# Diastereoselective 1,3-Dipolar Cycloadditions of Chiral Derivatives of 2-Oxoethanenitrile Oxide to Noncyclic Conjugated Symmetrical Alkenes

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Asymmetric 1,3-dipolar cycloadditions of chiral derivatives of the nitrile oxides **3a**–**3c** derived from (2*R*)-bornane-10,2-sultam, (2*R*)-10-(dicyclohexylsulfamoyl)isoborneol, and (1*R*)-8-phenylmenthol, to either (*E*)-stilbene **4** or dimethyl fumarate **5**, leading to the corresponding 4,5-dihydroisoxazoles **6a**–**6c** and **7a**–**7c** in both moderate yields and diastereoselectivities, are presented. All cycloadducts were converted into the corresponding methyl esters **8** and **9**, which were used for determination of their enantiomeric purities *via* chiral HPLC analyses. In the case of both stilbene cycloadducts **6a** and **6b**, their absolute configurations were determined by X-ray crystal-structure analyses. These [3+2] cycloadditions suggest the participation of the thermodynamically less stable $SO_2$/CO *syn*-conformer in the $\pi_y$ approach along the C=O bond of the linear nitrile oxide **3a**.

**Introduction.** – The asymmetric 1,3-dipolar cycloaddition of nitrile oxides to alkenes is a powerful tool for the stereocontrolled synthesis of 3-substituted 4,5-dihydroisoxazoles [1]. With respect to the easy cleavage of their weak hetero N–O bond [2] and their simple hydrolysis [3], these heterocycles have been proved useful in the synthesis of several pharmaceuticals [4] and natural products [5]. Intermolecular diastereoselective cycloadditions of achiral nitrile oxides to optically active dipolarophiles has attracted most interest [6]. The substituted acryloyl derivatives of chiral auxiliaries from the menthol [7], isoborneol [8], chiral sultams [9], sugars [10], steroids [11], chiral amides [12], or amine families [13] have already been reported. More recently, antibodies [14], enzymes [15], and chiral *Lewis* acids have been explored under either stoichiometric [16] or catalytic conditions [17]. There are few literature examples of diastereoselective 1,3-dipolar cycloadditions of optically active nitrile oxides [18][2]). Possibly, either the linearity of the dipole, its $\pi_z/\pi_y$ LUMO/HOMO[3]) and dipolarophile *re*/*si* faces modes of addition, or the distances between inducing and created stereocenters may account for the reported poor stereoselectivities. Recently, we have published a preliminary communication concerning the efficient preparation of the chiral nitrile oxide derived from (2*R*)-*N*-(glyoxyloyl)bornane-10,2-sultam (**1a**),

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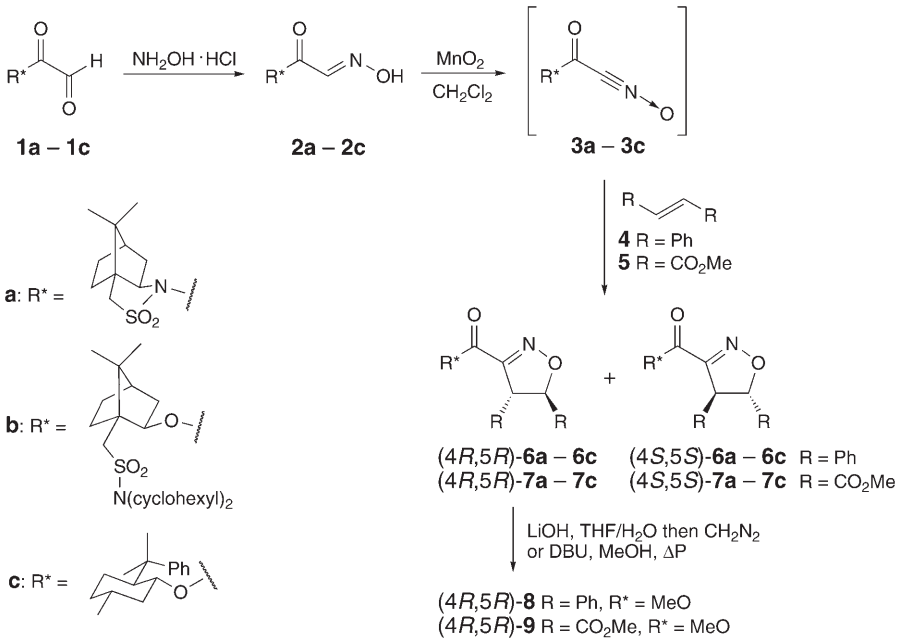
[2]) Furthermore, besides our own work [19–21], none of them are either directly conjugated to a carboxy moiety or directed by a recoverable chiral auxiliary.

[3]) For propargyl-allenyl type dipoles, formally, the carbonyl substituent may be conjugated to either the reactive $\pi 4_s$ or its orthogonal $\pi$ orbital [1].

and its 1,3-dipolar cycloadditions to noncyclic alkenes as dipolarophiles [19]. We then improved the preparation protocol and extended the cycloaddition of nitrile oxides **3a**–**3c** [20] to cyclic olefins [21]. We now report in detail the cycloadditions of these three dipoles to either (*E*)-stilbene **4** or dimethyl fumarate **5**, as symmetric noncyclic dipolarophiles of different electronic demand (*Scheme 1*).

*Scheme 1*




**Results.** – The chiral derivatives of ethanenitrile oxides were generated from aldoximes **2a**–**2c** *via* their mild oxidation with $MnO_2$, and were trapped *in situ* with either (*E*)-stilbene (**4**) or dimethyl fumarate (**5**) to furnish 4,5-dihydroisoxazoles **6** and **7**, respectively, as mixtures of diastereoisomers (30–48% de) in moderate-to-good yields (45–75%; *Table 1*).

Table 1. *Diastereoselectivities, Yields, and Absolute Configurations Determined after [3+2] Cycloadditions of* **3a**–**3c** *to Alkenes* **4** *and* **5**

| Nitrile oxide | (*E*)-Stilbene (**4**) | | | Methyl fumarate (**5**) | | |
|---|---|---|---|---|---|---|
| | de [%] | Yield [%] | Configuration | de [%] | Yield [%] | Configuration |
| **3a** | 48 | 57 | (4*S*,5*S*)-**6a** | 34 | 58 | (4*S*,5*S*)-**7a** |
| **3b** | 30 | 45 | (4*R*,5*R*)-**6b** | 43 | 60 | (4*S*,5*S*)-**7b** |
| **3c** | 38 | 67 | (4*R*,5*R*)-**6c** | 32 | 75 | (4*S*,5*S*)-**7c** |

The major (*E*)-stilbene cycloadduct (4*S*,5*S*)-**6a** was isolated as a single diastereoisomer after crystallization, and its absolute configuration was determined by X-ray-

analysis (*Fig. 1*, *Table 2*). This structure shows a particularly rare $SO_2$/C=O *syn*-conformation, already observed in the solid state in cases of peculiar steric crowding [22], or, eventually, when a heteroatom, possessing an electron lone pair, is located in the $\beta$-position[4]). The minor diastereoisomer (4*R*,5*R*)-**6a** could also be obtained in pure form from the mother liquor after column chromatography/crystallization.

