Stereoselective 1,3-Dipolar Cycloadditions to Heterocyclic Compounds

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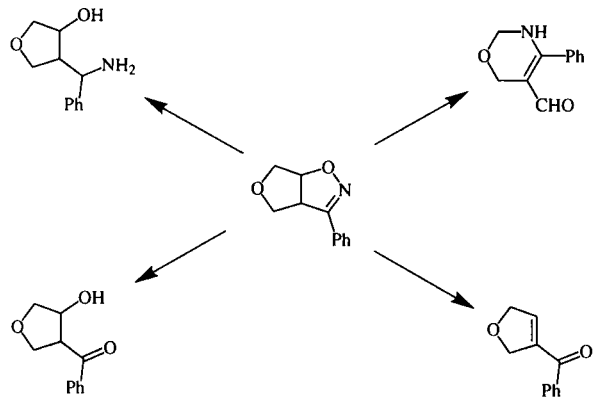
1. Introduction.

1,3-Dipolar cycloaddition reaction between an olefin and a nitrile oxide [1-3] and nitrone [3-6] offers one of the most powerful synthetic route to isoxazolines and isoxazolidines, respectively. Isoxazolines have been shown to be useful intermediates, especially for the synthesis of γ-amino alcohols [3], β-hydroxy carbonyl compounds and their derivatives [7-10]. Some years ago, we showed that the photorearrangement of isoxazolines can be made selectively (Scheme 1) [11].

Scheme 1

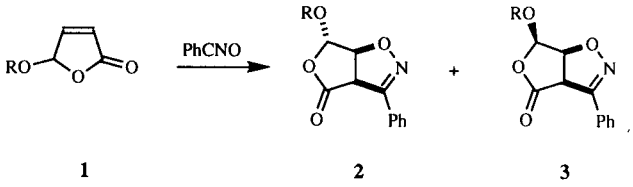


There is therefore renewed interest in their synthesis *via* 1,3-dipolar cycloaddition of nitrile oxides and nitrones to alkenes, with particular attention being focused on the factors influencing stereo- and regioselectivity. One of the key features of these cycloadditions is the *cis*-stereoselectivity, that transfers the stereochemical information of the alkene to the stereocenters of the heterocyclic ring. Thus, from (*E*)-alkenes 4,5-*trans* products are obtained, while (*Z*)-alkenes afford 4,5-*cis* compounds [1]. A large part of the research in this area in the last few years has dealt with the influence exerted by a stereocenter located in one of the two reactants upon the stereochemical outcome [12].

With our efforts to utilize heterocyclic compounds as dipolarophile component in 1,3-dipolar cycloaddition during the last years we have found that:

i) Arylnitrile oxides undergo highly regio- and stereoselective cycloadditions with 5-alkoxy- and 5-acetoxy-2(5*H*)-furanones **1** (R = Me, Et, Ac). In each case a single product **2** results from addition to the less hindered face of the furanone with an antiperiplanar relationship between the new C-C bond and R-oxy substituent (Scheme 2) [13,14]. The stereoselectivity was explained by Felkin-Anh-Houk (FAH) model reflecting also in this case of furanones the anomeric effect. Moreover, *syn* orientation of the oxygen containing substituent relative to the oxygen atom of nitrile oxide should lead to a greater repulsion in the transition state. On the other hand, *syn*-cycloaddition occurred in part only in the case of 5-hydroxy-2(5*H*)-furanone **1** (R = H), where a hydrogen bond in the transition state can be present. Thus, the hydroxy compound **1** yielded a 52:48 mixture of both *anti*-**2** and *syn*-**3** diastereoisomers (Scheme 2).

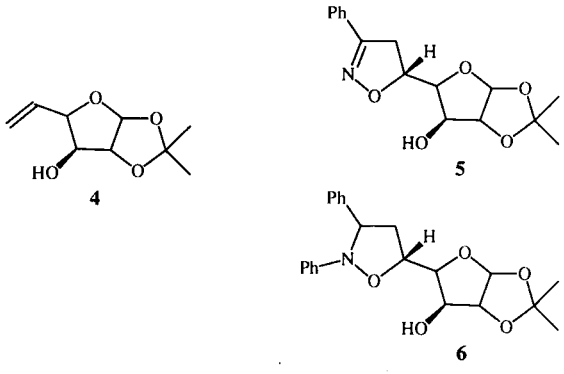
Scheme 2



1 **2** **3**

ii) The similar, highly stereoselective cycloaddition we have observed by the 1,3-dipolar cycloaddition of nitrile oxides [15] and nitrones [16] with 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**4**) (Scheme 3). The cycloaddition proceeded more than ≥95% π-facial selectivity, the major products were *anti*-adducts **5** and **6**. Assuming an *anti* attack, the stereochemical outcome of the cycloaddition has been rationalized in terms of the *inside* alkoxy effect in FAH model [81].

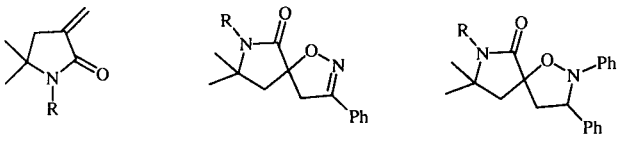
Scheme 3



4 **5** **6**

iii) Finally, we have found that, nitrile oxides [17,18] and nitrones [19,20] add regioselectively to the carbon-carbon double bond of α-methylenepyrrolidinones **7** giving exclusively the 5-substituted spiro-derivatives **8** and **9** (Scheme 4). AM1 calculations, show that the regio- and stereochemistry of the cycloaddition seems to be controlled by steric effects rather than by frontier orbital consideration [17-20].

Scheme 4



7 **8** **9**

The present lecture is devoted to regio- and stereoselectivity of nitrile oxide and of chiral/achiral nitrone cycloadditions with heterocyclic compounds having an *exo*- and *endo*-cyclic double bond, respectively, and in some cases also with model alkenes.

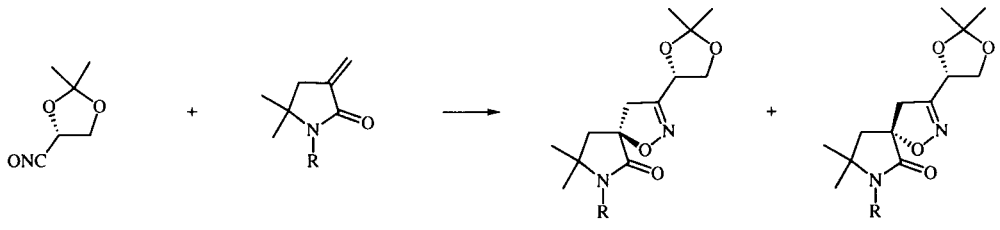
2. Cycloadditions to Heterocycles Possessing an *Exo*-cyclic C=C Bond.

In the framework of our project on the utilization of heterocyclic compounds as the dipolarophile component in 1,3-dipolar cycloaddition, we have chosen some heterocyclic compounds **7** [17], **13** and **17** [29-33] possessing an *exo*-cyclic double bond as a model system. The reaction with 1,3-dipoles could be of some mechanistic interest regarding the well known pecularity of the regioselectivity pattern in electron deficient dipolarophiles in such a reaction [2]. Now, I will show that heterocycles possessing an *exo*-cyclic double bond deserve special attention. The recent fundamental observation of the strong herbicidal activity of spirocyclic lactams [21], coupled with the absence of toxicity to microorganisms, and also that some spiroisoxazolines occur naturally - araplysillins [22] are inhibitors of ATPase - stimulated our interest in the synthesis of other spirocyclic derivatives. Perhaps the most developed methodology of the synthesis of spirocyclic systems, other than the spiroketals, are cycloadditions to *exo*-cyclic double bonds [23-28].

1,3-Dipolar cycloaddition of chiral glyceraldehyde-derived nitrile oxide **10** [3] and α-methylenepyrrolidinones **7** affords the mixture of diastereomeric spiroisoxazolines **11** and **12** in an approximate 50:50 ratio (Scheme 5) [29]. The asymmetric induction expected by the α-chiral center of nitrile oxide **10** has not been very effective, as has been also indicated by AM1 modeling of the respective transition states [29]. While product **11** (R = H) was preferred kinetically (difference in transition states energies is 3 kJ/mol), product **12** was more thermodynamic stable (ΔH_f =-1 kJ/mol).

Therefore, we have chosen chiral α-methylenepyrrolidinone **13** [30] as a heterocycle useful for the study of the factors controlling π-facial selectivity since the 5-substituents can systematically be varied [30-33]. Moreover, the regioselective elaboration of the latent amino functionality of spiroisoxazolines can be used for the preparation of chiral amino acid derivatives. The reaction of optically active pyrrolidinone **13** and stable mesitonitrile oxide (**14**) proceeded with the formation of *trans*- and *cis*-diastereoisomers **15** and **16** in a ratio of 67:33, in favor of the *trans* diastereomer **15** (Scheme 6) [29]. The attack of the 1,3-dipole occurred preferentially from the less hindered face of the dipolarophile **13**.

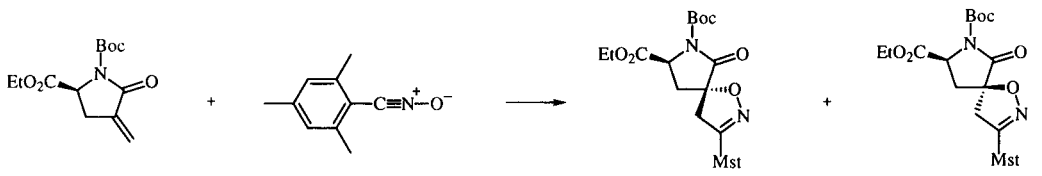
Scheme 5



10 **7** **11** **12**

a, R = H; **b**, R = *n*-Bu; **c**, R = $COCH_3$; **d**, R = Boc; **e**, R = $C(CH_3)=CH_2$

Scheme 6



13 14 15 16

The cycloaddition to the racemic α-methylene-γ-lactone **17** [31] proceeded analogously [29]. In this case, the predominant approach of the dipole also occurs *anti* to the phenyl substituent in the dipolarophile **17** (Scheme 7). The reaction of mesitonitrile oxide **14** with the methylenelactone **17** afforded a 90:10 mixture of cycloadducts **18** and **19**. Thus, we have found in all cases evidence for a predictable *anti*-diastereoselective 1,3-dipolar cycloaddition of arylnitrile oxide to substituted heterocyclic compounds possessing an *exo*-cyclic double bond [28,29].

