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Formation of Cycloadducts with Trans-Configurated Ester Groups from Nitrones and Dimethyl Maleate

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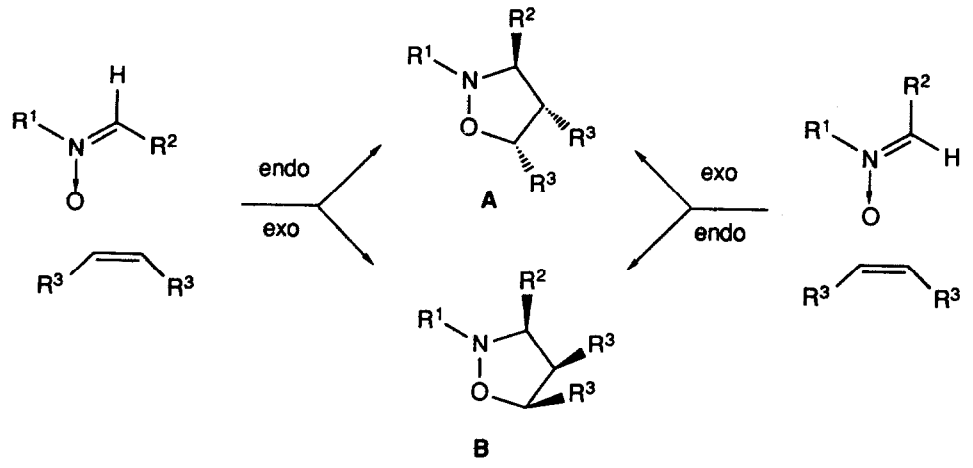
Abstract: In the 1.3-dipolar cycloaddition of the cyclic nitrone **1c** and the acyclic nitrones **8a-h**, **12a, b** with dimethyl maleate in refluxing chloroform not only the expected cycloadducts with cis-configuration of the two ester groups were formed but also such with trans-configuration. This phenomenon is not limited to chloroform, but was also observed in polar solvents as cyclohexane and n-hexane. However, there is no clue for either a non-concerted reaction course or a subsequent conversion of the cis-products to trans-product, in general. Rather, conversion of dimethyl maleate to dimethyl fumarate seems to be responsible for the formation of the trans-substituted cycloadducts. This conversion can be induced by small quantities of N-alkylhydroxylamine formed from slight decomposition of nitrones under the reaction conditions, or by small quantities of nitrone derivatives possessing a NOH moiety such as N-hydroxy enamine tautomers or nitrone dimers.

The 1.3-dipolar cycloaddition of various acyclic aldonitrones with acceptor-substituted alkynes revealed steric effects on the regioselectivity of the reaction.[1] This was attributed to the possibility that the reaction can proceed via transition states which are derived from the Z-configuration as well as from the E-configuration of the nitrones. In principle, similar steric effects are expected for the reaction of acyclic nitrones with alkenes. However, in this case the situation is more complicated, since now different stereoisomers can arise in addition to the different regiosisomers.[2] But the formation of two regioisomers can be circumvented by using disubstituted alkenes with identical substituents as dipolarophiles. By the reaction of such cis-alkenes with acyclic nitrones cycloadducts **A** can be formed either from the Z-nitrones by an endo-attack or from the E-nitrone by an exo-attack. On the other hand, formation of the cycloadduct **B** would result either from an exo-attack to the Z-form or from an endo-attack to the E-form.[3] Thus it would not be distinguishable, whether the cycloadducts arise preferently by exo- or endo-attack and what is the steric influence of substituents R^1 and R^2 on the reaction course.[4]

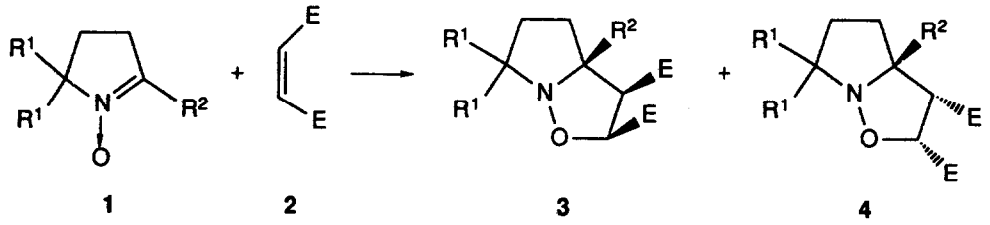
This is not true for cyclic nitrones which are fixed in the E-configuration. To this end we studied at first the reaction of some cyclic nitrones with dimethyl maleate (DMM) as well as with dimethyl fumarate (DMFU).

Surprisingly, we found that in the reaction of one of the cyclic nitrones not only the two expected products were formed, but also two additional adducts which were formally derived from the addition of DMFU. Extending our studies to the reaction of acyclic nitrones with DMM we found again cycloadducts with trans-figuration of the two ester groups among the reaction products. Thus, we were confronted with the question whether the 1.3-dipolar cycloaddition of these nitrones proceeds, at least partially, in a non-concerted way[5] or what else is the reason for the appearance of the wrong trans cycloadducts.



Cycloaddition of Cyclic Nitrones with Dimethyl Maleate (DMM) and Dimethyl Fumarate (DMFU)

The reaction of 1-pyrroline-N-oxide (**1a**) with DMM was already studied by Ali et al.[6] in chloroform at 50°C. They obtained a 83:17 mixture of cycloadducts **3a** and **4a**, which showed characteristic ^{1}H-NMR signals of the proton 3-H at 4.86 and 4.70 ppm, respectively. When we performed the reaction between nitrone **1b** and DMM in refluxing chloroform, compound **3b** resulting from exo-attack of the dipolarophile was the sole product. This was also found by Gandolfi et al.[7] when they studied this reaction in benzene at 20°C.

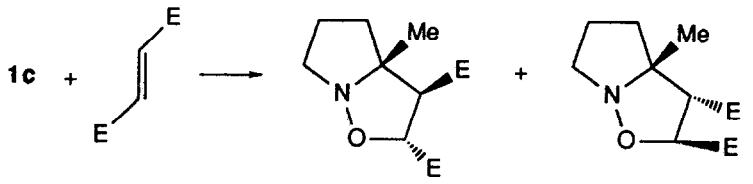


1 **2** **3** **4**

$E = CO_2Me$

	R^1	R^2
a	H	H
b	Me	H
c	H	Me

	R^1	R^2
d	Me	Me
e	Me	iPr



5 **6** **7**

$E = CO_2Me$

Surprisingly, the cycloaddition of nitrone **1c** with DMM afforded four products. Compounds **3c** and **4c** were formed in 38 and 52% yield of the isolated material, respectively, the two other products were shown to be the cycloadducts **6** and **7** (yield 3 and 6%, respectively). The latter were prepared independently by reaction of **1c** with DMFU in the ratio 32:68. After separation from the trans products **6** and **7**, a mixture of compounds **3c** and **4c** did not show any isomerization after further heating in chloroform for one week. Neither compound **4d** nor compound **4e** reacted with DMM under identical conditions.

The structures of compounds **3c** and **4c** were assigned by their 3-H chemical shifts (**3c**: 4.83 ppm, **4c**: 4.69 ppm) in analogy to the compounds **3a** and **4a** (**3a**: 4.86 ppm, **4a**: 4.70 ppm), where in each case the signal of the proton at the endo-side of the bicyclus appears at lower field. Further confirmation comes from the position of the ^{1}H-signal of the methyl group R^2 and of some of the ^{13}C-signals of the diastereomers **3c**, **4c**, **6** and **7** (see table 1). Thus the ^{1}H-signal as well as the ^{13}C-signal of the methyl group is shifted to higher field if the ester group is in cis-position (**3c**, **6**) compared to the compounds with the ester group in trans-position. In the same way the C-6 signal is shifted to higher field by a cis-standing ester group (**4c**, **7**).[8]

Table 1. Characteristic ^{1}H- and ^{13}C-NMR Chemical Shifts in $CDCl_3$ (in ppm)

	^{1}H (CH_3)	^{13}C (CH_3)	^{13}C (6-C)
3c	1.21	21.5	37.8
4c	1.34	24.7	32.4
6	1.20	21.8	35.5
7	1.35	23.6	32.9

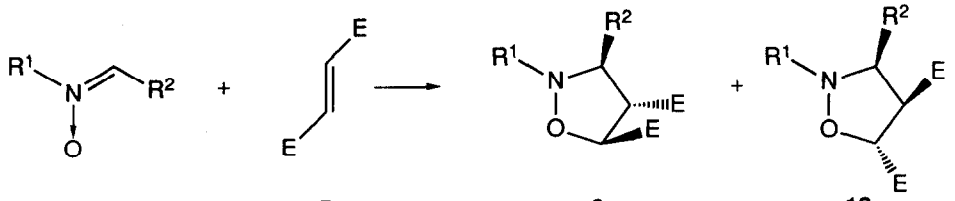
The behaviour of the cyclic nitrones **1** in the cycloaddition with DMM may be rationalized as follows: There are two opposite effects, a steric effect destabilizing the endo-transition state thus favouring the formation of exo-product and a non-steric effect (presumably electrostatic and similar interactions) which tends to favour the endo-approach.[9] In the case of nitrone **1a** the steric effect is decisive, thus the exo-product **3a** is the major product. Introduction of two methyl groups as substituents R^1 (**1b**) reinforces the steric destabilization of the endo-transition state, consequently **3b** is the sole product. Contrary, with a methyl group as substituent R^2 as in **1c** the exo-transition state is destabilized by steric interaction compared to **1a**, the endo-product **4c** being formed in excess relative to **3c**. The increasing steric destabilization in the case of nitrones **1d** and **1e** prevents the cycloaddition completely. In the reaction of **1c** with DMFU the steric hindrance for the formation of compound **7** should be less than for the formation of **6**, because in the former case one of the two ester groups is exo-orientated to the NO-moiety whereas it is endo-orientated in the latter case, while the steric interaction of the second ester group with the methylene moiety is not very different from that with the methyl group. The preferred formation of cycloadduct **7** is in line with this consideration.

