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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. Nitrone addition afforded isoxazolidines **27**, **28** and **34** with complete *anti*-facial- and regiochemistry, but with *endo-exo* selectivities up to 76%. Enantiomerically pure isoxazolidines 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.[2,4] The use of chiral 1,3-dipoles[5] and chiral dipolarophiles has been reported. Diazo compounds[6], nitrile oxides[7], nitrones[8] and azomethine ylides[9] have been added to activated chiral olefins. In several cases high diastereoselectivity was found.

We have demonstrated that γ-alkoxy 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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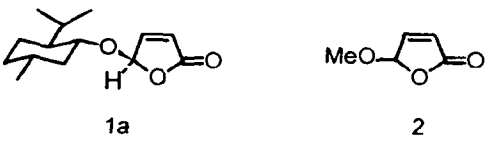
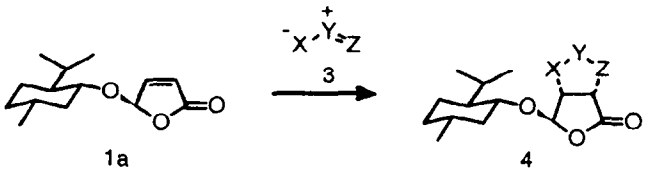
†Member of the EC Human Capital and Mobility Network "Stereoselective Organic Synthesis"



1a 2

Figure 1

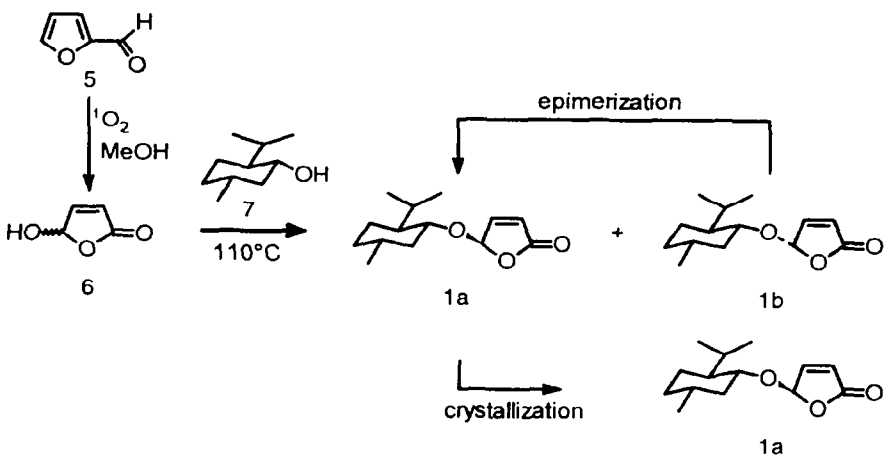


1a 4

Scheme 1

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

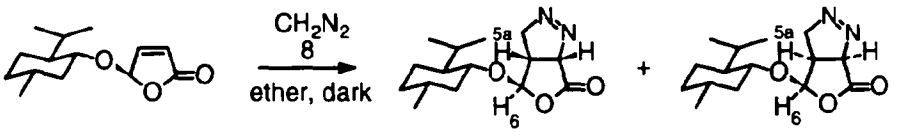
The starting material, 5-menthyloxy-2(5H)-furanone **1**, is readily prepared via methylene blue sensitized photooxidation of furfural[13], followed by acetalization with *l*-menthol (scheme 2). A mixture of diastereomeric 5-menthyloxy-2(5H)-furanones **1a** and **1b** in a 6 : 4 ratio is formed. Enantiomerically pure 5-(R)-menthyloxy-2(5H)-furanone **1a** is obtained *via* a crystallization-epimerization procedure.[9a] The major diastereoisomer **1a** 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 **1b** is driven by the continuous removal of the major crystalline isomer **1a** from the solution. The epimerization rate can be increased thermally or by acid catalysis. This epimerization-crystallization process allows the isolation of pure **1a** up to 80% yield (scheme 2).[14]



Scheme 2

Diazoalkane 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 H_6 and H_{5a} in the *anti*-isomer **9a** is smaller than 1.0 Hz, whereas the coupling constant between H_6 and H_{5a} in the *syn*-isomer **9b** is between 8.5 and 13.5 Hz. The spectrum shows a singlet for $H_{6(trans)}$, whereas $H_{6(cis)}$ has a coupling constant $J_{6,5a}$ of 6 Hz. Both diastereoisomers can be separated *via* crystallization.



1a 9a 9b

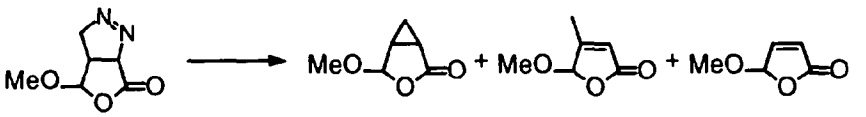
Scheme 3

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

entry	temperature	ratio	9a	9b
1	0 °C		55	45
2	-10 °C		60	40
3	-20 °C		68	32
4	-40 °C		72	28

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 N_2-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 pyrrolopyrazolines, e.g. 66% cyclopropane, 19% methyl compound and 15% cycloreversion.



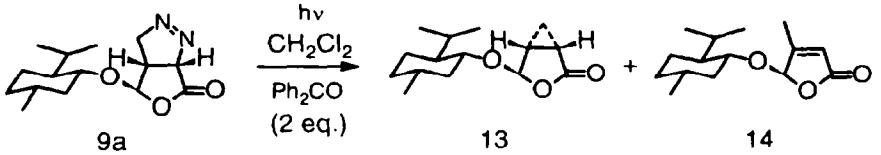
10 11 12 2

Scheme 4

Table 2: Influence of solvent and sensitizer on the photochemical formation of cyclopropane **11**.

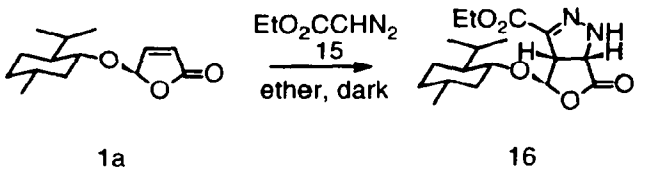
entry	solvent	benzophenone (eq.)	percentage (%) **11**	**12**	**2**
1	CH_2Cl_2	-	50	40	10
2	acetone	-	50	50	0
3	benzene	1	70	30	0
4	CH_2Cl_2	1	70	30	0
5	CH_2Cl_2	2	95	5	0

With this results in mind we subjected enantiomerically pure product **9a** to the same procedure. When **9a** was irradiated in CH_2Cl_2 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

In contrast to the diazomethane addition the addition of ethyl diazoacetate **15** to 5-(R)-menthyloxy-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.



