1,3-Dipolar Cycloadditions of a 2-Oxoethanenitrile Oxide Derived from (2*R*)-Bornane-10,2-sultam to Electronically Modified 4,4′-Disubstituted Stilbenes

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Thanks to its type-II dipole nature, we were able to demonstrate the higher reactivity of the SO_2/C=O *syn*-conformer for the uncatalyzed 1,3-dipolar cycloaddition of the 2-oxoethanenitrile oxide **2** derived from bornane-10,2-sultam to the symmetric 4,4′-disubstituted *trans*-stilbenes **3a**–**3i**. The C(α)-*si* dipolarophile π_y approach along the C=O bond precludes the use of the steric rules formerly expressed for this pseudo-C_2-symmetric auxiliary. The observed diastereoselectivity is related to the electronic nature of the dipolarophile and may be predicted on the basis of its σ_{para} *Hammett* constant. The absolute configuration was based on the X-ray structure analysis of cycloadduct (4*S*,5*S*)-**4b**, which exhibits an SO_2/C=O *anti*-conformation. Finally, the results obtained with *cis*-stilbene suggest a nonsynchronous mechanism.

Introduction. – Resulting from dipole interactions, *N*-acyl-substituted (2*R*)-bornane-10,2-sultam derivatives adopt essentially, in the solid state, the thermodynamically more stable SO_2/C=O *anti*-periplanar conformation[2]). More than a decade ago, we suggested that the *syn*-periplanar conformation could lead to a more reactive species in solution, and thus could eventually participate during the course of the reaction by displacing the *anti*/*syn* equilibrium[3]) [8][9]. This higher reactivity is believed to result from a better electronic alignment between the C=O moiety and the N lone pair (lp), favoring delocalization on the sultam moiety through a generalized anomeric stabilization of the N lp by the *anti*-periplanar S=O σ* MO [2]. Indeed, we found that the ΔhN pyramidal height is directly correlated with the S–N–C=O dihedral angle and reach local and global minima near *ca.* 170 and −10°, respectively [7][8]. For *syn*-periplanar conformations, where the C=O is bisecting the O=S=O angle, the S–N–C=O torsion angle only varies from *ca.* −19 to −9° and the ΔhN decreases from 0.133 to 0.066 Å, respectively [7]. Alternatively, in the sterically less constrained *anti*-conformation, this parameter decreases from *ca.* 0.40 to 0.11 Å, for a dihedral angle comprised between *ca.* 120 and 170°, respectively [7][8]. This widely

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[2]) For the first example of a *syn*-conformer chelated with $TiCl_4$, see [1].
[3]) For the first example of a nonchelated *syn*-conformer of **1a**, see [2]. For rare further *syn*-examples, see [3], as well as [4–7]. These latter represent *ca.* 3% of the *N*-acyl-substituted (2*R*)-bornane-10,2-sultam derivatives in the *CCDC* database (2008).

used chiral auxiliary [10] was earlier recognized as a disguised pseudo-C_2-symmetric promoter, reminiscent of a 2,5-disubstituted pyrrolidine [11]. As a consequence, it is particularly difficult to define whether the *anti*- or *syn*-conformer is responsible for the observed induction in the absence of chelation. It is indeed only very recently, by studying the asymmetric 1,3-dipolar cycloaddition of the 2-oxoethanenitrile oxide **2** derived from (2*R*)-bornane-10,2-sultam to symmetric alkenes, that we have been able to demonstrate the higher reactivity of the SO_2/C=O *syn*-conformer *syn*-**2** [6]. This evidence is supported by the fact that similar differences of energies have been calculated by means of a B3LYP/6-31G** DFT method [12] for the approaches of conformer *anti*-**2** to either the C(α)-*si* or -*re* faces of *trans*-stilbene ((*E*)-**3c**); on the contrary, the C(α)-*si* approach of this dipolarophile to conformer *syn*-**2** is favored, thus leading preferentially to the (4*S*,5*S*)-cycloadduct **4c**, as shown by the X-ray-analysis of its *syn*-conformer [6]. We also calculated that the LUMO of conformer *syn*-**2** is slightly lower in energy, as compared to its *anti*-conformer, and thus should react preferentially with electron-rich dipolarophiles. Alternatively, with a slightly higher HOMO energy, the type-II[4]) dipole *anti*-**2** should react faster with electron-poor dipolarophiles, such as the unreported 4,4′-dinitrostilbene **3h**, and thus result in a poorer diastereoselectivity. To confirm our hypothesis, we electronically modified the dipolarophile *trans*-stilbene (**3c**) at C(4) and C(4′), thus minimizing the steric requirements about the reactive centers and maintaining the symmetry, in order to avoid the formation of regioisomers. This comparative study is now presented in detail.

Results and Discussion. – Starting from the reported *N*-(glyoxyloyl)bornane-10,2-sultam **1b** [15], the obtained known crystalline aldoxime **1c** [16] was treated with the commercially available 4,4′-dimethoxystilbene **3a** in the presence of *N*-chlorosuccinimide (NCS) and $KHCO_3$ in $CHCl_3$ [17], to afford cycloadduct **4a** in 88% yield and 49% d.e. (*Scheme*, *Table 1*). The diastereoselectivity of the formation of **4a**–**4i** was determined with the crude reaction mixtures by 500-MHz-^{1}H-NMR analysis of the major *d* (H–C(4)) appearing between δ 4.72 and 4.82, with respect to that of the minor (4*R*,5*R*)-stereoisomer resonating systematically at higher field (δ *ca.* 4.48–4.58) [6], with a $\pm$2% precision[5]). When 4,4′-dimethylstilbene **3b** [18] was used, we isolated cycloadduct **4b** in 87% yield and 43% d.e. The sense of induction was ascertained by an X-ray crystal-structure analysis of the main stereoisomer (4*S*,5*S*)-**4b** (*Fig. 1*), after purification by crystallization from hexane/AcOEt 1:1, thus corroborating our previous results obtained with analogue (4*S*,5*S*)-**4c** [6].