However, the main question that arose at this point was why the trans-products **6** and **7**, with respect to the position of the two ester groups, were formed in reaction of **1c** with DMM. Did they arise by a non-concerted 1.3-dipolar cycloaddition caused by the increased steric hindrance of the formation of the new carbon-carbon bond?[5] Or are there some effects that gave rise to an isomerization of DMM to DMFU under the reaction conditions?[10] To this end we studied the reaction of DMM with several acyclic nitrones possessing

alkyl groups at the nitone carbon atom.[11] Reaction with DMFU was also undertaken to get the corresponding cycloadducts for comparison.

Cycloaddition of Acyclic Nitrones with Dimethyl Fumarate (DMFU)

The reaction of nitrones **8** with DMFU in refluxing chloroform afforded mostly isoxazolidines **9** as the sole cycloadducts. Only with nitrones **8d** and **8g** small amounts of the diasteromeric isoxazolidines **10d** and **10g** (20 and 10%, respectively) were formed along with compounds **9d** and **9g**.



8 **5** **9** **10**

E = CO_2Me

	R^1	R^2
a	Me	Et
b	Me	iPr
c	Me	tBu

	R^1	R^2
d	iPr	Et
e	iPr	iPr
f	iPr	tBu

	R^1	R^2
g	tBu	Et
h	tBu	iPr

The structure of **9g** was determined by an X-ray analysis,[12] confirming the all-trans position of the substituents at C-3, C-4 and C-5 (see Figure 1). Both ester groups occupy a quasi-axial position, the torsional angle between the ester groups was found to be 150.4°, whereas the torsional angle of the quasi-equatorial hydrogen atoms 4-H and 5-H is only 92.6°. Both these hydrogen atoms form an angle of approximately 30° with the respective ester group in the vicinal position. The tert-butyl group and the hydrogen atom 3-H are arranged in an almost ecliptic manner (torsional angle = 16.4°).

In solution the angle formed by the hydrogen atoms 4-H and 5-H differs from the angle in the crystalline state, because the ^{1}H-NMR coupling constant J 4/5 was found to be 4.8 Hz.[13] In the diastereomeric compound **10g**, however, J 4/5 increases to 10.3 Hz pointing to a quasi-axial position of these two hydrogen atoms. A similar situation arises for the diastereomers **9d** and **10d**, for which J 4/5 was found to be 5.9 and 8.8 Hz, respectively.

As was already found for cycloadducts **3c/4c** and **6/7**, the ^{13}C-signal of the methylene group of **9g** (R^2 = CH_2-CH_3) appears at lower field (δ = 29.7 ppm) since the ester group is in trans-position compared to **10g** (δ = 25.0 ppm), where it is in cis-position.

In addition, the stereochemistry of **9b**, **9c** and **9h** was confirmed by NOE effects. Irradiation with the frequency of the proton at the tertiary C-atom of the isopropyl group of **9b** and **9h** gave rise to an increase of the signal intensity of 4-H, as well as irradiation with the frequency of the tert-butyl protons of **9c** did. Comparison of the usual NMR data confirms the stereochemistry of the other compounds **9**.

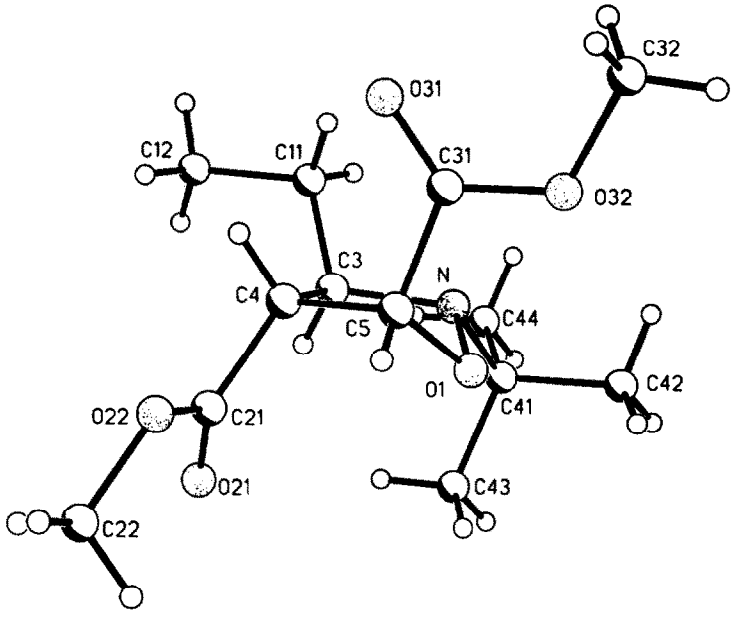
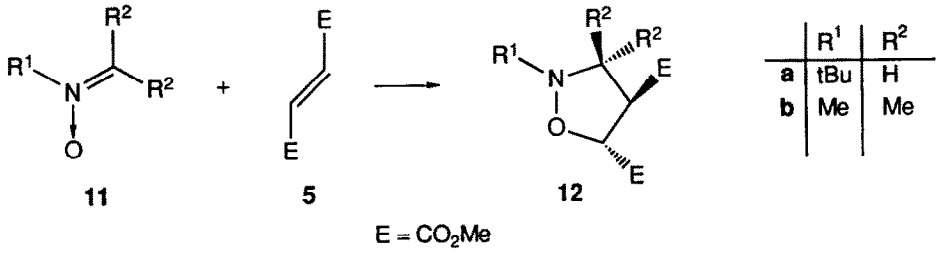


Figure 1. Molecular plot of 3*SR*,4*SR*,5*SR*-4.5-bis(methoxycarbonyl)-2-tert-butyl-3-ethyl-isoxazolidine (**9g**)

As expected reaction of nitrones **11a** and **11b** with DMFU in refluxing chloroform afforded cycloadducts **12a** and **12b**, respectively.



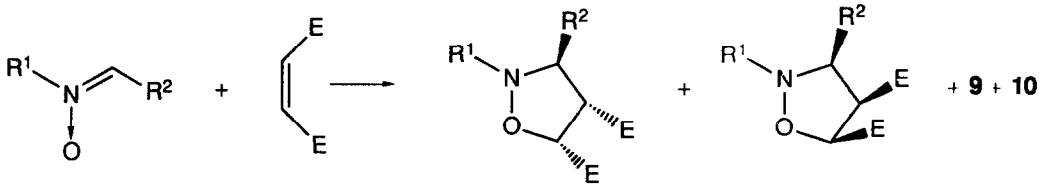
	R^1	R^2
a	tBu	H
b	Me	Me

The ^{1}H-NMR spectra of both cycloadducts reveal, however, a dynamic process of the molecules, indicated by line broadening of most of the signals at room temperature.[14] In the spectrum of **12a** in deuterochloroform at 213 K a doublet at 4.92 ppm (J = 4.4 Hz) was observed for the proton 5-H of the major conformer, along with a second doublet for a minor conformer which corresponds to a portion of less than 5%. At 337 K in 1.2-dideuterotetrachloroethane a single doublet arises at 4.64 ppm (J = 4.7 Hz), indicating that now the exchange between the two conformations is fast with respect to the NMR-time scale.

A similar situation arose for compound **12b**. Two doublets at 4.95 ppm (J = 6.4 Hz) and 5.08 ppm (J = 7.9 Hz) in the intensity ratio of 5:1 were observed for the 5-H proton of the two conformers at 213 K in deuterochloroform. With increasing temperature line broadening occurred gradually until at 307 K only a broad singlet at 4.89 ppm appeared. At 322 K the signal at 4.89 ppm was again split to a doublet (J = 7.0 Hz).

Cycloaddition of Acyclic Nitrones with Dimethyl Maleate (DMM)

Nitrones **8a-8l** were heated under reflux together with an equimolar quantity of DMM in chloroform as well as in cyclohexane or hexane for several hours. The ratio of the cycloadducts formed depends on the structure of the nitrone, but in some cases also on the solvent. The product ratios are summarized in table 2.



8 **2** **13** **14**

E = CO_2Me

	R^1	R^2
a	Me	Et
b	Me	iPr
c	Me	tBu

	R^1	R^2
d	iPr	Et
e	iPr	iPr
f	iPr	tBu

	R^1	R^2
g	tBu	Et
h	tBu	iPr
i	tBu	tBu

	R^1	R^2
k	Ph	Ph
l	tBu	Ph

Table 2. Product Ratios from Reaction of Nitrones **8** with DMM

Nitrone	**(13+14):(9+10)** in $CHCl_3$	**(13+14):(9+10)** in c-C_6H_{12}	**13:14**[a]
8a	85:15	90:10[b]	75:25
8b	85:15	90:10[b]	75:25[b]
8c	90:10	90:10	90:10
8d	85:15	c)	>95:<5
8e	90:10	c)	e)
8f	75:25	c)	e)
8g	<5:>95	80:20[d]	80:20[f]
8h	<5:>95	35:65	e)

a) The ratio **13:14** is independent of the solvent in most cases; b) n-hexane instead of cyclohexane; c) no trans-cycloadducts **9** and **10** could be detected; d) in n-hexane the ratio was 60:40; e) **14** could not be detected, f) in n-hexane the ratio was 70:30

In fact, 4.5-trans cycloadducts **9** and sometimes **10** were formed along with the expected 4.5-cis cycloadducts **13** and **14** with few exceptions. Relatively small quantities of 4.5-trans cycloadducts **9** arose from nitrones **8a-c**, the product ratio in chloroform at one hand and in cyclohexane or hexane on the other hand did not change considerably. No 4.5-trans cycloadducts were formed from nitrones **8d-f** in cyclohexane, whereas in chloroform between 10 and 25% of 4.5-trans cycloadducts could be detected. For the N-tert-butyl substituted nitrones **8g** and **h** the solvent effect was dramatic. In chloroform only less than 5% of 4.5-cis cycloadducts were detected from both nitrones. However, in cyclohexane and n-hexane still 80 and 60%, respectively, of the

expected 4.5-cis cycloadducts **13g/14g** were formed. But the sterically more congested nitrone **8h** afforded the cycloadducts**13h** (cis) and **9h** (trans) in a 35:65 ratio.

