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Studies on Cycloaddition Reactions of 2,2-Dimethyl-3,4-dihydro-2*H*-pyrrole N-Oxide and *N*-(benzylidene)methylamine *N*-oxide with α,β-Unsaturated Lactones & Esters.

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Abstract: Intermolecular asymmetric 1,3-dipolar cycloaddition of 2,2-dimethyl-3,4-dihydro-2*H*- pyrrole *N*-oxide and *N*-(benzylidene)methylamine *N*-oxide with optically active α,β-unsaturated esters **1,2,4** and **7-9** provided the corresponding diastereomers while chiral sugar lactones gave stereoselectively the cycloadducts **17a** and **17b** (in the case of dipolarophile **3**) and **18** in (the case of the dipolarophile **6**) with the acyclic nitrone **B**. The stereochemistry of the products has been established using high field **nmr** techniques. The regioselectivities of these reactions are inconsistent with **FMO** coefficients and are explained on the basis of charge distribution obtained through **AM1** calculations. © 1997 Elsevier Science Ltd.

[3+2] Cycloaddition of nitrones to alkenes has become a method of choice for syntheses of a wide variety of molecules.[1-3] According to Sustmann's classification,[4] the nitrone cycloaddition is a type II process and the product distribution is governed by both sets of HOMO-LUMO interactions. Steric factors and secondary orbital interactions usually dictate the stereochemical outcome of the cycloadditions.[5-7] A high degree of regio- and stereo-selectivity signifies the importance of this methodology. Cycloadditions of cyclic achiral nitrones with achiral unsaturated esters and lactones have been reported,[8] as has been a similar study on chiral unsaturated sugar lactones and acyclic nitrones.[9,10] However, the behavior of cyclic and acyclic achiral/chiral nitrones towards chiral unsaturated esters and lactones has received little attention.

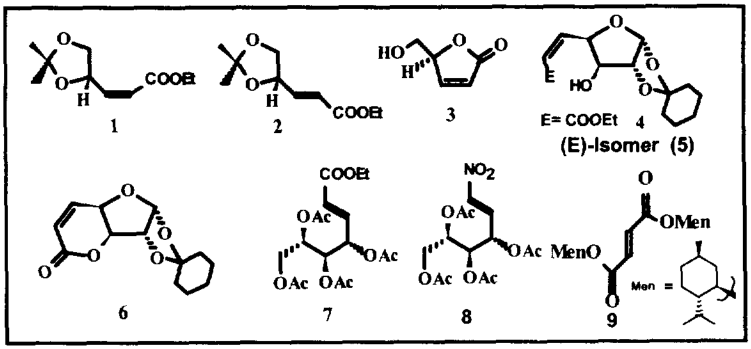
Recently, we reported the 1,3-dipolar cycloaddition of nitrone[11] and diazomethane[12] to enantiomerically pure esters and lactones with an alkoxy-substitutent in the γ-position leading to the regio and stereoselective formation of the isoxazolidines and pyrazolines. These results prompted us to investigate the addition of five membered cyclic nitrone and *C*-phenyl-*N*-methyl nitrone to various unsaturated esters and lactones and thereby to observe the regio- and stereo-chemical outcome as well as the diastereoselectivity of cycloaddition. Apart from selectivity aspects, the isoxazolidines formed should be of interest as precursors for the synthesis of a variety of amino alcohol derivatives.

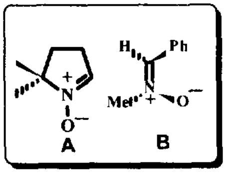
Intermolecular nitrone cycloaddition reactions on chiral electrophilic olefins were undertaken with the objective to evaluate the influence of steric and stereoelectronic factors on the outcome of this process. Chiral dipolarophiles were synthesised by utilising literature as well as our improved procedures. Some of the dipolarophiles were chosen as models for conformationally biased systems (E or Z) containing a center of chirality at the allylic carbon.

Section A: Cycloaddition of 2,2-dimethyl-3,4-dihydro-2*H*-pyrrole *N*-oxide (A)

Since the geometry of the nitrone is known to control the stereochemical outcome of products, it was decided to circumvent any complexity arising out of E-Z isomerisation of the nitrone during the reaction by employing 2,2-dimethyl-3,4-dihydro-2*H*-pyrrole *N*-oxide (**A**). This choice of nitrone may also enable us to relate the stereochemistry of the product directly with the *exo/endo*-selectivity of the cycloaddition. However, the present stereochemical study could introduce one more problem, *viz.* the difficulty associated with the unambiguous stereochemical assignment of adducts having three new stereogenic centers. A detailed configurational investigation of the cycloadducts based on 2D (^{1}H-^{1}H) COSY, NOESY and ^{1}H-^{13}C HETCOR techniques and cyclisation experiments have enabled us to establish unequivocally their stereochemistry and thereby to deduce the regio- and *exo/endo*- selectivity of these reactions.

For this purpose, some stereochemically well defined dipolarophiles (**1-9**) were synthesized and condensed with cyclic nitrone **A** and acyclic nitrone **B**. The choice of dipolarophiles was governed by the following considerations;

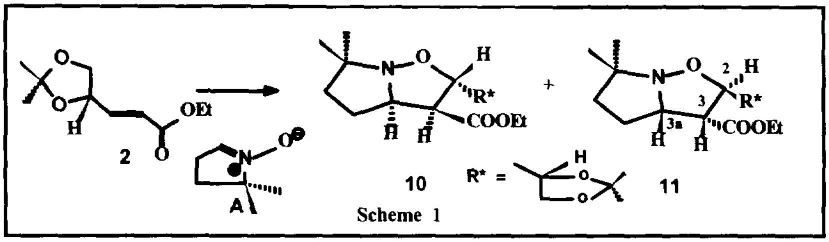




a) the remoteness of the stereogenic center from the site of addition, **b)** the nature and geometry of electrophilic olefins (E and Z) and **c)** the presence or absence of allylic acyloxy or alkoxy groups.

Compounds **1-3**,[13] and **7-8**[14] were synthesised according to the literature procedure with slight modification. The dipolarophiles **4-6** were synthesised from D-glucose following our previously described method.[15]

Reaction of nitrone **A** with dipolarophiles **1** and **3-6** were discussed earlier.[11a] The dipolarophile **1** provided three of the possible eight diastereomeric cycloadducts whereas the dipolarophile **3** and **6** provided only one of their respective adducts.[11a] The cycloaddition of **A** was attempted on **2** in refluxing chloroform (Scheme 1) and in benzene, but no reaction occurred. However, condensation of **A** with the dipolarophile **2** for 200h in refluxing toluene resulted in the formation of a mixture of cycloadducts **10** and **11** in equal proportions which were separated by column chromatography.

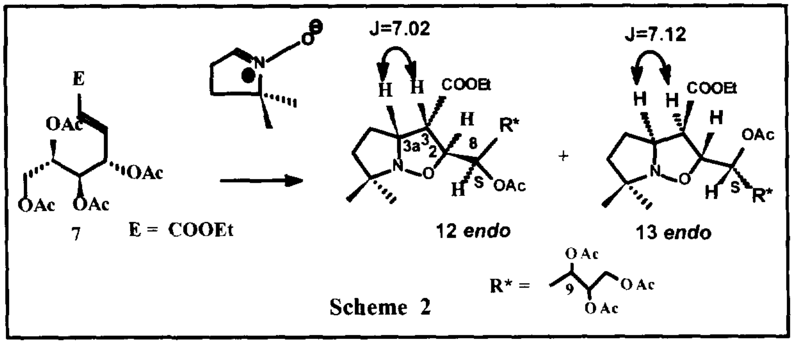


Scheme 1

The regiochemical features of the cycloadducts were readily deduced from the ^1H NMR spectrum of the pure cycloadducts. In each case, one proton double doublets at δ 4.31 and 4.37 corresponded to the H-2 proton of compounds **10** and **11**. For compound **10**, the H-3 proton appears as a double doublet at δ 3.64 with $J_{3,3a}$ 6.96 indicating it to be *cis* coupled with the H-3a. Since the nitrone addition is reported to take place with the retention of configuration, H-2 and H-3 should be *trans* oriented and hence the cyclisation experiment[11a] was not tried to find out the absolute stereochemistry.