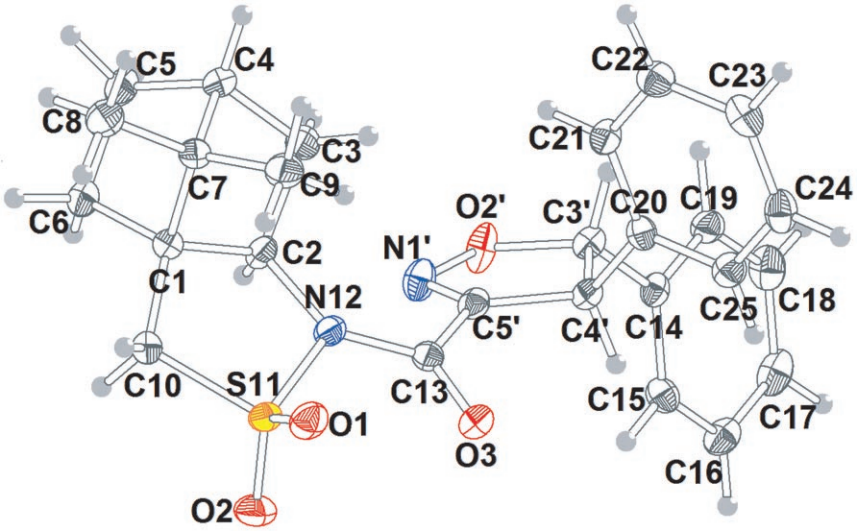



Fig. 1. *ORTEP View of cycloadduct (4S,5S)*-**6a** (arbitrary atom numbering). Ellipsoids are represented at the 50% probability level.

Similarly, the nitrile oxide **3b** also gave a crystalline major adduct (4*R*,5*R*)-**6b**, suitable for X-ray structural analysis (*Fig. 2*, *Table 2*).

The conversion, the extent, and the sense of asymmetric induction were initially estimated by $^1$H-NMR analysis of the crude cycloadducts and then confirmed by chiral HPLC analyses of the corresponding methyl esters **8** and **9**[5]), obtained either by saponification (LiOH, THF/$H_2O$ 5 : 2; 98%) and re-esterification ($CH_2N_2$, $Et_2O$; 70%) of **6a** and **7a**, or *via* a mild direct *trans*-esterification under high pressure (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), MeOH, 10 kbar, 98% [21][27]) of **6b** and **6c**, and **7b** and **7c** (*Scheme 1*). For cycloadducts **6a** and **7a**, both major diastereoisomers

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4) The simple presence of a heteroatom on a sp$^2$-hybridized $\alpha$-atom seems influential but not sufficient for imposing a $SO_2$/C=O *syn*-conformation [20][21][23]. Thus, for example, the crystalline unpublished (2*R*)-*N*-furfuroylbornane-10,2-sultam derivative exhibits an *anti*-conformation ($\Delta h$N 0.284 Å; S–N–C=O 139.00(11)°; O=C–C–O –17.98(19)°), contrasting with a *syn*-conformation of its *N*-picolinoyl analogue ($\Delta h$N 0.065 Å; S–N–C=O –11.5(3)°; O=C–C=N 128.1(2)°). In the case of **2a**, the O=C–C=N *anti*-s-*cis*-conformation involves an intermolecular H-bond with an intercalary molecule of $H_2O$ [20]. For (4*S*,5*S*)-**6a**, both $\Delta h$N and the S–N–C=O dihedral angle (*Table 2*) are larger than the previously reported examples (0.107 Å, –17.3° [21]; 0.083 Å, –9.3° [23]), and, thus, are fully consistent with the proportional correlation found for *anti*-conformers [24].

5) For the racemic analogous ethyl ester of **8**, see [25]; for racemic **9**, see [26].

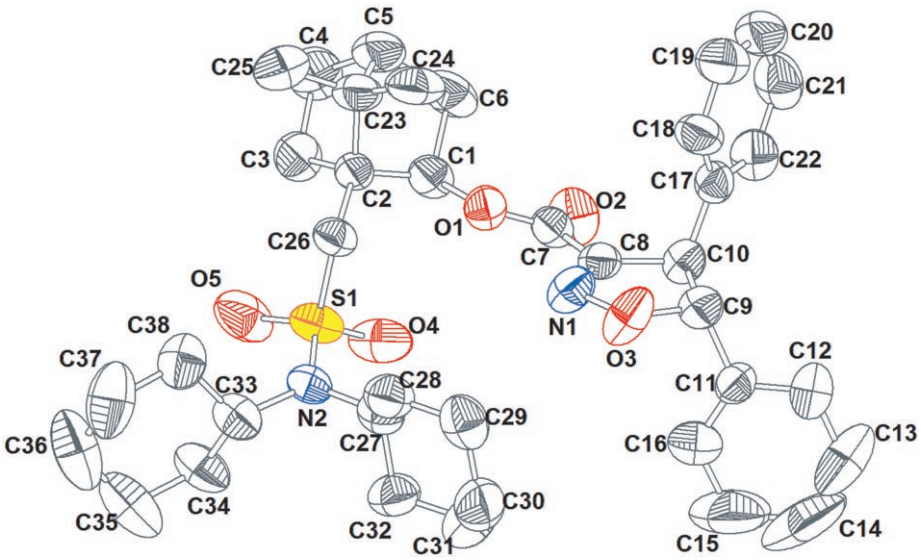


Fig. 2. *ORTEP View of cycloadduct (4*R,5R*)*-**6b** (arbitrary atom numbering). Ellipsoids are represented at the 50% probability level.

Table 2. *Selected Bond Lengths* [Å] *and Angles* [°] *for (4*S,5S*)*-**6a** *and (4*R,5R*)*-**6b**

| (4*S*,5*S*)-**6a** | | (4*R*,5*R*)-**6b** | |
|---|---|---|---|
| S=O(1) | 1.4249(10) | S=O(4) | 1.4219(21) |
| S=O(2) | 1.4308(11) | S=O(5) | 1.4532(20) |
| S–N | 1.7084(11) | S–N(2) | 1.6163(22) |
| S–C(10) | 1.7941(14) | S–C(26) | 1.7753(25) |
| N–C(2) | 1.4909(18) | | |
| N–C(13) | 1.3734(19) | | |
| N(1′)–O(2′) | 1.3897(15) | N(1)–O(3) | 1.3990(27) |
| C(13)=O(3) | 1.2150(17) | C(7)–O(2) | 1.1984(33) |
| O(1)=S=O(2) | 118.38(6) | O(4)=S=O(5) | 118.99(15) |
| C(2)–N–S | 112.64(9) | | |
| C(2)–N–C(13) | 128.65(11) | | |
| C(13)–N–S | 116.81(10) | | |
| C(2)–N–S=O(1) | −125.22(10) | | |
| C(2)–N–S=O(2) | 103.65(10) | | |
| C(3)–C(2)–N–S | 140.18(11) | | |
| S–N–C(13)=O(3) | −17.45(18) | | |
| N(1′)=C–C=O(3) | 141.91(14) | N(1)–C–C=O(2) | −160.27(29) |
| Δ*h*N(12) | 0.119(2) | | |
| Puckering parameter $q_2$ | 0.368 | | |
| S–N–C(2)–C(1)–C(10) $\phi_2$ | 90.3 | | |

show systematic and typical downfield-shifted signals of either benzylic (5.65 and 4.80 ppm) or $\alpha$-methoxycarbonyl (5.47 and 4.96 ppm) H-atom in the $^1$H-NMR

analyses, as compared to those of their minor diastereoisomers (5.60 and 4.57 ppm) and (5.40 and 4.62 ppm), respectively [21][28], thus indicating an identical configuration. For cycloadduct **6b**, a major signal appears at 4.68 ppm as compared to that of the minor diastereoisomer at 4.60 ppm, while for **7b** the image is inverted (minor at 4.75 ppm; major at 4.67 ppm)[6]). A comparison of chiral HPLC analyses of methyl esters **8**, obtained either from a single diastereoisomer or from the reaction mixtures, established that the configuration of the major cycloadduct **6c** is also (4*R*,5*R*). The configurations of the remaining products **7a**–**7c** are based on comparative $^1$H- and $^{13}$C-NMR analyses of the cycloadducts (**6a** and **6b** *vs.* **7a** and **7b**), as well as both chiral HPLC elution times and chiroptical properties of the corresponding methyl esters **9** (*Table 1*).