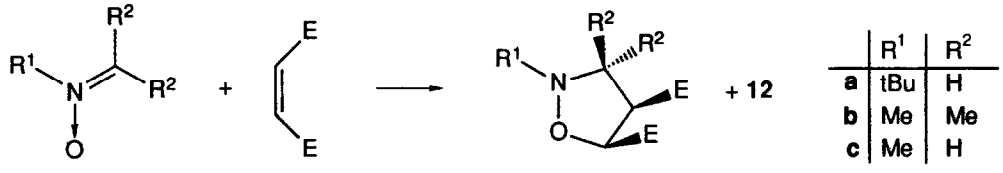
In contrast to these results the C-phenylnitrone **8k** yielded only a 3:1 mixture of the 4.5-cis cycloadducts **13k** and **14k** in refluxing chloroform.[15] Nitrones **8i** and **8l** did not react at all with DMM when the reaction mixture was refluxed in chloroform.

Only the diastereomeric cycloadducts formed from nitrones **8a-c** and **k** could be separated by chromatography. The product ratios in the reaction mixtures of the cycloadducts were determined from the relative intensity of the NMR signals of the proton 5-H. With the NMR data of the corresponding 4.5-trans cycloadducts **9** and **10** at hand these could be easily determined among the 4.5-cis cycloadducts **13** and **14**.

The distinction between **13** and **14** was possible by means of the chemical shift of protons 5-H. In the major compound **13** the signal of this proton appears at higher field compared to that of the minor compound **14**. This assignment was confirmed by NOE effects of **13c** and **13e**. Irradiation of **13c** (R^2 = tBu) with the resonance frequency of the tert-butyl protons caused an intensity increase of the signals of 3-H (3.4%), 4-H (4.8%) and 5-H (1.5%). A similar effect was observed when **13e** was irradiated with the resonance frequency of the central proton of the isopropyl group at C-3, giving rise to an intensity increase of the signals of 3-H (2.7%), 4-H (1.9%) and 5-H (0.5%).

Furthermore, the stereochemical assignment was confirmed by comparison of the ^{13}C-signals of the CH_2 group (R^2 = CH_3-CH_2) of **13a** (24.3 ppm) and **14a** (21.6 ppm), where the absorption at higher field indicates the cis-configuration of the ethyl and the ester group, as was already demonstrated for the diastereomeric pairs **3c/4c**, **6/7** and **9g/10g**.

Nitrone **11a**[16] is more reactive than nitrones **8**. Thus cycloaddition with DMM took place even at room temperature giving almost quantitatively the expected 4.5-cis cycloadduct **15a**. In refluxing chloroform and cyclohexane, however, the 4.5-trans cycloadduct **12a** was also formed, the ratio of **15a**:**12a** was 3:1 and 9:1, respectively. Cycloaddition of **11b**[17] with DMM afforded a mixture of **15b** and **12b** in the ratio of 3.4:1 in refluxing chloroform. Nitrone **11c**[18] which is only stable in solution was refluxed with DMM in methanol giving the 4.5-cis cycloadduct **11c** with at best traces of the corresponding 4.5-trans cycloadducts.



	R^1	R^2
a	tBu	H
b	Me	Me
c	Me	H

11 **2** **15**

E = CO_2Me

As in the case of the isoxazolidines **12a** and **b** two conformers could be observed for the isoxazolidines **15a-c** at lower temperatures by NMR spectroscopy. The spectrum of **15c** showed two doublets of the proton 5-H at 4.76 (8.8 Hz) and 4.96 ppm (9.4 Hz) in the ratio 1:1 at 213 K in deuterochloroform. Between 293 and

322 K they were fused to broad singlets, but in dideuterotetrachloroethane at 374 K a single sharp doublet at 4.65 ppm (8.9 Hz) appeared, indicating a fast interconversion of the two conformers at this temperature.

The rate of interconversion k between the two conformers was determined by full line shape analysis[19] of the signals of the N-CH_3 group in deuterochloroform in the temperature range from -40 to +49°C as given in table 3. From the temperature dependence of the free enthalpy of interconversion $\Delta G^{\neq}$ the following values were determined by means of the Gibbs-Helmholtz equation: $\Delta H^{\neq} = 80.3$ kJ · mol^{-1}, $\Delta S^{\neq} = 55.3$ J · mol^{-1} · K^{-1}.

Table 3. Rate Constants and Free Enthalpies for Conformer Interconversion of Compound **15c**

T(K)	k(s^{-1})	$\Delta G^{\neq}$ (kJ · mol^{-1})	T(K)	k(s^{-1})	$\Delta G^{\neq}$ (kJ · mol^{-1})
243	0.02	67.0	303	66.7	63.7
277	3.33	64.9	307	100	63.5
283	7.14	64.6	309	125	63.4
288	13.3	64.3	313	200	63.0
293	23.3	64.1	322	500	62.4
297	35.7	63.9			

Similar line broadening effects indicating the interconversion of two conformers were found in the ^{1}H NMR spectra of **15b** in deuterochloroform (213 K: doublets at 4.75 (9.4 Hz) and 4.62 ppm (9.6 Hz) ratio 2:1, 277 K: two broad singlets at 4.71 and 4.59 ppm, 307 K: one broad singlet at 4.63 ppm, 322 K: doublet at 4.63 ppm (9.5 Hz) and of **15a** in dideuterotetrachloroethane (252 K: doublets at 4.51 (8.9 Hz) and 4.62 ppm (8.6 Hz) ratio 3:1, 277 K: one broad singlet at 4.54 ppm, 337 K: doublet at 4.58 ppm (8.8 Hz)).

Discussion of the Formation of Cycloadducts with Trans-Orientated Ester Groups from Dimethyl Maleate (DMM)

Three possibilities have to be discussed to rationalize the formation of trans cycloadducts in the reaction of nitrones with DMM:

- The cycloaddition may proceed in a non-concerted course
- The cis cycloadduct formed initially may undergo partial conversion to the trans cycloadduct
- DMM may be converted directly to DMFU under the reaction conditions.

With respect to the first possibility we could not find any indication for a non-concerted process. Usually the cycloaddtion proceeds faster in less polar solvents as n-hexane or cyclohexane than in the more polar chloroform. This is a strong argument against a non-concerted process via a dipolar intermediate.[20] A mechanism with a diradical as intermediate cannot be ruled out absolutely, but the reaction was neither affected by radical initiators nor by radical traps.

With the exception of one special case to be discussed later the cis isoxazolidines were stable under the reaction conditions. Contrary, the formation of the trans isoxazolidines seems to be more easily reversible as was found for **9g** in refluxing chloroform as well as in n-hexane. However, there are some other examples for this trend in the literature.[21]

DMM was not converted to DMFU in refluxing chloroform after four days. On the other hand, heating of nitrone **8g** in chloroform afforded a small quantity of decomposition products after one day as was shown by

the ^{1}H-NMR spectra. After 10 days decomposition was considerable, tert-butylhydroxylamine being among the decomposition products. When the progress of the reaction between nitrone **8g** and DMM in refluxing n-hexane was followed by ^{1}H NMR spectroscopy, a ratio of 4.5-cis- to 4.5-trans isoxazolindes (**13g/14g**:**9/10g**) of 2:1 was observed after two hours at 40% turnover. At this time traces of DMFU were detected together with a small quantity of a compound which was identified as methyl 2-tert-butyl-5-oxo-isoxazolidine-3-carboxylate (**18**) by independent synthesis and comparison of the NMR data. The cis-trans ratio (**13/14g**:**9/10g**) decreased to 1.4:1 within 24 hours, when the reaction was almost quantitative. Further heating of the reaction mixture for up to five days did not change this ratio.

In refluxing chloroform the same reaction was slower. After two hours only about 15% of cycloadducts had been formed, the portion of 4.5-cis isoxazolidines being only in the order of 2%. After 24 hours about 70% of 4.5 trans-products (**9/10g**) had been formed, but the portion of the portion of the 4.5-cis products (**12/13g**) had been only insignificantly increased. At this time the formation of DMFU and compound **18** could be also observed.