Similarly, for the adduct **11**, H-3 proton absorbs at δ 3.59 with $J_{3,3a}$ 7.69 indicating a *cis* relationship between H-3 and H-3a proton. All the other protons viz., H-3a,4' and 5' appeared as a multiplet between δ 3.8 and 4.3 ppm. Both the products show a *cis* coupling between H-3 and H-3a and hence must have arisen via an *endo* transition state corresponding to the two diastereotopic faces of the dipolarophiles. The reaction was found to be regiospecific and probable products arising due to reverse nitrone cycloaddition were not observed. The above findings were confirmed by comparison with the related literature report.[16a]

We next studied the cycloaddition of dipole **A** with an enoate **7**, having a chiral allylic alkoxy moiety on a linear unit. Thus dipole **A** and dipolarophile **7** were refluxed in benzene and the reaction was monitored by t.l.c. The two cycloadducts formed in the ratio of 1:1.5 were separated by column chromatography and are designated as **12** and **13** in the increasing order of polarity (Scheme 2).



Scheme 2

The ^1H NMR data of both the compounds were well in agreement with the expected regiochemistry having higher chemical shift for the β carbonylic proton, H-2 (δ 4.29 for compound **12** and δ 4.44 for **13**) than the α carbonylic proton H-3 (δ 3.70 for **12** and δ 3.48 for **13**). The coupling constant value of 7.02 Hz for **12** and 7.12 Hz for **13** between H-3 and 3a denotes that H-3 is *cis* coupled with H-3a. This confirms the *endo* geometries of the cycloadducts. The *endo* stereochemistry for the ethoxycarbonyl at C-3 in **12** and **13** is reasonable since the steric strain due to the side chain and the pyrrolidine ring is relieved in this orientation.[16b] Also the transition state with 3-*endo* carbethoxy orientation has[16b] relatively less steric crowding as well as favorable secondary orbital interactions. The 1,3-dipolar cycloaddition reactions are known to proceed in an concerted fashion with the retention of olefinic substituent configuration. Therefore, the E-configuration of the dipolarophiles dictates that H-3 and H-2 should be *trans* to each other in both the compounds. These assignments were further confirmed by COSY experiments. The double doublet at δ 5.53 for the compound **12** was assigned to H-9 of the side chain, which showed a cross-peak connectivity with H-8 located at δ 5.28. The signal at δ 5.53 also showed a connectivity with H-2 at δ 4.29. The chemical shift of H-3 (δ 3.70) and H-3a (δ 4.05) could be worked out through the connectivities between H-2 and H-3 as well as between H-3 and H-3a respectively. ^{13}C NMR and DEPT experiments were performed to support the proposed structure for the compounds.[2] From the above analysis it was now possible to unequivocally assign the regiochemistry of both adducts.

Since the two cycloadducts are not the regiomers, they should differ only by the facial approach of the dipole in the transition state (Figure 1). Though the π-facial approach of the dipole is different, very little difference in the coupling constant and chemical shift of both the isomers was noticed. This could be due to the libration of the C-C single bond (Figure 2). The observed regiospecificity during the cycloaddition is totally in agreement with the earlier studies. Thus it could be concluded that adducts **12** and **13** have arisen as a result of differential π-facial attack of the dipole on the dipolarophile and are diastereomerically related to each other.

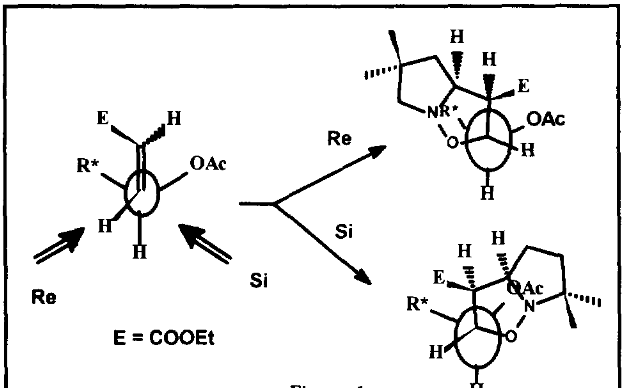


Figure 1

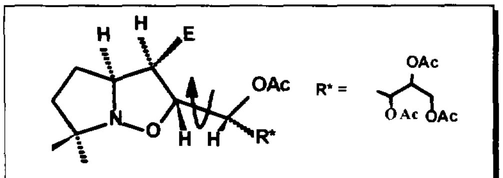
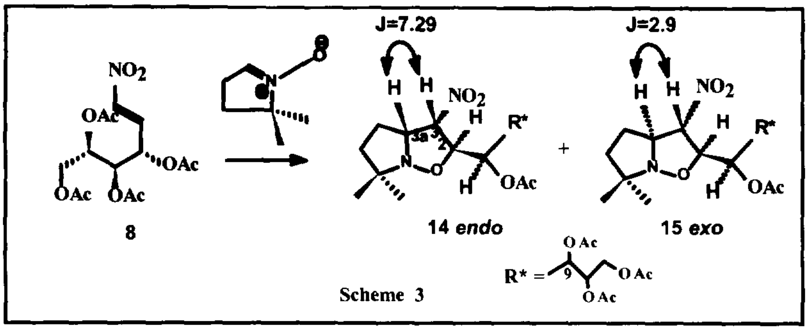


Figure 2

A similar dipolar cycloaddition of nitrone **A** with **8** was performed in benzene. Column chromatography of the crude mixture afforded two diastereomeric cycloadducts **14** and **15** in the ratio of 2:1, respectively (Scheme 3).



Scheme 3

The regiochemical features of the cycloaddition were readily deduced from the ^{1}H NMR spectrum of the pure cycloadduct. In each case a one proton double doublet was seen at δ 4.64 and 4.77 which corresponds to H-2 signals of the compound **14** and **15**, respectively. The alternative regiomeric cycloadducts were expected to show H-2 proton signals as doublets further down field due to the attachment of a nitro group. The regioselectivity of the process was further confirmed by the observed chemical shift of the H-3 proton of **14** and **15**, which appeared as double doublets at δ 5.52 and 5.48 respectively. The relative down field shift observed for H-3 in **14** and **15** compared to **12** and **13** can easily be attributed to the highly electronegative nitro substitution. The near identical value of $J_{2,3}$ (~3.02) in **14** and **15** supports the retention of the *trans* relationship of the E-dipolarophile.

A higher J value between H-3 and H-3a ($J_{3,3a}$ 7.29 Hz) in **14** shows that this product arises from a TS in which the NO_2 group of the dipolarophile and 1,3-dipole are *endo* oriented i.e., leading to a *cis* H-3a , H-3 relationship in the adduct. However, a lower J value of 2.9 Hz was observed between H-3a & H-3 for the cycloadduct **15**. This indicates that the cycloadduct accrues via the *exo* transition state. The greater preference for **14** over **15** may be accounted for by the higher steric crowding felt by the long side chain and the pyrrolidine ring in **15** than in **14**. Thus, based on mechanistic consideration and earlier analysis,[17] it could be concluded that unlike as in **12** and **13** obtained from **7**, the adducts **14** and **15** derived from **8** differ in orientation (*endo/exo*) rather than the facial topicity of the molecule.

Section B: Cycloaddtion of *N*-(benzylidene)methylamine *N*-oxide (B)

An olefin involving a stereocenter in the R* or Z^1 group (chart 1) may lead to eight diastereomers (only four of the 4-substituted regiomers are shown in chart 1) on treatment with the achiral nitrone through presumed cyclic *endo* and *exo*-transition states (with respect to Z^1).[18] However, the level of diastereoselectivity of this reaction chiefly depends on the structures of **X** and **Y** (Chart-1), which is usually unpredictable.[19]

In our continuing effort of examining the stereoselectivity of 1,3-dipolar nitrone addition to the chiral dipolarophile, we contemplated examining the role of alkoxy and vicinal diol controllers in discriminating between the diastereofaces of some of the above mentioned chiral unsaturated sugar lactones and esters with allyl oxygen moiety in the acyclic nitrone-olefin cycloaddition reaction. The regio-, and stereo-selectivity during 1,3-dipolar cycloadditions of these dipolarophiles were examined.

The reaction between nitrone **B** and dipole **1** was performed in toluene at reflux for 5 days, after trying in a few low boiling solvents. To our dismay, the cycloaddition afforded four of the eight possible isoxazolidines **16a,b,c** and **d** in moderate yield (Scheme 4). Out of the four products, the major adduct **16d** was isolated by column chromatography as a single compound and **16a**, **16b** and **16c** were collected together as a second fraction of a mixture of non-separable compounds.