**Discussion.** – Based on B3LYP/6-31G** DFT calculations [29], the LUMO of the nitrile oxides **3a**–**3c** interacts preferentially with the HOMO of (*E*)-stilbene **4**, while the situation is reversed with dimethyl fumarate **5**, due to the much smaller difference of energies in favor of the $HOMO_{dipole}-LUMO_{dipolarophile}$ interactions (*Table 3*). Furthermore, the nitrile oxide **3a** exists in both reactive conformations **A** (S–N–C=O 160.0°) and **B** (S–N–C=O −16.3°, *Figs. 3* and *4*), the *anti*-$SO_2$/C=O conformer **A** being thermodynamically more stable ($\Delta E = 3.33$ kcal/mol). On the other hand, the LUMO of conformer **B** is slightly lower in energy (0.004 Hartree, 2.7% for **4**) and thus possibly more reactive with (*E*)-stilbene (**4**), such participation being able, in some instances, to kinetically drive the equilibrium[7]).

Table 3. *FMO Differences of Energies* $\Delta$E [Hartree] *between Dipoles* **3a**–**3c**, *and Dipolarophiles* **4** *or* **5**

| | **4** | | **5**[a]) | |
|---|---|---|---|---|
| | $\Delta E(LUMO_3 - HOMO_4)$[b]) | $\Delta E(HOMO_3 - LUMO_4)$ | $\Delta E(LUMO_3 - HOMO_5)$ | $\Delta E(HOMO_3 - LUMO_5)$[b]) |
| *syn*-**3a** | *0.135* | 0.225 | 0.207 | 0.192 |
| *anti*-**3a** | 0.139 | 0.213 | 0.211 | *0.188* |
| **3b** | *0.145* | 0.197 | 0.218 | *0.164* |
| **3c** | *0.145* | 0.187 | 0.218 | *0.154* |

[a]) Values for the bis-s-*trans*-conformer. For the bis-s-*cis*-conformer, this difference is 0.01–0.02 (for $HOMO_3 - LUMO_5$) to 0.02–0.06 Hartree (for $LUMO_3 - HOMO_5$) higher in energy. [b]) In italics: smallest energy differences to be considered for either the LUMO/HOMO or HOMO/LUMO, and between *syn*/*anti* reactivities of **3**.

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6) This inversion is even more evident in the $^{13}$C-NMR data of **6b** (major: 93.4, 80.0 ppm; minor: 93.8, 80.5 ppm) as compared to those of **7b** (minor: 83.2, 80.6 ppm; major: 83.3, 80.9 ppm). Stereoisomers of cycloadduct **6c** could not be distinguished by NMR analyses.

7) *Kim et al.* invoked an electrostatic effect to rationalize the unexpected contra-steric stereoselectivity observed in the cycloaddition of acetonitrile oxide to *N*-acryloylbornane-10,2-sultam [9d]. We already mentioned (see Footnote 41 in [24]) that, despite an attempted systematic rotation, they completely omitted taking into account the possible more reactive $SO_2$/C=O *syn*-conformation in their rationalization.

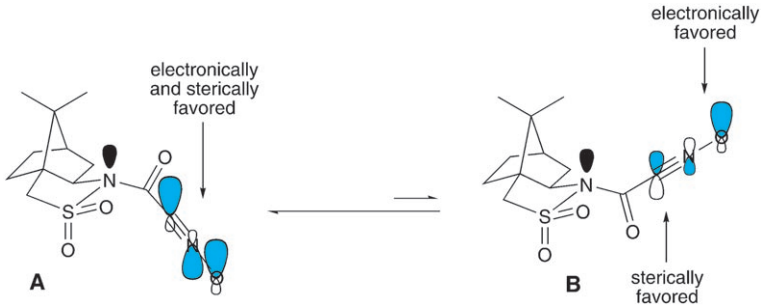


Fig. 3. *Thermodynamic, steric, and* $\pi_y$ *LUMO stereoelectronic preferences for* anti/syn *nitrile oxides* **3a**

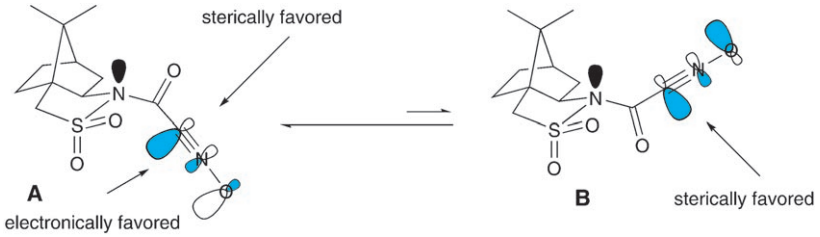


Fig. 4. *Thermodynamic, steric, and* $\pi_y$ *HOMO stereoelectronic preferences for* anti/syn *nitrile oxides* **3a**

Furthermore, the HOMO of the *anti*-conformer **A** is slightly higher in energy (0.005 Hartree, 2.5% for **5**) than its *syn*-conformer **B**[8]). Moreover, the sultam N lone pair (lp) slightly influences the atomic coefficients of the $\pi_z$ LUMO's orbitals and electronically favors the attacks of the alkenes from the top face, regardless of the conformation (*Fig. 3*).

As a consequence, the steric and stereoelectronic effects are mismatching in conformation **B**, whilst matching in conformation **A**, and, thus, are in contrast to an earlier rationalization given for [4 + 2] cycloadditions of *N*-alkenoyl or *N*-glyoxyloyl sultams derived from this auxiliary [24][32]. To the best of our knowledge, this is the second example of a $[_\pi 4_s + _\pi 2_s]$ cycloaddition [9d], which does not follow the simple steric rules imparted by the 'masked' $C_2$ symmetry of the bornane-10,2-sultam auxiliary, as expressed by *Kim* and *Curran* [33]. On the other hand, although these results match well with both the stereoelectronic influence of the N lp and the concurrent reactivity of the thermodynamically disfavored $SO_2$/C=O *syn*-conformer, which we had proposed more than a decade ago [24][32], we nevertheless wanted to claim that the unexpected (4*S*,5*S*)-configuration of **6a** is not resulting from a thermodynamic control, *via* retro-cycloaddition [24]. First of all, we treated the pure minor cycloadduct (4*R*,5*R*)-**6a**,