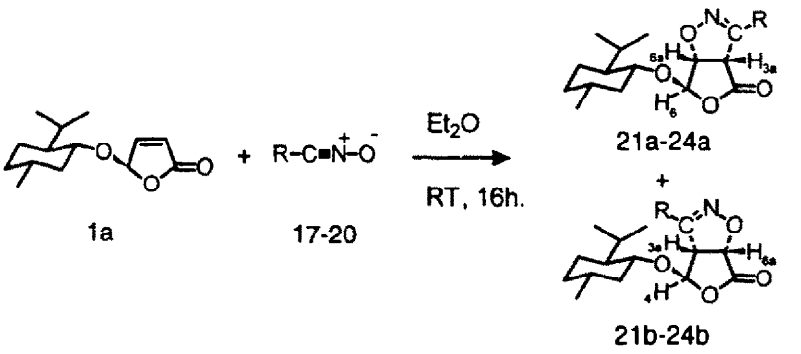
Scheme 6

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.[17] Subsequent chlorination using N-chlorosuccinimide gave the acids in high yield.[18]

The reactions with 5-(R)-menthyloxy-2(5H)-furanone **1a** were performed at room temperature in diethylether as the solvent with reaction times of 16 hours using 1.5 equivalents of nitrile oxide, to ensure that all the 5-(R)-menthyloxy-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 .



Scheme 7

Table 3: Chemical yield of isoxazoles **21a-24a**.

Nitrile oxide	R	Products	ratio a:b	Yield (%)[a]
17	Ph	**21a,b**	n.d.	67
18	p-ClC_6H_4	**22a,b**	90:10	64
19	p-$MeOC_6H_4$	**23a,b**	91:9	67
20	i-Pr	**24a,b**	92:8	65

[a]Chemical yield of isolated pure adducts **21a-24a**
[b]n.d · not determined

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 H_{3a} of **21a-24a** are shifted upfield compared to the absorptions for H_{6a} of **21b-24b** and furthermore the ^1H NMR absorptions of H_6 and H_{6a} of **21a-24a** are shifted downfield compared to the absorptions of H_4 and H_{3a} of **21b-24b** (note the difference in numbering of the different atoms in both regioisomers!). The upfield shift for H_{3a} of **21a-24a** compared to the ^1H NMR absorption for H_{6a} of **21b-24b** can be explained by the fact that for **21a-24a**, H_{3a} is located on the carbon next to the isoxazole imine, whereas H_{6a} 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 H_{6a} of **21a-24a** compared to H_{3a} 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 H_6 of **21a-24a** compared to that of H_4 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 H_{3a} and the *ortho*-aryl hydrogens in **21a-23a**. A similar enhancement for H_{6a} is absent in the NOESY-spectra of **21b-23b**.

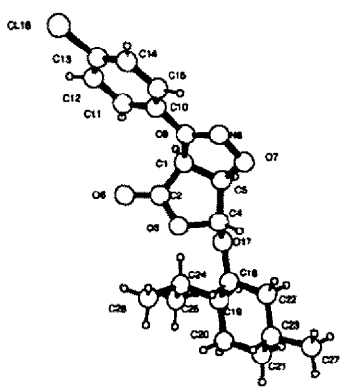


Figure 2: X-ray structure of **22a**

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 H_6 for **21a-24a** (H_4 for **21b-24b**), which implies a *trans* relationship between H_{6a} and H_6 (H_{3a} and H_4, 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 π-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]

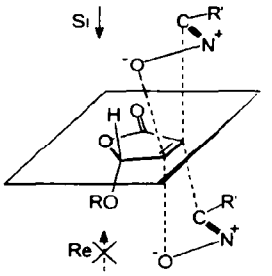
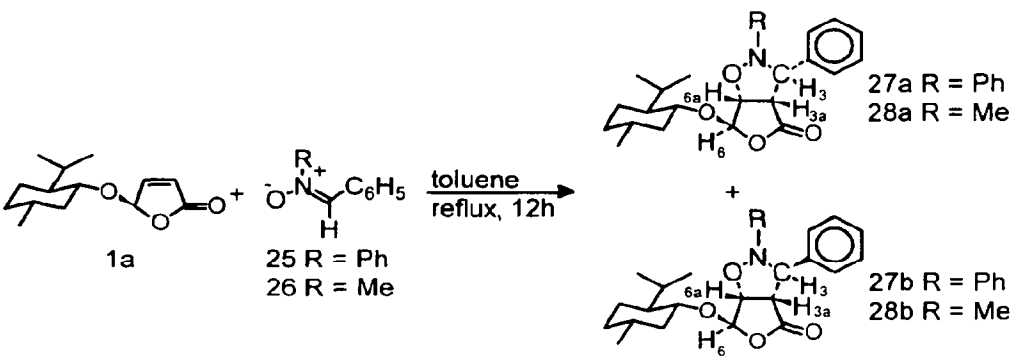


Figure 3

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

The NMR chemical shifts and coupling patterns of the protons at the bridgehead (H_{6a},H_{3a}) support the regiochemistry as indicated for all four compounds. In particular the upfield H_{3a} proton relative to the downfield H_{6a} 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 H_6 and H_{6a}. 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**).

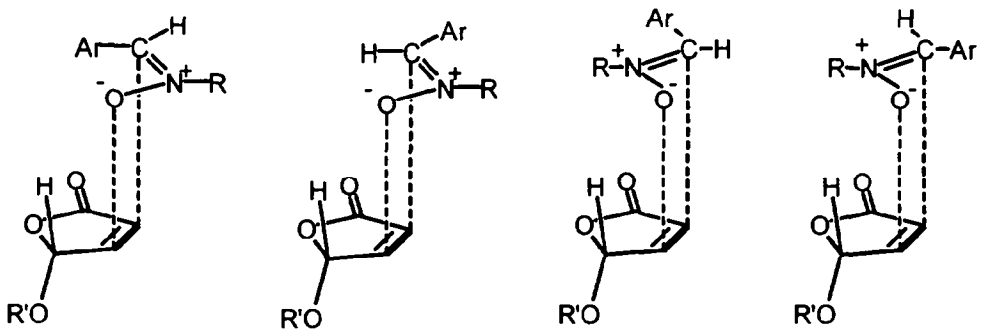


Figure 4

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.).[21] 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 nitrone, *i.e.* **27b**. Therefore this product was either formed by an *endo* approach of the *Z*-nitrone (**32**) or by the *exo* approach of the *E*-nitrone (**30**). The minor adduct **28a** with nitrone **25** was formed either by an *exo* approach of the *Z*-nitrone (**29**) or an *endo* approach of the *E*-nitrone (**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.[18b] Chmielewski and Panfil[18c] 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 nitrone (**25**) and 5-menthyloxy-2(5H)-furanone (**1a**) was formed through the *exo*-transition state of the nitrone in the *Z*-configuration (**29**), whereas the minor adduct was either formed by the *exo* attack of the *E*-nitrone (**31**), or by the *endo* attack of the *Z*-nitrone (**32**).