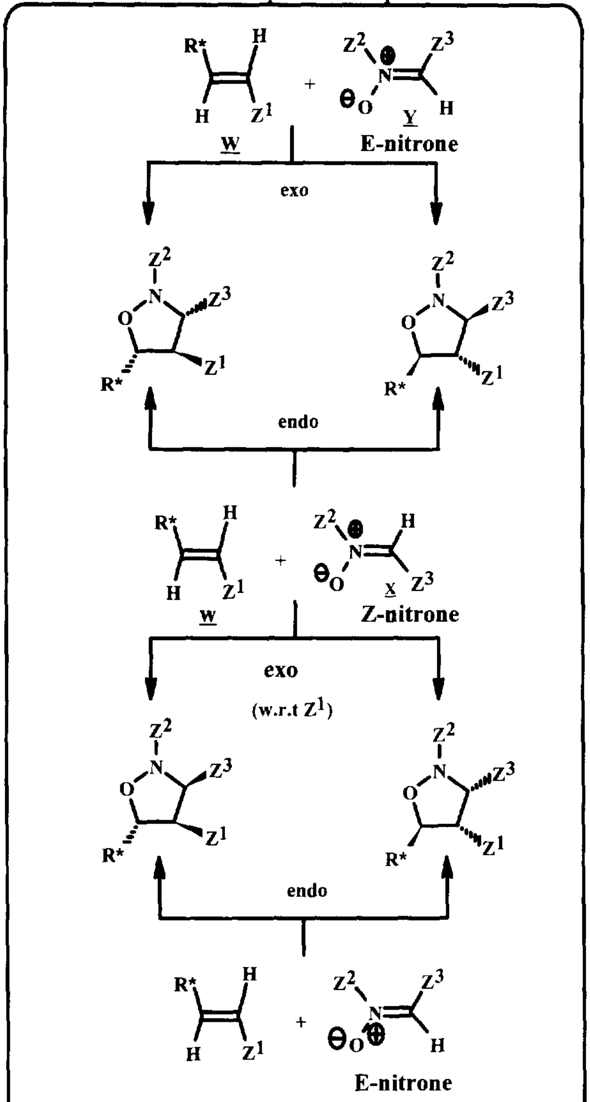
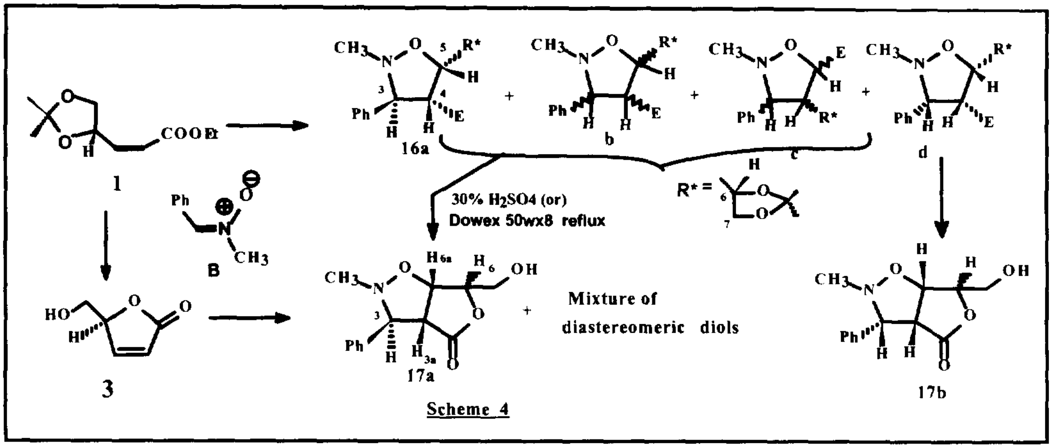


CHART 1

However, the ratio of these four adducts (1:1:1.5:2) was determined by taking into consideration the isolated yield of **16d** along with the weight of the second fraction and the ratio of **16a**, **16b** and **16c** in it by ^1H NMR spectrum. This was possible since the ethoxy methyl protons were well resolved in the spectrum of the second fraction.

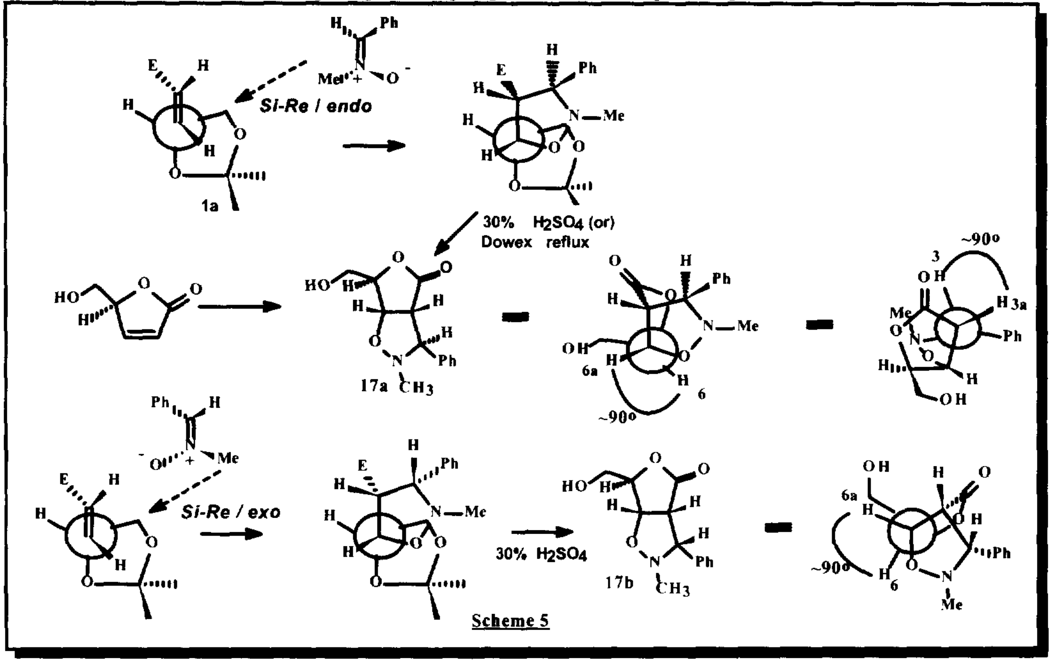


Scheme 4

The ^1H NMR chemical shifts and proton coupling constants helped in the assignment of relative dispositions of substituents in all four compounds. For compound **16d**, the down field appearing proton at δ 4.42 ppm assigned to H-5 is split as a double doublet with coupling constants 9.0 Hz and 9.2 Hz. A regiomeric product of **16**(16c) should have necessarily appeared as a doublet and hence is ruled out. Since both the coupling constants are large, 5-H is concluded to be *cis* coupled with H-4. This is in line with concerted addition of nitrone to Z-olefin. In particular, H-3 appearing at δ 4.09 as a doublet with J 9 Hz indicates the *cis* relationship between H-3 and H-4 and hence, an *exo* transition state.

For other diastereomers **16a** and **16b**, the H-4 protons appear as two triplets at δ 3.42 ppm with $J_{4,3}$ 9Hz and indicated the *exo* transition state. In all these cases, the facial approach of dipole as well as the relative stereochemistry between H-4 and H-6 or H-5 and H-6 could not be revealed by observing the coupling constant due to libration of C-4,C-6 (for compound **16c**) and C-5, C-6 (for compounds **16a,b** and **d**) sigma bonds. Hence, the adducts were lactonised using Dowex 50wx8 or H_2SO_4 (Scheme 4). From the lactonised mixture of **16a,b** and **c** only **17a** could be isolated in pure form, the remaining mixture comprising of the diols could not be resolved. The compound **16d** provided the adduct **17b**. This was further confirmed by reacting the nitrone **B** with the lactone **3** synthesised by the acid cyclisation of **1**. Fortunately, the reaction between the nitrone **B** and butenolide **3** in benzene reflux provided two isomers **17a** and **17b** (1.2:1) in 66% yield. The ^1H NMR spectrum of these adducts matched with the compounds isolated from the cyclisation experiment. The structures of lactones **17a** and **17b** were established as enumerated below.