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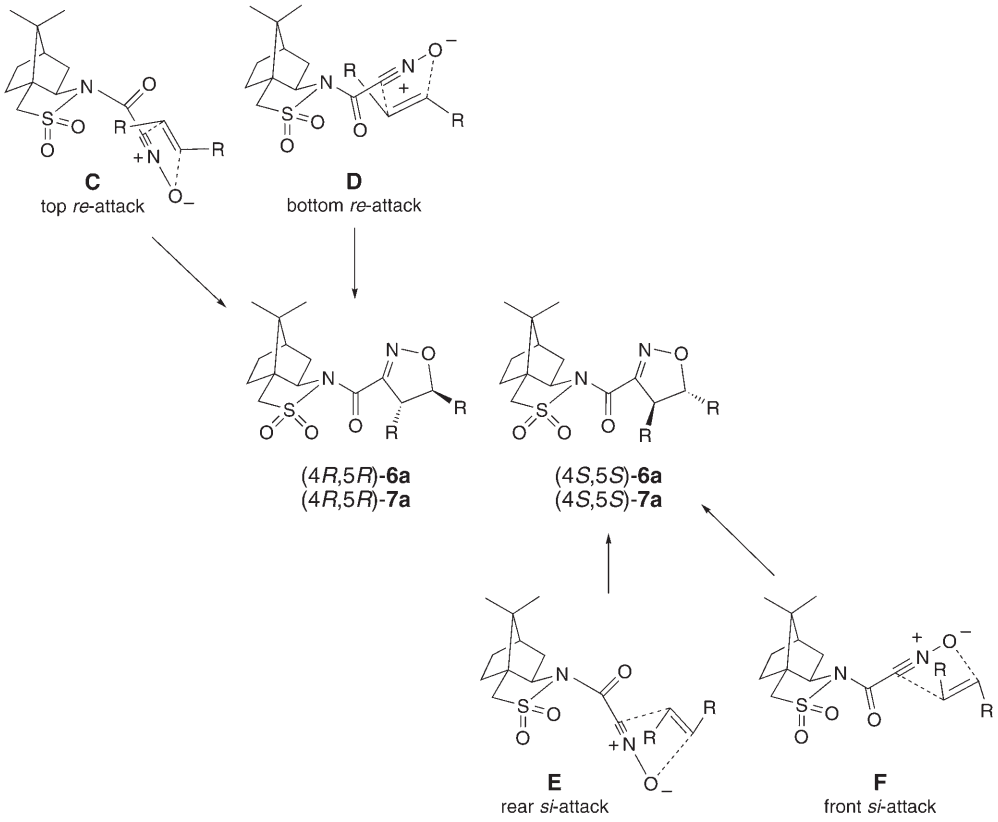
[8]) Dipoles **3** are of type II according to *Sustmann* and *Trill* [30], meaning that the similarity of the dipole and dipolarophile FMO energies implies that both the HOMO – LUMO or LUMO – HOMO interactions are important [31]. The preference may, besides the electronic nature of the dipolarophile, also depend from the electronic influence of **3a**, hence, for example, its $SO_2$/C=O *anti*-/*syn*-conformation.

isolated from the mother liquor, with additional stilbene in the presence of $MnO_2$, without noticing any modification in the diastereoisomer ratio. Alternatively, we also treated this stereoisomer with cyclohexene/$MnO_2$ and did not detect any traces of cross cycloadducts [21]. Thus, the kinetically controlled cycloadducts correspond either to the dipolarophile *si*-attack on the top face of the *syn*-conformer (**B**, $\pi_z$ attack) or to an alternative $\pi_y$ *si*-approach along the C=O bond[9]) (*Fig. 4*). Indeed, in the case of *anti*-conformer **A**, the olefin *re*-attack (*e.g.*, (*E*)-stilbene (**4**)) at the C($\alpha$)-atom is directed opposite to the pseudo-axial S=O(2)[10]). This would produce the (4*R*,5*R*)-diastereoisomer *via* transition state **C**. Analogously, the *re*-attack on the *syn*-conformer **B**, over transition state **D**, would lead to the same (4*R*,5*R*)-product (*Scheme 2*) [33].

Scheme 2. *Stereomodels for Rationalization of the [3+2] Cycloadditions of* **3a** *to* **4** *or* **5**




[9]) The dipolarophile trajectory, with an approach opposite to the C=O bond, is precluded either by the $SO_2$ moiety in conformation **A** (*Scheme 2*, **E**, front attack), or by the bornane skeleton in conformation **B** (**F**, rear attack).

[10]) Both the higher planarity of the N-atom and the pseudo-equatorial orientation of the S=O(1) (resulting from the C(9) steric influence [34]; *Fig. 1*) imposes a deformation of the sultam heterocyclic five-membered ring towards an envelope-like conformation, as expressed by the typical puckering parameter $\phi_2$ (*Table 2*, similar to both previously reported examples: $q_2 = 0.329$, $\phi_2 = 104.8$ [21]; $q_2 = 0.358$, $\phi_2 = 90.6$ [23]), as compared to $SO_2$/C=O *anti*-conformers [28a][34].

Alternatively, the dipolarophile may approach along the C=O bond to add in an orthogonal fashion to the $\pi_y$ orbitals (*i.e.*, **E** and **F**), thus leading to the observed opposite (4*S*,5*S*)-cycloadduct. Due to a steric interaction between the proximal R substituent of the dipolarophile and the (2*R*)-bornane-10,2-sultam auxiliary, the *si*-face transition state (TS#) **E** is favored over either its *anti*-$SO_2$/C=O *re*-face approach or TS# **F**.

Likewise, both configurations and diastereoselections for cycloadducts bearing either (2*R*)-10-(dicyclohexylsulfamoyl)isoborneol or 8-phenylmenthol as auxiliaries may be interpreted by either the dipole of less hindered *re*-face approaches of the dipolarophile as depicted in transition states **G** and **H**[11]) or by their corresponding orthogonal $\pi_y$ trajectories (**I** and **J**, *Scheme 3*). The reverse selectivity observed for **6b** and **7b** may eventually find its origin in either the steric or electronic differences between dipolarophiles **4** and **5**, as well as the possible $\pi_y$ approach *anti* to the C=O for **3c** (*Scheme 3*, approach **L**).

In view of these multiple possible stereochemical models, we decided to proceed to a systematic calculation of the TS# for cycloaddition of **3a** to **4**. Only one imaginary frequency was found for each TS#, and these results are summarized in *Table 4*[12]).

Table 4. *B3LYP/6-31G** DFT Values Calculated for the Cycloaddition of* **3a** *to Stilbene* **4** (see *Fig. 5* for TS#)

| Dipole conformer | $\Delta H_{form}$ [kcal/mol] | $\Delta H^{\#}$ ($\pi_y - re$) [kcal/mol] | $d$(C···C) [Å] | $d$(C···O) [Å] | $\Delta H^{\#}$ ($\pi_y - si$) [kcal/mol] | $d$(C···C) [Å] | $d$(C···O) [Å] |
|---|---|---|---|---|---|---|---|
| *syn*-**3a** | 3.33 | 42.74 | 2.17 | 2.64 | *41.36* | 2.15 | 2.69 |
| *anti*-**3a** | 0.00 | *41.03* | 2.18 | 2.57 | *41.01* | 2.15 | 2.62 |

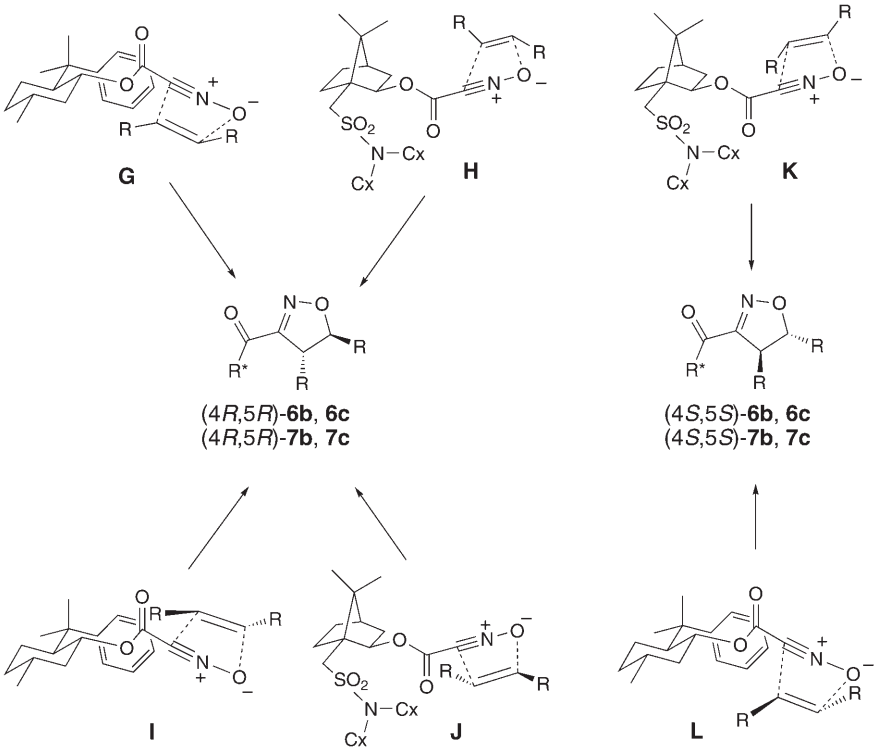
We were unable to finalize TS# based on the sole $\pi_z$ approaches of types **C** or **D**. The only calculable TS# originated from $\pi_y$ trajectories of types **E** and **F** (*Fig. 5*). If the lowest transition state (41.01 kcal/mol, **E**) corresponds well to the $\pi_y$ *si*-approach of **4** in the thermodynamically more stable *anti*-conformer **3a**, it is noteworthy that the same approach in the *syn*-conformer exhibits a $\Delta\Delta H^{\#}$ of 38.03 kcal/mol, thus suggesting a concurrent kinetic participation, with possible displacement of the thermodynamic *anti*/*syn* equilibrium. Implication of the *syn*-conformer **3a** is furthermore supported by the observed diastereoselectivity (48% de), since the exclusive participation of its *anti*-conformer should be practically unselective[13]). Although this corresponds to gas-phase calculations, without considering solvent effects, C···C and C···O forming bond distances suggest a non-synchronous concerted reaction mechanism, due to the steric