Hillman adducts **20a-d** (Scheme 8) [38-40]. The reactions are completely regioselective with only the 5-substituted isoxazolines being isolated - irrespective of the presence or absence of the Mg(II) additive [37]. The cycloadditions were first carried out in the absence of any Lewis acids (entries 1, 4, 6 and 11) - a single isomeric product (entry 11) or mixture of isomers (*de* ranging from >90% to 4%) were formed with the compounds **22a-d** obtained as the main products. The reactions also exhibit a moderate degree of stereocontrol, induced by the asymmetry of the

Scheme 7

17 14 18 19

3. Cycloadditions to Baylis-Hillman Adducts.

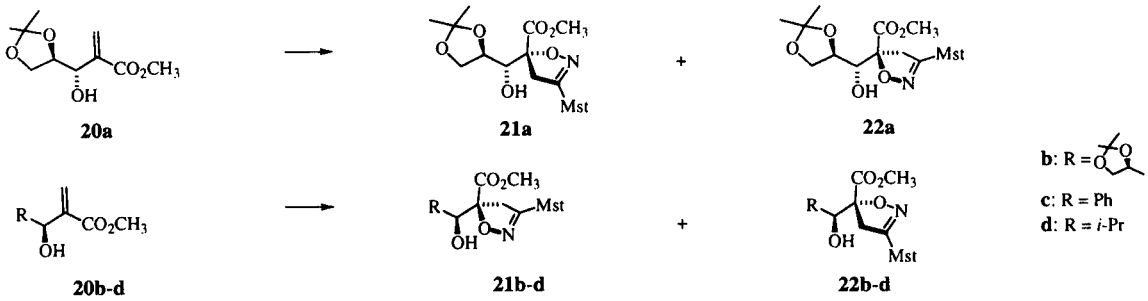
If a chiral alkene is used as the dipolarophile, two diastereoisomers can be formed by 1,3-dipolar cycloaddition [12]. Several models have been published which predict the structure of the major diastereoisomer [1-3]. However, if a 1,3-dipolar cycloaddition is used in a synthesis of a complex target molecule, the ratio of diastereoisomers may change or even reverse. S. Kanemasa *et al.* have described the first successful control of stereo- and regioselectivity in 1,3-dipolar cycloadditions of nitrile oxides by metal coordination [34,35]. The presence of magnesium ions dramatically accelerates nitrile oxide cycloadditions to allylic alcohols, improving both the regio- and stereoselectivity of the reaction. For example, cycloadditions to allylic alcohols bearing α-chirality produce *syn*-stereoisomers of isoxazolines selectively [34]. These reactions involve the formation of activated intermediates in which a nitrile oxide and allylic alkoxide coordinate to the magnesium ion [34-36].

We have investigated [37] the effect of the addition of methylmagnesium bromide on the stereoselectivity in cycloadditions of mesitonitrile oxide to chiral Baylis-

dipolarophile, but the stereocenter in the β-position has little effect on the diastereoisomeric ratio (22:78 for **20a** and 26:74 for **20b**).The structure of the major cycloadduct **22a** was determined by X-ray analysis and that of minor cycloadduct **21a** from X-ray diffraction of the product of lactonization [37].

The addition of methyl magnesium bromide to dipolar cycloadditions of mesitonitrile oxide to the Baylis-Hillman adducts **20a-d** affects and can even reverse the sense of induced stereoselectivity, 95:5 for **20a** (entry 2) and 85:15 for **20b** (entry 5) (Scheme 8) [37]. Addition of Grignard reagent to **20a-d** produces magnesium alkoxides which subsequently form complexes with mesitonitrile oxide. The stereochemical outcome of the cycloaddition in the absence of Grignard reagent has been rationalized in terms of the presence of hydrogen bonding in a Felkin-Anh-Houk model [41]. On the other hand, the reversal of the stereoselectivity presumably results from the formation of a chelated transition state with a geometry different from a "nonchelated" transition state (Scheme 9). The chelated transition state may arise from the coordination of both the 1,3-dipole and the dipolarophile by the same magnesium ion.

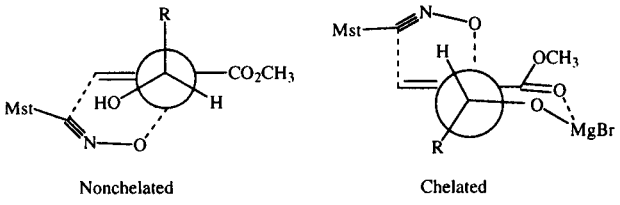
Scheme 8



Entry	Compound	Solvent [a]	Lewis Acid [b]	Time	Temperature	Yield %	Ratio **21**:**22** [c]
1.	**20a**	TOL	—	2 h	80°	89	22:78
2.	**20a**	DCM	MeMgBr	48 h	r.t.	50	>95:<5
3.	**20a**	CLB	MeMgBr	4 min	MW [d]	34	78:22
4.	**20b**	TOL	—	2 h	80°	92	26:74
5.	**20b**	DCM	MeMgBr	43 h	r.t.	62	85:15
6.	**20c**	TOL	—	4 h	80°	92	42:58
7.	**20c**	DCM	MeMgBr	24 h	r.t.	57	61:39
8.	**20c**	DCM	—	24 h	r.t.	96	48:52
9.	**20c**	CLB	MeMgBr	4 min	MW [d]	40	70:30
10.	**20c**	CLB	—	1.5 min	MW [d]	99	43:57
11.	**20d**	TOL	—	2 h	80°	99	<5:>95
12.	**20d**	DCM	MeMgBr	76 h	r.t.	35	>95:<5

[a] TOL: toluene; CLB: chlorobenzene; DCM: dichloromethane; [b] One equivalent of the MeMgBr was employed. The reaction was allowed to reach completion; [c] Determined by ^{1}H and/or ^{13}C nmr of crude reaction miexture; [d] Microwave irradiation.

Scheme 9



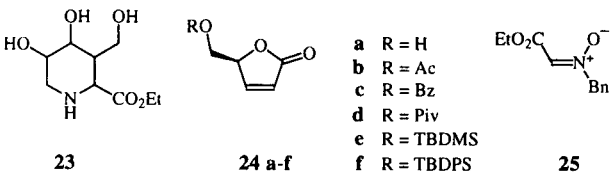
To the best of our knowledge this unusual reversal of the stereoselectivity of nitrile oxide cycloaddition in the presence of Lewis acids is a very rare phenomenon and has previously been observed in dipolar cycloaddition of nitrile oxides by Kanemasa [34] and recently by Page [42]. It is noteworthy that the attempts to accelerate the cycloaddition by microwave irradiation were successful (the reaction time decreased from days to less than 5 minutes) without loss of stereoselectivity in the nonchelated cycloadditions (entries 6 and 10), and with only a negligible decrease of stereoselectivity in the chelated reactions (entries 2, 3 and 7, 9, respectively) (Scheme 8) [37].

4. Nitrone Cycloadditions to Furanons.

With the goal of developing a simple route to polyhydroxylated derivatives of piperidine **23** [43] *via* an asymmetric 1,3-dipolar cycloaddition, we have designed (*S*)-5-hydroxymethyl-2(5*H*)-furanone (**24a**) [44] and its 5-*O*-substituted derivatives **24b-f** as templates for nitrone cycloadditions (Scheme 10). Reactions of nitrones with chiral heterocyclic dipolarophiles have received only limited studies [45-50]. In line with our above mentioned efforts to utilize heterocyclic compounds as dipolarophile component in 1,3-dipolar cycloaddition, we now report some results on the regio- and stereochemical outcome of the nitrone cycloaddition to the optically active lactone **24a** and its alkoxy substituted derivatives **24b-f** [51-53], having in mind that the N-O bond in the cycloadducts can be readily cleaved, to obtain a precursor for the synthesis of piperidine derivatives such as **23**.