The upfield proton H-3a for adduct **17a** appears as a doublet at δ 3.58 ppm (J 6.35 Hz) indicating a *cis* relationship between H-3a and H-6a. This establishes the *cis* fusion of rings A and B. Conspicuously the coupling between H-3a and H-3 is zero. Inspection of the models revealed that the protons at C-3 and C-3a form a dihedral angle of Ca.90° only in the *trans* orientation. This is also demonstrated by the observance of H-3 as a singlet at δ 3.69 ppm instead of a doublet (Scheme 5). These orientations of substituents are possible on *endo* approach of the dipole. According to Smadja[20] and Ortuno,[21] the more reactive conformer, **1a** determines the facial approach of the reactant with the product in the transition state. The more deshielded proton H-6a, which also probably makes an angle of 90° with H-6 and appears as a doublet at 4.91 ppm with $J_{6a,3a}$ 6.35 Hz, indicating the *antifacial* approach of the reactant in the transition state. This ultimately confirms that one of the products **16a**, accrues from ***Si-Re*** face of the dipolarophile with *antifacial* approach in an *endo* mode. The 2D COSY analysis of **17a** started with H-6a. H-6a appearing at δ 4.91 ppm showed a cross peak connectivity with H-3a centered at δ 3.58. A broad singlet centered at δ 4.63 ppm assigned for H-6 showed two cross peak connectivities with H-7 and H-7' centered at δ 3.80 and 3.96 ppm. There is no observable connectivity between H-6a and H-6 as well as between H-3 and H-3a indicating the poor coupling between the respective protons.



Scheme 5

This ultimately confirms that **16a** which is the precursor for **17a** is formed by addition of **A** to the dipolarophile from the ***Si-Re*** face with an *antifacial* approach in an *endo* mode.[22a] The structure of **16a** and **16d** differ only at the stereocenter involving the phenyl group. Remarkably, the $J_{3,4}$ coupling observed for both the molecules is around 9Hz and reflects that both the *cis* and *trans* coupling could be large.[22b]

For compound **17b,** the α-carbonylic proton H-3a, expected to be the most shielded proton, absorbs at δ 3.60 as a triplet with $J_{3a,3 \text{ and } 3a,6a}$ 8.06 Hz pointing to a *cis* relationship between all the mentioned protons, and hence, the *exo* transition state as depicted in scheme 2. The β-carbonylic proton H-6a resonates at higher chemical shift (δ 4.96 ppm) with a small coupling of $J_{6a,6}$ 2.69 Hz indicating the *trans* relationship between those two protons and hence, the adduct accrues from the ***Si-Re*** face of the dipolarophile **1** with an *exo* mode. Knowing the structures of **16a** and **16d,** adduct **16b** is concluded to be formed by attack of **A** on the ***Re-Si*** face of the dipolarophile. Since, the relative stereochemistry of H-3 and H-4 could not be determined merely by coupling between them ($J_{3,4}$ 9 Hz), the mode of approach of the dipole to the dipolarophile could not be ascertained.

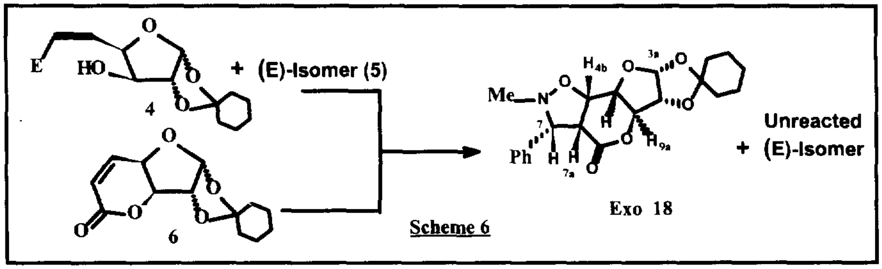
Similarly, from the ^{1}H NMR spectrum of the mixture **16a,b** and **c**, H-4 of **16c** at δ 3.1 ppm appears as a quartet ($J_{4,3} = J_{4,5} = J_{4,6}$ 9 Hz) which has its counter part H-5, appearing at δ 4.8 ppm as a doublet with coupling constant 9 Hz. This suggests the formation of C-5 ester substituted compound regiomeric with

16d. However, the structures of **16b** and **16c** could not be determined since the cyclisation experiment did not give us the expected cyclic compounds.

From our earlier observations[23] concerning the 1,3 dipolar cycloaddition of nitrone and simple olefin, we can assume that an *exo*-TS is eventually favored over *endo*. The proton of the isoxazolidine ring in relative *cis*-orientation is the consequence of the Z-configuration of nitrones and their *exo* approach to the dipolarophile. These results can also be explained by an *endo* approach of nitrone **B** in an *E* configuration. However, the difference in regiomeric distribution in case of cycloaddition of **1** with **B** is presumably dictated by the difference in steric factors in the regiomeric TS.[16] The mutual configuration can be proved by the large values of vicinal coupling constants between proton H-3, H-3a, and H-6a; which is indeed observed for adduct **17b.** The smaller value of $J_{3,3a}$ found for adduct **17a** indicates the *trans* configuration of the coupled proton and hence, an *endo*-geometry. From this reaction, it is concluded that the cycloaddition is regio- as well as face selective and the products **17a** and **17b** differ from each other only by the *endo/exo* mode of addition of dipole in the transition state.

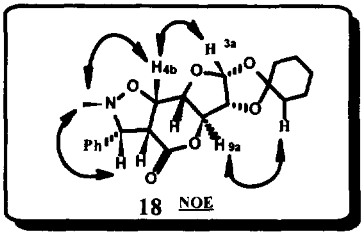
Attention was next turned to a chiral, six-membered unsaturated lactone, **6** and the esters, **4** and **5** which could serve as models for the synthesis of several optically active compounds. Very similar results were obtained compared to the furanone case, in the cycloaddition of the nitrone **B** to **4** and **5** under identical set of conditions.

The reaction of nitrone **B** with dipolarophile **4** afforded a single diastereomer **18** (Scheme 6) in 67% yield, where the absence of ethoxy methyl peak in ^1H NMR and absence of OH peak in IR confirms the formation of the cyclic adduct. In this adduct, the α-carbonylic proton H-7a which was more shielded by C=O group absorbs at δ 3.47 ppm as a double doublet with $J_{7,7a}$ 7.97 and $J_{7a,4b}$ 9.09, confirming the *cis* relationship between H-7 and H-7a and hence, an *exo* transition state. The *cis* fusion of the rings A and B was confirmed by the observed coupling constant between H-7a and H-4b. Similarly, the *antifacial* approach of the reactant in the TS could be confirmed by observing a coupling constant of 1.87 Hz between H-4b and H-4a. All these assignments were corroborated by ^{13}C and 2D NOESY experiments acquired with $\tau_m = 1$ s.



Scheme 6

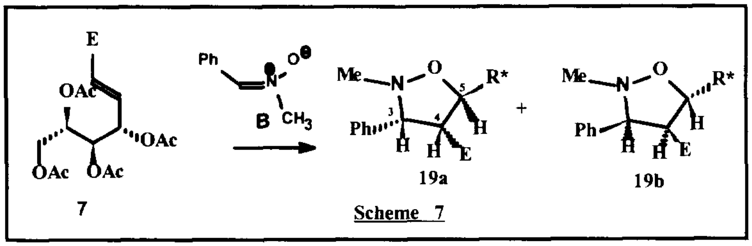
A similar result was observed on treating the pyranone **6** with the nitrone **B**. This resulted in essentially a single product which was identified as **18.** In the 2D NOESY spectrum of **18** a singlet centered at δ 2.59 assigned for N-CH_3 showed cross peak connectivities with H-7 and H-7a centered at δ 3.47. These assignments indicated a *cis* orientation of N-CH_3, H-7 and H-7a and hence an *exo* transition state (for Z-dipole). The more deshielded proton H-3a showed strong connectivities with H-4b and H-9b, indicating the *cis* relationship of these protons. Since H-9b as well as H-3a showed strong connectivities with H-4b, H-4b and H-4a should be *trans* coupled, because of the existing *trans* geometry between H-9a and H-9b in the lactone **6**.



18 NOE

Compound **18** can therefore arise either from the Z-nitrone reacting with the dipolarophile by an *exo* attack (Chart 1) or from the E-nitrone by an *endo* attack. As nitrone **B** is known[9,24,25] to exist predominantly in the Z form, therefore the former mode of attack is accepted. This is well in agreement with the reported values for other chiral lactones.[25] The addition of this dipole can be explained by chart 1 which shows the four possible modes of addition for a 4-substituted regiomer.