[11]) The reactive thermodynamically more stable conformation of these esters is assumed to have the carbonyloxy moiety *syn*-periplanar with respect to the C–H bond of the hydroxylic center [35], as exhibited by the X-ray structure analysis of (4*R*,5*R*)-**6b** (*Fig. 2*, C(1)–H). TS# **H** is, for example, sterically disfavored over TS# **J**.

[12]) Parallel results were also obtained by using the semi-empirical PM3 level of theory [36].

[13]) With an energy difference of 39.41 kcal/mol, the *re*-face approach of **4** to *syn*-**3a** is thus also kinetically in concurrence, and partially accounts for the presence of the minor stereoisomer (4*R*,5*R*)-**6a**.

Scheme 3. *Possible Approaches of the Dipolarophiles* **4** *or* **5** *to the Nitrile Oxides* **3b** *and* **3c**




and electronic influences of both the chiral auxiliary and the carbonyloxy moiety. No evaluation of the entropic contributions to the activation energies was attempted, since we were only interested in energy differences[14]).

**Conclusions.** – Six new diastereoisomeric pairs of isoxazoles bearing three types of recoverable chiral auxiliaries (85–94%) were synthesized and converted to their corresponding methyl esters **8** and **9**, which were readily separated by chiral HPLC. In addition to the linear geometry of the nitrile oxide, the $\pi$-facial approaches, with respect to steric and stereoelectronic factors, depend on both participating reactive *syn*-/*anti*-conformations as well as dipolarophile *re*-/*si*-approaches. TS[#] Calculations suggest that, due to the steric influence of the dipole **3a** and its type-II nature[8]), the secondary $HOMO_{dipole}-LUMO_{dipolarophile}$ interactions, in parallel to fumarate **5**, may eventually have an additional co-operative influence for stilbene **4**. Only moderate diastereoselectivities were obtained (30–48% de), due to the non-applicability of *Curran*'s steric rules [33], with respect to the dipolarophile trajectory, approaching along the C=O bond. Bornane-10,2-sultam and (dicyclohexylsulfamoyl) isoborneol are the most promising auxiliaries, due to both their crystallinity and relatively efficient

[14]) We assume that the entropic contribution is similar for each of the TS[#] and thus can be neglected.

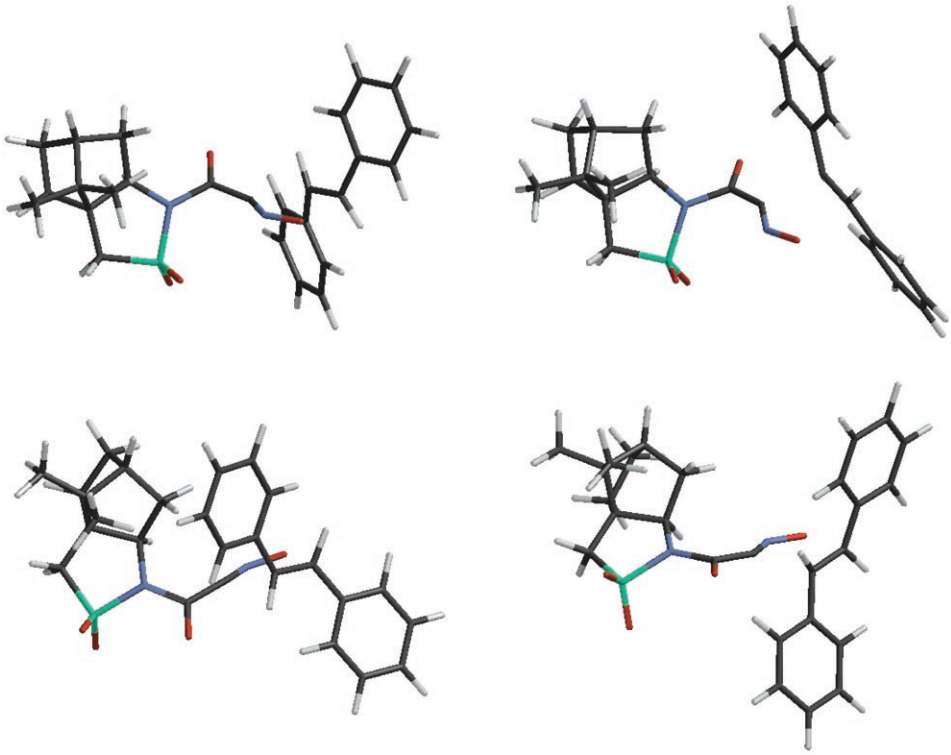


Fig. 5. *Transition states* **E**-anti-si (*top left*), **E**-anti-re (*top right*), **F**-syn-si (*bottom left*), *and* **F**-syn-re (*bottom right*)

chirality transfer. These results open the way for further investigations, including the application of more sterically/electronically demanding or non-symmetric olefins[15]), more effective chiral auxiliaries[16]), and hydroxylic or less polar solvents [21][37][38].

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[15]) Cycloaddition of methyl cinnamate to **3a** afforded in 66% yield a single regioisomer methyl (4*S*,5*S*)-4,5-dihydro-4-phenyl-3-[(tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzoisothiazol-1(4*H*)-yl)carbonyl]isoxazole-5-carboxylate with 51% de according to $^1$H-NMR analyses, whilst **3c** was less efficient with respect to both yield (62%) and diastereoselectivity (24% de for 5-methyl 3-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] (4*S*,5*S*)-4,5-dihydro-4-phenylisoxazole-3,5-dicarboxylate, according to comparative $^1$H-NMR analyses with **7c**). Electron-rich/-poor 4,4′-disubstituted stilbenes are also envisaged, since the former should preferentially interact with the more discriminative and reactive *syn*-conformer **3a**.

[16]) Interesting candidates could eventually be derived from either *cis*-isoketopinic acid or 8-hydroxy/bromo-isoborneol, or more simply, from *exo*-2,2-dimethylnorbornan-3-ol, and its substituted analogues or 8-naphthyl/neopentylmenthol.

## Experimental Part

*General*. See [39].