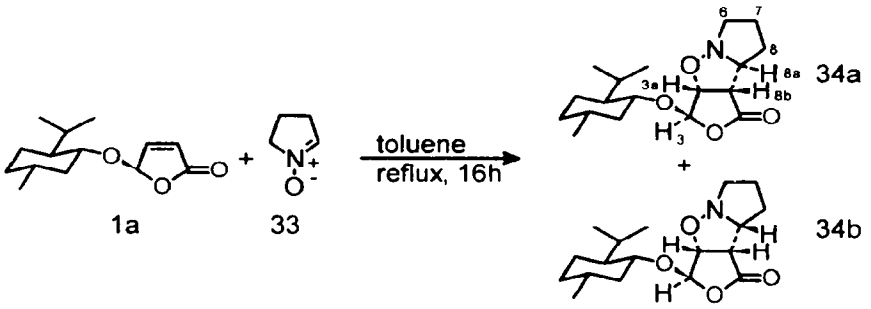
There is a significant barrier for rotation in nitrones, but it is not sufficient to prohibit *E-Z* interconversion of C-phenyl-N-methyl nitrone (scheme 9) under the reaction conditions (*i.e.* boiling toluene).[22]

Scheme 9

Furthermore, it is well known that the *E*-nitrone is more reactive than the *Z* form.[3] So the $E \rightleftarrows Z$ interconversion is in competition with the cycloaddition.[23] Assuming that addition of the C-phenyl-N-methyl nitrone (**26**) also takes place preferentially in the *exo* manner, this reaction should involve the *E* isomer of the nitrone (**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**).

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}.

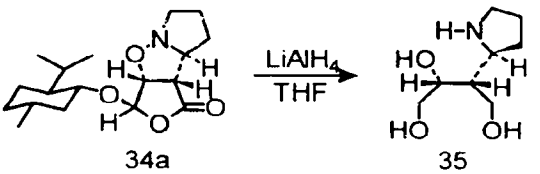
The 1,3-dipolar cycloaddition between 3-dihydro-2H-pyrrole-1-oxide (**33**) and **1a** was performed in toluene at reflux (scheme 10). Cycloadducts **34a** and **34b** were obtained in 85% yield and a 7:1 ratio. NMR analysis, as described above, showed that no regioisomers are formed. Again only *Si* 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.

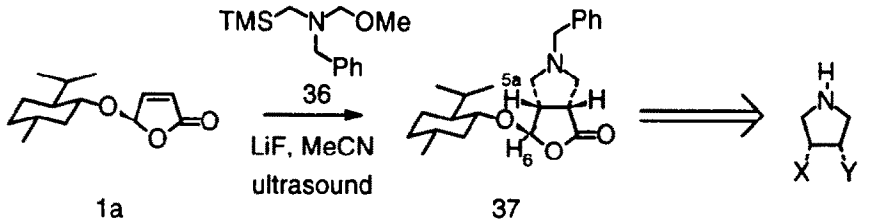


Scheme 11

All nitrone additions to optically pure 5-(R)-menthyloxy-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

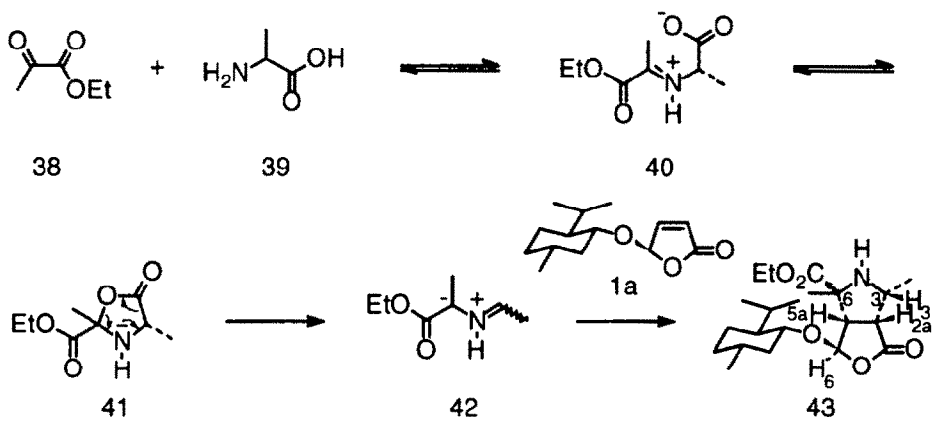
If azomethine ylides could be added to 5-(R)-menthyloxy-2(5H)-furanone **1a**, 3,4-*cis*-bis-functionalized pyrrolidines are accessible (scheme 12).



Scheme 12

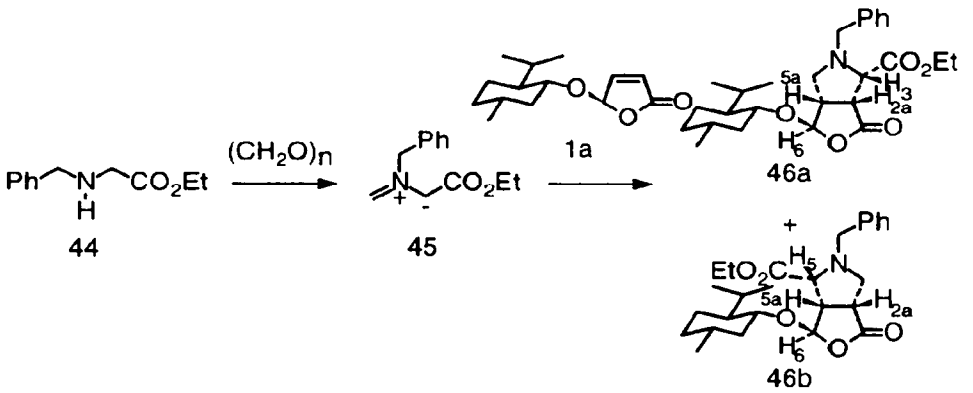
A suitable precursor for the 1,3-dipole in this reaction is N-methoxymethyl-N-(trimethylsilyl)benzylamine **36**, which was synthesized according to a literature procedure.[25] The reaction proceeds with lithium fluoride under ultrasonic conditions. These conditions are necessary due to the presence 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%.[26]

