 1,3-dipoles.

Conclusions

It can be concluded that optically active multifunctional (lactone annulated) pyrazolines, isoxazolines, isoxazolidines and pyrrolidines are accessible via 1,3-dipolar cycloadditions to γ-menthyl-γ-butenolide 1a. In several cases high regio- and diastereoselectivities are observed and by using optically pure 5(R)-menthyl-γ-butenolide 1a we are able to synthesize various optically pure heterocycles in modest to high yields.

EXPERIMENTAL SECTION

Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. $^1$H NMR spectra were recorded on a Varian Gemini-200 spectrometer (at 200 MHz) or a Varian VXR-300 spectrometer (at 300 MHz where indicated) using CDCl$_3$ as a solvent. Chemical shifts are denoted in δ units (ppm) relative to tetramethylsilane (TMS) as an internal standard at δ = 0.00 ppm. $^{13}$C NMR spectra were recorded on a Varian Gemini-200 spectrometer (at 50.289 MHz) or a Varian VXR-300 spectrometer (at 76.91 MHz where indicated) using CDCl$_3$ as solvent. The chemical shifts are denoted in δ units (ppm) with the solvent as an internal standard and converted to the TMS scale using δ (CDCl$_3$) = 76.91 ppm. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triplet), q (quartet), se (septet), m (multiplet) and br (broad). Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a 5 mL cell. High Resolution Mass Spectra (HRMS) were obtained on a AEI MS-902 mass spectrometer by Mr A. Kiewiet. Elemental analysis were performed in the
Microanalytical Department of this laboratory by Mr. H. Draayer, Mr. J. Ebels, Mr. J.E. Vos and Mr. J. Hommes. X-ray data collection was performed by Mr. F. van Bolhuis. All commercially available chemicals were obtained from Janssen Chimica or Aldrich and were used without further purification.

2a(S,R)5a(S,R)6(R)-3,4-diaza-6-methoxy-1-oxa-2-oxo-bicyclo[3.3.0]octene (9)

5-(R)-Methoxy-2(5H)-furanone 1a\textsuperscript{12} (1.05 g, 4.41 mmol) in 20 mL ether was cooled to 0°C, and 1.1 eq. diazomethane, in situ generated, by basic treatment of EXR (N,N'-dinitroso-N,N'-dimethyl terephlamide), was distilled directly as ethereal solution into the reaction mixture. The reaction mixture was stirred at 0°C for 16 h, while shielded from light. Nitrogen was bubbled through for 5 min. to remove the excess of diazomethane. After removal of the solvent under vacuum, 3,4-diaza-6-(R)-menthyloxy-1-oxa-2-oxo-bicyclo[3.3.0]octene 2a(S,R)5a(S,R)6(R)-3,4-diaza-6-menthyloxy-1-oxa-2-oxo-bicyclo[3.3.0]octene (9) was obtained as a mixture of 2 isomers in a ratio 55 : 45. Yield 1.23 g (4.41 mmol; 100%), m.p. 80-85°C; IR (KBr, cm\textsuperscript{-1}), 47.58 (d), 79.25 (d), 101.52 (d), 118.62 (d), 163.69 (d), 171.01 (s); \textsuperscript{1}H NMR (300 Mz, CDCl\textsubscript{3}): 4.7 (d, 1H, CH\textsubscript{3}), 2.1 (m, 2H, CC, (H-7)), 5.7 (s, 1H, OC, (H-5)), 6.2 (d, 1H, CC, (H-3)), 1.2 (m, 1H, CCC, (H-3)); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): 40.24 (t), 83.39 (t), 93.12 (d), 104.24 (d), 166.95 (s); high resolution mass spectra (HRMS) calcd. for C\textsubscript{15}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3}: 252.172, found: 252.173; Anal. calcd. for C\textsubscript{15}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3}: C, 64.43; H, 9.50; N, 9.99, found: C, 64.22; H, 8.68; N, 9.93.