All measurements of crystals were performed on a *KM4CCD* $\kappa$-axis diffractometer with graphite-monochromated Mo$K_\alpha$ radiation (*Table 5*). The crystal was positioned at 62 mm from the CCD camera. 825 frames were measured at 1° intervals with a counting time of 5 s for (4*S*,5*S*)-**6a** and 796 frames were measured at 1.6° intervals with a counting time of 5 s for (4*R*,5*R*)-**6b**. The data were corrected for *Lorentz* and polarization effects. Empirical correction for absorption was applied[17]) [40]. Data reduction and analysis were carried out with the *Oxford Diffraction* programs [40][41]. The structure was solved by direct methods [42] and refined using SHELXL [43]. The refinement was based on $F^2$ for all reflections except those with very negative $F^2$. Weighted *R* factors *wR* and all goodness-of-fit *S* values are based on $F^2$. Conventional *R* factors are based on *F* with *F* set to zero for negative $F^2$. The $F_o^2 > 2\sigma(F_o^2)$ criterion was used only for calculating *R* factors and is not relevant to the choice of reflections for the refinement. The *R* factors based on $F^2$ are about twice as large as those based on *F*. All H-atoms were located geometrically, and their positions and temperature factors were not refined. Scattering factors were taken from Tables 6.1.1.4 and 4.2.4.2 in [44]. The known configurations of the asymmetric centers were confirmed by the *Flack*-parameter refinement [45]. Crystallographic data (excluding structural factors) for (4*S*,5*S*)-**6a** and (4*R*,5*R*)-**6b** have been deposited as supplementary material with the *Cambridge Crystallographic Data Centre* and allocated the deposition number CCDC-639809 and -639810, resp. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EW, UK (fax: int. code +(1223)336-033; e-mail: depositcdc.cam.ac.uk). The *Cremer* and *Pople* puckering parameters [46] were calculated according to the literature [47].

*General Procedure for Cycloadditions.* To a soln. of oxime **2a**–**2c** (1.0 mmol) in $CH_2Cl_2$ (5 ml), $MnO_2$ (3 mmol) and either (*E*)-stilbene (**4**) or dimethyl fumarate (**5**; 3 mmol) was added at r.t. The progress of the reaction was monitored by TLC, and every 3 h more $MnO_2$ (3 mmol each time) was added. When the reaction was completed, after one or two additions, the solids were filtered off, the solvent was evaporated, and the residue was purified by CC ($SiO_2$; hexane/AcOEt 97:3 → 7:3).

*General Procedure for Saponification–Esterification of* **6a** *and* **7a**. To a soln. of cycloadduct **6a** or **7a** in THF/$H_2O$ 5:2 (6.3 ml/mmol) was added $LiOH \cdot H_2O$ (8.0 mol.-equiv.). After 30 min at 25°, the mixture was concentrated and extracted with $CH_2Cl_2$ to afford the chiral auxiliary in 85–94% yield. The aq. phase was acidified with 15% aq. HCl and extracted with $CH_2Cl_2$. This org. phase was dried ($MgSO_4$), concentrated, and esterified with a $CH_2N_2/Et_2O$ soln. to afford methyl ester **8** or **9** in 70–75% overall yield after purification by CC ($SiO_2$; hexane/AcOEt 97:3 → 9:1).

*General Procedure for Transesterification of the Cycloadducts.* In a *Teflon*® ampoule (2 ml) were placed the cycloadduct (**6b** and **6c**, and **7b** and **7c**) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 2.0 mol.-equiv.). The ampoule was filled with MeOH, closed, and placed in a high-pressure vessel, and the pressure was slowly increased to 10 kbar at 20°. After stabilization of pressure, the mixture was kept under these conditions for 20 h. After decompression, the solvent was evaporated, and the residue was purified by CC ($SiO_2$; hexane/AcOEt 97:3 → 9:1) to afford methyl ester **8** and **9** in 98% yield.

*1-{[(4S,5S)-4,5-Dihydro-4,5-diphenylisoxazol-3-yl]carbonyl}hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide* ((4*S*,5*S*)-**6a**). Obtained pure after crystallization from hexane/AcOEt 1:1. M.p. 190–191°. $[\alpha]_D^{22} = +225.0$ ($c = 1$, $CHCl_3$). IR (KBr): 2940, 1670, 1380, 1340, 1220, 1160, 1125, 925, 753, 735, 700. $^1$H-NMR: 7.40–7.25 (*m*, 10 H); 5.65 (*d*, *J* = 8.5, 1 H); 4.80 (*d*, *J* = 8.5, 1 H); 4.14–4.11 (*m*, 1 H); 3.45 (*AB*, *J* = 13.5, 51.5, 2 H); 2.09–1.82 (*m*, 5 H); 1.42–1.23 (*m*, 2 H); 1.10 (*s*, 3 H); 0.96 (*s*, 3 H). $^{13}$C-NMR: 159.3; 154.6; 138.9; 136.7; 129.2; 128.9; 128.8; 128.2; 128.1; 125.7; 92.9; 65.8; 61.9; 53.1; 48.8; 47.8; 45.3; 39.2; 33.3; 26.2; 21.4; 19.9. EI-MS: 464 (6, $M^+$), 294 (17), 242 (29), 180 (23), 135 (100), 93 (17). HR-EI-MS: 464.176952 ($[M+H]^+$, $C_{26}H_{28}N_2O_4S^+$; calc. 464.176975).

*(4*R*,5*R*)-**6a**. Obtained pure after crystallization from hexane/AcOEt 1:1 of the CC ($SiO_2$; hexane/AcOEt 97:3 to 7:3) purified mother liquor of (4*S*,5*S*)-**6a**. M.p. 175–176°. $[\alpha]_D^{22} = -228$ ($c = 1$, $CHCl_3$). IR (KBr): 3433, 2958, 1684, 1347, 1332, 1220, 1168, 1134, 1114, 933, 763, 701. $^1$H-NMR: 7.38–7.21 (*m*,

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[17]) CrysAlis RED [36]; empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

Table 5. *Crystal Data and Structure Refinement of Compounds (4*S,5S*)*-**6a** *and (4*R,5R*)*-**6b**

| | (4*S*,5*S*)-**6a** | (4*R*,5*R*)-**6b** |
|---|---|---|
| Empirical formula | $C_{26}H_{28}N_2O_4S$ | $C_{38}H_{50}N_2O_5S$ |
| $M_r$ | 464.56 | 646.87 |
| Temp. [K] | 293(2) | 293(2) |
| Wavelength [Å] | 0.71073 | 0.71073 |
| Crystal system | orthorhombic | monoclinic |
| Space group | $P2_12_12_1$ | $C_2$ |
| Unit-cell dimensions: | | |
| $a$ [Å] | 10.3696(7) | 19.568(5) |
| $b$ [Å] | 10.5733(8) | 11.523(3) |
| $c$ [Å] | 20.8790(14) | 16.685(4) |
| $\beta$ [°] | | 101.765(19) |
| $V$ [Å$^3$] | 2289.2(3) | 3683.1(16) |
| $Z$ | 4 | 4 |
| Density [Mg/m$^3$] | 1.348 | 1.167 |
| Absorpt. coeff. [mm$^{-1}$] | 0.178 | 0.131 |
| $F(000)$ electrons | 984 | 1392 |
| Crystal size [mm] | $0.58 \times 0.38 \times 0.17$ | $0.61 \times 0.40 \times 0.37$ |
| $\theta$ Range for data [°] | 2.74 to 28.65 | 2.68 to 25.25 |
| Index ranges | $-13 \le h \le 13$ | $-23 \le h \le 23$ |
| | $-13 \le k \le 13$ | $-13 \le k \le 13$ |
| | $-27 \le l \le 28$ | $-20 \le l \le 20$ |
| Reflections collected/unique | 29940/5608 | 30865/6678 |
| $R$(int) | 0.0226 | 0.0600 |
| Refinement method | Full-matrix least-squares on $F^2$ in both cases | |
| Data/restraints/parameters | 5608/0/388 | 6678/1/417 |
| Goodness-of-fit on $F^2$ | 0.990 | 0.715 |
| $R(F)$ ($I > 2\sigma(I)$) | | |
| $R_1$ | 0.0282 | 0.0372 |
| $wR_2$ | 0.0630 | 0.0643 |
| $wR(F^2)$ (all data) | | |
| $R_1$ | 0.0369 | 0.1144 |
| $wR_2$ | 0.0646 | 0.0738 |
| Abs. struct. parameter | −0.03(4) | 0.01(6) |
| Extinction coefficient | 0.0017(5) | not determined |
| Largest peak and holes [e Å$^{-3}$] | 0.261; −0.273 | 0.157; −0.137 |