A second azomethine ylide **42** was generated *in situ* from ethyl pyruvate **38** and alanine **39** (scheme 13).[27] After formation of the iminium ion **40** spontaneous decarboxylation takes place yielding the ylide **42**. The ylide **42** was subsequently reacted with 5-(R)-menthyloxy-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,[26] we presume that the *endo*-ester is formed as the major product.



Scheme 13

A third azomethine ylide, N-benzyl-α-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.[10b] Reaction with the less reactive 5-(R)-menthyloxy-2(5H)-furanone **1a**, yielded only 6% of N-phenyl-1-oxa-2-oxo-3-ethoxycarbonyl-4-aza-6-(R)-menthyloxy-[3.3.0]bicyclooctane **46a** and N-phenyl-1-oxa-2-oxo-5-ethoxycarbonyl-4-aza-6-(R)-menthyloxy-[3.3.0]bicyclooctane **46b** in the ratio 1 : 2 (scheme 13). The coupling constant $J_{H6,H5a}$ 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 $J_{H2a,H3}$ and $J_{H5a,H5}$ 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 ^1H NMR analysis it appeared that **46a** and **46b** are two regioisomers as indicated in scheme 14.



Scheme 14

AM1 calculations

In order to rationalize the contrary modes of addition of the ylides to the 5-(R)-menthyloxy-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 β-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 ethoxycarbonyl azomethine ylide the α-ester carbon atom is supposed to react with the β-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.

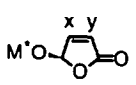
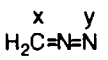
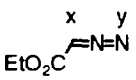
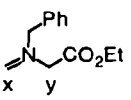
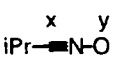
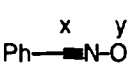
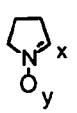
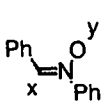
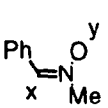
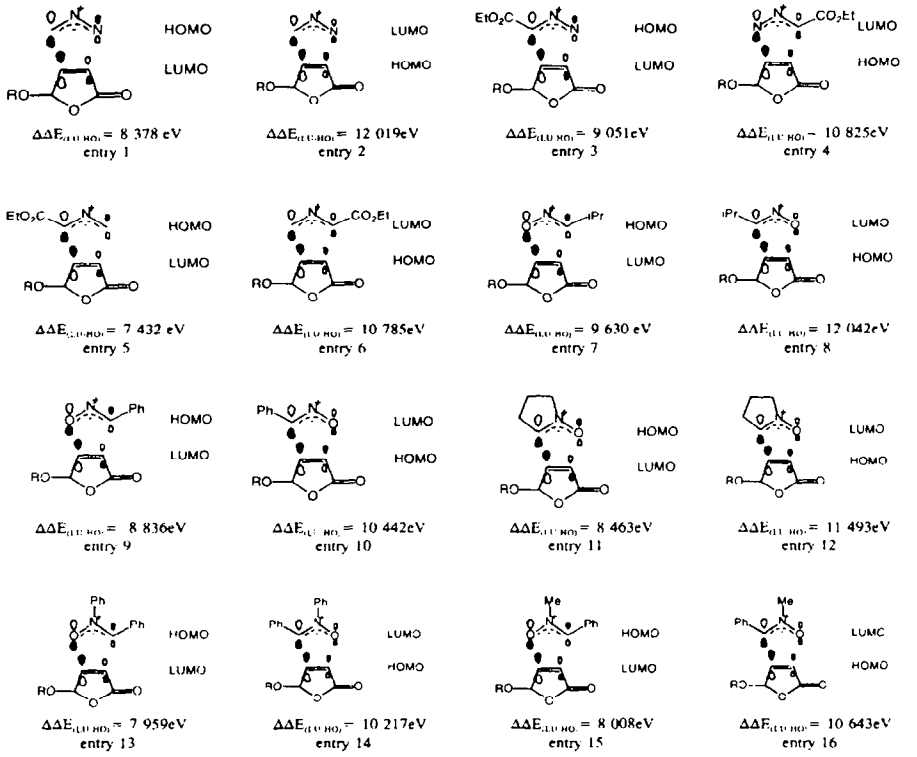
compound	ΔE HOMO (eV)	ΔE LUMO (eV)	HOMO x	HOMO y	LUMO x	LUMO y
	-10.945	-0.444	0.233	0.217	-0.332	0.281
	-8.822	1.074	0.761	-0.629	0.560	0.518
	-9.495	-0.120	-0.764	0.555	-0.351	-0.539
	-7.876	-0.160	-0.579	0.746	-0.592	-0.350
	-10.074	1.097	0.468	-0.573	-0 484	-0.256
	-9.380	-0.503	0.369	-0.491	-0.234	-0.215
	-8.907	0.548	-0.662	0.636	-0.613	-0.403
	-8.403	-0.728	0.482	-0.502	-0.360	-0.266
	-8.452	-0.302	0.479	-0.514	0.390	0.345