2a(S,R)5a(S,R)6(R)-3,4-diaza-6-(R)-menthyloxy-1-oxa-2-oxo-bicyclo[3.3.0]octene (9) (low temperature reaction)

In order to synthesize 3,4-diaza-6-(R)-menthyloxy-1-oxa-2-oxo-bicyclo[3.3.0]octene 9 at lower temperature the reaction mixture was kept at -10°C for 16 h. The diastereomeric ratio of 9 was 6 : 4. When the reaction was allowed to proceed at -20°C, a second eq. diazomethane was added after 48 h. and the reaction was allowed to proceed for another 48 h. The diastereomeric ratio of 9 was 2 : 1. When the reaction was allowed to proceed at -40°C the diazomethane addition procedure was repeated 4 times. The diastereomeric ratio of 9 was 18 : 7.

Photochemical conversion of 3,4-diaza-6-methoxy-1-oxa-2-oxo-bicyclo[3.3.0]octene (10)

3,4-Diaza-6-methoxy-1-oxa-2-oxo-bicyclo[3.3.0]octene 10 (20 mmol) was dissolved in 20 mL CH\textsubscript{2}Cl\textsubscript{2}, benzene or aceton and the indicated amount of benzophenone was added (see table 2). The mixture was irradiated using a Hanovia 150 W, 180-300 nm, UV-lamp for 2 h. at room temperature. After removal of the solvent the resulting oil was distilled using bulb-to-bulb equipment, giving 3,4-diaza-6-methoxy-1-oxa-2-oxo-2(5H)-furanone 2. \textsuperscript{1}H NMR (60 MHz, CDCl\textsubscript{3}, 11): 0.8 (s, 1H, CCH\textsubscript{3}, (H-3)), 1.2 (m, 1H, CCH\textsubscript{3}, (H-3)), 2.1 (m, 2H, CCH\textsubscript{3}, (H-2a, H-3a)), 3.5 CH\textsubscript{3}O (s, 3H, (H-5)), 5.1 (s, 1H, OCH\textsubscript{3}, (H-4)); \textsuperscript{1}H NMR (60 MHz, CDCl\textsubscript{3}, 12): 2.1 (s, 3H, CH\textsubscript{3}C, (H-7)), 3.5 (s, 3H, CH\textsubscript{3}O, (H-6)), 5.6 (s, 1H, OCH\textsubscript{3}, (H-5)), 5.8 (s, 1H, CCH\textsubscript{3}, (H-3)); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}, 2): 3.5 (s, 3H, CH\textsubscript{3}O, (H-6)), 5.8 (s, 1H, OCH\textsubscript{3}, (H-5)); high resolution mass spectra (HRMS) calcd. for C\textsubscript{13}H\textsubscript{21}O\textsubscript{2}: 252.172, found: 252.173; Anal. calcd. for C\textsubscript{13}H\textsubscript{21}O\textsubscript{2}: C, 64.43; H, 8.63; N, 9.99, found: C, 64.22; H, 8.68; N, 9.93.

4-methyl-5-(R)-menthyl-2(5H)-furanone (14)