10 H); 5.60 ($d$, $J$ = 7, 1 H); 4.57 ($d$, $J$ = 7, 1 H); 4.05–3.94 ($m$, 1 H); 3.47 ($AB$, $J$ = 14, 67.5, 2 H); 2.05–1.81 ($m$, 5 H); 1.43–1.22 ($m$, 2 H); 1.15 ($s$, Me); 0.97 ($s$, 3 H). $^{13}$C-NMR: 159.7; 153.1; 139.3; 138.1; 129.1; 128.8; 128.6; 128.1; 127.8; 125.7; 93.1; 65.8; 63.3; 53.4; 48.6; 47.8; 45.1; 38.6; 33.3; 26.3; 21.3; 19.9. HR-EI-MS: 487.1670 ([$M$ + Na]$^+$, $C_{26}H_{28}N_2O_4S^+$; calc. 487.1667).

*1-{[(Dicyclohexylamino)sulfonly]methyl}-7,7-dimethylbicyclo[2.2.1]hept-2-yl (4*R,5R*)-4,5-Dihydro-4,5-diphenylisoxazole-3-carboxylate* ((4*R*,5*R*)-**6b**). M.p. 189–192°. $[\alpha]_D^{23} = -259.1$ ($c$ = 1, $CHCl_3$). IR (KBr): 3432, 2932, 1724, 1454, 1326, 1166, 1143, 1048, 982, 756, 698, 576. $^1$H-NMR: 7.40–7.18 ($m$, 10 H); 5.55 ($d$, $J$ = 7, 1 H); 5.05–5.00 ($m$, 1 H); 4.68 ($d$, $J$ = 7, 1 H); 3.49 ($d$, $J$ = 13, 1 H); 3.38–3.22 ($m$, 2 H); 2.62 ($d$, $J$ = 13, 1 H); 2.04–1.52 ($m$, 20 H); 1.50–1.06 ($m$, 7 H); 1.04 ($s$, 3 H); 0.90 ($s$, 3 H). $^{13}$C-NMR: 158.9; 153.3; 139.5; 138.4; 129.3; 120.0; 128.7; 128.0; 127.4; 125.7; 93.3; 80.0; 61.2; 57.3; 53.3; 49.6; 49.1; 44.4; 39.7; 33.4; 32.3; 30.1; 27.0; 26.3; 25.3; 20.4; 19.9. LSI-MS (+; NBA 8 kV): 647 (8, [$M$ + H$^+$]), 380 (64), 228 (33), 180 (41), 135 (100), 83 (47). HR-EI-MS: 647.34878 ([$M$ + H]$^+$, $C_{38}H_{51}O_5N_2S^+$; calc. 647.35187).

*5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (4*R,*5*R*)-4,5-Dihydro-4,5-diphenylisoxazole-3-carboxylate* ((4*R*,5*R*)-**6c**). IR (film): 3030, 2957, 2923, 1729, 1585, 1495, 1454, 1316, 1218, 1126, 935, 757, 699. $^1$H-NMR: 7.47–6.98 (*m*, 15 H); 5.53 (*d*, *J* = 8, 1 H); 4.84–4.76 (*m*, 1 H); 3.52 (*d*, *J* = 8, 1 H); 1.91–1.26 (*m*, 7 H); 1.24 (*s*, 3 H); 1.12 (*s*, 3 H); 1.09–0.99 (*m*, 1 H); 0.71 (*s*, 3 H). $^{13}$C-NMR: 158.8; 153.4; 151.6; 139.4; 138.7; 129.0; 128.8; 127.7; 127.5; 125.4; 125.3; 93.4; 75.9; 60.3; 50.3; 40.6; 39.3; 34.2; 31.0; 29.1; 26.2; 23.4; 21.6. LSI-MS (+; NBA 8 kV): 482 (16, $[M+H]^+$), 268 (62), 215 (37), 119 (72), 105 (100). HR-EI-MS: 482.27102 ($[M+H]^+$, $C_{32}H_{36}NO_3^+$; calc. 482.26952).

*Dimethyl (4*S,*5*S*)-4,5-Dihydro-3-[(tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzothiazol-1(4*H*)-yl)carbonyl]isoxazole-4,5-dicarboxylate* ((4*S*,5*S*)-**7a**). IR (KBr): 2960, 1749, 1675, 1439, 1395, 1347, 1264, 1239, 1170, 1141, 1114. $^1$H-NMR: 5.44 (*AB*, *J* = 6.5, 37, 1 H); 4.96 (*d*, *J* = 6.5, 0.67 H); 4.615 (*d*, *J* = 6.5, 0.33 H); 4.21–4.19 (*m*, 0.67 H); 4.13–4.10 (*m*, 0.33 H); 3.84 (*s*, 3 H); 3.79 (*s*, 3 H); 3.48 (*AB*, *J* = 14.5, 47.5, 2 H); 2.11–1.86 (*m*, 5 H); 1.48–1.325 (*m*, 2 H); 1.275–1.21 (*m*, 3 H); 1.00 (*s*, 3 H). $^{13}$C-NMR: 167.9; 166.8; 159.3; 149.9; 81.7; 65.5; 56.8; 56.1; 53.6; 52.8; 49.3; 40.0; 45.3; 39.0; 33.0; 26.3; 21.1; 19.9. EI-MS: 428 (23, $M^+$), 214 (100), 172 (41), 57 (77), 43 (48). HR-EI-MS: 429.13047 ($[M+H]^+$, $C_{18}H_{25}N_2O_8S^+$; calc. 429.13315).

*3-(1-{[(Dicyclohexylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]hept-2-yl) 4,5-Dimethyl (4*S,*5*S*)-4,5-Dihydroisoxazole-3,4,5-tricarboxylate* ((4*S*,5*S*)-**7b**). IR (KBr): 3443, 2935, 1748, 1454, 1326, 1223, 1143, 1048, 982, 576. $^1$H-NMR: 5.40 (*d*, *J* = 6, 0.72 H); 5.34 (*d*, *J* = 6, 0.28 H); 5.18–5.06 (*m*, 1 H); 4.75 (*d*, *J* = 6, 0.28 H); 4.67 (*d*, *J* = 6, 0.72 H); 3.84 (*s*, 3 H); 3.80 (*s*, 3 H); 3.38 (*d*, *J* = 13, 1 H); 3.32–3.12 (*m*, 2 H); 2.63 (*d*, *J* = 13, 1 H); 2.01–1.50 (*m*, 20 H); 1.48–1.04 (*m*, 7 H); 1.01 (*s*, 3 H); 0.89 (*s*, 3 H). $^{13}$C-NMR: 168.0; 167.4; 158.0; 149.4; 83.3; 80.9; 57.4; 55.6; 53.5; 53.3; 49.7; 49.1; 44.5; 39.1; 33.1; 32.4; 30.2; 27.0; 26.3; 25.2; 20.3; 19.9. LSI-MS (+; NBA 8 kV): 611 (11, $[M+H]^+$), 380 (78), 228 (29), 154 (74), 135 (27), 83 (40). HR-EI-MS: 611.29859 ($[M+H]^+$, $C_{30}H_{47}O_9N_2S$; calc. 611.30023).