To verify, by comparison with **3c** [6], that this decreasing diastereoselectivity originates from electronic rather than steric reasons, we tested the 4,4′-difluorostilbene

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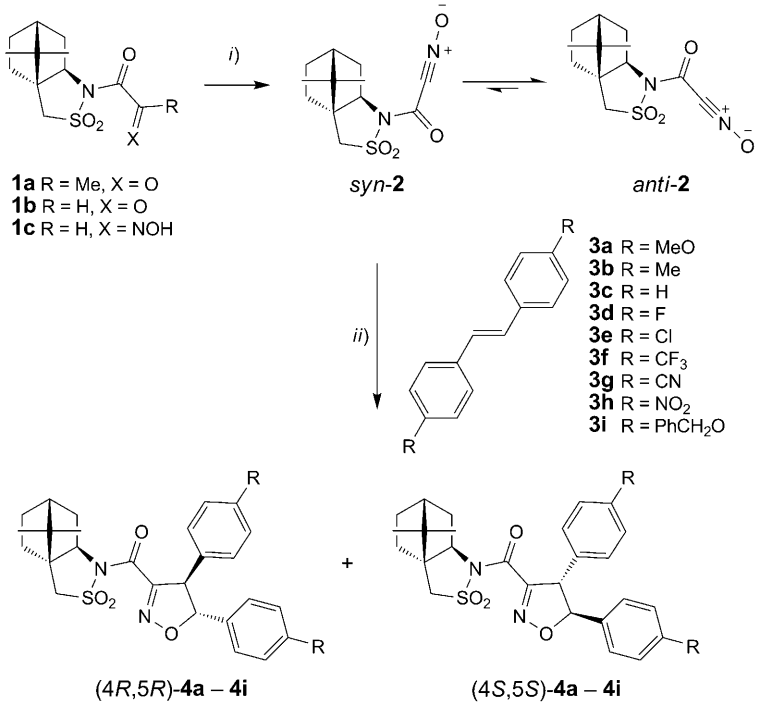
[4]) Dipoles **2** are of type II according to [13], meaning that the similarity of the dipole and dipolarophile FMO energies implies that both the HOMO–LUMO or LUMO–HOMO interactions are important [14]. The preference may, besides the electronic nature of the dipolarophile, also depend on the electronic influence of **2**, hence, for example, on its SO_2/C=O *anti*- or s*yn*-conformation.

[5]) The *d*s of H–C(5) similarly appear at δ 5.51–5.67 and 5.48–5.63 for the (4*S*,5*S*)- and (4*R*,5*R*)-stereoisomers **4a**–**4i**, respectively, but were not used for quantifications since they were not always baseline-separated.

Scheme



i) NCS, $CHCl_3$. *ii*) $KHCO_3$, $CHCl_3$, 20°, 6 h.

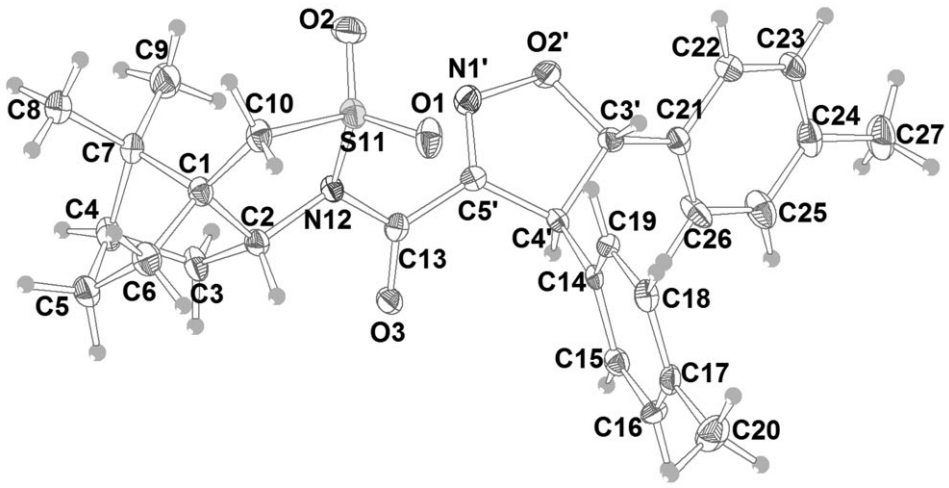


Fig. 1. *ORTEP Diagram of cycloadduct (4S,5S)*-**4b** (arbitrary atom numbering). Ellipsoids are represented at the 50% probability level.

Table 1. *HOMO and LUMO Energies* [Hartree] *and* Hammett *Constants of the 4,4′-Disubstituted* trans-*Stilbene Dipolarophiles* **3a**–**3i**, *with Respect to Diastereoisomer Excess* (d.e.), *Logarithm of the Diastereoisomer Ratio* (d.r.), *and Chemical Yield of the Cycloadducts* **4a**–**4i**

	Dipole **2**		*trans*-Stilbene **3** (R)								
	anti	*syn*	**3a** (MeO)	**3b** (Me)	**3c** (H)	**3d** (F)	**3e** (Cl)	**3f** (CF_3)	**3g** (CN)	**3h** (NO_2)	**3i** (BnO)
LUMO	−0.064	*−0.068*[a])	−0.037	−0.045	−0.050	−0.054	−0.065	−0.078	−0.097	**−0.115**[b])	−0.037
HOMO	**−0.271**	−0.275	*−0.181*	*−0.194*	*−0.203*	*−0.205*	*−0.212*	*−0.227*	*−0.235*	−0.245	*−0.188*
Hammett σ_p[c])			−0.27	−0.17	0.00	0.06	0.23	0.54	0.66	0.78	−0.42
Hammett σ_{sti}[d])			−0.12	−0.14	0.00	0.15	0.24	0.53	0.70	0.81	−0.41
d.e. [%]			49	43[e])	46	45	40	36	24		51
log(d.r.)[f])			0.466	0.399	0.432	0.421	0.368	0.327	0.213		0.489
Yield of **4**			88	87	90	65	56	53	20		40

[a]) $LUMO_{dipole} - HOMO_{dipolarophile}$. [b]) $HOMO_{dipole} - LUMO_{dipolarophile}$. [c]) Aromatic σ_{para}. [d]) *Hammett* constants of 4,4′-disubstituted *trans*-stilbenes. [e]) Constant after several repetitions. [f]) d.r. = [(4*S*,5*S*)-**4**]/[(4*R*,5*R*)-**4**].

(**3d**) [19][6]). In this case, the selectivity reached 45% d.e. (*Table 1*) which was confirmed by ^{19}F-NMR analysis. We then used 4,4′-dichlorostilbene (**3e**) [21] and isolated cycloadduct **4e** in 56% yield and 40% d.e. Dipolarophile **3f** (R = CF_3) [22] was also chosen as a quasi-isosteric analogue of **3b**, and its selectivity diminished to 36% d.e., as also confirmed by ^{19}F-NMR analysis. Finally, as expected from a concurrent unselective participation of conformer *anti*-**2**, the worst selectivity (24% d.e.) was observed with the electronically most deficient dipolarophile **3g** (R = CN) [23]. In this specific case, the reaction rate was so slow that dimerization of dipole **2** became a serious contaminating side reaction, and **4g** was isolated in only 20% yield after column-chromatography (CC; SiO_2) purification. We were unable to test **3h** (R = NO_2) as an inverse-electron-demand partner since we failed to synthesize it by the general procedures as earlier described for analogous substrates [24][7]). Furthermore, the chemical yield obtained from **3f** and the diastereoselectivity resulting from **3g** did not encourage us to continue pursuing this direction. At this point, to optimize the selectivity, we revisited an electron-rich dipolarophile, by testing the dibenzyl ether **3i** (R = $PhCH_2O$) [26]; in so doing, we could reach 51% d.e. As earlier emphasized, the diastereoselectivities were constant over time, and the cycloadducts **4** were stable under the reaction conditions [6].