Cycloaddition of chiral parent lactone **24a** to *N*-benzyl-*C*-ethoxycarbonyl nitrone (**25**) gave the three chromatographically separable isoxazolidines **26-28** in good yields [53]. There are eight possible products, comprising *exo*- and *endo*-isomers for each pair of regioisomers resulting from *anti*- and *syn*-face attacks related to the hydroxymethyl group. In all cases the cycloaddition occurs from

Scheme 10



23 24 a-f 25

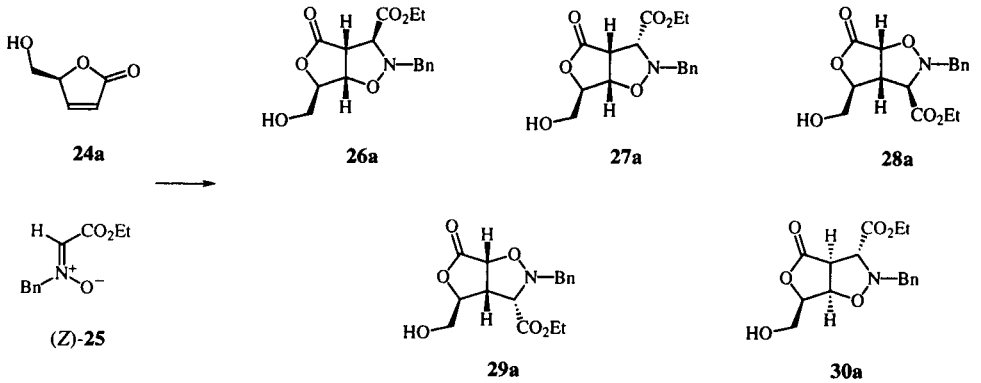
a R = H
b R = Ac
c R = Bz
d R = Piv
e R = TBDMS
f R = TBDPS

addition to the less hindered face of the furanone, with an antiperiplanar relationship between the new C-C bond and the inducing hydroxymethyl substituent. Only the diastereomeric adducts *exo*-**26a** and *endo*-**27a**, in which the oxygen of the 1,3-dipole has become attached to the β-carbon of the furanone, together with the corresponding minor regioisomer **28a** were formed. Neither *trans*-**29a** nor any of the other four possible adducts were detected in the crude reaction mixture (Scheme 11) [53].

mesitonitrile oxide was also found by Jäger *et al.* [3]. The high face-selectivity observed in the generation of each diastereoisomer **26a-28a** can be rationalized following inspection of Dreiding models. The transition states leading to the formation of the *anti* **26a-28a** experience no steric encumbrance when the dipole **25** approaches the lower face of the dipolarophile **24a** in an *anti* orientation and cycloadditon proceeds exclusively by this mode. Clearly steric factors are important in orientating the dipole **3** in the cycloaddition [53], and the presumed *syn*-directing effect of the hydroxymethyl group was not seen [3].

The isomer ratio of nitrone **25** cycloaddition to **24a** was found to be dependent upon the reaction solvent used (Scheme 11). Three structural features can influence the stereochemical outcome of nitrone/alkene cycloadditions: (*E*/*Z*)-nitrone isomerization about the C=N bond, alkene(nitrone) facial selectivity, and *endo*/*exo* preferences [4-6]. The formation of both major epimers **26a** and **27a** could be explained through the *endo* and *exo* approach shown in Scheme 12, the isoxazolidine **26a** arising from cycloaddition of *Z*-nitrone and *E*-nitrone through an

Scheme 11

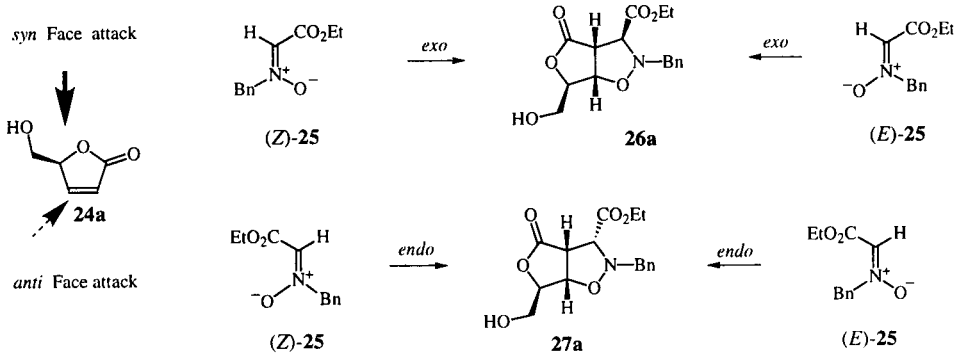


Entry	Compound	Solvent	Temperature	26	27	28	*E*/*Z* of 25
1	**24a**	CH_2Cl_2	40°	30	56	14	1.5
2	**24a**	MeOH	65°	36	46	18	0.1
3	**24a**	Benzene	80°	53	37	10	3.7
4	**24a**	DMSO	80°	40	42	18	0.26
5	**24a**	$Cl(CH_2)_2Cl$	80°	53	32	15	—
6	**24a**	1,4-Dioxane	MW [a]	64	23	10 [b]	—

[a] Microwave irradiation; [b] Additionally 3% of **30**.

Formation of the diastereoisomers **26a-28a** can be rationalized by involving a highly preferred approach of the nitrone **25** *anti* to the hydroxymethyl group in the transition state (Scheme 12). The dominance of the *anti*-mode of cycloaddition, is in accord with previous findings for cycloadditions of **24a** with a cyclic nitrone [49] and *C*,*N*-diarylnitrones [52], and comparable selectivity for *exo* transition state. On the other hand, the adduct **27a** could be formed by the *Z*-nitrone and *E*-nitrone reacting in the *endo* fashion [54,55]. The nitrone **25**, an ester-conjugated nitrone exists as an *E*/*Z* mixture in solution. In contrast to previous reports giving an *E*/*Z* isomer ratio at room temperature [56], we now report the *E*/*Z* ratio at reaction temperature (Scheme 11) [53]. Thus, the stereo-

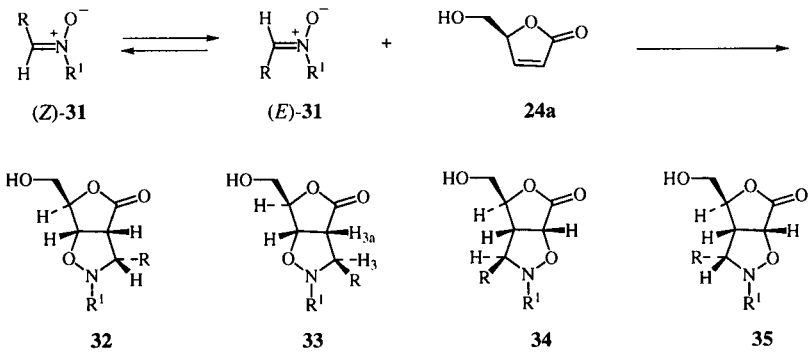
Scheme 12



selectivity observed in these cycloadditions reflects not only the steric hindrance in the corresponding *exo/endo* transition states but also the tendency of this nitrone to undergo the *E/Z* isomerization reaction [53]. Next, we investigated the optimization of the diastereoselectivity of this reaction by catalysis with Lewis acids [57-61] and with microwave irradiation [62]. The addition of Mg ion as a Lewis acid has no beneficial effect; indeed no isoxazolidines **26a-28a** were formed, only starting nitrone **25** being completely recovered. Attempts to accelerate the cycloaddition by microwave irradiation, however, were successful (the reaction time decreased from several hours to less than 10 minutes) with only a small change of stereoselectivity in favor of the *exo*-**26a** isomer (Scheme 11, entry 6). Moreover, in the case of microwave irradiation in dioxane a small amount of the unexpected *syn* adduct **30a** (3%) was also obtained after chromatography, in addition to the cycloadducts **26a-28a** [53].

Next, the regio- and stereoselectivity of cycloaddition of the lactone **24a** with arylnitrones **31** in different solvents was studied (Scheme 13) [52]. *C*-Aryl nitrones **31a-c** underwent highly regio- and face-selective cycloaddition with the lactone **24a**; the products **32** and **33** result from the approach *anti* to the hydroxymethyl group of the dipolarophile, the oxygen of the 1,3-dipole being attached to the β-carbon of the enone unit. On the other hand, cycloaddition of the LUMO-directing *C*-benzoyl nitrone **31d** also afforded one of the second possible regioisomers **34**. *Endo/exo* diastereoselectivity is affected significantly by the substituent on the nitrone **31** (Scheme 13, entries 2 and 3) and, by temperature too (entries 3 and 4) in the case of *C,N*-diphenyl nitrone (**31c**).

Scheme 13

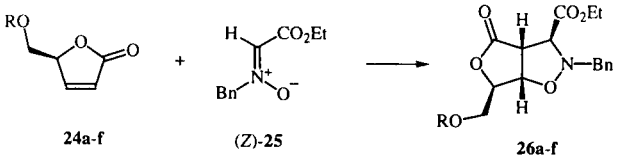


a R = Ph, R^1 = $PhCH_2$ **b** R = Mesityl, R^1 = Ph
c R = Ph, R^1 = Ph **d** R = PhCO, R^1 = Ph

Entry	Nitrone	Solvent	Temperature °C	Time Hours	Product 32	33	34
1	**31a**	Toluene	110	120	60	40	0
2	**31b**	Benzene	80	72	30	70	0
3	**31c**	Benzene	80	8	78	22	0
4	**31c**	Toluene	110	72	13	87	0
5	**31d**	Toluene	110	3	49	20	31
6	**31d**	CH_2Cl_2	25	168	40	32	28

Finally, the cycloaddition in benzene of the ethoxycarbonyl nitrone **25** with 5-*O*-substituted lactones **24b-f**, where R is Ac, Bz, Piv, TBDMS (*t*-BuMe$_2$Si) and TBDPS (*t*-BuPh$_2$Si), has been studied (Scheme 14) [53]. In each case only the *anti*-cycloadducts **26-28** were formed, confirming the key assumption that the template alkoxymethyl group would effectively shield the upper face of the lactones **24b-f**. The diastereoselectivity of cycloadditions to the 5-*O*-substituted lactones **24b-f** is dependent on the steric hindrance of lactone. The reaction compared to unsubstituted parent lactone **24a** proceeded more selectively in favor of *exo*-diastereoisomers **26b-f**, the selectivity increasing as the size of protected group attached to lactone increases: 53:37:10 for R = H and 83:15:2 for R = TBDPS (Scheme 14, entries 1 and 6) [53].