2a(S)5a(S)6(R)-3,4-Diaza-6-menthyl-1-oxa-2-oxo-bicyclo[3.3.0]octene 9a (1.8 g, 6.33 mmol) in 30 mL toluene was refluxed for 12 h. After removal of the solvent 1.6 g (6.33 mmol, 100%) diastereomerically pure 4-methyl-5-(R)-menthyl-2(5H)-furanone 14 was obtained as a white solid. m.p. 88.8-90.0°C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): 0.7-1.9 (m, 18H, CCH\textsubscript{3}, (H-mouthol)), 2.0 (s, 3H, CH\textsubscript{3}C, (H-17)), 3.6 (m, 1H, CCH\textsubscript{3}, (H-7)), 5.7 (s, 1H, OCH\textsubscript{3}, (H-5)), 5.8 (s, 1H, CH=C, (H-3)); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): 13.17 (q), 15.49 (q), 20.75 (q), 22.09 (q), 22.94 (t), 25.08 (d), 31.28 (d), 34.05 (t), 40.24 (t), 47.58 (d), 79.25 (d), 101.52 (d), 118.62 (d), 163.69 (d), 171.01 (s); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}): \textsuperscript{19}F = -109.9 (c= 1.0, CHCl\textsubscript{3}); HRMS calcd. for C\textsubscript{13}H\textsubscript{23}O\textsubscript{2}F: 258.165; found: 258.165; Anal. calcd. for C\textsubscript{13}H\textsubscript{23}O\textsubscript{2}F: C, 66.01; H, 9.04; F, 9.01, found: C, 66.00; H, 9.04; F, 9.11.
Photochemical conversion of 3,4-diaza-6-(R)-menthyl-1-oxa-2-oxo-bicyclo[3.3.0]octane (9a)

The irradiation of 3,4-diaza-6-(R)-menthyl-1-oxa-2-oxo-bicyclo[3.3.0]octane 9a was performed using the same procedure as used for 3,4-diaza-6-methyl-1-oxa-2-oxo-bicyclo[3.3.0]octane 10. A mixture consisting of 79% 4-(R)-menthyl-2-oxa-1-oxa[3.1.0]hexane 13 and 21% 4-methyl-5-(R)-menthyl-2-oxo-1-oxa-2(5H)-furanone 14 and benzophenone was obtained. The separation of the three compounds was not undertaken at this stage. 

1H NMR (13, 60 MHz, CDCl3): δ = 0.8-1.8 (m, 2H, (H-menthol)), 1.95-2.22 (m, 2H, (H-menthol)), 3.36 (dt, J = 10.5 Hz, 1H, OCHO, (H-3)), 3.5 (t, J = 9.0 Hz, 1H, OCHCC, (H-3)), 6.46-7.20 (m, 5H, (Ar)), 7.9 (br, 1H, N); 13C NMR: δ = 15.60 (q), 20.83 (q), 22.17 (q), 23.03 (t), 25.49 (d), 31.35 (d), 34.13 (t), 39.54 (t), 47.53 (d), 53.91 (d), 78.08 (d), 87.61 (d), 103.36 (d), 129.12 (d), 129.20 (d), 137.07 (s), 151.88 (s), 169.64 (s); [α]D20 = -208.1 (CHCl3, c = 1.00); HRMS calcd. for C21H22NO4Cl: 391.155, found: 391.155; Anal. calcd. for C21H22NO4: C, 64.20; H, 6.69; N, 3.57; Cl, 9.05; found: C, 64.20; H, 6.69; N, 3.57; Cl, 9.05.
3a(S)6(R)6a(R)-3-(4-methoxyphenyl)-6-methylxyloxy-3a,4,6,6a-tetrahydro-furo[3,4-d]isoxazol-4-one (23a)

Following the general procedure as given for 21. 5(R)-5-methylxyloxy-2(5H)-furanone 1a (0.50 g, 2.10 mmol) and p-methoxybenzaldehyde chloroxim (0.57 g, 3.10 mmol) afforded 23a, b (ratio 23a:23b = 91:9). After crystallization from MeOH 23a was obtained as white flakes (0.53 g, 1.37 mmol, 67%); m.p. = 168.8-168.9 °C; 1H NMR: δ 0.78-1.71 (m, 16H, CCHC, (H-menthol)); 2.02-2.20 (m, 2H, CCHC, (H-menthol)), 3.64 (dt, J = 10.7 Hz, J = 4.3 Hz, 1H, OCHC, (H-menthol)); 3.86 (s, 3H, OCH3), 4.68 (d, J = 9.0 Hz, 1H, CCHO, (H-6a)), 5.22 (d, J = 9.0 Hz, 1H, CCHO, (H-3a)), 5.83 (s, 1H, OCHO, (H-6)), 6.95 (d, J = 9.0 Hz, 2H, Ar), 7.89 (d, J = 9.0 Hz, 2H); 13C NMR: δ 15.63 (q), 20.85 (q), 22.18 (q), 23.04 (t), 25.48 (d), 31.34 (d), 34.21 (t), 39.57 (t), 47.60 (d), 56.91 (d), 71.42 (d); [α]D20 = -299.0 (CHCl3, c = 1.00); HRMS calcd. for C22H25NO4: 387.205, found: 387.205; Anal. calcd. for C22H25NO4: C, 66.82; H, 7.54; N, 3.61, found: C, 68.03; H, 7.54; N, 3.65.