Finally, we also tested pure (> 96%) *cis*-stilbene ((*Z*)-**3c**) as dipolarophile[8]) and could isolate in 30% yield a 3:7 mixture of *trans*- and *cis*-cycloadducts **4c**. The minor *trans*-pair, as well as the *cis*-cycloadducts were formed in *ca*. 44% d.e. in favor of the diastereoisomer (4*S*,5*S*)-**4c**, and *ca*. 28% d.e. in favor of the diastereoisomer (4*S*,5*R*)-**4c**, respectively. This latter ratio was determined by the integration of the ^{1}H-NMR signals of the 'benzyl' *d*s, appearing at lower field (δ 6.05 and 5.15, J = 11 Hz), for the main diastereoisomer, when compared to its minor counterpart (4*R*,5*S*)-**4c** (δ 5.96 and 4.80, J = 10 Hz). After CC (SiO_2) separation of the *trans*/*cis* mixture, the *cis*-adducts were crystallized from AcOEt/hexane 1:1 to afford the enriched minor (4*R*,5*S*)-**4c** (*cis*), as well as the analytically pure major *cis*-diastereoisomer (4*S*,5*R*)-**4c**. This latter was suitable for X-ray analyses, and hence for absolute-configuration determination (*Fig. 2*). It shows an SO_2/C=O *anti*-conformation with an S−N−C=O dihedral angle of 153.3(2)° and a ΔhN of 0.230 Å. As in the cases of both (4*S*,5*S*)-**4b** and (4*S*,5*S*)-**4c**, the C=O is *anti*-periplanar to the C(5′)=N(1′) bond. *cis*-Stilbene ((*Z*)-**3c**) appears isomerically stable under the reaction conditions, either in the presence or absence of dipole **2**. However, we cannot totally exclude a slow isomerization process, followed by a rapid cycloaddition, thus explaining the apparent absence of transient (*E*)-dipolarophile. Nevertheless, with respect to the absence of *trans*-stilbene (**3c**) in the remaining excess of dipolarophile, after completion of the reaction, these results are consistent with a nonsynchronous mechanism, as earlier suggested by calculations [6].

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[6]) An F-atom is sterically similar to an H-atom [20].

[7]) Owing to the strong oxidative reactive conditions, both OH- and N-containing substrates, such as the commercially available *trans*-stilbene-4,4′-diol (LUMO −0.039; HOMO −0.184), 4,4′-[(1*E*)-ethene-1,2-diyl]bis[pyridine] (LUMO −0.080; HOMO −0.238), or the known *trans*-4,4′-bis(dimethylamino)stilbene (=4,4′-[(1*E*)-ethene-1,2-diyl]bis[*N*,*N*-dimethylbenzenamine] [25] (LUMO −0.024; HOMO −0.158), proved to be unsuitable dipolarophiles in our hands, even under milder conditions using MnO_2 [6].

[8]) LUMO −0.043 and HOMO −0.209 Hartree.

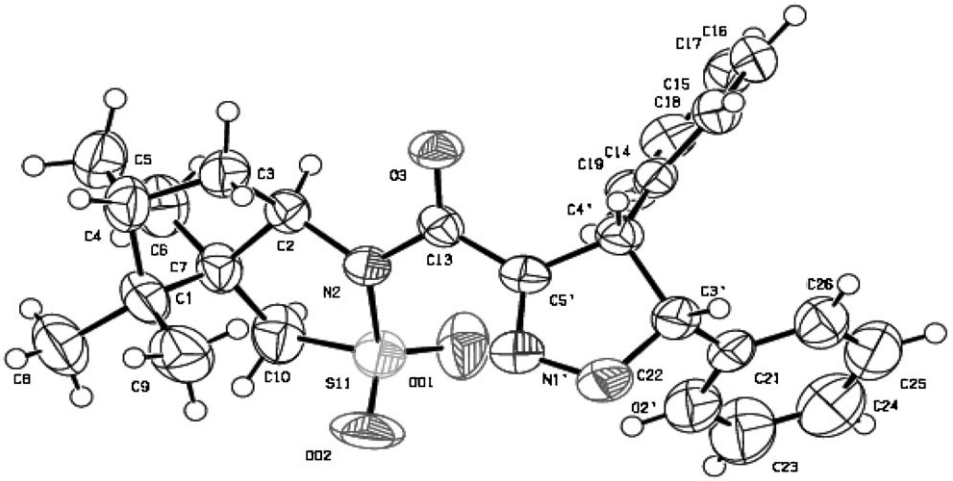

Fig. 2. *ORTEP Diagram of cycloadduct (4*S,5R*)*-**4c** (arbitrary atom numbering). Ellipsoids are represented at the 50% probability level.

In fact, we performed the X-ray structure analysis of (4*S*,5*S*)-**4b** (*Fig. 1*) because we expected to observe, as in the case of (4*S*,5*S*)-**4c** [6], the rare SO_2/C=O *syn*-conformation. Indeed, more than 97% of the X-ray structure analyses of bornane-10,2-sultam derivatives exhibit an SO_2/C=O *anti*-conformation, and we are aware of only six structures with *syn*-conformation [2][7], amongst which four possess a heteroatom lp in the β-position, and two of them are derived from dipole **2** [5][6]. The fact that (4*S*,5*S*)-**4b**[9]) shows an *anti*-conformation, in contrast to the *syn*-conformation of (4*S*,5*S*)-**4c**[10]), was surprising for us, and shows for these practically identical structures, that external secondary influences, such as the crystal-packing forces or the solvent polarity [27] are particularly important parameters for the control of the *syn*/*anti*-stability. A second example illustrating the differences in electronic alignments is given by the (2*R*)-*N*-picolinoylbornane-10,2-sultam derivative [6], which shows a ΔhN of 0.269 Å for an S−N−C=O angle of 144.57(15)°, as compared to 0.066 Å and −11.5(3)°, respectively, for its thermodynamically less stable (1.8 kcal/mol) *syn*-conformer [7].

From a conformational point of view, the S=O(2) substituent adopts a pseudo-equatorial orientation due to the steric influence of the Me(9) group [28]. For both (4*S*,5*S*)-**4b** and (4*S*,5*S*)-**4c**, the S=O(1) bond is slightly longer than the S=O(2) bond (see *Table 2* for (4*S*,5*S*)-**4b**, and *Fig. 1* for atom numbering), as expected from a stereoelectronic influence of the *anti*-periplanar N lone pair [29]. In the case of (4*S*,5*R*)-**4c**, the steric influence of the aromatic H−C(19) renders, in the crystalline state, the S=O(1) bond both less pseudoaxial and shorter (*Table 2* and *Fig. 2*). Interestingly, the O=S=O angle remains constant between the *anti*-conformation of (4*S*,5*S*)-**4b** and the *syn*-conformation of (4*S*,5*S*)-**4c** [6]. The Φ_2 puckering parameters for both five-membered sultam rings are in the range of those observed for both *syn*-

[9]) ΔhN = 0.264 Å and S−N−C=O = 148.29(11)°.