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-menthyloxy-butenolide **1a** In several cases high regio- and diastereoselectivities are observed and by using optically pure 5(R)-menthyloxy-2(5H)-furanone **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), ddd (double 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-menthyloxy-1-oxa-2-oxo-bicyclo[3.3.0]octene(9)
5-(R)-Menthyloxy-2(5H)-furanone **1a**[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 terephtalamide), 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 **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^{-1}): 2980 (CH), 1760 (C=O), 1580 (N=N); ^1H NMR (**9a**, 300Mz, $CDCl_3$): δ= 0.7-2.0 (m, 18H, CCHC, (H-menthol)), 2.8 (m, 1H, CCHC, (H-5a)), 3.5 (m, 1H, OCHC, (H-menthol)), 4.7 (m, J= 18.8 Hz, 1H, NCHHC, (H-5)), 4.9 (m, J= 18.8 Hz, 1H, NCHHC, (H-5)), 5.3 (d, J= 5.3 Hz, 1H, OCHCO, (H-6)), 5.7 (d, J= 9.0 Hz, 1H, (H-2a)); ^{13}C NMR (**9a**, 75 MHz, $CDCl_3$): δ= 15.48 (q), 20.75 (q), 22.08 (q), 22.84 (t), 25.28 (d), 31.20 (d), 34.02 (t), 39.19 (d), 39.54 (t), 47.50 (d), 77.64 (d), 83.39 (t), 93.12 (d), 104.24 (d), 166.95 (s); ^1H NMR (**9b**, 300Mz, $CDCl_3$): δ= 0.7-2.0 (m, 18H, CCHC, (H-menthol)), 3.1 (m, 1H, CCHC, (H-5a)), 3.5 (m, 1H, OCHCC, (H-8)), 4.3 (m, J= 18.3 Hz, J= 8.8 Hz, 1H, NCHHC, (H-5)), 5.3 (m, J= 18.3 Hz, 1H, NCHHC, (H-5)), 5.4 (m, J= 9.5 Hz, 1H, NCHHC, (H-2a)), 5.6 (d, J= 6.2 Hz, 1H, OCHOC, (H-6)); $[\alpha]_D^{20}$= -109.9 (c= 1.0, $CHCl_3$); HRMS calcd. for $C_{15}H_{24}O_3$ (M^+-N_2): 252.172, found: 252.173; Anal. calcd. for $C_{15}H_{24}N_2O_3$: C, 64.43; H, 8.63; 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 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_2Cl_2, benzene or acetone 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 4-methoxy-2-oxo-1-oxa[3.1.0]hexane **11**, 4-methyl-5-methoxy-2-oxo-1-oxa-2(5H)-furanone **12** and 5-methoxy-2-oxo-1-oxa-2(5H)-furanone **2**. ^1H NMR (60 MHz, $CDCl_3$, **11**): δ= 0.8 (m, 1H, CCHC, (H-3)), 1.2 (m, 1H, CCHC, (H-3)), 2.1 (m, 2H, CCHCC, (H-2a, H-3a)), 3.5 CH_3O, (s, 3H, (H-5)), 5.1 (s, 1H, OCHOC, (H-4)); ^1H NMR (60 MHz, $CDCl_3$, **12**): δ= 2.1 (s, 3H, CH_3C, (H-7)), 3.5 (s, 3H, CH_3O, (H-6)), 5.6 (s, 1H, OCHOC, (H-5)), 5.8 (s, 1H, CCHCC, (H-3)); ^1H NMR (60 MHz, $CDCl_3$, **2**): δ= 3.5 (s, 3H, CH_3O, (H-6)), 5.8 (s, 1H, OCHOC, (H-5)), 6.2 (d, 1H, CCHCC, (H-3)), 7.2 (d, 1H, CCHCC, (H-2)).

4-methyl-5-(R)-menthyloxy-2(5H)-furanone(14)
2a(S)5a(S)6(R)-3,4-Diaza-6-menthyloxy-1-oxa-2-oxo-bicyclo[3.3.0]octane **9a** (1.8 g, 6.3 mmol) in 30 mL toluene was refluxed for 12 h. After removal of the solvent 1.6 g (6.3 mmol, 100%) diastereomerically pure 4-methyl-5-(R)-menthyloxy-2(5H)-furanone **14** was obtained as a white solid. m.p. 88.8-90.0 °C; ^1H NMR (300 MHz, $CDCl_3$): δ= 0.7-1.9 (m, 18H, CCHC, (H-menthol)), 2.0 (s, 3H, CH_3C, (H-17)), 3.6 (m, 1H, OCHCC, (H-7)), 5.7 (s, 1H, OCHOC, (H-5)), 5.8 (s, 1H, CH=C, (H-3)); ^{13}C NMR (75 MHz, $CDCl_3$); δ= 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); $[\alpha]_D^{20}$= -130 (c= 1.0, $CHCl_3$); IR (KBr, cm^{-1}): 1780 (C=O); HRMS: calcd. for $C_{15}H_{24}O_3$: 252.174, found: 252.173. Anal. calcd. for $C_{15}H_{24}O_3$: C, 71.35; H, 9.58, found: C, 71.23; H, 9.50.

Photochemical conversion of 3,4-diaza-6-(R)-menthyloxy-1-oxa-2-oxo-bicyclo[3.3.0]octane (9a)
The irradiation of 3,4-diaza-6-(R)-menthyloxy-1-oxa-2-oxo-bicyclo[3.3.0]octane **9a** was performed using the same procedure as used for 3,4-diaza-6-methoxy-1-oxa-2-oxo-bicyclo[3.3.0]octane **10**. A mixture consisting of 79% 4-(R)-menthyloxy-2-oxo-1-oxa[3.1.0]hexane **13** and 21% 4-methyl-5-(R)-menthyloxy-2-oxo-1-oxa-2(5H)-furanone **14** and benzophenone was obtained. The separaration of the three compounds was not undertaken at this stage. ^{1}H NMR (**13**, 60 MHz, $CDCl_3$): δ= 0.8-1.8 (m, 20H, CCHC, (H-menthol), CCH_2C, (H-3)), 1.8-2.0 (m, 2H, CCHC, (H-2a), (H-3a)), 3.5 (m, 1H, OCHCC, (H-menthol)), 5.2 (s, 1H, OCHOC, (H-4)); Butenolide**14** was identical in all respects to **14** prepared as described above.