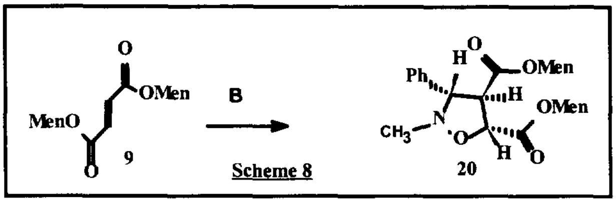
Next we undertook the cycloaddition of the acyclic nitrone **B** with the dipolarophile **7** derived from arabinose. Nitrone addition of this dipolarophile was performed in refluxing toluene. It provided a non-separable mixture of 1:1.6 ratio of two diastereomers **19a** & **19b** after five days (Scheme 7). Two triplets at δ 0.71 and 0.74 ppm assigned to $OCH_2C\underline{H}_3$ protons also indicated the formation of two diastereomers. Since the protons H-3 and H-4 appeared as a multiplet in the region of δ 3.65, the coupling constant between the nitrogen bearing methynic proton H-3 and the α-carbonylic proton H-4 could not be determined. Hence, the preferred facial approach, as well as the mode of addition (*exo/endo*) could not be resolved, but the proportion of the two isomers formed could be estimated from the integration of the H-5 proton signals resonating at δ 4.67 and 4.79. Absence of doublet at the deshielded region indicated that the C-4 ester substituted regiomer is not formed during cycloaddition.



Scheme 7

By literature analogy, these adducts could have arisen by an *exo* transition state geometry, because, the C-5 side chain cannot be *cis*-disposed with the C-3 phenyl ring due to the steric strain. Since H-5 and H-3 are *trans*, H-4 and H-3 should be in *cis* relation with each other in order to maintain the alkene geometry and hence, an *exo* transition state.

Conceptually, the formation of the two regiomers can be circumvented by using the disubstituted alkenes with identical substrates as dipolarophiles.[26] We have therefore, synthesised the chiral and symmetrically disubstituted dipolarophile **9**. The reaction between **B** and **9** was performed in benzene reflux for 2 days. The cycloaddition afforded in this case one of the four possible isoxazolidines, **20** (Scheme 8). As illustrated in Chart 1, the H-3 and H-4 *trans* isoxazolidine could arise from the E-nitrone reacting in an *exo* mode or from the Z-nitrone reacting in an *endo* mode. The proton H-5 flanked between ester and oxygen function appeared as a doublet with $J_{4,5}$ 4.73 denoting[26a] that it is *trans* coupled with H-4 as expected, which proves that the dipolar cycloaddition takes place with retention of configuration.[26a]



Scheme 8

In this case, unlike other examples, the steric effect is so decisive that it allows the nitrone to prefer the *endo* mode(Z-nitrone) of addition (3-phenyl and 4-menthyloxy are *trans*) so that steric crowding due to the *cis* phenyl and menthyloxy groups could be avoided. This was confirmed by observing the coupling constant between the H-3 and H-4 protons(J 8.54 Hz). Higher coupling values for *trans* geometry is in close agreement with the reported values for other dipolarophiles.[22,26a]

AM1 Studies:

Of the eight stereoisomeric products possible in almost all cases, only one, two or three were detected. The 3-substituted isomers (in the case of cyclic nitrone) and 4-substituted isomers (in the case of acyclic nitrone) were observed to be formed predominantly over the 2-substituted and 5-substituted ones. The origin of the stereo-selection is of interest. While a complex interplay of electronic and steric factors are likely to operate, it is useful to consider whether simplified descriptions can adequately reproduce the trends, especially the observed regiochemistry.

In order to rationalise the observed regioselectivities during the addition of cyclic nitrone A and acyclic nitrone **B** to dipolarophiles qualitatively, we have also performed **FMO** analysis using **AM1** calculated frontier orbitals.[9,27] All **HOMO-LUMO** orbital energies (Table 1) were obtained from **AM1** optimised geometries. The dominant orbital interaction can be discerned from these energies. Further, based on the usual assumption that atoms with the larger **HOMO** contribution are expected to interact more strongly with atoms with larger **LUMO** coefficient in the reaction partner, the regiochemistry can be predicted.

The computed frontier orbital energies of cyclic nitrone **A**, acyclic nitrone **B** and the dipolarophiles **1-3,6** and **7** (Table 1), reveal that the smaller **HOMO-LUMO** energy gap involves the **LUMO** of the dipolarophile and **HOMO** of the dipole. This is consistent with the qualitative expectation that the nitrones are electron rich and the dipolarophiles are electron deficient. The cycloadditions are thus dipole **HOMO** and dipolarophile **LUMO** controlled reactions. Regiochemistry should then correspond to complementarity of orbital coefficients in this set of frontier orbitals.

In all of these unsymmetrically substituted dipolarophiles, the larger **LUMO** coefficient is on the olefinic carbon β to the ester group. This is evident in the plots of the **LUMO**'s of **1** and **2** shown in figures 3 and 4. This trend is well known from calculations on similar dipolarophile at various levels of theory. The overall regiochemistry should then be governed by the polarization of the **HOMO** in the nitrone partner.

However, the frontier orbital predictions show large discrepancies in the case of nitrone, **A**. The **HOMO** is polarized only to a small extent. The oxygen atom of the nitrone **A** has a slightly smaller coefficient (Figure 5). Hence, poor regioselectivity is predicted, favoring the formation of 2-substituted fused isoxazolidines. This is against the observance of formation of 3-substituted isoxazolidines as major products on cycloaddition of **A** with **3**, **4** and **6**-**9**. The same preference for the ester group to be distal to the nitrone oxygen is observed in the case of addition of **A** and **2**. The cycloaddition products with **1** correspond to a mixture in which the 3-substituted regiomer predominates.[11] To explain this high regioselectivity, it has been suggested[5] that combination of the **LUMO** of nitrone with much larger difference in terminal coefficients with **HOMO** of the dipolarophiles is the chief governing force. On the basis of the above argument, the predominant formation of 3-substituted products is evident for dipolarophiles **1**-**3** (Table 1). However, for dipolarophiles **6** and **7**, having comparable atomic coefficients in **HOMO**, the same reasoning predicts a near equal distribution of 2 and 3-substituted adducts.

The **HOMO** of the acyclic nitrone, **B**, has a slight polarization (Table 1, fig 6), with the larger coefficient on oxygen. Hence, the acyclic nitrone **B** is expected to yield predominantly the 4-substituted isoxazolidine in cycloadditions with all the dipolarophiles examined. This conclusion is generally true. In reactions of **B** with **3**, **4**, **6** and **7**, the ester group is invariably away from the nitrone oxygen, consistent with the conclusion based on frontier orbital coefficients. In the case of the reaction with **1**, the predicted regioisomers are formed, although the opposite combinations are also produced in minor amount.

Evidently, factors other than frontier orbital coefficients need to be taken into account to explain the observed product distributions. Feringa and coworkers[9] arrived at a similar conclusion based on a limited study of frontier orbital coefficients in a few nitrone cycloaddition systems.

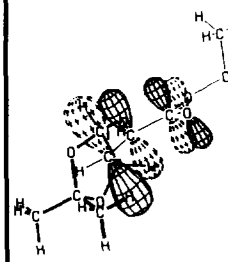


Figure 3
LUMO of **1**

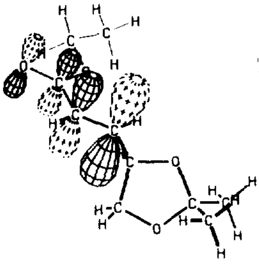


Figure 4
LUMO of **2**

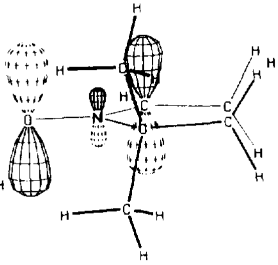


Figure 5
HOMO of **A**

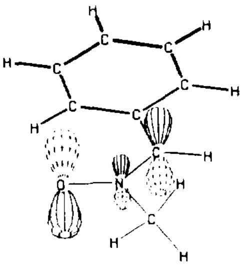
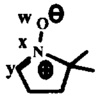
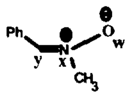
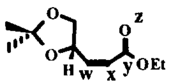
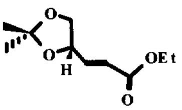
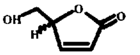
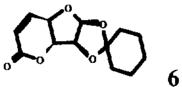
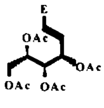


Figure 6
HOMO of **B**

Secondary orbital interactions may also be important in determining *exo/endo* selectivity. This factor may be important since the central nitrogen atom in the nitrone bears a fairly significant coefficient in the **HOMO** (Fig. 5, Table 1). In E-olefins with ester substituents, there is the possibility of additional stabilizing overlap between the non-reacting centers (Fig. 3 and 4) in the key frontier orbital interaction. This effect is likely to be overridden by stronger steric interaction in Z-olefins and also in the cyclic nitrone.