[10]) ΔhN = 0.119 Å and S−N−C=O = −17.45(18)°.

conformers (90.3° [6] to 104.8° [5]) and *anti*-conformers (77.4° [7][30] to 139.7° [31]). This contrasts with fenchane-8,2-sultams, which possess a modified envelope, with an S=O(2) substituent in the pseudoaxial orientation ($\Phi_2 = 252.4°$), despite the presence of a sterically more influent $Me_2C(3)$ moiety [28].

Table 2. *Selected Bond Lengths* [Å] *and Angles* [°] *of (4*S,*5*S*)*-**4b** *and (4*S,*5*R*)*-**4c**. For atom numbering, see *Figs. 1* and *2*.

	(4*S*,5*S*)-**4b**	(4*S*,5*R*)-**4c**
S=O(1)	1.4298(11)	1.413(3)
S=O(2)	1.4224(12)	1.428(3)
S–N	1.7092(12)	1.706(2)
S–C(10)	1.7907(15)	1.761(4)
N–C(2)	1.4873(18)	1.481(4)
N–C(13)	1.3821(18)	1.378(4)
C(13)=O(3)	1.2155(17)	1.223(3)
C(13)–C(5′)	1.487(2)	1.473(5)
O(1)=S=O(2)	118.42(7)	118.1(2)
C(2)–N–S	112.37(9)	112.15(19)
C(2)–N–C(13)	116.50(11)	117.1(2)
C(13)–N–S	122.21(10)	123.75(19)
C(5′)–N(1′)–O(2′)	108.59(12)	108.4(2)
C(2)–N–S=O(1)	108.08(10)	110.6(2)
C(2)–N–S=O(2)	−120.75(10)	−118.2(2)
C(3)–C(2)–N–S	139.17(11)	138.3(2)
O(3)=C(13)–C(5′)–N(1′)	138.78(14)	142.7(3)
N–C(13)–C(5′)–C(4′)	156.84(13)	155.5(3)
Puckering parameter q_2	0.344	0.345
S–N–C(2)–C(1)–C(10) Φ_2	98.76	102.38

The rationalization for the observed diastereoselectivity is based on earlier calculations suggesting a preferred π_y approach of the electron-rich (*E*)-dipolarophile C(α)-*si* face along the C=O bond of the more reactive dipole *syn*-**2** [6]. The unselective concurrent participation of nitrile oxide *anti*-**2** decreases the selectivity with respect to the increasing influence of its HOMO interaction with electron-deficient substrates. Due to the linearity of the nitrile oxide, and the unusual trajectory of the dipolarophile, the simple steric rules developed by *Kim* and *Curran* for this chiral auxiliary do not apply here [11]. Nevertheless, the predictability of the diastereoselectivity may be correlated with the *Hammett* σ_{para} electronic properties of the dipolarophiles **3a**–**3i**[11]) [33] by using *Eqn. 1* (d.r. = diastereoisomer ratio). A very similar correlation was found by using the 4,4′-disubstituted *trans*-stilbene electronic parameters (*Eqn. 2*) [34].

$$\log(\text{d.r.}) = -0.215\sigma_{para} + 0.406 \quad (1)$$

($R = 0.93$, standard deviation = 0.035, $n = 8$)

[11]) For a correlation between the σ^+_{para} *Hammett* parameter and the regioselectivity in enantiomer-catalyzed [3+2] cycloadditions of electronically modified nitrones, see [32].

$$\log(\text{d.r.}) = -0.222\sigma_{\text{stilbene}} + 0.416 \quad (2)$$

($R = 0.92$, standard deviation $= 0.036$, $n = 8$)

Nevertheless, we prefer to present the correlation with the more commonly used and accepted simple aromatic σ_{para} constants (*Fig. 3*). The *cis*-stilbene approach follows preferentially the same trajectory and results in the same configuration for the C(4) center.

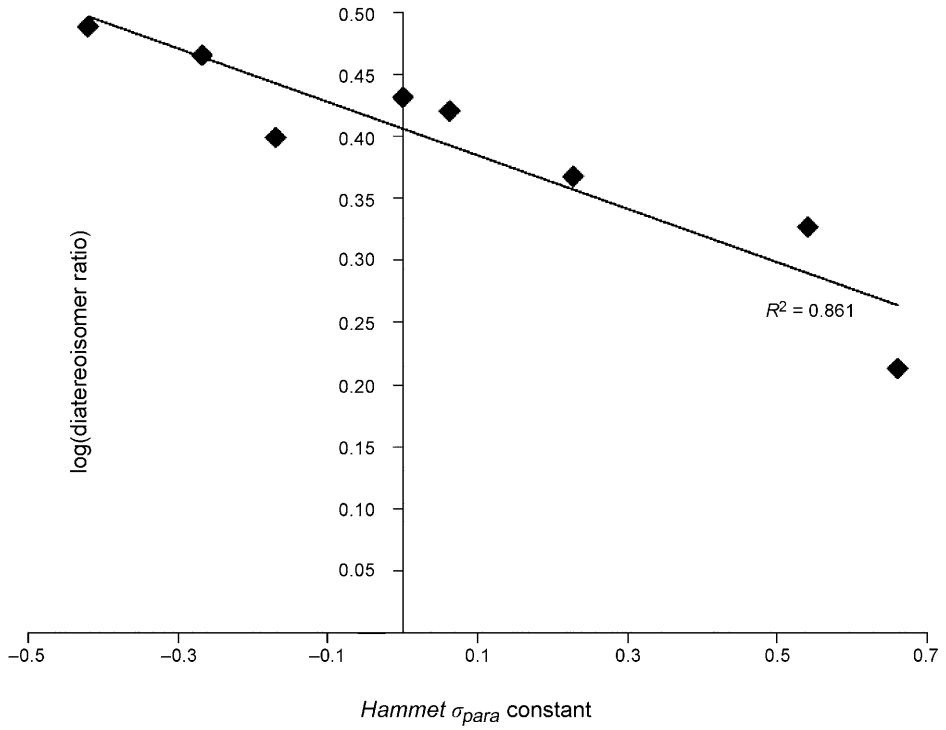

Fig. 3. *Diastereoselectivity* (log(diastereoisomer ratio)) *of the uncatalyzed 1,3-dipolar cycloaddition of dipole* **2** *and 4,4′-disubstituted* trans-*stilbenes* **3a**–**3i** *as a function of their* Hammett *aromatic constant* σ_{para}

Conclusions. – The uncatalyzed 1,3-dipolar cycloaddition of 2-oxoethanenitrile oxide **2** derived from (2*R*)-bornane-10,2-sultam to the symmetric 4,4′-disubstituted *trans*-stilbenes **3a**–**3i** follows the *Acree–Curtin–Hammett* principle [35]. The higher reactivity of the minor conformer *syn*-**2** results from a better alignment of the electronic π-system, between both the oxo and the N lp of the sultam moiety. The stereoelectronic properties of such sultam derivatives differ fundamentally from those of simple chiral amides or pyrrolidines, by their N lp anomeric stabilization with the *anti*-periplanar

[11]) For a correlation between the σ^{+}_{para} *Hammett* parameter and the regioselectivity in enantiomer-catalyzed [3 + 2] cycloadditions of electronically modified nitrones, see [32].