Scheme 14



24a-f (Z)-**25** **26a-f**

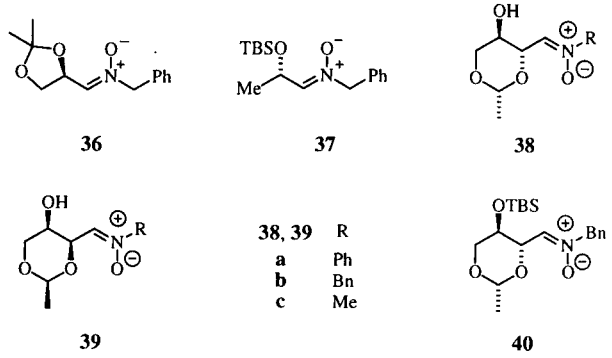
a R = H **d** R = Piv
b R = Ac **e** R = TBDMS
c R = Bz **f** R = TBDPS

Entry	Compound	Solvent	Temperature	26	27	28	*E*/*Z*
1	**24a**	Benzene	80°	53	37	10	3.7
2	**24b**	Benzene	80°	64	25	11	3.7
3	**24c**	Benzene	80°	72	20	9	3.7
4	**24d**	Benzene	80°	78	17	5	3.7
5	**24e**	Benzene	80°	81	19	—	3.7
6	**24f**	Benzene	80°	83	15	2	3.7

5. Cycloadditions of Chiral Nitrones.

Cyclic glycosides are important as enzyme inhibitors and as chiral synthons suitable for the synthesis of many natural products. These properties have stimulated interest in the synthesis of glycoside analogues [54]. Since the 1,3-dipolar cycloaddition has a nearly singular capability of establishing large numbers of stereochemical centers in one synthetic step and a large part of the research of stereocontrolled versions of 1,3-dipolar cycloaddition in the last few years dealt with the influence exert by a stereocenter located in either one of the two cycloaddends [12] we have focused our attention to the preparation of chiral nitrones. Among the chiral nitrones a fundamental role is played by *N*-sugar-derived nitrones [5,6]. Only scattered reports deal with nitrones possessing a chiral substituent at their carbon atom [54,63-72]. The following part of my lecture is devoted to the stereoselectivity of 1,3-dipolar cycloadditions of *C*-(α-alkoxy)-substituted chiral nitrones **36-40**, having in mind also in this case, that N-O bond of isoxazolidine cycloadducts can readily be cleaved, to obtain a precursor for the synthesis of natural products such as polyhydroxylated derivatives of pyrolizidines. The nitrones **36-40** (Scheme 15) were prepared in pure state from the corresponding aldehydes by treatment with *N*-substituted hydroxylamines. The *Z*-configuration of the nitrones was verified by an nOe experiment. The nitrones **38-40** derived from protected aldotetroses [71,72], succesfully used as nitrile oxide precursors [73], have been prepared by us in order to study this systematically.

Scheme 15



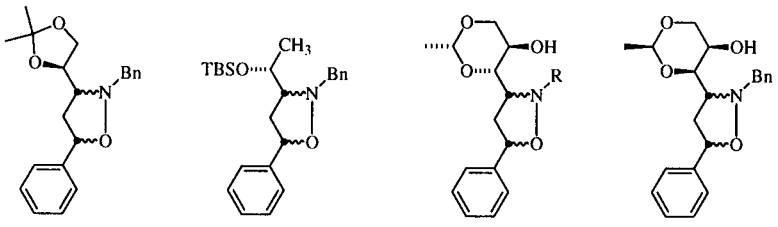
36 **37** **38**

39 **40**

38, 39 R
a Ph
b Bn
c Me

There are eight possible products, including *cis*- and *trans*-isomers for each pair of regioisomers, deriving from *anti* and *syn* attacks. The cycloaddition of nitrones **36-40** with styrene in boiling toluene afforded the corresponding isoxazolidines as a mixture of 3-4 diastereoisomers in excellent yield. Regioselectivity of cycloadditions also was very high: the 5-substituted isoxazolidines were formed exclusively (Scheme 16). The stereoselectivity was dependent on the steric hindrance of the nitrone. The

Scheme 16



selectivity increases as the sizes of *C*-"chiral" group and *N*-alkyl group attached to the nitrone increase. The best diastereoselectivity was achieved by using *N*-benzylnitrones **38-40** derived from protected aldotetroses (Scheme 15). New stereocenters being generated in the cycloaddition, therefore, four diastereomeric cycloadducts were possible for each case (Scheme 16).

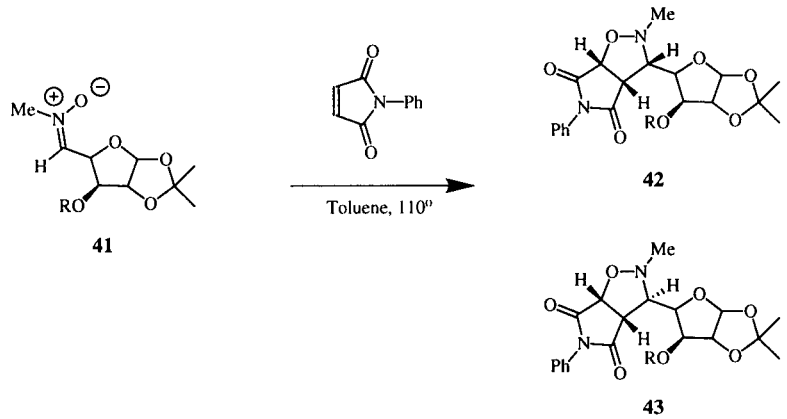
The stereoselectivity of nitrone cycloaddition to an alkene is difficult to predict, and would appear to be dependent on minor structural changes in either component [1,2,54]. Dipolar cycloaddition of α-alkoxy substituted nitrones had been shown to occur preferentially *via* a transition state in which the developing carbon-carbon bond would avoid steric interaction with the bulky group of the reactants [74]. Some years ago, we have demonstrated how small a structural change in the nitrone may be to effect a significant change in the stereoselectivity of cycloaddition [54,68]. We had found that 3-hydroxynitrone **41** (R = H) reacted with *N*-phenylmaleimide in toluene at 110° to give exclusively *syn*-isoxazolidines **42** (H-3/H-3a *syn* relationship). In contrast, the 3-acetoxynitrone **41** (R = Ac) gave the *anti*-isoxazolidine **43** as the solo products (H-3/3a-H *anti* relationship) (Scheme 17). The stereochemical outcome has been explained by *endo* attack for the acetoxynitrone **41**, which is sterically preferred, since the repulsions between the incoming *N*-phenylmaleimide and the sugar moiety are avoided, whereas *exo* attack for the hydroxynitrone **41**, stereoelectronically preferred through the hydrogen bond between the pentose hydroxy group and one of the carbonyl groups of the *N*-phenylmaleimide [54,68].

For the glyceraldehyde-derived nitrone **36**, the diastereoselectivity of the cycloaddition to styrene was found 73 (**44**):11 (**45**):9 (**46**):7 (**47**) (Scheme 18) [70]. The major product **44** was found to have the relative configurations *erythro* C-3/C-4' and *cis* C-3/C-5. It likely derives *via* a less hindered *endo* attack and in an antiperiplanar manner with respect to the largest methylene group of the dioxolane ring (Scheme 19). As has been mentioned above, dipolar cycloaddition of chiral nitrones had been shown to occur preferentially *via* a transition state in which the developing carbon-carbon bond avoids steric interaction with the most bulky group [74]. The cycloaddition with the L-lactaldehyde-derived nitrone was less selective and the stereoisomeric products **48-51** were found in a ratio of 39 (**48**):30 (**49**):20 (**50**):11 (**51**) (Scheme 20) [70].

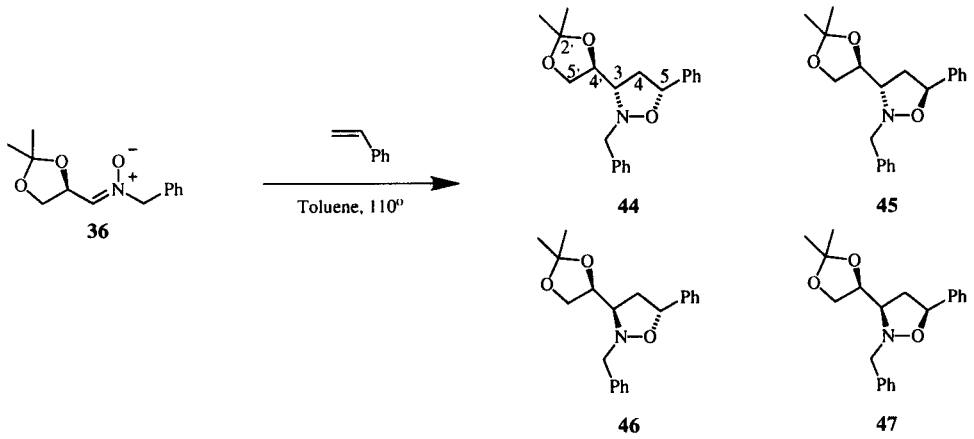
On the other hand, the cycloaddition of the nitrones **38a-c** derived from erythrose, which have been prepared from D-glucose, proceeded with higher yields and was more selective [71,72]. 2,4-*O*-Ethylidene-D-erythrose (**52**) was prepared from 4,6-*O*-ethylidene-D-glucose [75-77] (readily available from D-glucose in 70% yield) by oxidation with periodate in almost quantitative yield (Scheme 21). The protected β-hydroxyaldehyde **52** was isolated as a crystalline dimer [77-80]. Reformation of the monomer **52** was facilitated in our case by adding a catalytic amount of 2-pyridone [80], and the aldehyde **52** underwent smooth condensation with the respective hydroxylamine in increased yield (50% *versus* 73% for nitrone **38b**).

The ratio of the diastereoisomers **53-56** was dependent on the substituent located at the nitrogen atom of the nitrone (Scheme 22). The X-ray analysis established the product configuration. In this case the major product **53** was also found to have C-3/C-4' *erythro* and C-3/C-5 *cis* configuration, indicating formation from a cycloaddition which had occurred on the more sterically accessible face of the *Z*-nitrone, *via* an *endo* transition state with antiperiplanar relationship of the phenyl and *N*-alkyl(aryl) group [72].