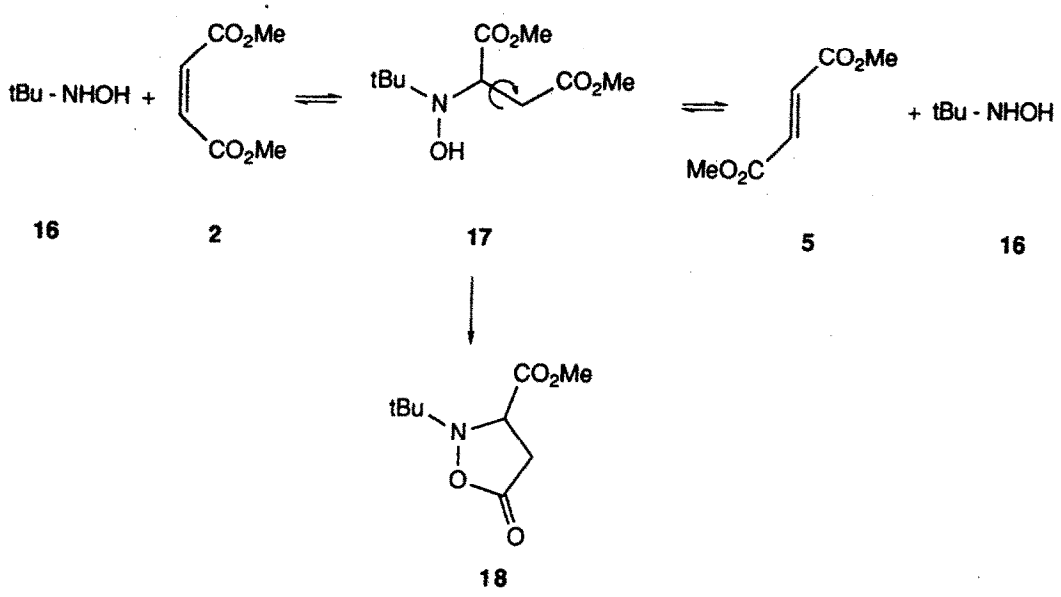
Thus it must be concluded, that under these reaction conditions conversion of DMM to DMFU occurs by means of traces of N-tert-butylhydroxylamine formed by partial decomposition of nitrone **8g**. Since DMFU is more reactive in 1.3-dipolar cycloaddition than DMM,[22] it undergoes cycloaddition with the nitrone as it is formed, so that it cannot accumulate to a larger extent in the reaction mixture. Formation of **18** could be observed also during the reaction between nitrone **8h** and DMM along with some DMFU.

To prove the effect of N-tert-butylhydroxylamine on the reaction course we added a small quantity to the mixture of nitrone **8g** and DMM in n-hexane. After heating the mixture for two hours half of the unreacted DMM had been converted to DMFU. Under these conditions the reaction proceeded much faster, so that after four hours only a small quantity of DMFU and traces of nitrone **8g** could be detected. The ratio of 4.5-cis to 4.5-trans isoxazolidines was found to be 1:5 compared to 1.4:1 without addition of N-tert-butylhydroxylamine. With this finding in mind we made sure that the starting nitrone was free of N-tert-butylhydroxylamine as well as that the solvent chloroform was free of acid and water.

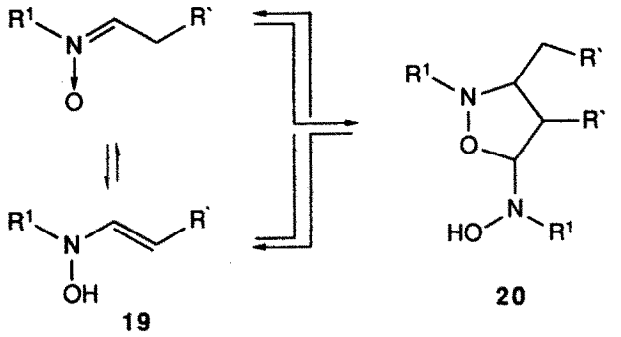
The conversion of DMM to DMFU by N-tert-butylhydroxylamine was proved independently. When the reaction of the hydroxylamine with DMM performed in deuterochloroform at room temperature was followed by ^{1}H-NMR spectroscopy, at first addition product **17** could be detected. Then the signals of DMFU appeared and sometimes later the formation of isoxazolidinone **18** was indicated.

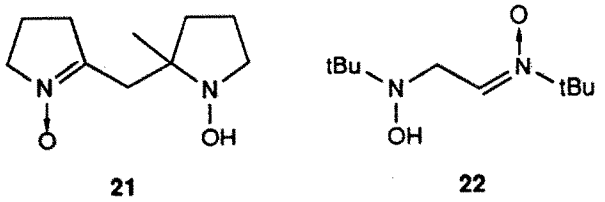
Obviously, compound **17** plays the crucial role in the conversion of DMM to the thermodynamically more stable DMFU. In particular at the temperature of the boiling solvents there may be a large number of conversions **2** $\rightarrow$ **17** $\rightarrow$ **5** by one molecule of N-tert-butylhydroxylamine before it is consumed for the formation of one molecule of **18**.

On the other hand, with other nitrones than **8g** and **8h** we were not able to detect a corresponding isoxazolidinone as by-product of the cycloaddition. Thus a second possibility has to be considered to rationalize the conversion of DMM to DMFU. Similar to the reversible addition of primary N-alkylhydroxylamines as N-tert-butylhydroxylamine to DMM giving intermediates like **17**, secondary N.N-dialkylhydroxylamines can add to the double bond of DMM forming a CO-bonded intermediate which can subsequently eliminate DMFU. Thus, for instance, a 1:1 mixture of DMM and N-hydroxypiperidine in deuterochloroform revealed the conversion of 20% of DMM to DMFU after two days at room temperature.



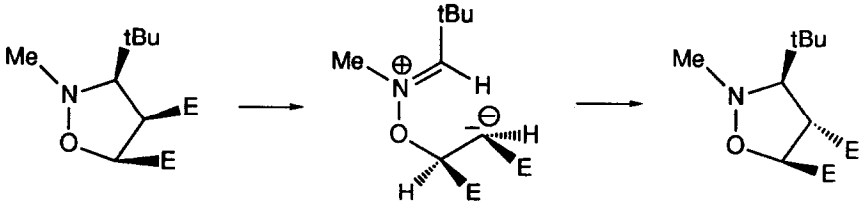
Since most of the nitrones **8** as well as **11b** are able to form tautomeric N-hydroxyenamines **19** and "nitrone dimers" **20**,[23] possessing a N.N-dialkylhydroxylamine moiety the existence of small quantities of these compounds in equilibrium with the parent nitrones also could be the reason for some conversion of DMM to DMFU. The corresponding N-hydroxyenamine and dimer **21** can be formed also from the cyclic nitrone **1c**.[24] Formation of a dimeric form **22** in equilibrium with nitrone **11c** seems possible.





However, this possibility does not exist for nitrones **8c, f, i, k** and **l**. In fact, nitrone **8k** does not give the wrong 4.5-trans isoxazolidine. **8i** and **8l** do not at all react with DMM under the reaction conditions applied by us. Furthermore, we could not observe any conversion of DMM to DMFU with the latter nitrones, the educts being isolated unchanged.

Nitrones **8c** and **f**, however, afforded some 4.5-trans isoxazolidines in reaction with DMM. Studying the reaction of **8c** with DMM in boiling deuterochloroform we found a slight decrease of the quantity of the 4.5-cis isoxazolidine **14c** during the reaction course. Thus we assume that the sterically hindered **14c** undergoes partially a ring opening to a dipolar intermediate **23** which after rotation about the C.C-single bond forms the thermodynamically more stable 4.5-trans isoxazolidine **9c** by ring closure.



14c **23** **9c**

Experimental Part

Elemental analyses were performed by the division Routine-Analytik, Fachbereich Chemie, University of Marburg. Spectra were recorded with following instruments: NMR: ^{1}H-NMR 300 MHz Bruker AC 300 if not quoted otherwise, or Bruker AM 400, Bruker AMX 500; ^{13}C-NMR 75 MHz Bruker AC 300. Solvent $CDCl_3$, internal standard residue of ^{1}H (δ = 7.25 ppm) or ^{13}C of $CDCl_3$ (δ = 77.0 ppm) MS: Varian CH 7 (EI) and 711 (FD). - IR: Beckman IR 33.

The solvents were dried by usual procedures. Chloroform was dried over $CaCl_2$, distilled off and then again dried with active Al_2O_3. In a second procedure chloroform was at first treated with conc. H_2SO_4, subsequently washed with water, then dried over $CaCl_2$, distilled off and finally dried over molecular sieves 4 A. The chloroform treated in these two different ways did not show any differences on the product ratios.

The nitrones were prepared as described in reference 1. See also for references cited there.

General procedure of the 1.3-dipolar cycloaddition. A solution of the nitrone **1**, **8** or **11a** and an equimolar portion of dimethyl maleate or dimethyl fumarate in 20 ml of the solvent (chloroform, cyclohexane or n-hexene) was refluxed for several days. After removal of the solvent under reduced pressure the residue was washed with 4 ml of cold diethyl ether and dried under vacuum (1 Torr). Then the reaction product was purified by column chromatography with a mixture of diethyl ether and petroleum ether as solvent. Separation of diastereomers was only achieved with the isoxazolidines **3c/4c**, **9g/10g**, **13a/14a** and **13b/14b**. The ratio of the diastereomers formed was determined from the ^{1}H NMR spectra by comparison of the integral ratio of the proton signals 3-H for products **3**, **4**, **6**, **7** and 5-H for products **9**, **10**, **12-15**.

(3SR,4RS,5RS)-3.4-Bis(methoxycarbonyl)-8.8-dimethyl-2-oxa-1-azabicyclo[3.3.0]octane (3b): Solvent chloroform, reaction time 2 d, yield 98%, colourless solid, mp 43-45° C from Et_2O/petroleum ether. $C_{12}H_{19}NO_5$ (257.3) Calcd C 56.01 H 7.44 N 5.44 Found C 55.61 H 7.18 N 5.25. - MS(EI): m/e = 257 (24%, M^+) - IR (KBr): 1750 cm^{-1}. - ^{1}H-NMR (400 MHz): 1.07 (s, 3H, CH_3); 1.35 (s, 3H, CH_3); 1.60 (m, 2H, 7-H); 1.85 (m, 1H, 6-H); 2.24 (m, 1H, 6-H); 3.41 (dd, ^{3}J = 4.0, respectively, 7.5 Hz, 1H, 4-H); 3.73 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); 4.24 (dt, t ^{3}J = 4.0, respectively, d 9.3 Hz, 1H, 5-H); 4.77 (d, ^{3}J = 7.5 Hz, 1H, 3-H).