S=O σ^* antibonding orbital [2][36]. Although the dipolarophile π_y trajectory along the C=O bond precludes the use of the steric rules formerly expressed for this pseudo-C_2-symmetric auxiliary [11], the observed diastereoselectivity is related to the electronic nature of the dipolarophiles **3a**–**3i** and may be predicted on the basis of either their σ_{para} or σ_{stilbene} *Hammett* parameters. The sense of induction resulting from a C(α)-*si* approach of the *trans*-stilbene derivatives **3a**–**3i** is consistent with the X-ray structure of cycloadduct (4*S*,5*S*)-**4b**, which exhibits an SO_2/C=O *anti*-conformation, in contrast to the *syn*-conformation of (4*S*,5*S*)-**4c** [6]. A nonsynchronous mechanism is suggested by both calculations [6] and experimental evidences resulting from the cycloaddition of the dipolarophile *cis*-stilbene ((*Z*)-**3c**).

Financial support from the *Ministry of Science and Higher Education* (Grant PBZ-KBN-126/T09/06) is gratefully acknowledged. The X-ray crystal-structure data of (4*S*,5*S*)-**4b** were recorded in the Crystallographic Unit of the Physical Chemistry Laboratory at the Chemistry Department of the University of Warsaw, and those of (4*S*,5*R*)-**4c** in the Crystallographic Unit Laboratory at the Institute of Organic Chemistry, Polish Academy of Sciences of Warsaw.

Experimental Part

1. *General.* See [37].

2. *X-Ray Crystal-Structure Analyses.* All crystal measurements for (4*S*,5*S*)-**4b** (*Fig. 1*) were performed with a *KM4CCD* κ-axis diffractometer and graphite-monochromated MoK_α radiation. The crystal was positioned at 62 mm from the CCD camera, and 1800 frames were measured at 1° intervals with a counting time of 5 s. The data were corrected for *Lorentz* and polarization effects. Empirical correction for absorption was applied (with spherical harmonics, implemented in the SCALE3 ABSPACK scaling algorithm) [38]. All crystal measurements for (4*S*,5*R*)-**4c** (*Fig. 2*) were performed with a *Bruker-APEX-II-CCD* diffractometer and graphite-monochromated CuK_α radiation. The data for both compounds are listed in *Table 3*. Both data and absorptions were uncorrected. Data reduction and analysis were carried out with the *Oxford Diffraction Ltd.* programs [38]. The structures were solved by direct methods [39] and refined with SHELXL [40]. The refinement was based on F^2 for all reflections, except for those with very negative F^2. Weighted *R* factors *wR* and all goodness-of-fit *S* values were based on F^2. Conventional *R* factors were 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 was not relevant to the choice of reflections for the refinement. The *R* factors based on F^2 were 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 [41]. The known configurations of the asymmetric centers were confirmed by the *Flack*-parameter refinement [42]. CCDC-667773 and CCDC-697551 contain the supplementary crystallographic data for (4*S*,5*S*)-**4b** and (4*S*,5*R*)-**4c**, resp. Copies of the data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif. The *Cremer* and *Pople* puckering parameters [43] were calculated according to [44].

3. *Cycloadditions.* 3.1. *General Procedure.* To a soln. of aldoxime **1c** (0.26 mmol) in $CHCl_3$ (10 ml), NCS (0.26 mmol) was added at r.t. After 15 min, the appropriate *trans*-stilbene **3a**–**3i** (0.39 mmol) and $KHCO_3$ (0.39 mmol) were added, and the progress of the reaction was monitored by TLC until disappearance of the aldoxime. When the reaction was complete (max. 6 h), the mixture was washed with H_2O, the org. phase dried ($MgSO_4$) and concentrated, and the residue purified by CC (SiO_2, hexane/AcOEt 9:1 → 7:3): **4a**–**4i** (yields in *Table 1*).

3.2. *[(4*S*,5*S*)-4,5-Dihydro-4,5-bis(4-methoxyphenyl)isoxazol-3-yl][(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]methanone* ((4*S*,5*S*)-**4a**): IR: 2960, 2838, 1670, 1613, 1515, 1463, 1346, 1251, 1171, 1033, 829, 540. ^{1}H-NMR: 7.24–7.14 (*m*, 4 H); 6.9–6.85 (*m*, 4 H); 5.53 (*d*, *J* = 8.5, 1 H); 4.74 (*d*, *J* = 8.5, 1 H); 4.12 (*t*, *J* = 6, 1 H); 3.80 (*s*, 3 H); 3.37 (*s*, 3 H); 3.51, 3.40 (*AB*, *J* = 13.5, 76.0, 2 H); 2.4–1.82 (*m*, 5 H); 1.42–1.23 (*m*, 2 H); 1.11 (*s*, 3 H); 0.96 (*s*, 3 H).

Table 3. *Crystal Data and Structure Refinement of Compounds (4*S*,5*S*)*-**4b** *and (4*S*,5*R*)*-**4c***

	(4*S*,5*S*)-**4b**	(4*S*,5*R*)-**4c**
Empirical formula	$C_{28}H_{32}N_2O_4S$	$C_{26}H_{28}N_2O_4S$
M_r	492.62	464.57
Temp. [K]	100(2)	293(2)
Wavelength [Å]	0.71073	1.54178
Crystal system	triclinic	monoclinic
Space group	P_1	$P2_1$
Unit-cell dimensions		
a [Å]	6.8185(8)	12.5563(6)
b [Å]	9.1335(11)	7.6086(3)
c [Å]	10.6932(13)	12.9634(6)
α [°]	101.398(10)	90.00
β [°]	104.797(11)	108.200(3)
γ [°]	92.823(9)	90.00
V [Å^3]	627.65(13)	1176.51(9)
Z	1	2
Density [Mg/m^3]	1.303	1.311
Absorpt. coeff. [mm^{-1}]	0.166	1.511
$F(000)$ electrons	262	492
Crystal size [mm]	$0.45 \times 0.35 \times 0.12$	$0.83 \times 0.54 \times 0.50$
θ Range for data [°]	2.70 to 28.73	14.88 to 55.52
Index ranges	$-9 \le h \le 9$, $-12 \le k \le 12$, $-14 \le l \le 14$	$-13 \le h \le 10$, $-6 \le k \le 7$, $-10 \le l \le 12$
Reflect. collected/unique	17980/5990	1768/1666
R(int)	0.0193	0.0155
Refinement method	full-matrix least-squares on F^2	
Data/restraints/parameters	5990/3/321	1666/1/301
Goodness-of-fit on F^2	0.989	0.896
$R(F)$ ($I > 2\sigma(I)$)		
R_1	0.0293	0.0303
wR_2	0.0635	0.0822
$wR(F^2)$ (all data)		
R_1	0.0367	0.0312
wR_2	0.0646	0.0828
Abs. struct. parameter	−0.04(4)	0.04(2)
Extinction coefficient	0.012(2)	0.035(5)
Largest peak and holes [e · Å^{-3}]	0.223; −0.292	0.105; −0.120

^{13}C-NMR: 160.1; 159.5; 155.0; 131.0; 129.4; 127.6; 114.7; 114.4; 66.0; 61.1; 55.5; 55.4; 53.3; 48.9; 48.0; 45.5; 39.3; 33.4; 26.4; 21.6; 20.1. HR-MS: 547.1876 ($C_{28}H_{32}N_2NaO_6S^+$; calc. 547.1879).