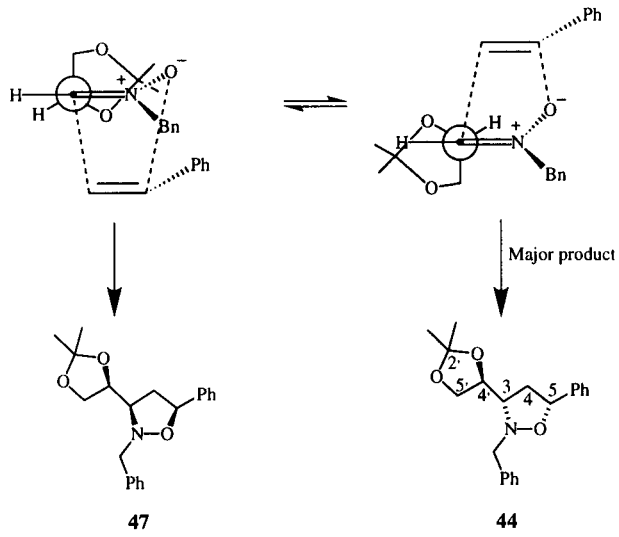
Scheme 17



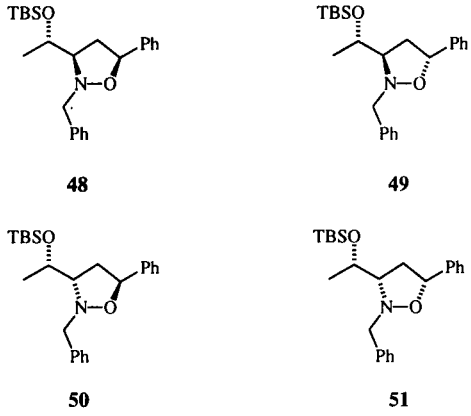
Scheme 18



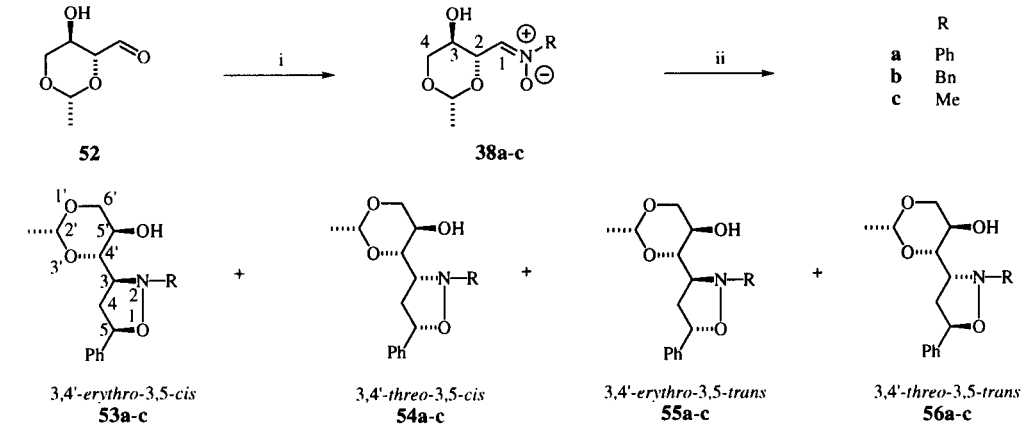
Scheme 19



Scheme 20



Scheme 21

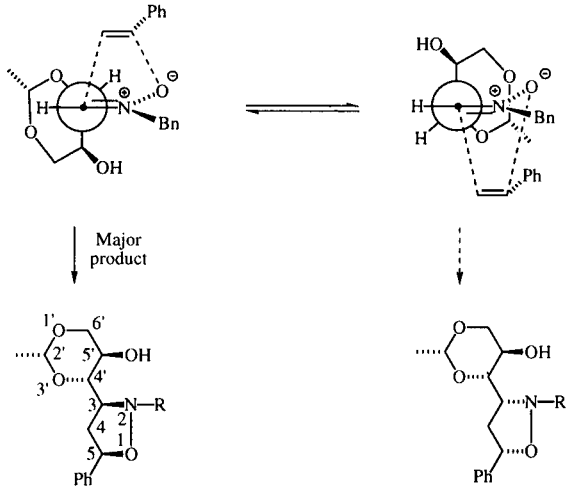


i. RNHOH, CH_2Cl_2, 2-Pyridone (cat.), r.t.; ii. Styrene, Toluene, 110°.

The first prefix *erythro (anti)* or *threo (syn)* denotes the relative relation at C-3 and C-4', and the second, *cis* or *trans*, the relationship between C-3 and C-5 atoms. The high diastereoselectivity found with **38b** and styrene can be ascribed to the more favored approach of the dipole **38b** to styrene, to give **53b** (*erythro-cis*) and **54b** (*threo-cis*) as depicted in Scheme 22. It is reasonable that the attack of (*Z*)-**38b** proceeds *via* the less hindered *endo* transition state and in an antiperiplanar manner with respect to the largest group (RCHOH) of the heterocyclic acetal to give the major product **53b** possessing C-3/C-4' *erythro* and C-3/C-5 *cis* configuration. The more pronounced steric hindrance present in the approach leading to the *threo-cis* diastereomer **54b** might explain the observed ratio *erythro/threo* 88:12 (Scheme 22) [72].

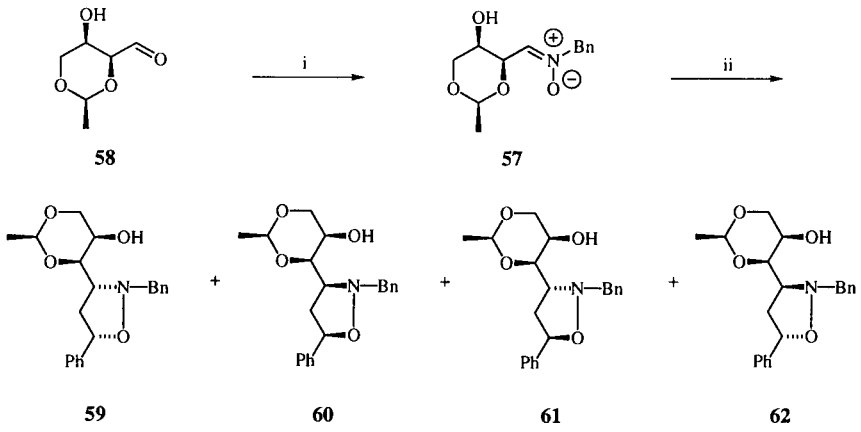
The best results in this series have been obtained in the cycloaddition with the nitrone **57**, derived from the threose (prepared from D-galactose) and the stereoisomers **59-62** were found in the ratio of 90 (**59**):5 (**60**):3 (**61**):2 (**62**) (Scheme 23) [73]. The desired D-*threo* nitrone **57** was prepared in moderate yield from 2,4-*O*-ethylidene-D-threose **58**, which is readily available from D-galactose [82].

Scheme 22



Entry	Nitrone	Yield (%)	*erythro-cis* **53**	*threo-cis* **54**	*erythro-trans* **55**	*threo-trans* **56**	*erythro:threo*	*cis:trans*
1	**38a**	94	82	9	5	4	87:13	91:9
2	**38b**	82	81	12	7	—	88:12	93:7
3	**38c**	85	69	17	10	4	79:21	86:14
4	**57**	84	90	5	3	2	93:7	95:5
5	**36**	78	73	11	9	7	82:18	84:16
6	**37**	89	39	30	20	11	59:41	69:31

Scheme 23



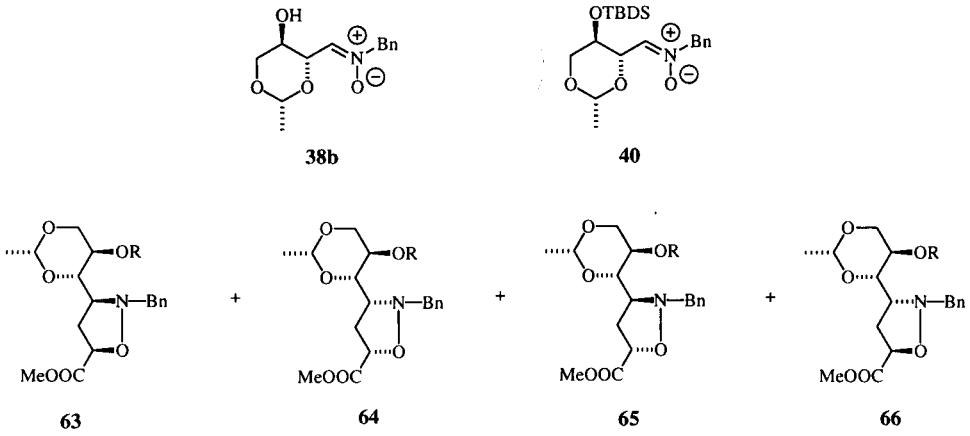
i. BnNHOH, CH_2Cl_2, 2-Pyridone, r.t.; ii. Styrene, Toluene, 110°

These suggested transition states can also explain the observed preponderance of the *cis* adducts (C-3/C-5) *vs.* the *trans* products (C-3/C-5). The ratios found: 93:7 (*N*-Bn), 91:9 (*N*-Ph), and 86:14 (*N*-Me) (Scheme 22, entries 1-3), point out that the steric hindrance between the phenyl group in the dipolarophile and the *N*-substituent in the dipole in the *exo* approach, leading to the 3,5-*trans*-isoxazolidine adducts **55** and **56**, is responsible for the high diastereoselectivity of the nitrones **38a-c** in the order **38b** (*N*-Bn) >**38a** (*N*-Ph) >**38c** (*N*-Me). This explanation, that steric factors are clearly important for the orientation of the dipoles **38a-c** in the cycloaddition to styrene, is also supported by the fact, that the cycloaddition of the D-*threo* nitrone **57** proceeds with the best *anti*-facial (93:7) and *endo*-facial (95:5) preference in this series (entry 4). The results, on the stereoselectivity of the chiral nitrones **36** and **37** to styrene, are in accord with the aforementioned importance of steric factors (Scheme 22, entries 5 and 6) [70-72].