2a(S)5a(S)6(R)-3,4-diaza-5-ethoxycarbonyl-6-menthyloxy-2(5H)-furanone (16).
(R)-5-Menthyloxy-2(5H)-furanone **1a** (1.0 g, 4.2 mmol), ethyldiazoacetate (0.55 g, 4.8 mmol) and 10 mL dioxane were heated at 95-105 °C for 12 h. After removal of the solvent the residue was crystallized from a 3:2 mixture of ether:petroleum ether 40-60, yielding 1.0 g (2.8 mmol, 67%) of 3,4-diaza-4-ene-5-ethoxycarbonyl-6-(R)-menthyloxy-2(5H)-furanone **16**. m.p. 147.1-149.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.8-2.1 (m, 18H, CCHC, (H-menthol), 1.4 (t, J= 6 Hz, 3H, CCH_3, (H-20)), 3.6 (m, 1H, OCHCC, (H-menthol)), 4.0 (d, J= 10 Hz, 1H, CCHC, (H-5a)), 4.4 (q, J= 6 Hz, 2H, OCH_2C, (H-19)), 4.8 (d, J= 10 Hz, 1H, CCHC, (H-2a)), 5.9 (s, 1H, OCHOC, (H-6)), 7.3 (br, 1H, NH, (H-3)), ^{13}C NMR (75 MHz, $CDCl_3$); δ= 14.00 (q), 15.31 (q), 20.62 (q), 21.97 (q), 22.80 (t), 25.24 (d), 31.15 (d), 33.97 (t), 39.66 (t), 47.28 (d), 53.17 (d), 60.75 (d), 61.48 (t), 78.12 (d), 102.19 (d), 138.97 (s, C-5); 161.27 (s), 174.31 (s); IR (KBr, cm^{-1}): 3350 (NH); 2950 (CH); 1790 (C=O); 1750 (C=O); $[\alpha]_D^{20}$= +87.3 (c= 1.0, $CHCl_3$).

3a(S)6(R)6a(R)-3-phenyl-6-menthyloxy-3a,4,6,6a-tetrahydro-furo[3,4d]isoxazol-4-one (21a)
To a stirred solution of 5(R)-5-menthyloxy-2(5H)-furanone **1a** (0.50 g, 2.1 mmol) and benzaldehyde chloroxime (0.5 g, 3.2 mmol, 1.5 eq.) in Et_2O (50 mL) was added very slowly triethylamine (0.65 g, 6.4 mmol, 3 eq.) dissolved in ether (50 mL). After stirring for 16 h at room temperature H_2O (100 mL) was added, the Et_2O layer was separated and the H_2O layer was washed with Et_2O (1 x 50 mL). The combined organic layers were dried ($NaSO_4$) and evaporated to afford a brown oil (**21a,b**). After column chromatography (SiO_2, ether:pentane = 1:9) and crystallization from diethylether, pure **21a** was obtained as a white solid, in 67% yield. m.p.= 127.3-129.6 °C; ^{1}H NMR: δ= 0.8-2.1 (m, 18H, CCHC, (H menthol)), 3.38 (dt, J= 10.5 Hz, J= 4.1 Hz, 1H, OCHCC, (H-menthol)), 4.60 (d, J= 8.0 Hz, 1H, CCHC, (H-3a)), 5.26 (d, J= 8.0 Hz, 1H, CCHO, (H-6a)), 5.73 (s, 1H, OCHO, (H-6)), 7.20 (m, 5H, Ar); ^{13}C NMR: δ= 15.40 (q), 20.63 (q), 21.97 (q), 22.80 (t), 25.25 (d), 31.10 (d), 33.93 (t), 39.30 (t), 47.32 (d), 53.73 (d), 77.74 (d), 81.79 (d), 103.08 (d), 127.74 (d), 128.59 (d), 128.80 (d), 130.75 (s, Ar), 152.55 (s), 169.56 (s); $[\alpha]_D^{20}$ = -218.3 ($CHCl_3$, c= 1.00); HRMS calcd. for $C_{21}H_{27}NO_4$: 357.193, found: 357.194.

3a(S)6(R)6a(R)-3-(4-chlorophenyl)-6-menthyloxy-3a,4,6,6a-tetrahydro-furo[3,4d]isoxazol-4-one (22a)
Following the general procedure as given for **21**, 5(R)-5-menthyloxy-2(5H)-furanone (0.83 g, 3.48 mmol) and p-chloro-benzaldehyde chloroxime (0.99 g, 5.21 mmol) afforded **22a,b** (ratio **22a**:**22b** = 90:10) Crystallization from MeOH yielded **22a** (0.87 g, 2.23 mmol, 64 %) as white needles; m.p.= 167.0-167.6 °C; ^{1}H NMR: δ= 0.78-1.57 (m, 14H, CCHC, (H-menthol)), 1.64-1.73 (m, 2H, CCHC, (H-menthol)), 1.95-2.22 (m, 2H, (H-menthol)), 3.36 (dt, J= 10.5 Hz, J= 4.1 Hz, 1H, OCHC, (H-menthol)), 4.70 (d, J= 9.0 Hz, 1H, CCHC, (H-3a)), 5.27 (d, J= 9.0 Hz, 1H, CCHO, (H-6a)), 5.85 (s, 1H, OCHO, (H-6)), 7.43 (d, J= 8.8 Hz, 2H, Ar), 7.90 (d, J= 8.8 Hz, 2H, Ar); ^{13}C-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), 125.30 (s), 129.12 (d), 129.20 (d), 137.07 (s), 151.88 (s), 169.64 (s); $[\alpha]_D^{20}$ = -208.1 ($CHCl_3$, c= 1.00); HRMS calcd. for $C_{21}H_{26}NO_4Cl$: 391.155, found: 391.155; Anal. calcd for $C_{21}H_{26}NO_4Cl$: C, 64.36; H, 6.69; N, 3.57; Cl, 9.05, found: C, 64.20; H, 6.69; N, 3.59; Cl, 9.05.

3a(S)6(R)6a(R)-3-(4-methoxyphenyl)-6-menthyloxy-3a,4,6,6a-tetrahydro-furo[3,4d]isoxazol-4-one (23a)

Following the general procedure as given for **21**, 5(R)-5-menthyloxy-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; ^{1}H NMR: δ= 0.78-1.71 (m, 16H, CCHC, (H-menthol)), 2.02-2.22 (m, 2H, CCHC, (H-menthol)), 3.64 (dt, J= 10.7 Hz, J= 4.3 Hz, 1H, OCHC, (H-menthol)), 3.86 (s, 3H, OCH_3), 4.68 (d, J= 9.0 Hz, 1H, CCHC, (H-3a)), 5.22 (d, J= 9.0 Hz, 1H, CCHO, (H-6a)), 5.83 (s, 1H, OCHO, (H-6)), 6.95 (d, J= 9.0 Hz, 2H, Ar), 7.89 (d, J = 9.0 Hz, 2H); ^{13}C NMR: δ= 15.63 (q), 20.85 (q), 22.18 (q), 23.04 (t), 25.47 (d), 31.35 (d), 34.16 (d), 39.55 (t), 47.55 (d), 54.24 (d), 55.33 (q), 77.96 (d), 87.11 (d), 103.34 (d), 114.23 (d), 119.22 (s), 129.62 (d), 152,26 (s), 161.65 (s), 169.94 (s); $[\alpha]_D^{20}$= -299.0 ($CHCl_3$, c= 1.00); HRMS calcd. for $C_{22}H_{29}NO_5$: 387.205, found: 387.205; Anal. calcd. for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61, found: C, 68.03; H, 7.54; N; 3.65.