*4,5-Dimethyl 3-[5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] (4*S,*5*S*)-4,5-Dihydroisoxazole-3,4,5-tricarboxylate* ((4*S*,5*S*)-**7c**). IR (film): 2956, 2925, 2870, 1744, 1716, 1598, 1496, 1438, 1369, 1222, 1125, 1019, 935, 764, 702. $^1$H-NMR: 7.31–7.03 (*m*, 5 H); 5.28 (*d*, *J* = 7, 0.34 H); 5.25 (*d*, *J* = 7, 0.66 H); 5.06–4.94 (*m*, 1 H); 4.54 (*d*, *J* = 7, 0.34 H); 3.93 (*d*, *J* = 7, 0.66 H); 3.90 (*s*, 1.02 H); 3.89 (*s*, 1.98 H); 3.79 (*s*, 1.02 H); 3.75 (*s*, 1.98 H); 2.14–1.40 (*m*, 7 H); 1.34 (*s*, 3 H); 1.24 (*s*, 3 H); 1.21–0.98 (*m*, 1 H); 0.89 (*s*, 3 H). $^{13}$C-NMR: 168.0; 167.7; 158.5; 151.1; 149.1; 128.0; 125.6; 125.2; 83.4; 76.8; 55.2; 54.9; 53.2; 50.4; 41.4; 39.7; 34.3; 31.3; 28.1; 26.5; 24.7; 21.7. LSI-MS (+; NBA 8 kV): 468 (18, $[M+Na]^+$), 446 (59, $[M+H]^+$), 215 (68), 172 (46), 119 (84), 105 (100), 91 (17). HR-EI-MS: 446.21742 ($[M+H]^+$, $C_{24}H_{32}NO_7^+$; calc. 446.21788).

*Methyl (4*R,*5*R*)-4,5-Dihydro-4,5-diphenylisoxazole-3-carboxylate* (**8**). *Chiracel OD* (hexane/AcO$^i$Pr 96:4, 1.5 ml/min): (4*R*,5*R*)-**8**, 7.3 min; (4*S*,5*S*)-**8**, 9.4 min. $[\alpha]_D^{20} = -44.5$ (*c* = 1.0, $CHCl_3$, obtained from pure crystallized (4*R*,5*R*)-**6b**). IR (KBr): 3434, 2952, 1728, 1590, 1438, 1361, 1220, 1123, 942, 928, 804, 764, 700. $^1$H-NMR: 7.44–7.21 (*m*, 10 H); 5.67 (*d*, *J* = 6, 1 H); 4.54 (*d*, *J* = 6, 1 H); 3.78 (*s*, 3 H). $^{13}$C-NMR: 160.4; 152.8; 139.4; 138.2; 129.4; 129.0; 128.75; 128.2; 127.4; 125.25; 93.6; 61.2; 52.8. HR-EI-MS: 282.1139 ($[M+H]^+$, $C_{17}H_{15}NO_3^+$; calc. 282.1130).

*Trimethyl (4*S,*5*S*)-4,5-Dihydroisoxazole-3,4,5-tricarboxylate* (**9**). *Chiracel OJ-H* (hexane/AcO$^i$Pr 90:10, 1.0 ml/min): (4*R*,5*R*)-**9**, 57.5 min; (4*S*,5*S*)-**9**, 62.4 min. $[\alpha]_D^{20} = +1.3$ (*c* = 1.0, $CHCl_3$, obtained from (4*S*,5*S*)-**7a**). IR: 3445, 2959, 1761, 1742, 1715, 1602, 1449, 1407, 1378, 1246, 1221, 1197, 1176, 1135, 995, 957, 931, 814. $^1$H-NMR: 4.40 (*d*, *J* = 6.2, 1 H); 4.67 (*d*, *J* = 6.2, 1 H); 3.92 (*s*, 3 H); 3.84 (*s*, 3 H); 3.81 (*s*, 3 H). $^{13}$C-NMR: 167.6; 159.5; 148.9; 83.6; 55.1; 53.45; 53.3; 29.7. HR-EI-MS: 246.1967 ($[M+H]^+$, $C_9H_{12}NO_7^+$; calc. 246.1978).

*Methyl (4*S,*5*S*)-4,5-Dihydro-4-phenyl-3-[(tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzoisothiazol-1(4*H*)-yl)carbonyl]isoxazole-5-carboxylate*[15]). Obtained in 66% yield as a solid from **3a** and methyl cinnamate. IR (KBr): 2959, 2885, 1745, 1671, 1592, 1457, 1346, 1264, 1237, 1170, 1140, 933, 757, 699, 559, 533, 492. $^1$H-NMR: 7.42–7.33 (*m*, 5 H); 5.92 (*d*, *J* = 8.5, 1 H); 4.63 (*d*, *J* = 8.5, 1 H); 4.30–4.24 (*m*, 1 H); 3.79 (*s*, 3 H); 3.49 (*AB*, *J* = 14, 42.5, 2 H); 2.24–1.88 (*m*, 5 H); 1.47–1.35 (*m*, 2 H); 1.26 (*s*, 3 H); 1.01 (*s*, 3 H). $^{13}$C-NMR: 168.2; 158.6; 149.9; 138.0; 129.0; 125.8; 87.1; 65.6; 60.3; 53.3; 52.8; 49.4; 48.0; 45.4; 39.3; 33.2; 26.3; 21.2; 20.0. EI-MS: 446 (21, $M^+$), 214 (82), 178 (100), 135 (27), 105 (35), 93 (32), 77 (17), 83 (27). HR-EI-MS: 446.15176 ($M^+$, $C_{22}H_{26}N_2O_6S^+$; calc. 446.15116).

*5-Methyl 3-[(1*R,2S,5R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl] (4*S,5S*)-4,5-Dihydro-4-phenylisoxazole-3,5-dicarboxylate*[15]). Obtained in 62% yield as an oil from **3c** and methyl cinnamate. IR: 2956, 2925, 2870, 1743, 1714, 1591, 1496, 1455, 1369, 1221, 1126, 1030, 937, 762, 700. $^1$H-NMR: 7.48–7.00 (*m*, 10 H); 5.83 (*d*, *J* = 9, 0.38 H); 5.75 (*d*, *J* = 9, 0.62 H); 5.09–4.94 (*m*, 1 H); 4.18 (*d*, *J* = 9, 0.38 H); 3.80 (*s*, 1.14 H); 3.75 (*s*, 1.86 H); 3.39 (*d*, *J* = 9, 0.62 H); 2.16–1.39 (*m*, 7 H); 1.36 (*s*, 1.14 H); 1.32 (*s*, 1.86 H); 1.28 (*s*, 1.14 H); 1.19 (*s*, 1.86 H); 1.18–0.92 (*m*, 1 H); 0.89 (*s*, 3 H). $^{13}$C-NMR: 169.0; 158.4; 151.3; 149.2; 138.0; 129.0; 128.9; 127.9; 125.6; 125.5; 125.2; 83.7; 76.3; 59.0; 53.2; 50.3; 41.5; 39.5; 34.3; 31.3; 28.8; 26.4; 23.9; 21.8. LSI-MS: 486 (58, $[M+Na]^+$), 464 (17, $[M+H]^+$), 215 (68), 119 (83), 105 (100), 91 (26). HR-EI-MS: 486.22554 ($[M+Na]^+$, $C_{28}H_{33}NaO_5^+$; calc. 486.22564).

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