3a(R)6(S)6a(R)-6-methylxyloxy-3-(1-methylethyl)-3a,4,6,6a-tetrahydro-furo[3,4-d]isoxazol-4-one (24a)

Following the general procedure as given for 21. 5(R)-5-methylxyloxy-2(5H)-furanone 1a (0.80 g, 3.30 mmol) and isobutylaldehyde chloroxim (0.60 g, 4.50 mmol) afforded 24a, b (ratio 24a:24b = 92:8). Purification by column chromatography (SiO2, hexane:ethyl acetate = 9:1) and subsequent bulb to bulb distillation (bath temperature 80°C, 0.01 mm Hg) yielded 24a (0.66 g, 2.05 mmol, 62%) as a viscous oil; 1H NMR: δ 0.78-1.37 (m, 14H, CCHC, (H-menthol)), 1.24 (d, J = 6.8 Hz, 3H, CCH3), 1.26 (d, J = 6.8 Hz, 3H, CCH3), 1.60-1.68 (m, 2H, CCHC, (H-menthol)), 1.95-2.12 (m, 2H, CCHC, (H-menthol)), 2.87 (se, J = 6.8 Hz, 1H, CCHCH3), 3.55 (dt, J = 10.7 Hz, J = 4.3 Hz, 1H, OCHC, (H-menthol)), 4.26 (d, J = 9.0 Hz, 1H, CCHC, (H-3a)), 5.02 (d, J = 9.0 Hz, 1H, OCHC, (H-6a)), 5.68 (s, 1H, OCHC, (H-6)), 11.50 (s, 1H, OCHO, (H-6a)); 13C NMR: δ 15.58 (q), 19.10 (q), 20.43 (q), 20.79 (q), 22.12 (q), 22.97 (t), 25.39 (d), 26.53 (d), 31.32 (d), 34.12 (t), 39.54 (t), 47.51 (d), 55.22 (d), 78.07 (d), 85.94 (d), 104.50 (d), 158.83 (s), 169.97 (s); [α]D20 = -98.34 (CHCl3, c = 1.00); HRMS calcd. for C18H21NO3: 323.210, found: 323.210; Anal. calcd. for C18H21NO3: C, 66.85; N, 4.33; H, 9.04. found: C, 66.88; N, 4.47; H, 9.03.
3(R)3a(S)6(R)6a(R)-3-phenyl-6-menthylxyo-2-methyl-3,3a,6,6a-tetrahydro-4H-furo[3,4-d]isoxazol-4-one 28b
3(S)3a(S)6(R)6a(R)-3-phenyl-6-menthylxyo-2-methyl-3,3a,6,6a-tetrahydro-4H-furo[3,4-d]isoxazol-4-one 28a