Minor stereoisomer (signals deduced from the crude mixture): ^{1}H-NMR: 7.28–7.14 (*m*, 4 H); 6.9–6.85 (*m*, 4 H); 5.49 (*d*, *J* = 7, 1 H); 4.52 (*d*, *J* = 6, 1 H); 4.00 (*t*, *J* = 6.5, 1 H); 3.80 (*s*, 3 H); 3.79 (*s*, 3 H); 3.55, 3.42 (*AB*, *J* = 14, 2 H); 2.4–1.82 (*m*, 5 H); 1.42–1.23 (*m*, 2 H); 1.16 (*s*, 3 H); 0.97 (*s*, 3 H). ^{13}C-NMR: 160.0; 159.4; 153.5; 131.6; 129.1; 128.9; 127.6; 114.6; 114.3; 66.0; 62.6; 55.5; 55.4; 53.6; 48.8; 47.9; 45.3; 38.8; 33.4; 26.5; 21.5; 20.1.

3.3. *[(4*S*,5*S*)-4,5-Dihydro-4,5-bis(4-methylphenyl)isoxazol-3-yl][(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]methanone* ((4*S*,5*S*)-**4b**): Obtained pure in *ca.* 44% yield after crystallization from hexane/AcOEt 1:1. M.p. 197–199°. $[\alpha]_D^{20} = +28.8$ ($c =$

1.0, $CHCl_3$). IR: 2959, 2939, 2917, 1666, 1572, 1518, 1413, 1387, 1348, 1196, 1169, 1136, 1113, 1060, 922, 813, 746, 559, 531. ^{1}H-NMR: 7.17–7.14 (*m*, 8 H); 5.57 (*d*, *J* = 9, 1 H); 4.74 (*d*, *J* = 9, 1 H); 4.12 (*t*, *J* = 6, 1 H); 3.50, 3.40 (*AB*, *J* = 13, 2 H); 2.35 (*s*, 3 H); 2.32 (*s*, 3 H); 2.09–1.82 (*m*, 5 H); 1.42–1.23 (*m*, 2 H); 1.11 (*s*, 3 H); 0.96 (*s*, 3 H). ^{13}C-NMR: 159.6; 154.9; 138.8; 138.0; 136.1; 134.0; 130.0; 129.7; 128.2; 93.3; 66.0: 61.7; 53.2; 48.9; 48.0; 45.5; 39.4; 33.5; 26.4; 21.6; 21.3; 20.1. HR-MS: 515.1976 $C_{28}H_{32}N_2NaO_4S$;calc. 515.1981).

Minor stereoisomer (signals deduced from the crude mixture): ^{1}H-NMR: 7.17–7.14 (*m*, 8 H); 5.54 (*d*, *J* = 6.5, 1 H); 4.52 (*d*, *J* = 6.5, 1 H); 4.00 (*t*, *J* = 6.5, 1 H); 3.54, 3.41 (*AB*, *J* = 13.5, 2 H); 2.345 (*s*, 3 H); 2.34 (*s*, 3 H); 2.09–1.82 (*m*, 5 H); 1.42–1.23 (*m*, 2 H); 1.16 (*s*, 3 H); 0.97 (*s*, 3 H). ^{13}C-NMR: 160.0; 153.4; 138.6; 137.9; 136.6; 135.4; 130.0; 129.7; 127.8; 126.0; 93.4; 66.0; 63.1; 53.6; 48.8; 48.0; 45.3; 38.9; 33.5; 26.5; 21.5; 21.4; 20.1.

3.4. *[(4*S*,5*S*)-4,5-Dihydro-4,5-diphenylisoxazol-3-yl][(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]methanone* ((4*S*,5*S*)-**4c**): Obtained pure after crystallization from hexane/AcOEt 1:1. For data, see [6].

3.5. *[(4*S*,5*R*)-4,5-Dihydro-4,5-diphenylisoxazol-3-yl][(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]methanone* ((4*S*,5*R*)-**4c**): Obtained pure from (*Z*)-**3c** after crystallization from hexane/AcOEt 1:1. M.p. 237–238°. $[\alpha]_D^{20} = -76.5$ (*c* = 1.0, $CHCl_3$). IR(KBr): 3005, 2957, 2922, 2876, 1669, 1579, 1456, 1389, 1346, 1206, 1169, 1114, 1080, 1060, 923, 910, 772, 753, 727, 694, 550, 534. ^{1}H-NMR: 7.09–7.03 (*m*, 8 H); 6.89–6.85 (*m*, 2 H); 6.05 (*d*, *J* = 11, 1 H); 5.15 (*d*, *J* = 11, 1 H); 4.17–4.1 (*m*, 1 H); 3.55, 3.43 (*AB*, *J* = 13.6, 2 H); 2.15–1.83 (*m*, 5 H); 1.42–1.26 (*m*, 2 H); 1.11 (*s*, 3 H); 0.98 (*s*, 3 H). ^{13}C-NMR: 159.35; 156.3; 134.7; 132.8; 129.4; 128.4; 128.0; 127.9; 127.8; 126.8; 88.9; 66.1; 57.9; 53.4; 48.9; 48.0; 45.5; 39.2; 33.5; 26.4; 21.5; 20.1. HR-MS: 465.1789 ($C_{26}H_{29}N_3O_4S^+$; calc. 465.5861).

Minor stereoisomer (signals deduced from the enriched *cis*-isomer mixture): ^{1}H-NMR: 7.09–7.03 (*m*, 8 H); 6.89–6.85 (*m*, 2 H); 5.96 (*d*, *J* = 10, 1 H); 4.80 (*d*, *J* = 10, 1 H); 4.13–4.03 (*m*, 1 H); 3.11 (*s*, 2 H); 2.15–1.83 (*m*, 5 H); 1.42–1.26 (*m*, 2 H); 1.10 (*s*, 3 H); 0.97 (*s*, 3 H). ^{13}C-NMR: 159.35; 156.3; 133.2; 132.8; 129.0; 128.4; 128.0; 127.9; 127.8; 127.0; 88.8; 66.1: 57.8; 53.4; 48.9; 48.0; 45.5; 39.2; 33.4; 26.4; 21.5; 20.1.

