Synthetic and Spectroscopic Investigation of *N*-Acylated Sulfoximines[±]

Christian P. R. Hackenberger, Gerhard Raabe, and Carsten Bolm*[a]

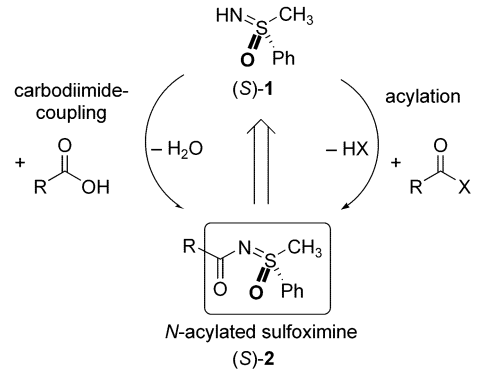
Abstract: *N*-Acylated sulfoximines display unique chemical properties. Various derivatives have been synthesized and investigated by NMR and IR spectroscopy. The results of these studies suggest that the bond between the sulfoximine nitrogen atom and the carbonyl group has a less pronounced double-bond character than the corresponding bond in an amide. This assumption is supported by the first X-ray crystal structure of a sulfoximidoyl derivative. Ab initio calculations (MP2/6-311++G**) provide further insight into the electronic nature of the *N*-acyl fragment. Studies of the chemical behavior of *N*-acylated sulfoximines indicate the presence of a highly electrophilic carbonyl group. Thus, the N–C(O) bond can easily be cleaved under mild basic conditions, and the acidity of the hydrogen atoms α to the sulfoximine carbonyl group is high. As a consequence of the latter property, *endo*,*endo*-sulfoximidoyl norbornene derivatives readily isomerize to their *endo*,*exo* counterparts, and sulfoximine-containing pseudopeptides can easily epimerize at the stereogenic center next to the N–C(O) carbonyl group.

Keywords: acylation · amides · hydrolysis · sulfodiimines · sulfoximines

Introduction

Since their first discovery more than fifty years ago,[1] sulfoximines have found widespread interest in the chemical community.[2] They have extensively been used as chiral directing groups in asymmetric synthesis,[3,4] and owing to their biological activity[1,5] interesting pharmaceutical applications of sulfoximines have been found.[6] For their synthesis several preparative routes have been developed.[2] Most of them start from the corresponding sulfide and involve sequential oxidation and imination steps.[7] In this manner *S*-methyl-*S*-phenyl-sulfoximine (**1**), which is a key intermediate for more complex molecules, can easily be prepared in multigram quantities.[8] Both enantiomeric forms of **1** are then available by a well-established, efficient resolution of racemic **1** with camphor-10-sulfonic acid.

Whereas *N*-alkyl-[9] and *N*-arylsulfoximines[10] have extensively been used in synthesis, *N*-acylated derivatives such as **2**, the so-called sulfoximidoyls, have received much less attention. Considering the ease of their preparation by simple acylation reactions (Scheme 1)[11] this is most surprising. The few literature examples include the synthesis of thiadiazene heterocycles by Jones, Sammes et al.,[12] the development of lactam analogues by Williams and Cram,[13] and a recent stereoselective cycloaddition by Mascareñas et al.[14] We utilized sulfoximidoyls for the preparation of *N*-alkylated sulfoximines[9b] and incorporated them as key components in sulfoximine-based pseudopeptides such as **3**.[15] In the latter case we observed that bis(sulfoximine) units induced turn conformations in nonpolar solutions.[16]



Scheme 1. Synthesis of *N*-acylated sulfoximines.

In the course of studies on pseudotripeptide **3** we were surprised to find unusual chemical shifts for the ^{13}C NMR carbonyl resonances of the sulfoximidoyl moiety and the amide carbonyl group in the β position to the sulfur atom. Whereas the former resonated at $\delta = 180.5$ ppm, the latter gave a signal at $\delta = 159.7$ ppm.[17] Since these values are significantly different from those of standard amide carbonyl

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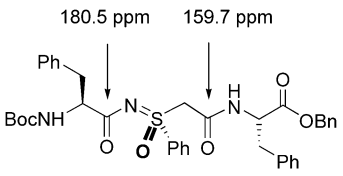

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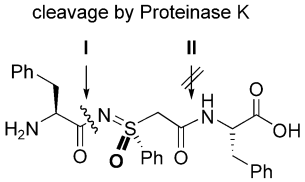

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signals in α-peptides ($\delta \approx$ 170 ppm), we wondered about the reactivity of the two carbonyl groups and the consequences thereof for the chemical properties of **3**. Maybe the unusual chemical shifts were indicative of a specific reactivity pattern that could be exploited for selective modification of **3**. Initial enzymatic cleavage experiments with proteinase K and pseudotripeptide **4** as substrate confirmed this assumption.[18] Whereas bond **I** in **4** was readily cleaved by the enzyme, bond **II** remained intact. Compared to a standard peptidic amide bond, **II** even exhibited increased stability.