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

Following the general procedure as given for **21**, 5(R)-5-menthyloxy-2(5H)-furanone **1a** (0.80 g, 3.30 mmol) and isobutyraldehyde chloroxime (0.60 g, 4.50 mmol) afforded **24a,b** (ratio **24a**:**24b**= 92:8). Purification by column chromatography (SiO_2, 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; ^{1}H NMR: δ= 0.78-1.37 (m, 14H, CCHC, (H-menthol)), 1.24 (d, J= 6.8 Hz, 3H, CCH_3), 1.26 (d, J= 6.8 Hz, 3H, CCH_3), 1.60-1.68 (m, 2H, CCHC, (H-menthol)), 1.95-2.15 (m, 2H, CCHC, (H-menthol)), 2.87 (se, J= 6.8 Hz, 1H, $CCHCH_3$), 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, (H6)); ^{13}C 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); $[\alpha]_D^{20}$ = -98.34 ($CHCl_3$, c= 1.00); HRMS calcd. for $C_{18}H_{29}NO_4$: 323.210, found: 323.210; Anal. calcd. for $C_{18}H_{29}NO_4$: C, 66.85; N, 4.33; H, 9.04. found: C, 66.88; N, 4.47; H, 9.03.

3(S)3a(S)6(R)6a(R)-3-phenyl-6-menthyloxy-2-phenyl-3,3a,6,6a-tetrahydro-4H-furo[3,4-d]isoxazol-4-one (27a)

3(R)3a(S)6(R)6a(R)-3-phenyl-6-menthyloxy-2-phenyl-3,3a,6,6a-tetrahydro-4H-furo[3,4-d]isoxazol-4-one (27b)

5(R)-5-Menthyloxy-2(5H)-furanone **1a** (1.0 g, 4.0 mmol) and C-phenyl-N-phenyl nitrone **25** (0.91 g, 4.60 mmol) were stirred in 50 mL toluene under reflux for 12 h.. After evaporation of the solvent, **27a,b** was obtained as a mixture of diastereoisomers (ratio **27a**:**27b**= 13:7). Column chromatography (SiO_2, hexane:ether = 9:1) afforded: **27b** (0.45 g, 1.04 mmol, 25%) as white crystals m.p.= 110.5-112.5 °C; ^{1}H NMR: δ= 0.77-1.75 (m, 16H, CCHC, (H-menthol)), 2.07-2.29 (m, 2H, CCHC, (H-menthol)), 3.61 (dt, J= 10.5 Hz, J= 4.1 Hz, 1H, OCHC, (H-menthol)), 3.90 (dd, J= 7.7 Hz, J= 9.0 Hz, 1H, CCHC, (H-3a)), 4.85 (d, J= 9.0 Hz, 1H, NCHC, (H-3)), 4.89 (dd, J= 1.3 Hz, J= 7.7 Hz, 1H, OCHC, (H-6a)), 5.88 (d, J= 1.3 Hz, 1H, OCHO, (H-6)), 7.04-7.48 (m, 10H, Ar); ^{13}C NMR: δ= 15.65 (q), 20.88 (q), 22.28 (q), 23,10 (t), 25.39 (d), 31.39 (d), 34.27 (t), 39.70 (t), 47.67 (d), 55.31 (d), 72.23 (d), 77.65 (d), 82.86 (d), 103.10 (d), 118.18 (d), 124.37 (d), 127.76 (d), 128.59 (d), 128.71 (d), 128.84 (d), 134.93 (s), 148.20 (s), 172.00 (s); $[\alpha]_D^{20}$= -232.4 (c= 0.5; $CHCl_3$); **27a** (1.00 g, 2.30 mmol, 55 %) as white crystals: m.p.= 118.4-119.6 °C; ^{1}H NMR: δ= 0.77-1.75 (m, 16H, CCHC, (H-menthol)), 2.01-2.25 (m, 2H, CCHC, (H-menthol)), 3.65 (dt, J= 10.5 Hz, J= 4.1 Hz, 1H, OCHC, (H-menthol)), 3.71 (dd, J= 6.0 Hz, J= 2.6 Hz, 1H, CCHC, (H-3a)), 4.86 (d, J= 6.0 Hz, 1H, OCHC, 1H, (H-6a)), 5.03 (d, J= 2.6 Hz, 1H, NCHC, (H-3)), 5.85 (s, 1H, OCHO, (H-6)), 6.93-7.52 (m, 10H, Ar); ^{13}C NMR: δ= 15.89 (q), 20.84 (q), 22.24 (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), 77.27 (d), 81.40 (d), 101.24 (d), 116.18 (d), 122.90 (d), 127.00 (d), 128.21 (d), 128.71 (d), 129.00 (d), 138.93 (s), 148.08 (s), 175.40 (s); $[\alpha]_D^{20}$= -62.2 (c= 0.5; $CHCl_3$); HRMS calcd. for $C_{27}H_{33}NO_4$: 435.242, found: 435.241.

3(R)3a(S)6(R)6a(R)-3-phenyl-6-menthyloxy-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-menthyloxy-2-methyl-3,3a,6,6a-tetrahydro-4H-furo[3,4-d]isoxazol-4-one 28a

5(R)-Menthyloxy-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 (SiO_2, 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= 0.75-1.06 (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, NCH_3), 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, CCHC, (H-3a)), 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); ^{13}C NMR (75.43 MHz, DMSO-d6, 120 °C): δ= 15.38 (q), 19.83 (q), 21.16 (q), 22.71 (t), 24.77 (d), 30.19 (d), 33.33 (t), 39.60 (t), 41.04 (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); $[\alpha]_D^{20}$= -139.0 (c= 1.0, $CHCl_3$); 28a (0.42 g, 1.13 mmol, 26.8 %) as white crystals; m.p.= 167.0-167.2 °C; ^1H NMR: δ= 0.73-1.72 (m, 16H, CCHC, (H-menthol)), 2.03-2.25 (m, 2H, CCHC, (H-menthol)), 2.63 (s, 3H, NCH_3), 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, CCHC, (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); ^{13}C-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); $[\alpha]_D^{20}$= -290.0 (c= 0.4; $CHCl_3$); HRMS calcd. for $C_{22}H_{31}NO_4$: 373.225, found: 373.225; Anal calcd. for $C_{22}H_{31}NO_4$: 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-Menthyloxy-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-menthyloxy-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, NCHHC), 3.37 (ddd, J= 13.7 Hz, J=7.3 Hz, J= 3.8 Hz, 1H, NCHHC), 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)); ^{13}C 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), 103.61 (d), 175.65 (s).