5(R)-Menthylxyo-2(5H)-furanone 1a (1.0 g., 4.2 mmol) and C-phenyl-N-methyl nitrone 26 (0.68 g., 5.0 mmol, 1.2 eq.) were stirred at reflux in 50 mL toluene for 12 h. After evaporation of the solvent 28a,b was obtained as a mixture of diastereoisomers.20 Both isomers were separated by column chromatography (SiO2, ethyl acetate/hexane= 9:1). 28b Was obtained as a yellowish wax (0.94 g. 2.52 mmol, 60%); 1H NMR (300 MHz, DMSO-d6, 120 °C); δ 7.5-1.0 (m, 12H, CCHC, (H-menthol)), 1.21-1.28 (m, 1H, CCHC, (H-menthol)), 1.39-1.46 (m, 1H, CCHC, (H-menthol)), 1.60-1.69 (m, 2H, CCHC, (H-menthol)), 2.00-2.22 (m, 2H, CCHC, (H-menthol)), 2.49 (s, 3H, NCH3), 3.65 (dt, J = 10.5 Hz, J = 4.1 Hz, 1H, OCHC, (H-menthol)), 3.77 (dd, J = 6.4 Hz, J = 3.9 Hz, 1H, OCHC, (H-menthol)), 3.94 (d, J = 3.9 Hz, 1H, NCHC, (H-3)), 4.67 (d, J = 6.4 Hz, 1H, OCHC, (H-6a)), 5.70 (s, 1H, OCHO, (H-6)), 7.34-7.40 (m, 5H, Ar); 13C NMR (75.43 MHz, DMSO-d6, 120 °C); δ 15.38 (q), 19.83 (q), 21.16 (q), 22.11 (t), 24.77 (d), 30.19 (d), 33.33 (t), 39.60 (q), 46.70 (d), 55.47 (d), 73.98 (d), 76.97 (d), 81.31 (d), 101.37 (d), 127.46 (d), 127.51 (d), 127.83 (d), 136.39 (s), 174.68 (s); [α]D20 = -139.0 (c = 1.0, CHCl3); 7a (0.42 g. 1.13 mmol, 26.8 %) as white crystals; m.p. = 167.0-167.2 °C; 1H NMR: δ = 0.73-1.12 (m, 16H, CCHC, (H-menthol)), 2.03-2.25 (m, 2H, CCHC, (H-menthol)), 2.63 (s, 3H, NCH3), 3.57 (dt, J = 10.7 Hz, J = 4.3 Hz, 1H, OCHC, (H-menthol)), 3.63 (dd, J = 8.1 Hz, J = 7.7 Hz, 1H, OCHC, (H-3a)), 3.79 (d, J = 8.1 Hz, 1H, NCHC, (H-3)), 4.65 (d, J = 7.7 Hz, 1H, OCHC, (H-6a)), 5.75 (s, 1H, OCHO, (H-6)), 7.26-7.40 (m, 5H, Ar); 13C NMR: δ = 15.82 (q), 20.85 (q), 22.21 (q), 23.04 (t), 25.26 (d), 31.39 (d), 34.24 (t), 39.76 (t), 42.61 (q), 47.63 (d), 54.81 (d), 75.56 (d), 77.71 (d), 81.91 (d), 104.91 (d), 128.02 (d), 128.64 (d), 133.35 (s), 172.51 (s); [α]D20 = -290.0 (% 0.4; CHCl3); HRMS calcd. for C19H15NO2: 373.225, found: 373.225; Anal. calcd. for C19H15NO2: C, 70.73; N, 3.75; H, 8.37, found: C, 70.39; N, 3.75; H, 8.27.

3(R)3a(R)8a(S)8b(S)-3-Methylxyo-1,3,3a,6,7,8,8a,8b-octahydro-furo[3,4-d]-pyrrolo[1,2-b]-isoxazol-1-one (34a)