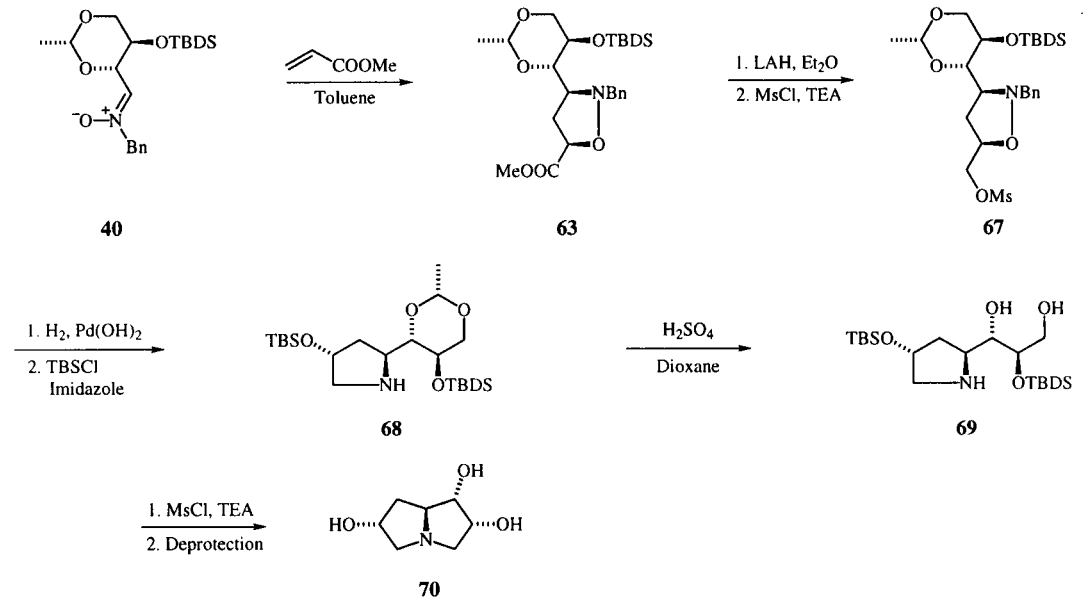
The cycloaddition of the nitrone **38b** with methyl acrylate was less selective and the stereoisomers **63-66** were found in the ratio of 48 (**63**):29 (**64**):18 (**65**):5 (**66**) [83]. We have dramatically improved this selectivity by protecting β-hydroxy group of this nitrone with a *t*-butyldimethylsilyl group (87:6:5:2). The protected D-*erythro* nitrone **40** gave the major adduct **63** (R = TBDS) in 83% yield (Scheme 24) [83].

In Scheme 25 we show an efficient synthesis of polyhydroxylated derivatives of pyrolizidines **70** related to *australine*, *alexine* and *hastanecine* [84-87] *via* an asymmet-

Scheme 24



Scheme 25



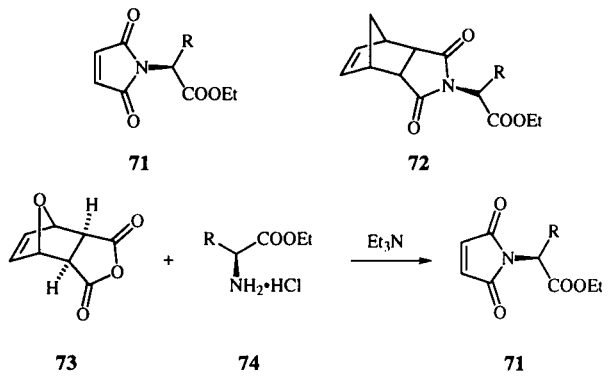
ric 1,3-dipolar cycloaddition between a nitrone **40** derived from erythrose protected with *t*-butyldimethylsilyl group, which was more selective then unprotected nitrone (83% *vs.* 48%), and methyl acrylate [83]. The key feature of the synthesis involves *anti*-diastereoselective 1,3-dipolar cycloaddition followed by subsequent reduction for cleavage of the N-O bond of chromatographically separated major adduct **63** together with the removal of the benzyl group in the protected isoxazolidine **67** (Scheme 25) [83]. Thus, the cycloaddition of the *C*-(α-alkoxy)-substituted chiral nitrones to alkenes would appear to proceed with useful stereoselectivity, but the nature of the stereoselectivity is dependent upon the precise functionality present in the nitrone.

6. Chiral Maleimides.

In the last part of my lecture I would like to present the preparation of chiral maleimides **71** derived from chiral amino acids. Although the maleimide moiety can be used in synthesis, for example as a Michael acceptor, a dienophile as well as a dipolarophile, there are few reports for the synthesis of such *N*-substituted chiral maleimides [88]. To the best of our knowledge, the chiral maleimides **71** derived from amino acids have not been described before. Most methods for the preparation of maleimides involve the reaction of an amine with maleic anhydride, followed by dehydration of the intermediate maleamic acid, usually promoted by acids, which is not successful in the case of amino acids. Recently, Biagini and co-workers [89] published a simple synthesis of amino acids derivatives **72**, which contains the norbornene moiety. Some years ago we have described that oxabicyclic derivatives react with 1,3-dipoles to give the products where furan has been extruded [90]. Since the method using a maleic anhydride in the case of amino acid derivatives was not successful, we have chosen the oxabicyclic anhydride **73**, the readily available *exo*-Diels-Alder adduct of furan and maleic anhydride, as a vehicle which in turn reacted with hydrochlorides of amino acids **74a-f** in the presence of Et_3N with release of furan to give the novel chiral maleimides **71a-f** in moderate to good yield (40-60%) (Scheme 26) [91]. For comparison, the yields reported for detailed application of the Biagini method [89] used for norbornyl derivatives in all cases were low (Method A), and for (*S*)-alanine **71a** and (*S*)-valine **71b** derivatives this synthetic route was not successful. We have found a simplified method. The reaction mixture was purified by column chromatography (Method B). Simplification of this synthetic step increased the yields of all derivatives and we have also isolated maleimide derivatives of (*S*)-alanine (**71a**), (*S*)-valine (**71b**) and of (*S*)-tryptophane (**71f**) in moderate yield (Scheme 26) [91].

As a second product in all cases the chiral fumaric acid *N*-substituted monoamides **76** were formed (20-60%) (Scheme 27). The structure of one of these compounds

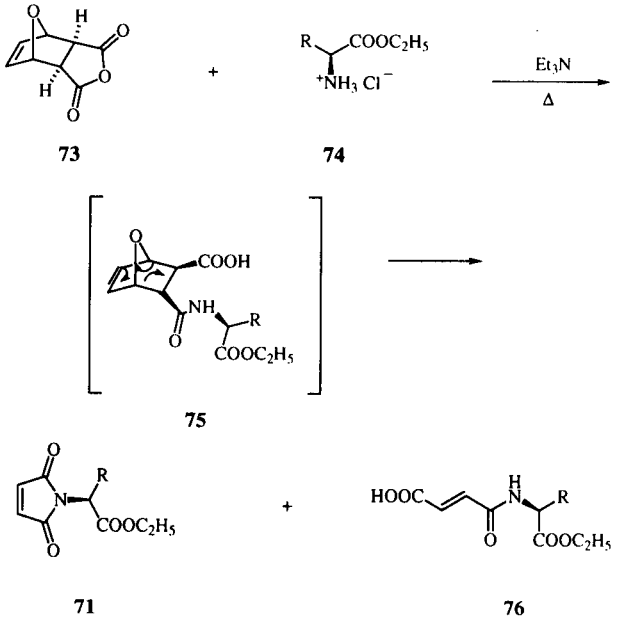
Scheme 26



Compound	R	Method A Yield (%)	Method B Yield (%)
71a	(*S*)-Ala	< 5	28
71b	(*S*)-Val	< 5	50
71c	(*S*)-Leu	24	44
71d	(*S*)-Ser	16	[a]
71e	(*S*)-Asp	39	62
71f	(*S*)-Trp	[a]	50
71g	(*S*)-Isoleu	[a]	[a]

[a] This method was not tried.

Scheme 27



(*E*)-**76** was clearly proven by ^1H nmr spectroscopy (large coupling constant $J_{2,3}$ = 14-16 Hz). We have found that a protocol for such preparation of maleimides **71** is given with temperatures above 90°. Performing the reaction by heating in benzene, only signals for the uncyclized intermediate **75** were detected. We suppose that at high temperature two competitive reactions are possible. The uncyclized maleamic acid derivatives **75** can cyclize to form the corresponding oxatricyclic derivatives which undergo *retro*-Diels-Alder reaction and the respective chiral maleimides **71** are formed; or the intermediates **75** can isomerize by treatment with Et_3N to give *trans*-**75** and hence the more stable fumaramides **76** on cycloreversion (Scheme 27) [91].

The compounds related to the amides **76** are rare and similar to some natural antibiotics (Scheme 28) [92-95]. Despite important biological properties, there are only a few reports on the synthesis of such analogues of active fumaric acid derivatives [94,95]. Most methods involve reactions of fumaric acid chloride or ester [94], or enzymatic routes [95]. Therefore, we have focused our interest on finding some new methods for the synthesis of such fumarates **76**, possessing potential biological activity. As has been mentioned before, the use of Et_3N as a base in the reaction of hydrochlorides of amino acid derivatives with oxabicyclic anhydride **73** leads to the formation of two products, maleimides **71** and fumaramides **76**. We have therefore tried to use other bases for faster epimerization of **75**. Indeed, when triethylamine was replaced with pyridine at the same conditions only derivatives of fumaric acid amide **76** were isolated (Scheme 28) [96].