3.6. *[(4*S*,5*S*)-4,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-yl][(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]methanone* ((4*S*,5*S*)-**4d**): IR: 2960, 2940, 2887, 1668, 1606, 1512, 1388, 1347, 1228, 1169, 1160, 1136, 1114, 924, 835, 558, 539. ^{1}H-NMR: 7.3–7.2 (*m*, 4 H); 7.1–7.03 (*m*, 4 H); 5.57 (*d*, *J* = 9, 1 H); 4.75 (*d*, *J* = 9, 1 H); 4.08 (*t*, *J* = 6, 1 H); 3.53, 3.41 (*AB*, *J* = 13.5, 2 H); 2.07–1.84 (*m*, 5 H); 1.4–1.2 (*m*, 2 H); 1.13 (*s*, 3 H); 0.97 (*s*, 3 H). ^{13}C-NMR: 164.1; 163.8; 162.2; 161.8; 159.8; 154.7; 134.6 (*J* = 3); 132.4 (*J* = 3); 130.1 (*J* = 8.3); 127.9 (*J* = 8.3); 116.5; 116.4; 116.3; 116.1; 92.6; 66.0; 53.4; 48.9; 48.0; 45.3; 39.1; 36.3; 33.5; 26.4; 21.6; 20.1. ^{19}F-NMR: −112.84 (*m*, 1 F); −113.70 (*m*, 1 F). HR-MS: 523.1481 ($C_{26}H_{26}F_2N_2NaO_4S^+$; calc. 523.1479).

Minor stereoisomer (signals deduced from the crude mixture): ^{1}H-NMR: 7.3–7.2 (*m*, 4 H); 7.1–7.03 (*m*, 4 H); 5.52 (*d*, *J* = 7, 1 H); 4.52 (*d*, *J* = 7, 1 H); 4.03 (*t*, *J* = 6, 1 H); 3.56, 3.42 (*AB*, *J* = 13.5, 2 H); 2.07–1.84 (*m*, 5 H); 1.4–1.2 (*m*, 2 H); 1.16 (*s*, 3 H); 0.98 (*s*, 3 H). ^{13}C-NMR: 164.1; 163.8; 162.1; 161.7; 159.5; 153.1; 135.1 (*J* = 3); 133.8 (*J* = 3); 129.6 (*J* = 8.3); 127.9 (*J* = 8.3); 116.4; 116.3; 116.1; 116.0; 92.5; 61.5; 53.6; 50.5; 45.5; 44.9; 38.6; 33.5; 32.1; 26.5; 21.5; 20.1. ^{19}F-NMR: −113.20 (*m*, 1 F); −113.94 (*m*, 1 F).

3.7. *[(4*S*,5*S*)-4,5-Bis(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl][(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]methanone* ((4*S*,5*S*)-**4e**): IR: 2961, 2884, 1668, 1599, 1493, 1347, 1219, 1169, 1092, 1015, 928, 817, 535. ^{1}H-NMR: 7.37–7.15 (*m*, 8 H); 5.55 (*d*, *J* = 8.9, 1 H); 4.72 (*d*, *J* = 8.9, 1 H); 4.07 (*t*, *J* = 6, 1 H); 3.54, 3.41 (*AB*, *J* = 13.7, 2 H); 2.32 (*s*, 3 H); 2.27 (*s*, 3 H); 2.1–1.85 (*m*, 5 H); 1.4–1.21 (*m*, 2 H); 1.14 (*s*, 3 H); 0.97 (*s*, 3 H). ^{13}C-NMR: 159.7; 154.5; 137.6; 137.1; 135.0; 134.6; 129.8; 129.7; 129.4; 127.4; 92.4; 66.1; 61.8; 53.5; 48.9; 48.0; 45.5; 39.1; 33.5; 26.4; 21.7; 20.1. MS: 555.2 (100), 557.2 (38). HR-MS: 555.0887 ($C_{26}H_{26}Cl_2N_2NaO_4S^+$; calc. 555.0888).

Minor stereoisomer (signals deduced from the crude mixture): ^{1}H-NMR: 7.37–7.15 (*m*, 8 H); 5.52 (*d*, *J* = 6.5, 1 H); 4.49 (*d*, *J* = 6.5, 1 H); 3.98 (*t*, *J* = 6.2, 1 H); 3.55, 3.41 (*AB*, *J* = 13.5, 2 H); 2.32 (*s*, 3 H); 2.31 (*s*, 3 H); 2.1–1.85 (*m*, 5 H); 1.4–1.21 (*m*, 2 H); 1.16 (*s*, 3 H); 0.98 (*s*, 3 H). ^{13}C-NMR: 159.5; 152.9; 138.0; 136.4; 135.0; 134.9; 134.4; 129.6; 129.3; 129.2; 127.4; 92.3; 66.0; 63.0; 53.6; 48.8; 48.0; 45.3; 38.6; 33.5; 26.5; 21.5; 20.1.

3.8. *{(4*S*,5*S*)-4,5-Dihydro-4,5-bis[4-(trifluoromethyl)phenyl]isoxazol-3-yl}[(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]methanone* ((4*S*,5*S*)-**4f**): IR: 2963, 2887, 1669, 1620, 1422, 1348, 1325, 1169, 1129, 1113, 1069, 1018, 832. ^{1}H-NMR: 7.68–7.64 (*m*, 4 H); 7.5–6.96 (*m*, 4 H); 5.67 (*d*, *J* = 9, 1 H); 4.82 (*d*, *J* = 9, 1 H); 4.06 (*dt*, *J* = 4.5, 1.5, 1 H); 3.56, 3.42 (*AB*, *J* = 14, 2 H); 2.3 (*m*, 1 H); 2.05–1.85 (*m*, 5 H); 1.4–1.22 (*m*, 4 H); 1.15 (*s*, 3 H); 0.98 (*s*, 3 H). ^{13}C-NMR: 159.6; 154.2; 142.4; 140.3; 138.0; 128.9; 126.3 (*q*, *J* = 3.9); 92.2; 66.2; 62.3; 53.6; 48.9; 48.0; 45.6; 38.6; 33.6; 26.4; 21.7. ^{19}F-NMR: −62.90 (*s*, 3 F); −62.94 (*s*, 3 F). HR-MS: 623.1415 ($C_{28}H_{26}F_6N_2NaO_4S^+$; calc. 623.1415).

Minor stereoisomer (signals deduced from the crude mixture): ^{1}H-NMR: 7.68–7.64 (*m*, 4 H); 7.5–6.96 (*m*, 4 H); 5.63 (*d*, *J* = 6, 1 H); 4.58 (*d*, *J* = 6, 1 H); 3.97 (*t*, *J* = 6, 1 H); 3.57, 3.42 (*AB*, *J* = 13.5, 2 H); 2.3 (*m*, 1 H); 2.05–1.85 (*m*, 5 H); 1.4–1.22 (*m*, 4 H); 1.16 (*s*, 3 H); (0.98 (*s*, 3 H). ^{13}C-NMR: 159.3; 152.6; 142.8; 141.7; 136.7; 128.4; 126.6 (*q*, *J* = 3.9); 92.1; 66.0; 63.4; 53.6; 48.9; 48.0; 45.3; 39.0; 33.6; 26.5; 21.5. ^{19}F-NMR: −62.87 (*s*, 3 F); −62.88 (*s*, 3 F).