Z-3.4-Bis(methoxycarbonyl)-5-methyl-2-oxa-1-azabicyclo[3.3.0]octane: Product mixture **3c/4c** (ratio 38:53): Solvent chloroform, reaction time 14 d, yield 62% after separation from **6/7** (ratio 3:6), yellow oil. $C_{11}H_{17}NO_5$ (243.3) Calcd C 54.31 H 7.04 N 5.76 Found C 54.21 H 7.04 N 5.70 - MS(EI): m/e = 243 (19%, M^+) - IR (neat): 1750 cm^{-1}. Separation by chromatography, solvent: chloroform/ethyl acetate 3:1 afforded *3SR,4RS,5RS* diastereomer **3c**: ^{1}H-NMR: 1.21 (s, 3H, CH_3); 1.42 - 2.21 (m, 4H, 6-H, 7-H); 3.12 (m, 1H, 8-H); 3.47 (m, 1H, 8-H); 3.68 (d, ^3J = 8.2 Hz, 1H, 4-H); 3.72 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 4.83 (d, ^3J = 8.2 Hz, 1H, 3-H).- *3RS,4RS,5RS*-diastereomer **4c**: ^{1}H-NMR: 1.34 (s, 3H, CH_3); 1.41 - 2.27 (m, 4H, 6-H, 7-H); 3.07 (dt, ^3J = 8.4 respectively, d 14.4 Hz, 1H, 8-H); 3.51 (m, 1H, 8-H); 3.63 (d, ^3J = 8.8 Hz, 1H, 4-H); 3.70 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 4.69 (d, ^3J = 8.8 Hz, 1H, 3-H).

*E-3.4-Bis(methoxycarbonyl)-5-methyl-2-oxa-1-azabicyclo[3.3.0]octane:*Product mixture **6/7** (ratio 32:68): solvent chloroform, reaction time 14 d , yield 42%, brown oil. - $C_{11}H_{17}NO_5$ (243,3) Calcd. C 54.31 H 7.04 N 5.76 Found C 53.98 H 7.08 N 5.77. - MS(EI): m/e = 243 (19%; M^+). - IR(neat): 1750 cm^{-1}. - *3RS,4RS,5RS*-diastereomer **6**: ^{1}H-NMR: 1.20 (s, 3H, CH_3); 1.47 -1.91 (m, 4H, 6-H, 7-H); 3.06 - 3.53 (m, 2H, 8-H); 3.49 (d, ^3J = 8.9 Hz, 1H, 4-H); 3.79 (s, 6H, OCH_3); 5.00 (d, ^3J = 8.9 Hz, 1H, 3-H). - *3SR,4SR,5RS*-diastereomer **7**: ^{1}H-NMR: 1,35 (s, 3H, CH_3); 1.47 - 1.91 (m, 4H, 6-H, 7-H); 3.06 - 3.53 (m, 2H, 8-H); 3.71 (d, ^3J=5.7 Hz, 1H, 4-H); 43.79 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 4.96 (d, ^3J=5.7 Hz, 1H; 3-H).

Table 4. ^{13}C NMR data of 3.4-Bis(methoxycarbonyl)-2-oxa-1-azabicyclo[3.3.0]octanes (chemical shift in ppm, solvent $CDCl_3$)

	R^1	R^2	C-3(d)	C-4(d)	C-5(s)	C-6(t)	C-7(t)	C-8(t)	R^2(q)	C=O (s)	OCH_3(q)
3b	Me	H[a)]	76.9	57.9	66.3(d)	35.6	31.1	68.4(s)	-	170.0, 170.0	52.0, 52.0
3c	H	Me	76.1	60.5	74.8	37.8	23.1	55.4	21.5	169.9, 170.3	51.9, 52.2
4c	H	Me	75.3	59.9	75.2	32.4	24.0	53.7	24.7	168.9, 169.8	51.7, 51.7
6c	H	Me	78.8	59.1	74.7	35.5	21.6	54.9	21.8	165.2, 169.9	52.1, 52.4
7c	H	Me	75.3	60.6	75.7	32.9	16.4	54.0	23.6	170.6, 171.8	52.1, 52.4

a) R^1 = CH_3: δ = 23.5 and 26.4 ppm

(3SR,4SR,5SR)-4.5-Bis(methoxycarbonyl)-3-ethyl-2-methyl-isoxazolidine (9a): Solvent chloroform, reaction time 2d, yield 87%, yellow oil. - $C_{10}H_{17}NO_5$ (231.3) Calcd. C 51.94 H 7.41 N 6.06 Found C 52.35 H 7.40 N 6.15. - MS(EI): m/e = 231 (25%; M^+). - IR(neat): 1740 cm^{-1}. - ^{1}H-NMR: 0.98 (t, ^3J = 7.5 Hz, 3H, CH_3); 1.60 (m, 1H, HCH); 1.70 (m, 1H, HCH); 2.74 (s, 3H, NCH_3); 2.80 (m, 1H, 3-H); 3.56 (dd, ^3J = 4.5 Hz respectively 7.5 Hz, 1H, 4-H); 3.79 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 4.83 (d, ^3J = 4.5 Hz, 1H, 5-H).

(3SR,4SR,5SR)-4.5-Bis(methoxycarbonyl)-3-isopropyl-2-methyl-isoxazolidine (9b): Solvent chloroform, reaction time 2d, yield 83%, yellow oil. - $C_{11}H_{19}NO_5$ (245.3) Calcd. C 53.87 H 7.81 N 5.71 Found C 53.83 H 7.70 N 5.54. - MS(EI): m/e = 245 (12%; M^+). - IR(neat): 1740 cm^{-1}. - ^{1}H-NMR: 0.89 (d, ^3J = 6.8 Hz, 3H, $CH(C\underline{H}_3)_2$); 0.94 (d, ^3J = 6.9 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.79 (oct, ^3J = 6.8 Hz, 1H, $C\underline{H}(CH_3)_2$); 2.71 (s, 3H, NCH_3); 2.82 (dd, ^3J = 6.3, respectively 6.8 Hz, 1H, 3-H); 3.56 (dd, ^3J = 4.8, respectively, 6.3 Hz, 1H, 4-H); 3.73 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); 4.83 (d, ^3J = 4.8 Hz, 1H, 5-H).

(3SR,4SR,5SR)-4.5-Bis(methoxycarbonyl)-3-tert-butyl-2-methyl-isoxazolidine (9c): Solvent chloroform, reaction time 2 d, yield 85%, yellow oil. - $C_{12}H_{21}NO_5$ (259.3) Calcd. C 55.59 H 8.16 N 5.40 Found C 54.85 H 7.89 N 5.50. - MS(EI): m/e = 259 (30%; M^+). - IR(neat): 1750 cm^{-1}. - ^{1}H-NMR: 0.89 (s, 9H, $C(CH_3)_3$); 2.77 (s, 3H, CH_3); 2.91 (d, ^3J = 4.9 Hz, 1H, 3-H); 3.50 (dd, ^3J = 4.9, respectively, 7.6 Hz, 1H, 4-H); 3.75 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 5.04 (d, ^3J = 7.6 Hz, 1H, 5-H).

E-4.5-Bis(methoxycarbonyl)-3-ethyl-2-isopropyl-isoxazolidine: Product mixture **9d/10d** (ratio 80:20): solvent chloroform, reaction time 3d, yield 86%, brown oil. - $C_{12}H_{21}NO_5$ (259.3) Calcd. C 55.59 H 8.16 N 5.40 Found C 55.34 H 8.18 N 5.72. -

MS(EI): m/e = 259 (59%; M^+). - IR(neat): 1740 cm^{-1}. - *3SR,4SR,5SR*-diastereomer **9d**: ^{1}H-NMR: 0.94 (t, ^{3}J = 7.4 Hz, 3H, CH_3); 1.06 (d, ^{3}J = 6.3 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.13 (d, ^{3}J = 6.2 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.47-1.75 (m, 2H, CH_2); 3.01 (hpt, ^{3}J = 6.2 Hz, 1H, $C\underline{H}(CH_3)_2$); 3.39 (m, 2H, 3-H, 4-H); 3.76 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 4.87 (d, ^{3}J = 5.9 Hz, 1H, 5-H). - *3SR,4RS,5RS*-diastereomer (**10d**): ^{1}H-NMR: 4.89 (d, ^{3}J = 8.8 Hz, 1H, 5-H). The other signals could not be identified.

(3SR,4SR,5SR)-4.5-Bis(methoxycarbonyl)-2.3-diisopropyl-isoxazolidine (9e): Solvent chloroform, reaction time 4d, yield 84%, yellow oil. - $C_{13}H_{23}NO_5$ (273.3) Calcd. C 57.12 H 8.48 N 5.12 Found C 57.04 H 8.47 N 5.10. - MS(EI): m/e = 273 (42%; M^+). - IR(neat): 1750 cm^{-1}. - ^{1}H-NMR: 0.95 (d, ^{3}J = 6.8 Hz, 3H, $CH(C\underline{H}_3)_2$); 0.98 (d, ^{3}J = 6.8 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.01 (d, ^{3}J = 6.1 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.14 (d, ^{3}J = 6.1 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.75 (m, 1H, $C\underline{H}(CH_3)_2$); 3.01 (hpt, ^{3}J = 6.1 Hz, 1H, $C\underline{H}(CH_3)_2$); 3.26 (dd, ^{3}J = 3.7 respectively, 7.6 Hz, 1H, 3-H); 3.47 (dd, ^{3}J = 3.7 respectively 7.2 Hz, 1H, 4-H); 3.76 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 4.91 (d, ^{3}J = 7.2 Hz, 1H, 5-H).