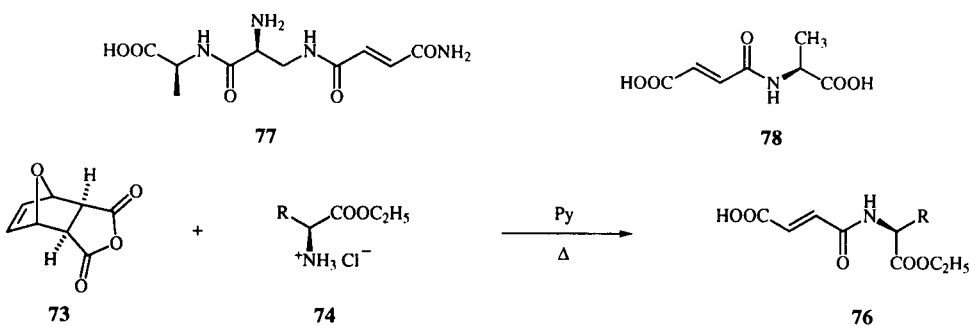
Our efforts in increasing the yields of maleimides were rewarded by the reaction of the oxabicyclic anhydride **73** with chiral amino acids **79** in water. Using microwave irradiation, we obtained good to excellent yields of maleimides **80** (Scheme 29) [97]. In contrast to the previously mentioned reaction conditions, the transformation was successful also with free amino acids. Based on this, we have obtained excellent yields of maleimides **80** using water as a solvent by conventional heating (Scheme 30) [97]. Thus, a new route for the synthesis of novel chiral maleimides **71**, **80**, and chiral fumaramides **76** related to natural antibiotics have been developed. This synthetic approach is short and uses only readily available and cheap starting materials and reagents.

Next, some nitrile oxide cycloadditions with the chiral imides **71** were tested with the aim to investigate the asymmetric induction in these additions. The mixture of stereoisomers, however was observed with poor to moderate stereoselectivity. The ratios of diastereomers show some dependence on the *N*-substituent of maleimide skeleton **71**. 1,3-Dipolar cycloadditions of nitrile oxides and nitrones proceeded with moderate diastereoselectivity. Further studies are currently in progress.

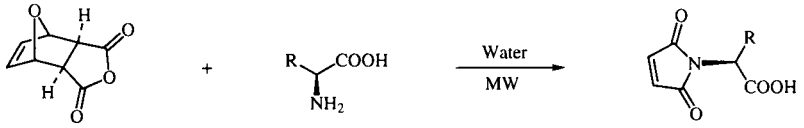
Acknowledgements.

I am pleased to express my sincere gratitude to my research students and other co-workers for their enthusiasm. Their names are mentioned in the list of references. The authors are grateful to the Slovak Grant Agency (No. I/4210/97) and Volkswagen-Stiftung (especially to Dr. A. Fliess) for financial support. V. O., J. K. and I. B. thank the Volkswagen-Stiftung for providing research stays at the University of Stuttgart (VW Special Programme, Project I/72948).

Scheme 28



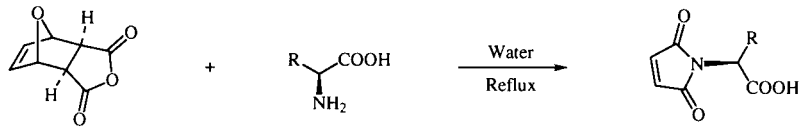
Scheme 29



73 79 80

R	Power	Time	Yield %
Gly	500 W	4 x 35 sec	80
(*S*)-Ala	500 W	4 x 35 sec	60
(*S*)-Val	500 W	5 x 35 sec	71
(*S*)-Leu	500 W	4 x 35 sec	85
(*S*)-Ile	500 W	5 x 60 sec	81
(*S*)-Ser	500 W	5 x 45 sec	92
(*S*)-Trp	500 W	2 x 60 sec	72

Scheme 30



73 79 80

R	Time	Yield %
Gly	2 h	86
(*S*)-Ala	2 h	85
(*S*)-Val	2 h	91
(*S*)-Leu	2 h	93
(*S*)-Ile	2 h	83
(*S*)-Asp	2 h	92
(*S*)-Trp	2 h	75

REFERENCES AND NOTES

[1] A. Padwa, 1,3-Dipolar Cycloaddition Chemistry, Vol **2**, A. Padwa, ed, John Wiley & Sons, New York, 1984, pp 277-406.

[2] K. B. G. Torssell, Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis, Verlag Chemie, New York, 1988.

[3a] V. Jäger, I. Müller, R. Schohe, M. Frey, R. Ehrler, B. Häfele and D. Schröter, *Lect. Heterocyclic Chem.*, **8**, 79 (1985); [b] V. Jäger, V. Buss and W. Schwab, *Tetrahedron Letters*, 3133 (1978).

[4] J. J. Tufariello, in 1,3-Dipolar Cycloaddition Chemistry, Vol **2**, A. Padwa, ed, John Wiley & Sons, New York, 1984, pp 83-168.

[5] M. Frederickson, *Tetrahedron*, **53**, 403 (1997).

[6] K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, 863 (1998).

[7] P. Grünanger and P. Vita-Finzi, Isoxazoles, Part One. In The Chemistry of Heterocyclic Compounds, E. C. Taylor and A. Weissberger, eds, Wiley, New York, 1991.

[8] S. A. Lang, Jr. and Y.-I. Lin, Comprehensive Heterocyclic Chemistry, Vol **6**, K. T. Potts, ed, Pergamon Press, Oxford, 1984, Chapter 4.16.

[9] W. Carruthers, Cycloaddition Reactions in Organic Synthesis, Pergamon Press, Oxford, 1990, pp 285-297.

[10] S. Kanemasa and O. Tsuge, *Heterocycles*, **30**, 719 (1990).

[11] L'. Fišera, The Photochemistry of Isoxazolines, In Chemistry of Heterocyclic Compounds, J. Kováč and P. Zálupský, eds, Elsevier, 1988, p 12.

[12] L. Raimondi, *Gazz. Chim. Italiana*, **127**, 167 (1997).

[13] L'. Fišera and P. Oravec, *Coll. Czech. Chem. Commun.*, **52**, 1315 (1987).

[14] P. Oravec, L'. Fišera and R. Gažo, *Monatsh. Chem.*, **122**, 165 (1991).

[15a] U. A. R. Al-Timari and L'. Fišera, *Carbohydrate Res.*, **218**, 121 (1991); [b] V. Jäger, R. Franz, W. Schwab, B. Häfele, D. Schröter, D. Schäfer, W. Hümmer, E. Guntrum and B. Seidel, Stereoselectivity of Isoxazoline Formation in Nitrile Oxide Cycloadditions to Chiral Enitols and Pentenolides, In Chemistry of Heterocyclic Compounds, J. Kováč and P. Zálupský, eds, Elsevier, 1988, p 58.

[16] U. A. R. Al-Timari, L'. Fišera, I. Goljer and P. Ertl, *Carbohydrate Res.*, **226**, 49 (1992).

[17] P. Oravec, L'. Fišera, P. Ertl and D. Végh, *Monatsh. Chem.*, **122**, 821 (1991).

[18] L. Jarošková, L'. Fišera, J. Maláková, N. Prónayová and P. Ertl, *Chem. Papers*, **48**, 404 (1994).

[19] P. Oravec, L'. Fišera, I. Goljer and P. Ertl, *Monatsh. Chem.*, **122**, 977 (1991).

[20] L. Jarošková, L'. Fišera, I. Matejková, P. Ertl and N. Prónayová, *Monatsh. Chem.*, **125**, 1413 (1994).

[21] J. Kobayashi, M. Tsuda, K. Agemi, H. Shigemori, M. Ishibashi, T. Sasaki and Y. Mikami, *Tetrahedron*, **47**, 6617 (1991).

[22] A. Longeon, M. Guoyot and J. Vacelet, *Experimentia*, **46**, 548 (1990).

[23] L'. Fišera, M. Konopíková, P. Ertl and N. Prónayová, *Monatsh. Chem.*, **125**, 301 (1994).

[24] L'. Fišera, F. Sauter, J. Fröhlich, Y. Feng, P. Ertl and K. Mereiter, *Monatsh. Chem.*, **125**, 553 (1994).

[25] L'. Fišera, F. Sauter, J. Fröhlich, Y. Feng and K. Mereiter, *Monatsh. Chem.*, **125**, 909 (1994).

[26] J. Fröhlich, L'. Fišera, F. Sauter, Y. Feng and P. Ertl, *Monatsh. Chem.*, **126**, 75 (1995).

[27] L'. Fišera, L. Jarošková, I. Matejková and H. Heimgartner, *Heterocycles*, **40**, 271 (1995).

[28] L'. Fišera, L. Jarošková, A. Lévai, E. Jedlovská, G. Tóth and M. Poláková, *Heterocycles*, **45**, 1651 (1997).

[29a] P. Mičúch, L'. Fišera, V. Ondruš and P. Ertl, *Molecules*, **2**, 57 (1997); [b] R. Anulewicz-Ostrowska, E. Pietka, T. M. Krygowski, P. Mičúch and L'. Fišera, *Polish. J. Chem.*, **73**, 727 (1999).

[30] C. Belaud, C. Roussakis, Y. Letourneux, N. E. Alami and J. Villieras, *Synth. Commun.*, **15**, 1233 (1985).

[31] N. Petragnani, H. M. C. Ferraz and G. V. J. Silvia, *Synthesis*, 157 (1986).

[32] S. K. Panday, D. Griffart-Brunet and N. Langlois, *Tetrahedron Letters*, **35**, 6673 (1994).

[33] C. Papageorgiou and C. Benezra, *J. Org. Chem.*, **50**, 157 (1985).

[34] S. Kanemasa, M. Nishiuchi, A. Kamimura and K. Hori, *J. Am. Chem. Soc.*, **116**, 2324 (1994).

[35] S. Kanemasa and S. Kobayashi, *Bull. Chem. Soc. Japan*, **66**, 2685 (1993).

[36] Y. Ukaji, K. Sada and K. Inomata, *Chem. Letters*, 1847 (1993).