3.9. *[(4*S*,5*S*)-4,5-Bis(4-cyanophenyl)-4,5-dihydroisoxazol-3-yl][(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]methanone* (=*4,4′-{(4*S*,5*S*)-4,5-Dihydro-3-{[(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzothiazol-1(4*H*)-yl]carbonyl}isoxazole-4,5-diyl}bis[benzonitrile]*; (4*S*,5*S*)-**4g**): IR: 2957, 2925, 2854, 2229, 1666, 1466, 1343, 1223, 1169, 1138, 1115, 917. ^{1}H-NMR: 7.8–7.6 (*m*, 4 H); 7.5–7.3 (*m*, 4 H); 5.66 (*d*, *J* = 8.5, 1 H); 4.80 (*d*, *J* = 8.5, 1 H); 4.04 (*dt*, *J* = 8, 5, 1 H); 3.58–3.39 (*m*, 2 H); 2.4–1.8 (*m*, 3 H); 1.5–1.2 (*m*, 4 H); 1.18 (*s*, 3 H); 1.00 (*s*, 3 H). ^{13}C-NMR: 159.3; 153.7; 143.2; 141.0; 133.2; 133.0; 129.1; 126.4; 118.2; 118.1; 113.1; 112.8; 91.5; 66.0; 62.2; 53.4; 48.8; 47.8; 45.3; 38.7; 33.3; 29.7; 26.2; 21.5; 19.9. MS: 591.2 (100); 304.3 (30).

Minor stereoisomer[12]) (signals deduced from the crude mixture): ^{1}H-NMR: 7.8–7.6 (*m*, 4 H); 7.5–7.3 (*m*, 4 H); 5.62 (*d*, *J* = 5.5, 1 H); 4.54 (*d*, *J* = 5.5, 1 H); 3.96 (*t*, *J* = 6.5, 1 H); 3.48 (*m*, 2 H); 2.4–1.8 (*m*, 3 H); 1.5–1.2 (*m*, 4 H); 1.12 (*s*, 3 H); 0.99 (*s*, 3 H). ^{13}C-NMR: 158.9; 152.2; 143.6; 142.5; 133.1; 132.9; 128.5; 126.4; 118.3; 118.2; 112.9; 112.6; 91.3; 65.8; 63.2; 53.5; 48.7; 47.8; 45.2; 38.3; 33.3; 29.6; 26.3; 21.3; 19.9.

3.10. *{(4*S*,5*S*)-4,5-Dihydro-4,5-bis[4-(phenylmethoxy)phenyl]isoxazol-3-yl}[(3a*S*,6*R*,7a*R*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]methanone* ((4*S*,5*S*)-**4i**): IR: 2957, 2925, 1669, 1610, 1512, 1454, 1344, 1246, 1176, 1137, 1025, 828, 740, 697, 539. ^{1}H-NMR: 6.8–7.5 (*m*, 18 H); 5.53 (*d*, *J* = 8.8, 1 H); 5.05 (*d*, *J* = 5.2, 2 H); 4.75 (*d*, *J* = 8.8, 1 H); 4.0–4.14 (*m*, 1 H); 3.36–3.55 (*m*, 2 H); 3.10 (*d*, *J* = 2.6, 2 H); 2.2–2.35 (*m*, 2 H); 1.7–2.1 (*m*, 2 H); 1.2–1.4 (*m*, 3 H); 1.13 (*s*, 3 H); 0.93 (*s*, 3 H). ^{13}C-NMR: 159.2; 158.7; 154.8; 129.3; 128.6; 128.0; 127.5; 115.5; 115.23; 92.9; 71.0; 70.5; 65.8; 62.9; 60.9; 53.1; 50.4; 48.7; 47.8; 47.5; 45.4; 44.7; 39.2; 36.1; 33.3; 31.9; 29.7; 26.8; 26.2; 21.4; 20.5. HR-MS: 699.2506 ($C_{40}H_{40}N_2NaO_6S^+$; calc. 699.2505).

Minor stereoisomer (signals deduced from the crude mixture): ^{1}H-NMR: 6.8–7.5 (*m*, 18 H); 5.50 (*d*, *J* = 6.8, 1 H); 5.05 (*d*, *J* = 5.2, 2 H); 4.52 (*d*, *J* = 6.8, 1 H); 4.0–4.14 (*m*, 1 H); 3.36–3.55 (*m*, 2 H); 3.10 (*d*, *J* = 2.6, 2 H); 2.2–2.35 (*m*, 2 H); 1.7–2.1 (*m*, 2 H); 1.2–1.4 (*m*, 3 H); 1.10 (*s*, 3 H); 0.96 (*s*, 3 H). ^{13}C-NMR: 159.1; 158.6; 153.3; 129.5; 129.0; 126.9; 126.4; 115.4; 115.1; 93.0; 72.5; 70.5; 64.4; 62.4; 60.9; 55.1; 53.4; 48.8; 47.8; 47.4; 45.1; 44.4; 38.6; 34.5; 32.8; 31.9; 29.4; 27.0; 26.3; 21.3; 20.5.

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12) Isolated; besides *ca.* 50% yield of (3a*S*,3′a*S*,6*R*,6′*R*,7a*R*,7′a*R*)-1,1′-[(2-oxidofurazan-2,4-diyl)bis(carbonyl)]bis[hexahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazole]: M.p.: 196–197°. $[\alpha]_D^{20} = -198.7$ (*c* = 1.0, $CHCl_3$). IR: 2987, 2962, 2895, 1700, 1670, 1630, 1475, 1470, 1462, 1380, 1350, 1300, 1250, 1175, 1150, 1075, 1062, 1050, 825, 762, 550, 500. ^{1}H-NMR: 4.35 (*dd*, *J* = 4.5, 7, 1 H); 4.04 (*dd*, *J* = 5, 8, 1 H); 3.52–3.42 (*m*, 4 H); 2.42–2.31 (*m*, 2 H); 2.05–1.90 (*m*, 8 H); 1.45–1.36 (*m*, 4 H); 1.23 (*s*, 3 H); 1.13 (*s*, 3 H); 1.00 (*s*, 3 H); 0.96 (*s*, 3 H). ^{13}C-NMR: 154.5; 151.8; 149.6; 65.3; 64.8; 52.9; 52.4; 50.0; 49.3; 48.1; 47.9; 45.5; 44.7; 39.2; 36.9; 33.3; 32.9; 26.4; 26.3; 20.9; 20.4; 20.1; 20.0.

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