(3SR,4SR,5SR)-4.5-Bis(methoxycarbonyl)-3-tert-butyl-2-isopropyl-isoxazolidine (9f): Solvent chloroform, reaction time 6 d, yield 55%, colourless oil. - $C_{14}H_{25}NO_5$ (287.4) Calcd. C 58.52 H 8.77 N 4.87 Found C 58.52 H 8.60 N 4.94. - MS(EI): m/e = 287 (4%; M^+). - IR(neat): 1750 cm^{-1}. - ^{1}H-NMR: 0.94 (s, 9H, $C(CH_3)_3$); 1.02 (d, ^{3}J = 6.0 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.16 (d, ^{3}J = 6.2 Hz, 3H, $CH(C\underline{H}_3)_2$); 3.10 (hpt, ^{3}J = 6.1 Hz, 1H, $C\underline{H}(CH_3)_2$); 3.27 (d, ^{3}J = 3.8 Hz, 1H, 3-H); 3.54 (dd, ^{3}J = 3.8 respectively 8.2 Hz, 1H, 4-H); 3.77 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 4.93 (d, ^{3}J = 8.2 Hz, 1H, 5-H).

E-4.5-Bis(methoxycarbonyl)-2-tert-butyl-3-ethyl-isoxazolidine: Product mixture **9g/10g** (ratio 90:10): solvent chloroform, reaction time 3 d, yield 75%. - $C_{13}H_{23}NO_5$ (273.3) Calcd. C 57.12 H 8.48 N 5.12 Found C 56.74 H 8.31 N 4.96. - MS(EI): m/e = 273 (6%; M^+). - IR(neat): 1740 cm^{-1}. Separation by chromatography, solvent Et_2O/petroleum ether afforded: *3SR,4SR,5SR*-diastereomer **9g**: white solid, mp 48°C, Et_2O/petroleum ether. - ^{1}H-NMR: 0.88 (t, ^{3}J = 7.5 Hz, 3H, CH_3); 1.05 (s, 9H, $C(CH_3)_3$); 1.47 (m, 1H, HCH); 1.57 (m, 1H, HCH); 3.37 (dt, d ^{3}J = 4.6 respectively, t 8.8 Hz, 1H, 3-H); 3.45 (t, ^{3}J = 4.8 Hz, 1H, 4-H); 3.71 (s, 3H, OCH_3); 3.74 (s, 3H, OCH_3); 4.82 (d, ^{3}J = 4.8 Hz, 1H, 5-H). - *3SR,4RS,5RS*-diastereomer **10g**: yellow oil. - ^{1}H-NMR: 0.88 (t, ^{3}J = 7.5 Hz, 3H, CH_3); 1.05 (s, 9H, $C(CH_3)_3$); 1.25-1.65 (m, 2H, CH_2); 3.47 (ddd, 1H, ^{3}J = 3.8, 8.0, respectively 10.0 Hz, 1H, 3-H); 3.63 (dd, ^{3}J = 8.0 respectively, 10.3 Hz, 1H, 4-H); 3.68 (s, 3H, OCH_3); 3.72 (s, 3H, OCH_3); 4.76 (d, ^{3}J = 10.3 Hz, 1 H, 5-H).

3SR,4SR,5SR)-4.5-Bis(methoxycarbonyl)-2-tert-butyl-3-isopropyl-isoxazolidine (9h): Solvent chloroform, reaction time 4 d, yield 71%, colourless oil. - $C_{14}H_{25}NO_5$ (287.4) Calcd. C 58.52 H 8.77 N 4.87 Found C 58.37 H 8.83 N 5.07. - MS(EI): m/e = 287 (2%; M^+). - IR(neat): 1740 cm^{-1}.- ^{1}H-NMR: 0.92 (d, ^{3}J = 4.4 Hz, 3H, $CH(C\underline{H}_3)_2$); 0.95 (d, ^{3}J = 4.3 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.11 (s, 9H, $C(CH_3)_3$); 1.81 (m, 1H, $C\underline{H}(CH_3)_2$); 3.48 (t, ^{3}J = 5.2 Hz, 1H, 3-H); 3.57 (dd, ^{3}J = 5.0 respectively 6.6 Hz, 1H, 4-H); 3.75 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 4.92 (d, ^{3}J = 6.6 Hz, 1H, 5-H).

(4SR,5SR)-4.5-Bis(methoxycarbonyl)-2-tert-butyl-isoxazolidine (12a): Solvent chloroform, reaction time 2 d, yield 87%, colourless oil. - $C_{11}H_{19}NO_5$ (245.3) Calcd. C 53.87 H 7.81 N 5.71 Found C 53.16 H 7.78 N 5.45. - MS(EI): m/e = 245 (41%; M^+). - IR(neat): 1750 cm^{-1}.- ^{1}H-NMR: 1.14 (s, 9H, $C(CH_3)_3$); 2.87 (m, broad, 1H, 3-H); 3.27 (m, broad, 1H, 3-H); 3.77 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 4.78 (d, ^{3}J = 4.6 Hz, 1H, 5-H). The signal of 4-H largely broadened at room temperature and superimposed by the signals at 3.77 and 3.79 cannot be located exactly.

(4SR,5SR)-4.5-Bis(methoxycarbonyl)-2.3.3-trimethyl-isoxazolidine (12b): Solvent chloroform, reaction time 3 d, yield 76%, colourless oil. - $C_{10}H_{17}NO_5$ (231.1) Calcd. C 51.94 H 7.41 N 6.06 Found C 51.02 H 7.31 N 6.23. - MS(EI): m/e = 231 (24%; M^+). - IR(neat): 1750 cm^{-1}.- ^{1}H-NMR: 0.93 (s, broad, 3H, CH_3); 1.25 (s, 3H, CH_3); 2.51 (s, 3H, CH_3); 3.40 (d, broad, ^{3}J appr. 6.9 Hz, 1H, 4-H); 3.71 (s, 3H, OCH_3); 3.72 (s, 3H, OCH_3); 4.80 (s, broad, 1H, 5-H). - ^{13}C-NMR: 14.3 (q, broad, CH_3); 24.0 (q, broad, CH_3); 36.0 (q, broad, CH_3); 52.2 (q, J = 146.1 Hz, 2·OCH_3); 55.0-70.0 (broad, C-4 and C-3); 74.6 (d, broad, C-5); 171.8 (s, 2·$C\underline{O}_2CH_3$).

The following reactions with dimethyl maleate were performed in cyclohexane or n-hexane as well as in chloroform:

Z-4.5-Bis(methoxycarbonyl)-3-ethyl-2-methyl-isoxazolidine: Product mixture **13a/14a** (ratio 75:25): solvent n-hexane, reaction time 3 d, yield 75% after separation from **9a**, yellow oil. - $C_{10}H_{17}NO_5$ (231.3) Calcd. C 51.94 H 7.41 N 6.06 Found C 52.04 H 7.42 N 6.30. - MS(EI): m/e = 231 (21%; M^+). - IR(neat): 1740 cm^{-1}.- Separation by chromatography (Et_2O/petroleum ether) afforded: *3SR,4SR,5RS* diastereomer **13a**: ^{1}H-NMR (500 MHz): 0.96 (t, ^3J = 7.5 Hz, 3H, CH_3); 1.56 (m, 1H, CH_2); 1.65 (m, 1H, CH_2); 2.80 (s, 3H, NCH_3); 2.88 (m, broad, 1H, 3-H); 3.42 (t, ^3J = 8.5 Hz, 1H, 4-H); 3.69 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3); 4.68 (d, ^3J = 9.0 Hz, broad, 1H, 5-H). - *3SR,4RS,5SR*-diastereomer **14a**: ^{1}H-NMR: 1.02 (t, ^3J = 7.4 Hz, 3H, CH_3); 1.41 (m, 1H, CH_2); 1.59 (m, 1H, CH_2); 2.75 (s, 3H, NCH_3); 2.80 (m, broad, 1H, 3-H); 3.71 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 3.93 (dd, ^3J = 7.0 respectively, 8.9 Hz, 1H, 4-H); 4.80 (d, ^3J = 8.9 Hz, 1H, 5-H).

Z-4.5-Bis(methoxycarbonyl)-3-isopropyl-2-methyl-isoxazolidine: Product mixture **13b/14b** (ratio 75:25): solvent n-hexane, reaction time 3 d, yield 74% after separation from **9b**, colourless solid. - $C_{11}H_{19}NO_5$ (245.3) Calcd. C 53.87 H 7.81 N 5.71 Found C 53.90 H 7.84 N 5.69. - MS(FD): m/e = 245 (100%; M^+). - IR(neat): 1740 cm^{-1}.- Separation by chromatography (Et_2O/petroleum ether) afforded: *3SR,4SR,5RS*-diastereomer **13b**: ^{1}H-NMR: 0.96 (d, ^3J = 3.0 Hz, 3H, $CH(C\underline{H}_3)_2$); 0.98 (d, ^3J = 2.9 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.86 (m, 1H, $C\underline{H}(CH_3)_2$); 2.82 (s, 3H, NCH_3); 2.89 (t, ^3J = 7.0 Hz, 1H, 3-H); 3.49 (dd, ^3J = 7.0 respectively 8.2 Hz, 1H, 4-H); 3.70 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 4.62 (d, ^3J = 8.2 Hz, 1H, 5-H). - *3SR,4RS,5SR*-diastereomer **14b**: ^{1}H-NMR: 0.94 (d, ^3J = 5.0 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.04 (d, ^3J = 6.7 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.93 (m, 1H, $C\underline{H}(CH_3)_2$); 2.82 (s, 4H, NCH_3 respectively, 3-H); 3.72 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 3.85 (t, ^3J = 7.3 Hz, 1H, 4-H); 4.89 (d, ^3J = 7.3 Hz, 1H, 5-H).