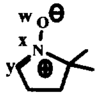
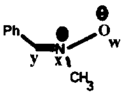
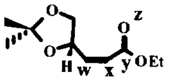
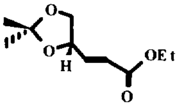
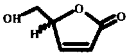
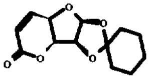
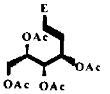
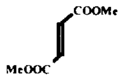
Table 1: AM1 calculated frontier molecular orbital energies (eV) and atomic orbital coefficients

Dipole/Dipolarophile		ϵ(eV)	w	x	y	z
 A	HOMO LUMO	-8.81 0.70	0.64 0.41	-0.27 -0.63	-0.66 +0.61	
 B	HOMO LUMO	-8.45 -0.30	-0.51 0.35	0.28 -0.50	0.48 0.39	
 1	HOMO LUMO	-10.45 -0.22	0.26 -0.65	0.34 0.49		
 2	HOMO LUMO	-10.57 -0.20	-0.35 -0.61	-0.42 0.47	0.02 0.36	0.17 -0.30
 3	HOMO LUMO	-10.86 -0.47	0.43 -0.66	0.52 0.53	-0.02 0.36	-0.36 -0.31
 6	HOMO LUMO	-10.58 -0.54	0.07 0.65	0.08 -0.53	-0.01 -0.36	-0.15 0.32
 E= COOEt 7	HOMO LUMO	-10.87 -0.22	0.23 0.47	-0.22 -0.44	0.03 -0.29	

An alternative model for predicting regiochemistry in cycloadditions of polarised substrates is by analysing electrostatic interactions. In general, the dipole is electron rich and the dipolarophile is electron deficient. Therefore, maximum stabilisation of the transition state results by matching the nucleophilic surface of the dipole with the electrophilic surface of the dipolarophile.[28] While rigorously computed electrostatic potential maps would yield the most reliable predictions, correct regiochemistry can often be arrived at from the calculated charge distributions.

The computed charge distributions in the dipolarophiles follow the expected pattern (Table 2). The olefinic carbon beta to the ester group has a smaller negative charge than the alpha carbon. This is the polarization resulting from the electron withdrawing effect of the ester group. In the nitrone, the oxygen atom carries a much larger negative charge compared to the carbon end.

Table 2: AM1 calculated charge distributions

Dipole and Dipolarophile	W	X	Y	Z
 A	-0.44	0.31	-0.30	
 B	-0.45	-0.23	-0.23	
 1	-0.07	-0.20	0.34	-0.28
 2	-0.08	-0.20	0.34	-0.35
 3	-0.12	-0.20	0.32	-0.27
 6	-0.09	-0.20	0.33	-0.28
 7	-0.13	-0.18	0.33	-0.31
	-0.07	-0.21	0.33	-0.28

For minimising electrostatic repulsions and to maximise the electrostatic complementarity of dipole and dipolarophile (Figure 7), the preferred regio-isomers would correspond to the nitrone oxygen being added to the olefinic carbon beta to the ester group. The products observed in the additions to **2**, **3**, **4** and **5** correspond to this regiochemistry. Only in the addition of **A** to **1**, one isomer with the opposite regiochemistry[11a] is isolated and that too as a minor product.

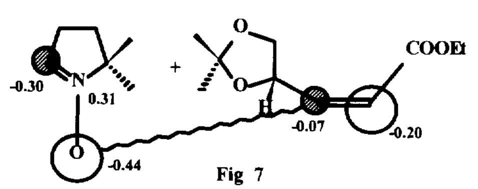


Fig 7

The regiochemistry of the products derived from cycloaddition of the acyclic nitrone **B** with **3**, **4** and **6** remains the same as in the case of cycloaddition with cyclic nitrone **A**.[2,11,29] Only in the addition of **B** to **1**, one isomer with the opposite regiochemistry, **16c**, is formed as a minor product.

Evidently, the electrostatic interactions have significant contribution to total energy stabilization, and hence, in influencing and determining regiochemistry of product obtained from sugar derived dipolarophiles. The same cannot be generated for FMO interaction since in some of the cases, viz., addition of **A** to **6** and **7**, the qualitative assessment shows equal stabilization for either of the regiomeric products. The *endo* selectivity in additions to E-alkenes, **2** and **7** can be best explained by stabilizing secondary orbital interactions involving FMO interaction. The secondary orbital stabilization is more than offset by steric reasons in the case of Z-alkenes **1**,**3** and **6** leading to products from *exo*-transition states.

The **HOMO** of **B** is calculated to be higher in energy than that of **A**. Hence, the stabilizing frontier orbital interaction involving the acyclic nitrone **B** is indicated to be stronger than that of the cyclic nitrone **A**. This is inconsistent with the experimental trend; the cyclic nitrone reacts faster than the acyclic nitrone to provide the adducts.

Overall, the frontier orbital description is too approximate to account for all the experimental trends in regioselectivity and rates. The orbital polarization is often small and often in differing directions compared to the products observed. This is not surprising in view of the complex nature of the reactant partners. However, the preferred regiochemistry can be understood in virtually all cases by considering electrostatic interactions and the large variations in computed charge distributions. Strong electrostatic interactions which can override frontier orbital preferences are probably present which influence the regioselectivity in nitrone cycloadditions. Quantitative computational methods on isomeric transition states are likely to be the most appropriate means for rationalizing the observed results.

Experimental:

All the solvents were dried and distilled before use. The organic extracts were dried over anhydrous Na_2SO_4. IR spectra were recorded on a Perkin Elmer 688 Spectrometer. NMR spectra were recorded on a Varian VXR 300S, Varian FT 60A or Varian 100 spectrometer using $CDCl_3$ as the solvent containing TMS as an internal standard. Chemical shifts (δ) are expressed as ppm down field with respect to TMS. J values are expressed in Hz. Optical rotations were measured with a Shimadzu digital polarimeter. HPLC purifications and analyses were performed on a Dupont 8800 series chromatographic system with gradient controller. GLC analyses were carried out on Shimadzu 15A chromatograph. Mass spectra were recorded on a CEC-21-110B double focusing mass spectrometer operating at 70eV using the direct inlet system. Analytical samples were dried in vacuum desiccator at room temperature for 12h. Microanalyses were performed on Carlo Erba Model 1106 elemental analyser.

Reaction of Nitrone A with dipolarophile 2

Nitrone **A** (0.59g, 5.22 mmol) was dissolved in 25 ml of dry toluene and a solution of the dipolarophile **2** (0.7g, 3.5mmol) in toluene was added dropwise. The reaction mixture was refluxed for 200h. The formation of two products was indicated by t.l.c. (Rf values of 0.4 and 0.5, 20% EtOAc: hexane). The reaction mixture was chromatographed over silica gel eluting with 10%-EtOAc-hexane to afford the products **10** and **11** in the ratio 1:1.

Yield : 55%;

Compound 10

$[\alpha]_D^{28}$ = + 82.4 (c 0.85, $CHCl_3$);

ν_{max} (KBr)/cm^{-1}: 3000, 1760, 1390, 1380;

^1H NMR (300 MHz) δ : 1.04-1.43(s, $(CH_3)_2$,1.28(t, $OCH_2C\underline{H}_3$),1.56-1.97(m, H-4,5), 3.64 (dd, 1H, J = 7.14, 6.96Hz, H-3), 3.72-4.26(m, H-3a,4',5', $OC\underline{H}_2CH_3$), 4.31(dd, 1H, J = 7.14, 7.32Hz, H-2);

MS,m/z 313(M^+), 298(M^+ 15, 100%);

Anal. Calcd for $C_{16}H_{27}O_5N$ (313): C:61.32 %,H:8.68%, N:4.46 %, Found C:61.42%, H:8.32%, N:4.35 %.