To answer the question whether this behavior is enzyme-specific or general, we studied the properties of the N–C(O) bond (bond **I** in **4**) and evaluated its stability under various reaction conditions. Furthermore, we hoped to establish a clear picture of the electronic nature of the sulfoximidoyl moiety, which could help to explain the unusual ^{13}C NMR chemical shifts of the carbonyl groups.

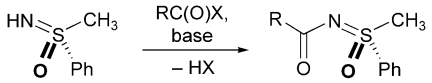
Results

As shown in Scheme 1, there are two general approaches for the synthesis of *N*-acylated sulfoximines such as **2**. They both start from *NH*-sulfoximines, which are acylated by treatment with acyl halides (or anhydrides) or subjected to carbodiimide-mediated coupling with carboxylic acids. The reactions of *NH*-sulfoximine **1** will be presented in three groups: couplings with simple acyl halides (Table 1), carbodiimide-mediated reactions with amino acid derivatives (Table 2), and acylations with other carboxylic acids including bicyclic hemiesters (Table 3). Relevant literature results are included in the tables to allow a more detailed analysis of the significant IR and ^{13}C NMR data.

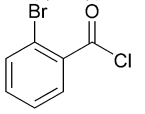
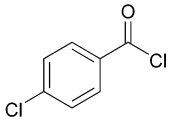
Table 1 summarizes the results of the syntheses of sulfoximidoyl derivatives (*S*)-**2a–h** from (*S*)-**1** and simple acyl halides (or anhydrides) in the presence of base. Generally, the desired products were obtained in excellent yields.

The ^{13}C NMR carbonyl signals of (*S*)-**2a–h** span a range of about 30 ppm. Compounds with aliphatic R groups give signals at $\delta \approx 180$ ppm, and those with aromatic substituents at $\delta \approx 175$ ppm. The most upfield ^{13}C NMR carbonyl resonances for the N–C(O) group of (*S*)-**2** were found for sulfoximidoyls bearing the electron-donating *tert*-butoxide substituent ($\delta = 157.7$ ppm) and, surprisingly, the CF_3 group ($\delta = 164.3$ ppm).

Table 1. Preparations of sulfoximidoyl derivatives through acylation reactions of *NH*-sulfoximines with acyl halides.



1 2

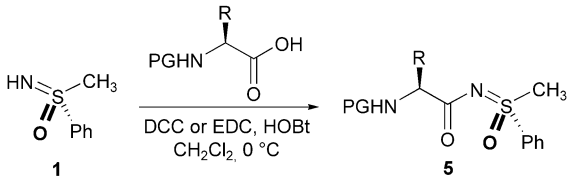
Entry	Acylating agent	Reaction conditions	Product	Yield [%]	$\delta(^{13}C)$ for N–C(O) [ppm]
1[a]	CH_3COBr	NEt_3, CH_2Cl_2, 0 °C	**2a**	99	179.9
2[a]	$(CH_3)_3CCOCl$	NEt_3, CH_2Cl_2, 0 °C	**2b**	98	188.3
3	CH_3CH_2COCl	NEt_3, CH_2Cl_2, 0 °C	**2c**	89	183.7
4[a]	$CH_3(CH_2)_6COCl$	NEt_3, CH_2Cl_2, 0 °C	**2d**	87	183.2
5[a]		pyridine, CH_2Cl_2, 0 °C	**2e**	97	175.1
6[a]		pyridine, CH_2Cl_2, 0 °C	**2f**	97	173.2
7[b]	Boc_2O	KO*t*Bu, THF, 0 °C	**2g**	98	157.7
8	$(CF_3CO)_2O$	NEt_3, CH_2Cl_2, 0 °C	**2h**	68	164.3

[a] Taken from ref. [9b]. [b] Taken from ref. [15b].

Characteristic IR signals for sulfoximines bearing aliphatic acyl groups were detected in the range of 1635–1641 cm^{-1}. For example, **2c** gave absorptions at 1638 cm^{-1} in $CHCl_3$ and at 1635 cm^{-1} in KBr. In the latter case an additional very weak signal appeared at 1581 cm^{-1}.

With regard to enzymatic-cleavage experiments, the properties of sulfoximidoyls stemming from couplings between *NH*-sulfoximines and protected amino acids[15] are particularly interesting. Although sulfoximines are rather weak nucleophiles,[19] standard DCC- and EDC-mediated couplings afforded the desired products **5** in good to very good yields (Table 2). Acylation of either enantiomer of **1** with natural amino acids proceeded without any detectable racemization and led to stereochemically homogeneous sulfoximidoyls. Only in couplings with phenylglycine were two diastereomeric products in a ratio of 2:1 identified by NMR spectroscopy (Table 2, entries 8 and 9). Apparently, the stereogenic center at the α-carbon atom of the N–C(O) group of **5g** had partially epimerized. Even though the (benzylic) hydrogen atom at this position is known to be rather acidic, the high degree of epimerization was unexpected, since Carpino et al. applied similar DCC/HOBt conditions in couplings of phenylglycine derivatives to give dipeptides, and in this case only 10% of isomerization was detected.[20] We therefore hypothesized that the higher tendency of the sulfoximidoyls **5** to epimerize must be attributed to the presence of the sul-