Z-4.5-Bis(methoxycarbonyl)-3-tert-butyl-2-methyl-isoxazolidine: Product mixture **13c/14c** (ratio 90:10): solvent cyclohexane, reaction time 3 d, yield 72% after separation from **9c**, yellow brown oil. - $C_{12}H_{21}NO_5$ (259.3) Calcd. C 55.59 H 8.16 N 5.40 Found C 55.62 H 7.91 N 5.41. - MS(EI): m/e = 259 (29%; M^+). - IR(neat): 1750 cm^{-1}.- *3SR,4SR,5RS*-diastereomer **13c**: ^{1}H-NMR: 0.93 (s, 9H, $C(CH_3)_3$) 2.88 (s, 3H, CH_3); 2.91 (d, ^3J = 4.0 Hz, 1H, 3-H); 3.49 (dd, ^3J = 4.0 Hz respectively, 7.5 Hz, 1H, 4-H); 3.73 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 4.57 (d, ^3J = 7.5 Hz, 1H, 5-H). - *3SR,4RS,5SR*-diastereomer **14c**: ^{1}H-NMR: 4.88 (d, ^3J = 5.9 Hz, 1H, 5-H). The other signals could not be identified.

Z-4.5-Bis(methoxycarbonyl)-3-ethyl-2-isopropyl-isoxazolidine: Product mixture **13d/14d** (ratio >95:<5): solvent cyclohexane, reaction time 3 d, yield 84%, brown oil. - $C_{12}H_{21}NO_5$ (259.3) Calcd. C 55.59 H 8.16 N 5.40 Found C 55.69 H 7.79 N 5.47. - MS(EI): m/e = 259 (42%; M^+). - IR(neat): 1750 cm^{-1}.- *3SR,4SR,5RS*-diastereomer **13d**: ^{1}H-NMR: 0.96 (t, ^3J = 7.5 Hz, 3H, CH_3); 1.14 (d, ^3J = 6.5 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.19 (d, ^3J = 6.2 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.44 - 1.79 (m, 2H, CH_2); 3.17 (hpt, ^3J = 6.3 Hz, 1H, $C\underline{H}(CH_3)_2$); 3.39 (m, 2H, 3-H, 4-H); 3.69 (s, 3H, OCH_3); 3.74 (s, 3H, OCH_3); 4.66 (d, ^3J = 7.6 Hz, 1H, 5-H). - *3SR,4RS,5SR*-diastereomer **14d**: ^{1}H-NMR: 4.68 (d, ^3J = 9.6 Hz, 1H, 5-H). The other signals could not be identified.

(3SR,4SR,5RS)-4.5-Bis(methoxycarbonyl)-2.3-diisopropyl-isoxazolidine (13e): Solvent cyclohexane, reaction time 4 d, yield 92%, dark yellow oil. - $C_{13}H_{23}NO_5$ (273.3) Calcd. C 57.12 H 8.48 N 5.12 Found C 58.00 H 8.48 N 5.08. - MS(EI): m/e = 273 (71%; M^+). - IR(neat): 1750 cm^{-1}.- ^{1}H-NMR: 0.96 (d, ^3J = 6.9 Hz, 6H, $CH(C\underline{H}_3)_2$); 1.13 (d, ^3J = 6.5 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.21 (d, ^3J = 6.1 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.79 (m, 1H, $C\underline{H}(CH_3)_2$); 3.16 (d, ^3J = 6.3 Hz, 1H, $C\underline{H}(CH_3)_2$); 3.36 (dd, ^3J = 4.3 respectively, 6.3 Hz, 1H, 3-H); 3.50 (dd, ^3J = 4.3 respectively, 8.3 Hz, 1H, 4-H); 3.69 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3); 4.62 (d, ^3J = 8.3 Hz, 1H, 5-H).

(3SR,4SR,5RS)-4.5-Bis(methoxycarbonyl)-3-tert-butyl-2-isopropyl-isoxazolidine (13f): Solvent cyclohexane, reaction time 7 d, yield 52%, colourless oil. - $C_{14}H_{25}NO_5$ (287.4) Calcd. C 58.52 H 8.77 N 4.87 Found C 58.29 H 8.90 N 4.82. - MS(EI): m/e = 287 (6%; M^+). - IR(neat): 1750 cm^{-1}.- ^{1}H-NMR: 0.94 (s, 9H, $C(C\underline{H}_3)_3$); 1.04 (d, ^3J = 5.8 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.23 (d, ^3J = 6.0 Hz, 3H, $CH(C\underline{H}_3)_2$); 3.24 (hpt, ^3J = 6.1 Hz, 1H, $C\underline{H}(CH_3)_2$); 3.45 (d, ^3J = 2.4 Hz, 1H, 3-H); 3.66 (dd, ^3J = 2.4 respectively 9.6 Hz, 1H, 4-H); 3.71 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 4.70 (d, ^3J = 9.6 Hz, 1H, 5-H).

Z-4.5-Bis(methoxycarbonyl)-2-tert-butyl-3-ethyl-isoxazolidine: Product mixture **13g/14g** (ratio 80:20): solvent cyclohexane, reaction time 4d, yield 54%, colourless oil. - $C_{13}H_{23}NO_5$ (273.3) Calcd. C 57.13 H 8.48 N 5.12 Found C 57.03 H 8.21 N 5.10. - MS(EI): m/e = 273 (14%; M^+). - IR(neat): 1750 cm^{-1}. - *3SR,4SR,5RS*-diastereomer **13g**: ^{1}H-NMR(500 MHz): 0.92 (t, ^{3}J = 7.5 Hz, 3H, CH_3); 1.08 (s, 9H, $C(CH_3)_3$); 1.14 - 1.64 (m, 2H, CH_2); 3.21 (dd, ^{3}J = 2.9 respectively 6.0 Hz, 1H, 4-H); 3.28 (dt, ^{3}J = 2.9 respectively 10.1 Hz, 1H, 3-H); 3.60 (s, 3H, OCH_3); 3.70 (s, 3H, OCH_3); 4.50 (d, ^{3}J = 6.0 Hz, 1H, 5-H). - *3SR,4RS,5SR*-diastereomer **14g**: 1H-NMR: 4.73 (d, ^{3}J = 9.8 Hz, 1H, 5-H). The other signals could not be identified.

Table 5. ^{13}C-NMR data of 4.5-Bis-(methoxycarbonyl)isoxazolidines, Chemical shifts in ppm, Solvent $CDCl_3$

	R^1	R^2	C-3(d)	C-4(d)	C-5(d)	R^1	R^2	C=O (s)	OCH_3(q)
9a	Me	Et	72.8	55.6	76.6	43.2(q)	9.4(q), 24.1(t)	171.0,171.9	52.2,52.2
9b	Me	iPr	76.9	52.7	77.3	43.9(q)	17.1(q), 29.4(d)	170.3,172.3	52.0,52.0
9c	Me	tBu	78.9	53.7	81.6	46.6(q)	26.6(q), 34.8(s)	169.7,173.2	52.7,52.8
9d	iPr	Et	56.6	53.0	77.3	18.3(q),20.8(q),67.6(d)	10.6(q), 27.6(t)	170.3,172.4	52.4,52.4
9e	iPr	iPr	54.3	53.0	78.2	19.6(q),20.8(q),72.7(d)	18.6(q),19.1(q),32.0(d)	169.7,172.7	52.2,52.2
9f	iPr	tBu	53.7	52.9	78.7	19.3(q),21.3(q),76.5(d)	26.6(q), 34.6(s)	169.3,173.3	52.4,52.4
9g	tBu	Et	63.7	57.1	78.2	26.1(q), 59.2(s)	10.3(q), 29.7(t)	171.0,172.0	52.6,52.6
9h	tBu	iPr	67.3	54.1	79.6	26.5(q), 59.3(s)	16.7(q),19.4(q),32.6(d)	170.0,171.8	52.2,52.2
10g	tBu	Et	62.0	54.8	77.9	26.5(q), 59.2(s)	11.1(q), 25.0(t)	169.2,170.2	52.0,52.3
12a	tBu	H	50.1(t)	50.7	76.4	25.1(q), 57.1(s)	-	172.0,172.0	52.5,52.5
13a	Me	Et	72.7	56.1	76.6	43.9(q)	9.7(q), 24.3(t)	169., 171.2	52.2,52.2
13b	Me	iPr	76.5	52.3	76.8	43.0(q)	16.6(q),19.2(q),28.8(d)	168.5 171.5	51.7,51.8
13c	Me	tBu	78.1	53.4	79.8	47.9(q)	26.4(q), 34.0 (s)	169.1,171.9	52.2,52.2
13d	iPr	Et	55.7	54.6	76.7	17.8(q),20.8(q),66.2(d)	9.8(q), 26.6(t)	169.3,171.0	51.8,51.9
13e	iPr	iPr	54.3	52.6	77.6	19.6(q),21.3(q),70.4(d)	17.2(q),18.1(q),30.9(d)	169.6,171.9	51.9,52.1
13f	iPr	tBu	55.0	52.6	79.7	19.6(q),21.7(q),74.1(d)	26.3(q),34.1(s)	170.5,172.1	51.7,51.7
13g	tBu	Et	63.9	55.2	75.0	25.8(q), 58.3(s)	10.4(q), 30.1(t)	168.4,171.1	51.9,52.0
13k	tBu	iPr	66.9	50.6	75.7	25.9(q), 58.4(s)	15.3(q),19.7(q),32.0(d)	168.3,171.6	51.9,52.0
14a	Me	Et	73.0	54.6	75.5	43.6(q)	11.1(q), 21.6(t)	169.9,170.4	51.9,52.2
14b	Me	iPr	76.2	54.7	77.0	46.7(q)	20.1(q),20.4(q),28.7(d)	169.0,169.5	52.1,52.4
15a	tBu	H	49.2	50.2	75.7	21.5(q), 57.5(s)	-	169.5,170.3	51.9,51.9
15c	Me	H	58.8/59.4	50.0/50.8	76.7	45.1(q)	-	169.2,170.3	52.1,52.1