2(R)2'(S)3(R)-3-pyrrolidin-2'-yl-butane-1,2,4-triol (35)

To a solution of isoxazolidine **34a** (2.00 g, 6.2 mmol) in 200 mL of dry THF was added $LiAlH_4$ (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 ($NaSO_4$) 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, CCHHC), 1.87-2.06 (m, 2H, CCHHC), 2.55 (m, 1H, CCHCC), 2.96-3.26 (m, 2H, NCH_2C), 3.52 (m, 1H, NCHC), 3.67-3.92 (m, 4H, OCH_2C), 4.19-4.27 (dd, J= 4.7 Hz, J= 6.4 Hz, 2H, OCHC), 4.0 (br, 4H, NH, OH); ^{13}C 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); $[\alpha]_D^{20}$= -81.6 (c= 0.75, $CHCl_3$); HRMS calcd. for $C_8H_{15}NO_3$ (M^+-H_2): 173.105, found 173.105.

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

5-(R)-Menthyloxy-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 Na_2SO_4. After removal of the solvent the product was purified by column chromatography (SiO_2; 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; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.70-2.04 (m, 18H, CCHC, (H-menthol)), 2.37 (m, 2H, CCHC, (H-2a, H-5a)), 2.70 (m, 1H, NCHHC, H-3), 2.90 (m, 1H, NCHHC, (H-3)), 3.13 (m, 1H, NCHHC, (H-5)), 3.21 (m, 1H, NCHHC, (H-5)), 3.44-3.66 (m, 3H, (H-menthol, H-benzyl)), 5.27 (s, 1H, OCHOC, (H-6)), 7.24 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 15.554 (q), 20.812 (q), 22.155 (q), 23.070 (t), 25.360 (d), 31.250 (d), 34.211 (t), 39.755 (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), 128.277 (d), 138.075 (s), 176.365 (s); HRMS calcd. for $C_{22}H_{33}NO_3$: 371.246, found: 371.244; $[\alpha]_{436}^{20}$= 241.3 (c= 1.0; CH_2Cl_2).

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)-Menthyloxy-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 (SiO_2: ether; SiO_2: ethyl acetate:hexane:triethylamine 4:15:1; and SiO_2: ether:hexane 2:1). Yield: 0.346 g (0.91 mmol: 37%) of 4-aza-3,5-dimethyl-3-ethoxycarbonyl-6-menthyloxy-7-oxa-8-oxobicyclo[3.3.0]octane **43** as a yellow oil (mixture of 2 isomers); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.70-2.14 (m, 27H, CCHC, (H-menthol, 3xCH_3), 2.20-2.60 (br, 1H, NH), 2.82 (dd, J= 2.9 Hz, J= 8.4 Hz, 1H, CCHC, (H-5a)), 3.22 (dd, J= 8.4 Hz, J= 8.4 Hz, 1H, CCHC, (H-2a)), 3.45 (dt, J= 10.7 Hz, J= 4.27 Hz, 1H, OCHCC, (H-7)), 3.63 (dq, J= 8.4 Hz, J= 6.7 Hz, 1H, (H-3)), 4.08-4.38 (m, 2H, OCH_2C), 5.17 (d, J= 2.2 Hz, 0.08H, OCHOC, (H-6)), 5.25 (d, J= 2.9 Hz, 0.92H, OCHOC, (H-6)); ^{13}C NMR (75 MHz, $CDCl_3$): 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), 49.51 (d), 54.04 (d), 57.77 (d), 61.50 (t), 76.88 (d), 172.59, 174.35 (s,s).

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

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

5-(R)-Menthyloxy-2(5H)-furanone **1a** (0.595 g, 2.5 mmol), N-benzyl-ethyl glycine **44** (0.965 g, 5.0 mmol, 2.0 eq.) and paraformaldehyde (0.375 g, 12.5 mmol, 5.0 eq.) were refluxed in toluene under Dean-Stark conditions for 16 h.. Subsequently paraformaldehyde (0.450 g, 15 mmol, 6.0 eq.) was added and the mixture was refluxed for another 24 h.. After removal of the solvent the residue was purified using repeated column chromatography (SiO_2: ether; SiO_2: ethyl acetate:hexane:triethylamine 4:15:1; and SiO_2: ether:hexane 1:9). Yield: 62 mg (6%) of 4-aza-4-benzyl-3-ethoxycarbonyl-6-(R)-menthyloxy-7-oxa-8-oxobicyclo[3.3.0]octane **46a** and 4-aza-4-benzyl-5-ethoxycarbonyl-6-(R)-menthyloxy-7-oxa-8-oxobicyclo[3.3.0]octane **46b**. ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 0.74-2.12 (m, 21H, CCHC, (H-menthol, CH_3), 2.41-2.51 (m, 1H, CCHC, (H-2a)), 2.95-3.07 (m, 1H, CCHC, (H-5a)), 3.12-3.44 (m, 4H, NCHC, (H-5, H-3, H-benzyl)), 3.50 (dt, J= 10 Hz, J= 4 Hz, 1H, OCHCC, (H-menthol)), 4.04-4.12 (m, 1H, NCHC, (H-3, H-5)), 4.12-4.36 (m, 2H, OCH_2C), 5.41 (d, J= 2.6 Hz, 0.36H, OCHOC, (H-6)), 5.50 (d, J= 2.2 Hz, 0.64H, (H-6)), 7.21-7.41 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, 2 isomers): δ= 14.01, 14.13 (q); 15.55 (q); 20.75 (q); 22.08 (q); 22.94 (t); 25.24 (d); 31.12, 31.16 (d); 34.12 (t); 39.78 (t); 42.39, 44.33 (d); 47.47, 47.54 (d); 47.60, 48.27 (d); 55.16, 55.42 (d,t); 56.57, 56.68 (t); 61.04, 61.16 (t); 67.33, 67.54 (d,t); 77.14, 77.25 (d); 101.34, 105.25 (d); 127.21-128.82 (d,d,d); 136.58, 136.91 (s); 169.20, 169.66 (s); 174.30, 177.03 (s). MS: m/e= 443 (M^+).

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