Compound 11

$[\alpha]_D^{28}$ = - 85.5 (c 0.62, $CHCl_3$);

ν_{max} (KBr)/cm^{-1}: 3000, 1760, 1390, 1380;

^1H NMR (300 MHz) δ : 1.06-1.48(s, $(CH_3)_2)$,1.27(t, $OCH_2C\underline{H}_3$), 1.58-2.25(m, H-4,5), 3.59(dd, 1H, J = 7.26, 7.69Hz, H-3),3.88(dd, 1H, H-4'), 3.99(dd, 1H, H-4'), 4.02-4.35(m, H-3a,5', $OC\underline{H}_2CH_3$), 4.37(dd, 1H, H-2);

Anal. Calcd for $C_{16}H_{27}O_5N$ (313): C:61.32 %,H:8.68%, N:4.46 %, Found C:61.51%, H:8.49%, N:4.57 %.

Reaction of Nitrone A with dipolarophile 7

Nitrone **A** (0.176g, 1.56 mmol) was dissolved in 25 ml of dry benzene. To this a solution of dipolarophile **7** (0.5g, 1.3 mmol) in benzene was added dropwise . The reaction mixture was refluxed for 100h. Formation of two products was indicated by the t.l.c with very close R_f values of 0.5 and 0.45. The reaction mixture was chromatographed over silica gel using 25%-EtOAc-hexane to afford the products **12** and **13** in the ratio 1:1.5. These compounds were oily in nature. The two diastereomers had similar IR and mass spectral features. Yield (85%).

Compound 12

$[\alpha]_D^{30}$ = + 73.7 (c 0.88,$CHCl_3$);

ν_{max} (neat)/cm^{-1}: 3000, 1730, 1380;

^1H NMR (300 MHz) δ : 1.04 & 1.25(s, $(CH_3)_2)$, 1.26 (t, $OCH_2C\underline{H}_3$), 1.32-1.94(m, H-4,5), 2.02-2.13(4s, $OCOC\underline{H}_3$), 3.70(t, 1H, J = 7.02, 6.86 Hz, H-3), 4.05(m, 1H, H-3a), 4.14(m,2H, $OC\underline{H}_2CH_3$), 4.22(m, 2H, H-11), 4.29(dd, 1H, J = 8.7, 6.8 Hz, H-2), 5.19(m,1H, H-10), 5.28(dd,1H, J = 3.05, 8.7Hz, H-8), 5.53(dd, 1H, J = 3.05, 8.4, H-9);

^{13}C NMR(75 MHz) δ: 14.13, 20.60-20.74 (4 $OCO\underline{C}H3$), 23.84, 26.70, 27.20, 35.76, 55.61, 60.97, 62.22, 66.66, 68.34, 68.82, 69.41, 71.72, 74.77, 169.16-170.52($\underline{C}$=O);

MS m/z, 502(M^{+1}, 78), 501(100), 485(64), 329(47), 241(23), 162(33), 130(40), 113(84), 81(67), 55(45);

Anal. Calcd for $C_{23}H_{35}O_{11}N$ (501.5): C:55.08%, H:7.03%, N:2.79%, Found C:55.23%, H:7.12%, N:2.61%.

Compound 13

$[\alpha]_D^{30}$ = - 31.6 (c 0.10,$CHCl_3$);

^1H NMR (300 MHz) δ : 1.03 & 1.25(s, $(CH_3)_2)$, 1.27 (t, $OCH_2C\underline{H}_3$), 1.33-1.93(m, H-4,5), 2.02-2.12(4s, $OCOC\underline{H}_3$), 3.48(t, 1H, J = 7.12 Hz, H-3), 4.06(m, 1H, H-3a), 4.17(m,2H, $OC\underline{H}_2CH_3$), 4.20(m, 2H, H-11), 4.44(dd, 1H, J = 7.12, 5.34 Hz, H-2), 5.17(m,1H, H-10), 5.42(m,2H, H-8, H-9);

^{13}C NMR(75 MHz) δ: 14.13, 20.67-20.83 (4 $OCO\underline{C}H_3$), 23.79, 27.04, 27.21, 36.14, 53.30, 61.17, 61.89, 66.02, 68.53, 68.87, 68.90, 69.37, 76.36, 169.81-170.54($\underline{C}$=O);

MS m/z, 502(M^{+1});

Anal. Calcd for $C_{23}H_{35}O_{11}N$ (501.5): C:55.08%, H:7.03%, N:2.79%, Found C:55.22%, H:7.15%, N:2.66%.

Reaction of Nitrone A with dipolarophile 8

A solution containing nitrone **A** (0.136 g, 1.2 mmol) and dipolarophile (0.4 g, 1.2 mmol) in benzene (25ml) was refluxed for 100h. After removal of the solvent the yellow residue was chromatographed using 15% EtOAc-hexane to afford the major diastereomer **14**. Subsequent continued elusion with EtOAc afforded the minor isomer **15** as colorless oil with overall yield of 81%.

Compound 14

$[\alpha]_D^{30}$ = + 34.5(c 2.99,$CHCl_3$); ν_{max} (neat)/cm^{-1}: 3000, 1550, 1370;

^1H NMR (300 MHz) δ : 1.06 & 1.30(s, $(CH_3)_2$), 1.65(m,2H, H-4), 2.02-2.12(4s, $OCOC\underline{H}_3$), 2.17 (m,2H, H-5), 4.24(dd,1H,H-3a), 4.25(dd,1H, H-11), 4.64(dd, 1H, H-2), 5.19(ddd,1H,H-10), 5.46(dd,1H, H-8), 5.51(dd,1H, H-9), 5.52(dd, 1H, H-3);

MS m/z, 475(M^+, 100), 435(40), 425(30), 379(25), 336(10);

Anal. Calcd for $C_{20}H_{30}O_{11}N_2$(474.5):C:50.63%,H:6.37%, N:5.90%, Found C:50.72%, H:6.19%, N:5.74%.

Compound 15

$[\alpha]_D^{30}$ = - 38.8(c 1.445,$CHCl_3$) ;

^1H NMR (300 MHz) δ : 1.06 & 1.30(s, $(CH_3)_2$), 1.66(m,2H, H-4), 2.02-2.10(4s, $OCOC\underline{H}_3$), 2.12 (m,2H, H-5), 4.10(dd,1H,H-11), 4.22(m,1H, H-3a), 4.77(dd, 1H, H-2), 5.19(m,1H,H-10), 5.44(dd,1H, H-9), 5.48(dd,1H, H-3), 5.54(dd, 1H, H-8);

MS: m/z, 475(M^+);

Anal. Calcd for $C_{20}H_{30}O_{11}N_2$(474.5):C:50.63%,H:6.37%, N:5.90%, Found C:50.74%, H:6.24%, N:5.81%.

Reaction of Nitrone B with dipolarophile 1

Nitrone **B** (0.52g, 3.8mmol) was dissolved in 25 ml of dry toluene and a solution of the dipolarophile 1 (0.7g, 3.5mmol) in toluene was added dropwise. The reaction mixture was refluxed for 120h. The formation of product was indicated by t.l.c. (20% EtOAc-hexane). The reaction mixture was chromatographed over silica gel eluting with 15% EtOAc-hexane to afford the products **16a,b,c & d** in the ratio of 1:1:1.5:2. The compounds were oily in nature. The four diastereomers had similar IR and mass spectral features. Yield: 60%;

Cycloadducts 16a, 16b & 16c: Ethyl 5-[2,2-dimethyl-1,3-dioxalane-4-yl-2-methyl-3-phenyl-isoxazolidine-4-carboxylate.

ν_{max} (KBr)/cm^{-1}: 3000, 2800, 1740;

^{1}HNMR(300MHz, $CDCl_3$) δ: 0.78,0.79 & 0.81(t,3x3H, $OCH_2C\underline{H}_3$),1.1-1.5(s,$(CH_3)_2$), 2.6-2.7(3s, N-CH_3), 3.1(q,1H, J = 9.0Hz, H-4 of 16c), 3.42(2t, 2H, J = 9.0Hz, H-4 of 16a & b), 3.7-4.4(m), 4.8(d,1H, J = 9.0Hz, H-5 of 16c), 7.2-7.4(m, Ar-H);

MS : m/z, 335 (M^+).

Cycloadduct 16d:

ν_{max} (KBr)/cm^{-1}: 3000, 2800, 1740;

^{1}HNMR(300MHz, CDCl$_3$) δ: 0.81(t,3H, OCH$_2$C$\underline{H}_3$), 1.37 and 1.48(s, (CH$_3$)$_2$), 2.74(s, N-CH$_3$), 3.47(dd, 1H, J = 6.0,9.0, H-8), 3.62-3.76(m,3H, H-4 & OC$\underline{H}_2$CH$_3$), 3.95(dd,1H, J = 6.0,9.0Hz, H-7), 4.09(d,1H, J = 9.0Hz, H-3), 4.42(dd,1H, J = 9.0,9.2Hz, H-5), 4.84(m,1H, H-6), 7.2-7.4(m,Ar-H);

Anal. Calcd for $C_{18}H_{25}O_5N$ (335.4): C:64.46%, H:7.51%, N:4.17%, Found C:64.59%, H:7.62%, N:4.03%.