(3SR,4SR,5RS)-4.5-Bis(methoxycarbonyl)-2-tert-butyl-3-isopropyl-isoxazolidine (**13h** mixed with **9h**) (ratio 35:65): Solvent cyclohexane, reaction time 4 d, yield **13h** 23%, colourless oil. - $C_{14}H_{25}NO_5$ (287.4) Calcd. C 58.52 H 8.77 N 4.87 Found C 58.14 H 8.68 N 4.89. - MS(EI): m/e = 287 (2%; M^+). - IR(neat): 1750 cm^{-1}.- ^{1}H-NMR (500 MHz): 0.93 (d, 3H, $CH(C\underline{H}_3)_2$); 1.01 (d, ^{3}J = 6.8 Hz, 3H, $CH(C\underline{H}_3)_2$); 1.14 (s, 9H, $C(CH_3)_3$); 1.82 (m, 1H, $C\underline{H}(CH_3)_2$); 3.35 (dd, ^{3}J = 2.9 respectively, 6.0 Hz, 1H, 4-H); 3.37 (t, ^{3}J = 3.1 Hz, 1H, 3-H); 3.68 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 4.47 (d, ^{3}J = 6.0 Hz, 1H, 5-H).

(4SR,5RS)-4.5-Bis(methoxycarbonyl)-2-tert-butyl-isoxazolidine (15a): Solvent chloroform, reaction time 2 d at room temperature, yield 84%, colourless oil. - $C_{11}H_{19}NO_5$ (245.3) Calcd. C 53.87 H 7.81 N 5.71 Found C 53.80 H 7.57 N 5.50. - MS(EI): m/e = 245 (40%; M^+). - IR(neat): 1750 cm^{-1}.- ^{1}H-NMR: 1.16 (s, 9H, $C(CH_3)_3$); 3.26 (m, broad, 2H, 3-H); 3.27 , 3.70 (s,

3H, OCH_3); 3.74 (s, 3H, OCH_3); 4.69 (d, ^3J = 8.8 Hz, 1H, 5-H). The signal of 4-H largely broadened at room temperature and superimposed by the signals at 3.70 and 3.74 cannot be located exactly.

(4SR,5RS)-4.5-Bis(methoxycarbonyl)-2.3.3-trimethyl-isoxazolidine (**15b**) mixed with **12b** (ratio 3.4:1): Solvent chloroform, reaction time 3 d, yield **15b** 57%, colourless oil.- $C_{10}H_{17}NO_5$ (231.3) Calcd. C 51.94 H 7.41 N 6.06 Found C 51.08 H 7.28 N 6.20. - MS(EI): m/e = 231 (19%; M^+). - IR(neat): 1750 cm^{-1}. The signals of the ^1H- and ^{13}C-NMR spectra are largely broadened at room temperature, so that an umambiguous assignment is not possible.

(4SR,5RS)-4.5-Bis(methoxycarbonyl)-2-methyl-isoxazolidine (15c): To a solution of N-methyl-methylenamine-N-oxide in methanol prepared from N-methylhydroxylamine hydrochloride, formalin and triethylamine at room temperature, an approximately equimolar portion of dimethyl maleate was added. The reaction mixture was refluxed for 2 days. After removal of the solvent the residue was treated with diethyl ether. The remaining triethylamine hydrochloride was filtered off, the ethereal solution was dried with $MgSO_4$ and thereafter the solvent was evaporated. The residue was dried under vacuum (1 Torr) and subsequently purified by chromatography with Et_2O/petroleum ether, yielding 42% of a colourless oil. - $C_8H_{13}NO_5$ (203.2) Calcd. C 47.29 H 6.45 N 6.89 Found C 47.19 H 6.50 N 6.84. - MS(EI): m/e = 203 (73%; M^+). - IR(neat): 1750 cm^{-1}. .- ^1H-NMR (500 MHz, 322 K): 2.78 (s, broad, 5H, 3-H and CH_3); 3.69 (s, 3H, broad OCH_3); 3.73 (s, 3H, OCH_3); 3.78 (q, broad, 1H, 4-H); 4.73 (s, broad, 1H, 5-H).

2-t-Butyl-3-methoxycarbonyl-isoxazolidin-5-one (18). A solution of N-tert-butylhydroxylamine (1.0 g 11.1 mmol) and dimethyl maleate (1.6 g, 11.1 mmol) in chloroform (50 ml) was refluxed for one day. Evaporation of the solvent and recrystallization from diethyl ether affords **18** in 85% yield (1.88 g) as a white solid, mp 42°C from diethyl ether. $C_9H_{15}NO_4$ (201.2) Calcd C 53.27 H 7.51 N6.96 Found C 53.37 H 7.55 N 6.87. - MS (EI): m/e = 201 (4%, M^+). - IR (KBr): 1780, 1740 cm^{-1}. - ^1H-NMR: 1.15 (s, 9H, $C(CH_3)_3$); 2.94 (dd, ^3J = 9.5, ^2J = 17.8 Hz, 1H, 4-H); 3.08 (dd, ^3J = 6.5, ^2J = 17.8 Hz, 1H, 4-H); 3.78 (s, 3H, OCH_3); 4.16 (dd, ^3J = 6.5 and 9.5 Hz, 1H, 3-H).- ^{13}C-NMR: 24.9 (q, J = 126.2 Hz, $C(\underline{C}H_3)_3$); 33.4 (t, J = 137.5 Hz, CH_2); 52.9 (q, J = 148,0 Hz, OCH_3); 59.2 (d, J = 144.0 Hz, CH); 61.6 (s, $\underline{C}(CH_3)_3$); 170.7 (s, CO_2CH_3); 173.7 (s, CO).

Dimethyl 2-(N-tert-butyl-hydroxyamino)succinate 17: could be detected by ^1H-NMR spectroscopy when N-tert-butylhydroxylamine and dimethyl maleate reacted in deuterochloroform at room temperature. ^1H-NMR: 1.12 (s, 9H, $C(CH_3)_3$); 2.82 (d, ^3J = 6.8 Hz, 2H, CH_2); 3.61 (s, 3H, OCH_3); 3.66 (s, 3H, OCH_3); 4.10 (t, ^3J = 6.8 Hz, 1H, CH); 6.30 (s, broad, 1H, OH).

Crystal structure determination of 9g. Suitable crystals were grown and submitted to crystal X-ray analysis. Intensity data were collected in ω-scan mode on a Enraf-Nonius CAD4 diffractometer at T = 188 K with graphite monochromated Cu K_α radiation (Unit cell: a = 8.953 (4) Å, b = 9.469 (3) Å, α = 68.34(4)°, ß = 83.35(3)°, γ = 83.06°, V = 748 $Å^3$, space group P1).

The structure was solved by Direct methods and subsequent difference Fourier syntheses. The full matrix least square refinement with anisotropic displacement factors for all atoms except the hydrogen atoms yielded a R-factor of 5.8 for 2144 reflections with $I<5\sigma$. The H atoms were refined using a riding model with fixed temperature factors. For structure solution, refinement, tables and graphic representation the program system Shelxtl[25] were used, the least square planes were calculated with the help of the program PLATON.[26]

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References and Footnotes

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2. See for instance: Tufariello, J.J. in *1.3 Dipolar Cycloaddition Chemistry*, Padwa, A. (Ed.) Chapter 9, Wiley - Interscience New York, **1984**, pp. 108-114.
3. See ref. 2, pp 112-113.
4. In this context it should be mentioned that C-alkylnitrones possessing at least one hydrogen atom at ß-position are expected to undergo Z,E-isomerization much more easily than those without a hydrogen atom at this position, in particular C-arylnitrones, because in the former case the isomerization can proceed via the tautomeric N-hydroxy-enamine form by rotation about its CN-single bond. Though the E-isomer of most of the aldonitrons cannot be detected by NMR-spectroscopy (Aurich, H.G., Franzke, M., Kesselheim, H.P. *Tetrahedron*, **1992**, *48*, 663-668), reactions via transition states derived from E-isomer must be considered seriously, see ref. 2 and 1.
5. There was a considerable discussion about the question whether such reactions as 1.3-dipolar cycloadditions proceed as concerted or as stepwise processes. However, at present the idea of a concerted mechanism seems to be generally accepted. For a short summary see ref. 2, pp. 98-101.
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11. Most of the acyclic nitrones supplied so far in 1.3-dipolar cycloaddition reactions were those without a hydrogen atom at the ß-position (C-aryl nitrones etc.). See for instance, the compilation in Confalone, P.N:, Huie, E.M. The [3+2]Nitrone Olefin Cycloaddition Reaction in *Organic Reactions*, A.S. Kende (Ed. in Chief) Vol. 36, Chapter 1, John Wiley and Sons, New York **1988**, pp. 68-117, in particular pp. 83-86.
12. The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
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