Following the general procedure as described for 27, 5(R)-5-methylxyo-2(5H)-furanone (1.00 g, 4.20 mmol) and 3,4-dihydro-2H-pyrrole-1-oxide (0.39 g, 4.60 mmol, 1.1 eq.) afforded 34 (ratio 34a:34b = 7:1) as a mixture of diastereoisomers. Column chromatography afforded 34a (1.15 g, 3.57 mmol, 85%) as white crystals; 1H NMR: δ 0.75-2.20 (m, 22H, CCHC, (H-menthol)), 3.04 (dt, J = 13.7 Hz, J = 8.1 Hz, 1H, NCHC), 3.37 (dd, J = 13.7 Hz, J = 7.3 Hz, J = 3.8 Hz, 1H, NCHC), 3.50 (d, 6.8 Hz, 1H, CCHC, (H-8b)), 3.55 (dt, J = 10.5 Hz, J = 4.1 Hz, 1H, OCHC, (H-menthol)), 3.86 (t, J = 7.5 Hz, 1H, NCHC, (H-8a)), 4.53 (d, J = 6.8 Hz, 1H, OCHC, (H-6a)), 5.61 (s, 1H, OCHO, (H-6)); 13C NMR: δ = 15.64 (q), 20.82 (q), 22.18 (q), 23.04 (t), 24.21 (t), 25.45 (d), 30.02 (t), 31.29 (d), 34.21 (t), 39.64 (t), 47.57 (d), 54.46 (d), 56.46 (t), 70.23 (d), 77.40 (d), 81.21 (d), 104.91 (d), 127.23 (d), 128.64 (d), 133.35 (s), 172.51 (s); [α]D20 = -290.0 (% 0.4; CHCl3); HRMS calcd. for C19H15NO2: 373.225, found: 373.225; Anal. calcd. for C19H15NO2: C, 70.73; N, 3.75; H, 8.37, found: C, 70.39; N, 3.75; H, 8.27.

2(R)2′(S)3(R)-3-pyrrolidin-2′-yl-butyte-1,2,4-triolel(35)

To a solution of isoxazolidine 34a (2.00 g. 6.2 mmol) in 200 mL of dry THF was added LiAlH4 (571 mg) very slowly. After stirring for 2 hours 6 mL of water were added. The solids were filtered and extracted with THF (Soxhlet). The combined THF fractions were dried (NaSO4) and evaporated. The remaining oil was crystallized from ethyl acetate/hexane leaving the menthol in solution and obtaining the aminotriol (35) as yellowish crystals (830 mg, 4.7 mmol, 77%); m.p. = 91.3-93.1 °C; 1H NMR: δ = 1.63-1.83 (m, 2H, CCHC), 1.87-2.06 (m, 2H, CCHC), 2.35 (m, 1H, NCHC), 2.67-3.17 (m, 4H, OCH2C), 4.19-4.27 (dd, J = 4.7 Hz, J = 6.4 Hz, 2H, OCHC), 4.0 (br, 4H, NH, OH); 13C NMR: δ = 22.74 (t), 31.42 (t), 54.36 (d), 57.03 (t), 60.68 (t), 61.25 (t), 67.56 (d), 78.86 (d); [α]D20 = -81.6 (% 0.75, CHCl3); HRMS calcd. for C8H15NO3 (M+H2): 173.105, found 173.105.

2a(R)5a(S)6a(R)-4-aza-4-benzil-6-menthylxyo-1-oxa-2-oxo-bicyclo[3.3.0]octane(37)