[37] P. Mičúch, L'. Fišera, M. K. Cyrański and T. M. Krygowski, *Tetrahedron Letters*, **40**, 167 (1999).

[38] A. Bernardi, M. G. Beretta, L. Colombo, C. Gennari, G. Poli, and C. Scolastico, *J. Org. Chem.*, **50**, 4442 (1985).

[39] C. Papageorgiou and C. Benezra, *J. Org. Chem.*, **50**, 157 (1985).

[40] A. Foucaud and F. E. Guemmout, *Bull. Soc. Chim. France*, 403 (1989).

[41] K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jäger, R. Schohe and F. R. Fronczek, *J. Am. Chem. Soc.*, **106**, 3880 (1984).

[42] P. C. B. Page, M. Purdle and D. Lathbury, *Tetrahedron*, **53**, 7365 (1997).

[43] Dictionary of Natural Compounds, Vol **4**, Chapman and Hall, London, 1994.

[44] B. Häfele and V. Jäger, *Liebigs. Ann. Chem.*, 85 (1987).

[45] I. Panfil, C. Belzecki, Z. Urbanczyk-Lipkowska and M. Chmielewski, *Tetrahedron*, **47**, 10087 (1991).

[46] M. T. Rispens, E. Keller, B. DeLange, R. W. J. Zijlstra and B. L. Feringa, *Tetrahedron: Asymmetry*, **5**, 607 (1994).

[47] N. Langlois, N. V. Bac, N. Dahuron, J.-M. Delcroix, A. Deyine, D. Griffart-Brunet, A. Chiaroni and C. Riche, *Tetrahedron*, **51**, 3571 (1995).

[48] A. J. Blake, T. A. Cook, A. C. Forsyth, R. O. Gould and R. M. Paton, *Tetrahedron*, **48**, 8053 (1992).

[49] S. Baskaran and G. K. Trivedi, *J. Chem. Res. (S)*, 308 (1995).

[50] L'. Fišera, V. Jäger, L. Jarošková, J. Kubáň and V. Ondruš, *Khim. Geterotcykl. Soedin.*, 1350 (1995).

[51] V. Ondruš, M. Orság, L'. Fišera, and N. Prónayová, *Chem. Papers*, **51**, 161 (1997).

[52] V. Ondruš, M. Orság, L'. Fišera and N. Prónayová, *Chem. Papers*, **51**, 372 (1997).

[53] V. Ondruš, M. Orság, L'. Fišera, and N. Prónayová, *Tetrahedron*, **55**, 10425 (1999).

[54] L'. Fišera, U. A. R. Al-Timari and P. Ertl, in Cycloadditions in Carbohydrate Chemistry, R. M. Giuliano, ed, ACS Monograph, Am. Chem. Soc., Washington, 1992, p 158.

[55] M. Cinquini and F. Cozzi, in Stereoselective Synthesis, Vol **E 21c**, Houben-Weyl, G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, eds, Thieme Stuttgart, New York, 1995, p 2953.

[56] S. Kanemasa and T. Tsuruoka, *Chem. Letters*, 49 (1995).

[57] K. V. Gothelf and K. A. Jorgensen, *J. Org. Chem.*, **59**, 5687 (1994).

[58] S. Kanemasa, T. Tsuruoka and H. Yamamoto, *Tetrahedron Letters*, **36**, 5019 (1995).

[59] J.-P. G. Seerden, M. M. M. Boren and H. W. Scheeren, *Tetrahedron*, **53**, 11843 (1997).

[60] K. V. Gothelf and K. A. Jorgensen, *Acta Chem. Scand.*, **50**, 652 (1996).

[61] K. V. Gothelf, R. G. Hazell and K. A. Jorgensen, *J. Org. Chem.*, **61**, 346 (1996).

[62] S. S. Bari, A. K. Bose, A. G. Chaudhary, M. S. Manhas, V. S. Raju and E. W. Robb, *J. Chem. Educ.*, **69**, 938 (1992).

[63] B. Bernet and A. Vasella, *Helv. Chim. Acta.*, **62**, 2411 (1979).

[64] A. Brandi, S. Cicchi, A. Goti and K. M. Pietrusiewicz, *Tetrahedron: Asymmetry*, **2**, 1063 (1991).

[65] S. Saito, T. Ishikawa, N. Kishimoto, T. Kohara and T. Moriwake, *Synlett*, 282 (1994).

[66] T. Kametani, S. D. Chu and T. Honda, *Heterocycles*, **25**, 241 (1987).

[67] E. G. Baggiolini, J. A. Iacobelli, B. M. Hennesy, A. D. Batcho, J. F. Sereno and M. R. Uskokovic, *J. Org. Chem.*, **51**, 3098 (1986).

[68] U. A. R. Al-Timari, L'. Fišera, P. Ertl, I. Goljer and N. Prónayová, *Monatsh. Chem.*, **123**, 999 (1992).

[69a] A. Dondoni, S. Franco, F. Junquera, F. Merchán, P. Merino and T. Tejero, *Synth. Commun.*, **24**, 2537 (1994); [b] P. Merino, E. Castillo, S. Franco, F. L. Merchan and T. Tejero, *J. Org. Chem.*, **63**, 2371 (1998).

[70] J. Kubáň, I. Blanáriková, L'. Fišera and N. Prónayová, *Chem. Papers*, **51**, 378 (1997).

[71] J. Kubáň, I. Blanáriková, M. Fengler-Veith, V. Jäger and L'. Fišera, *Chem. Papers*, **52**, 780 (1998).

[72] J. Kubáň, I. Blanáriková, L'. Fišera, L. Jarošková, M. Fengler-Veith, V. Jäger, J. Kožíšek O. Humpa, N. Prónayová and V. Langer, *Tetrahedron*, **55**, 9501 (1999).

[73] V. Jäger, B. Häfele, R. Müller, T. Leibold, D. J. Zimmermann and M. Fengler-Veith, unpublished results.

[74a] P. DeShong, C. M. Dicken, J. M. Leginus and R. R. Whittle, *J. Am. Chem. Soc.* **106**, 5598 (1984); [b] M. J. Fray, R. H. Jones and E. J. Thomas, *J. Chem. Soc. Perkin Trans. 1*, 2753 (1985).

[75] R. C. Hockett, D. V. Collins and A. Scattergood, *J. Am. Chem. Soc.*, **73**, 599 (1951).

[76] R. Barker and D. L. MacDonald, *J. Am. Chem. Soc.*, **82**, 2301 (1960).

[77a] M. Fengler-Veith, O. Schwardt, U. Kautz, B. Krämer and V. Jäger, *Org. Synth.*, accepted for checking; [b] M. Fengler-Veith, Dissertation, Universität Stuttgart, 1996.

[78] J. R. Hauske and H. Rapoport, *J. Org. Chem.*, **44**, 2472 (1979).

[79] V. Jäger, R. Müller, T. Leibold, M. Hein, M. Schwarz, M. Fengler, L. Jarošková, M. Pätzel, P.-Y. LeRoy, *Bull. Soc. Chim. Belgium* **103**, 491 (1994).

[80] V. Jäger and M. Fengler-Veith, unpublished results.

[81] K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jäger, R. Schohe and F. R. Fronczek, *J. Am. Chem. Soc.*, **106**, 3880 (1984).

[82a] D. H. Ball and J. K. N. Jones, *J. Chem. Soc.*, 905 (1958); [b] D. H. Ball, *J. Org. Chem.* **31**, 220 (1966).

[83] J. Kubáň, I. Blanáriková, Ľ. Fišera, M. Fengler-Veith, V. Jäger, O. Humpa and N. Prónayová, unpublished results; J. Kubáň, Dissertation, Slovak University of Technology, 1999.

[84] S. E. Denmark, A. R. Hurd and H. J. Sacha, *J. Org. Chem.*, **62**, 1668 (1997).

[85] A. E. McGaig, K. P. Meldrum and R. H. Wightman, *Tetrahedron*, **54**, 9429 (1998).

[86] A. Hall, K. P. Meldrum, P. R. Therond and R. H. Wightman, *Synlett*, 123 (1997).

[87] R. Müller, T. Leibold, M. Pätzel and V. Jäger, *Angew. Chem. Int. Ed. Engl.*, 1295 (1994).

[88] N. E. Searle, U. S. Patent 2,444,536 (1948); *Chem. Abstr.*, **42**, 7340 (1948).

[89] S. C. G. Biagini, S. M. Bush, V. C. Gibson, L. Mazzariol, M. North, W. G. Teasdale, C. M. Williams, G. Zagotto and D. Zamuner, *Tetrahedron*, **51**, 7247 (1995).

[90] Ľ. Fišera, F. Považanec, P. Zálupský, J. Kováč and D. Pavlovič, *Coll. Czech. Chem. Commun.*, **48**, 3144 (1983).

[91] V. Ondruš and Ľ. Fišera, *Molecules*, **2**, 49 (1997).

[92] H. B. Maruyama, Y. Suhara, J. Suzuki-Watanabe, Y. Maeshima, N. Shimizu, M. Ogura-Hamada, H. Fujimoto and K. Takano, *J. Antibiot.*, **28**, 636 (1975).

[93] Y. Suhara, H. B. Maruyama, Y. Kotoh, Y. Miyasaka, K. Yokose, H. Shirai, K. Takano, P. Quitt and P. Lanz, *J. Antibiot.*, **28**, 648 (1975).

[94] J. L. van der Baan, J. W. F. K. Barnick and F. Bickelhaupt, *J. Antibiot.*, **36**, 784 (1983).

[95] D. Rossi, A. Calcagni and A. Romeo, *J. Org. Chem.* **44**, 2222 (1979).

[96] V. Ondruš, Ľ. Fišera and N. Prónayová, *Chem. Papers*, **51**, 164 (1997).

[97] V. Ondruš, Ľ. Fišera and V. Bradáč, unpublished results.