Reaction of Nitrone B with lactone 3

The same reaction conditions as above (solvent: benzene) were utilised for the cyclic dipolarophile **3** using (0.18g, 1.61mmol) nitrone **B** and 0.23g (1.70mmol) of dipolarophile **3**. The reaction mixture was chromatographed over silica gel using 25% EtOAc-hexane to afford the products **17a** and **17b** in the ratio 1.2:1 (Yield : 66%).

Cycloadduct 17a; 3(α),3a(β),6(α),6a(β)-tetrahydro-6-hydroxymethyl-2-methyl-3-phenyl-4H-furo[3,4-d]isoxol-4-one

$[\alpha]_D^{31}$= +94.4(c 0.45,CHCl$_3$);

^{1}HNMR(300MHz, CDCl$_3$) δ: 2.63(s, 3H, N-Me), 3.58(d, 1H, $J_{3a,6a}$ = 6.35Hz, H-3a), 3.69(bs, 1H, H-3), 3.80(dd, 1H, $J_{7,7}$ = 12.67Hz, $J_{7,6}$ = 6.35 Hz, H-7), 3.96 (dd, 1H, J = 12.67Hz, $J_{7',6}$ = 2.44Hz, H-7'), 4.63(bs, 1H, H-6). 4.91(d, 1H, $J_{6a,3a}$ = 6.35Hz, H-6a), 7.26-7.7(m, 5H, Ar);

MS: m/z, 249(M$^+$, 87), 172(37), 134(100), 118(50), 91(43), 77(67), 42(80), 31(71).

Cycloadduct 17b:

$[\alpha]_D^{30}$ = - 88.5(c 0.26,CHCl$_3$);

^{1}HNMR(300MHz, CDCl$_3$) δ: 2.61(s, 3H, N-Me), 3.60(t, $J_{3,3a}$ = $J_{3a,6a}$ = 8.06Hz, 1H, H-3a), 3.79(m, 2H, H-3,7), 3.98 (dd, 1H, $J_{7,7'}$ = 12.93Hz, $J_{7',6}$ = 2.44Hz, H-7'), 4.71(dd,1H, $J_{6,7}$ = 8.06Hz, $J_{6,6a}$ = 2.69 Hz,H-6), 4.96(dd, 1H, $J_{6a,6}$ = 2.69Hz, $J_{6a,3a}$ = 8.06Hz, H-6a), 7.26-7.39 (m, 5H, Ar);

^{13}CMR(75 MHz, CDCl$_3$) δ : 42.58 (d, 3a), 55.38 (d, 6), 62.68(t, 7), 75.70(d,6), 78.06 (q, 8), 85.78 (d, 6a), 127.77-128.86 (5d, Ar), 133.56(s, Ar), 174.0(s,4);

Anal. Calcd for $C_{13}H_{15}O_4N$ (249.3): C:62.64%, H:6.06%, N:5.61%, Found C:62.78%, H:6.17%, N:5.50%.

Reaction of Nitrone B with 4 and 6

Nitrone **B**(0.07g, 0.5mmol) was dissolved in 25 ml of dry benzene and a solution of dipolarophile **6** (0.1g, 0.4mmmol) in benzene was added dropwise. The reaction mixture was refluxed for 30h. Formation of the product was indicated by t.l.c. (R_f 0.6, 25%-EtOAc-hexane). The reaction mixture was chromatographed over silica gel eluting with 15%-EtOAc-hexane to afford the product **18** (67%).

Similar reaction conditions were adopted for dipolarophile **4** and in this case, the unreacted E-isomer **(5)** was isolated by column chromatography.

3a(R),5a(S),5b(R),8a(R),9a(S),9b(S),-hexahydro-2(3H)-methyl-3(R)-phenyl-spiro[cyclohexane-1',7[4H][1,3]dioxalo[5'',4'':4',5']furo[2',3':5,6]pyrano[3,4-d]isoxazole]-4-one (18)

ν_{max} (KBr)/cm^{-1}: 3000, 1740, 1390, 1380;

^{1}HNMR(300MHz, CDCl$_3$) δ: 1.25-1.77(m,10H), 2.59(s,N-Me), 3.47(dd,2H,H-7,7a, $J_{7,7a}$ = 7.97Hz, $J_{7a,4b}$ = 9.09Hz) , 4.40(dd,1H,$J_{4a,4b}$ = 1.87,2.22Hz,H-4a), 4.74(m,2H,H-4b,9b), 5.02(d, J = 1.87Hz,1H,H-9a), 5.89(d, J = 3.71Hz,1H, H-3a);

^{13}CMR(75 MHz, CDCl$_3$) δ : 23.24(t), 23.55(t),24.51(t), 35.38(t), 35.87(t), 42.26(d), 52.86(d), 70.81(d), 72.70(d), 77.15(d), 80.58(q), 82.86(d), 103.83(d), 113.38(s), 127.8(d), 128.67(d), 135.64(s), 167.05(s);

MS: m/z, 388(M^{+1}, 100%), 288(5), 270(8);

Anal. Calcd for $C_{21}H_{25}O_6N_2$(387.4): C:65.10%, H:6.50%, N:3.61%, Found C:65.01%, H:6.61%, N:3.52%.

Reaction of Nitrone B with 7

The reaction was carried out as described above using toluene as solvent for five days to provide **19a** and **19b**. Ratio; 1 : 1.6.

ν_{max} (KBr)/cm^{-1}: 3010, 2800, 1730, 1620, 1520,1390;

^{1}HNMR(300MHz, $CDCl_3$) δ: 0.71 & 0.74(2t, $OCH_2C\underline{H}_3$), 2.04-2.16(s, 2 x 4 $COCH_3$), 2.57(s, 2 x 3H, N-CH_3), 3.51-3.79(m, 2 x 4H, H-3, H-4 & $OC\underline{H}_2CH_3$), 4.06-4.28(m, 2 x2H, H-9), 4.67(t, 1H, J = 6.41Hz, H-5), 4.79(dd, 1H, J = 5.68, 7.33Hz, H-5'), 5.16(m, 2 x 1H, H-8), 5.45 (m, 2x 2H, H-6,7);

^{13}CMR(75 MHz, $CDCl_3$) δ : 14.24 & 14.33(O-$COCH_2C\underline{H}_3$), 20.73-21.15($OCOC\underline{H}_3$), 42.90, 59.41-78.11(OCH & OCH_2), 123.87-140.90(Ar), 169.63-171.40(C=O).

Reaction of Nitrone B with 9
Dimenthyl-2-methyl-3-phenyl-isoxazolidine-4,5-dicarboxylate (20)

A solution of dipolarophile **9** (0.75g 1.9mmol) and the nitrone **B**(0.34g, 2.5mmol) in benzene (25 ml) was refluxed for 2 days. Presence of the product was indicated by t.l.c. (rf 0.5, 20% EtOAc-hexane). After removal of the solvent, the crude product was chromatographed using 10% EtOAc-hexane to afford the compound **20** in 70% yield .

$[\alpha]_D^{31}$= -19.9(c 1.0, $CHCl_3$);

^{1}HNMR(300MHz, $CDCl_3$) δ: 0.64-2.08(m, menthol-H), 2.60(S, N-CH_3, 3H), 3.70(d, 1H, J = 8.54Hz, H-3), 3.78(dd, 1H, J = 4.73, 8.54Hz, H-4), 4.62 & 4.81(td, 2H, O-CH-menthol), 4.85(d, 1H, J = 4.73Hz, H-5);

^{13}CMR(75 MHz, $CDCl_3$) δ : 170.87(s), 170.66(s), 127-136(Ar), 75-77(d &t) 60.68(d), 47.11(d), 46.64(d), 42.44(q), 40.71(t), 34.06 & 34.21(t), 31.38 & 31.30(d), 15.89-26.0(q,d,t, menthol unit);

MS: m/z, 527(M^+, 25), 344(20), 206(30), 162(100), 118(50), 83(75), 43(100);

Anal. Calcd for $C_{32}H_{49}O_5N$(527.4): C:72.82%, H:9.35%, N:2.65%, Found C:72.64%, H:9.41%, N:2.45%.

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