5-(R)-Menthylxyo-2(5H)-furanone 1a (1.0 g, 4.2 mmol), N-methoxymethyl-N-(trimethylsilyl)benzylamine 36 (1.5 g, 6.3 mmol, 1.5 eq.) and lithium fluoride (0.225 g, 9.8 mmol, 2.3 eq.) were dissolved in 10 mL
acetonitrile and treated for 50 min. with a Branson Sonifier Cell Disruptor B15. The reaction mixture was poured into water and extracted 3 times with ether. The combined organic layers were washed with brine and dried with Na₂SO₄. After removal of the solvent the product was purified by column chromatography (SiO₂; ethyl acetate:hexane 1:9); yield 1.26 g (3.4 mmol; 81%) diastereomERICally pure 4-aza-4-benzyl-6-menthylOxy-1-oxa-2-oxo-bicyclo[3.3.0]octane 37; m.p.= 71.8-72.8 °C. ¹H NMR (300 MHz, CDCl₃): δ= 0.70-2.04 (m, 18H, CH₃, (H-5a)), 4.62-4.85 (m, 2H, (H-2a)), 2.37 (m, 2H, CH₂, (H-3)), 3.13 (m, 1H, CH₂, (H-3a)), 3.21 (m, 1H, CH₂, (H-5a)), 3.44-3.66 (m, 3H, (H-menthol, H-benzyl)), 5.27 (s, 1H, OCHO, (H-6)), 7.24 (m, 5H, Ar); ¹³C NMR (75 MHz, CDCl₃): δ= 15.554 (q), 20.812 (q), 22.154 (q), 23.070 (q), 25.360 (d), 31.250 (d), 34.211 (t), 39.78 (t), 44.039 (d), 45.290 (d), 47.640 (d), 57.071 (t), 57.528 (t), 58.567 (t), 76.818 (d), 105.264 (d), 127.026 (d), 128.216 (d), 138.075 (s), 176.365 (s); HRMS calcd. for C₂₀H₂₆NO₃: 371.246, found: 371.244; [α]²⁰° = 241.3 (c= 1.0; CH₂Cl₂).

2a(R)5(R,S)5a(S)6(R)-4-aza-3,5-dimethyl-3-ethoxycarbonyl-6-(R)-menthylOxy-1-oxa-2-oxo-bicyclo[3.3.0]octane 43

5-(R)-MenthOxy-2(5H)-furanone 1a (0.590 g, 2.5 mmol), alanine 39 (0.440 g, 5.0 mmol, 2.0 eq.) and ethylpyruvate 38 (0.580 g, 5.0 mmol, 2.0 eq.) were dissolved in 25 mL DMF. The reaction mixture was heated at 110 °C for 16 h. After removal of the solvent, the solid was purified by repeated column chromatography using subsequently (SiO₂; ether; SiO₂; ethyl acetate:hexane 4:1:5:1; and SiO₂; ether:hexane 2:1). Yield: 0.346 g (9.1 mmol; 37%) of 4-aza-3,5-dimethyl-3-ethoxycarbonyl-6-menthOxy-7-oxa-8-oxo-bicyclo[3.3.0]octane 43 as a yellow oil (mixture of 2 isomers); ¹H NMR (300 MHz, CDCl₃): δ= 0.70-2.14 (m, 27H, CC, (H-2a)), 2.37 (m, 2H, CC, (H-menthol)), 3.13 (m, 1H, NC, (H-3)), 3.50 (dt, J= 2.6 Hz, 0.64H, (H-6)), 7.21-7.41 (m, 5H, Ar); ¹³C NMR (75 MHz, CDCl₃): δ= 13.94 (q), 15.44 (q), 16.56 (q), 20.70 (q), 22.03 (q), 22.84 (t), 24.56, 25.11 (d,q), 31.04 (d), 34.06 (t), 39.51 (t), 40.68 (s), 47.59 (d), 49.45 (d), 54.04 (d), 57.77 (d), 61.50 (t), 76.88 (d), 172.59, 174.35 (s,s).

2a(R)5(S)5a(S)6(R)-4-aza-4-benzyl-3-ethoxycarbonyl-6-menthylOxy-1-oxa-2-oxo-bicyclo[3.3.0]octane (46a)

2a(R)5(S)5a(S)6(R)-4-aza-4-benzyl-5-ethoxycarbonyl-6-menthylOxy-1-oxa-2-oxo-bicyclo[3.3.0]octane (46b)

Asymmetric 1,3-dipolar cycloadditions
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21. This temperature dependency can be explained by a conformational interchange of the isoxazolidine structures which is occurring on NMR timescale at room temperature. When the temperature is raised to 120 °C only one of the possible conformational isomers predominates.


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