Table 2. Preparations of sulfoximidoyl derivatives through couplings of *NH*-sulfoximine **1** with protected amino acids.[a]



1 5

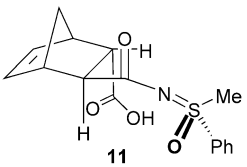
Entry	Boc-protected amino acid	Protecting group	Carbodiimide	Product	Yield [%]	$\delta(^{13}C)$ for N–C(O) [ppm]
1	L-tyrosine	benzyl	DCC	L,(*S*)-**5a**	97	180.3
2	L-lysine	Cbz	DCC	L,(*S*)-**5b**	88	181.3
3	L-lysine	Boc	DCC	L,(*S*)-**5c**	78	181.2
4	L-hydroxyproline	acetyl	DCC	L,(*S*)-**5d**	91	180.9
5	L-hydroxyproline	acetyl	DCC	L,(*R*)-**5d**	94	181.2
6	L-serine	acetyl	DCC	L,(*S*)-**5e**	56	177.2
7	L-histidine	benzyl	EDC	L,(*S*)-**5f**	48[b]	180.7
8	D-phenylglycine	–	EDC	D/L(*R*)-**5g**	91[c]	178.4
9	D-phenylglycine	–	DCC	D/L(*S*)-**5g**	90[c]	178.4

[a] In all cases (*S*)-**1** was used, except in entries 5 and 8, where (*R*)-**1** served as substrate. [b] Workup by extraction without column chromatography. [c] Epimerization of the product was observed (d.r. = 2:1).

foximine group, which increases the acidity of the hydrogen atoms next to the N–C(O) group.

Carbodiimide-mediated couplings were also utilized for the synthesis of sulfoximidoyls with sterically more demanding R groups. As shown in Table 3, products **10** were generally obtained in high yields.

Surprisingly, however, in the EDC-mediated coupling of *endo*,*endo*-norbornene dicarboxylic acid monomethyl ester (**8**) and its saturated analogue **9**, epimerization at C3 occurred and led to predominant formation of the corresponding *endo*,*exo* monoesters **10c** and **10d**, respectively.[21] The transformations of **8** and **9** are noteworthy for two reasons. First, since the *endo*,*endo* isomers of both starting materials are readily available as single enantiomers by asymmetric alkaloid-mediated alcoholysis of the corresponding anhydrides,[22] the observed isomerization now allows conversion of these *endo*,*endo* isomers to their *endo*,*exo* counterparts. Second, the epimerization conditions are remarkably mild, and even the weak base DMAP is sufficient to induce this transformation. This contrasts with amides, for which much stronger bases such as lithium amides are required for such isomerizations.[23] Since DCC couplings of *endo*,*endo*-**8** with amino acids cleanly afford *endo*,*endo* products,[24] it can be excluded that the epimerization occurs at the stage of the intermediately formed active ester.



11

Saponification of methyl ester **10c** with aqueous NaOH afforded sulfoximidoyl carboxylic acid **11** in 85% yield. Recrystallization of **11** from ethanol gave crystals which were suitable for X-ray crystal structure analysis (Figure 1).[25] To the best of our knowledge, this is the first solid-state structure of a sulfoximidoyl derivative determined by this technique. The structural details of **11** and their relevance to the chemical reactivity of sulfoximidoyls are discussed below.

Next, the chemical stability of the N–C(O) bond under acidic and basic conditions was probed with sulfoximidoyl **2c** as test substrate. The results are summarized in Table 4. Apparently, the sulfoximidoyl bond of **2c** is rapidly cleaved when the compound is treated with 10 N HCl (Table 4, entry 2). The hydrolysis occurs much more slowly with dilute HCl (1 N; Table 4, entry 1). Most interestingly, treatment with TFA does not lead to N–C(O) cleavage at room temperature, and more vigorous reaction conditions lead only to partial destruction of **2c** (Table 4, entries 3 and 4).

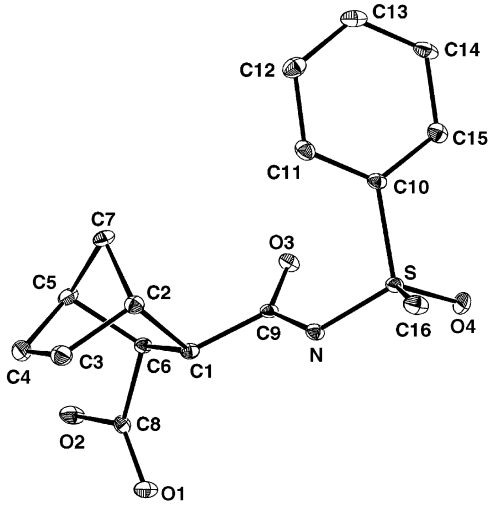
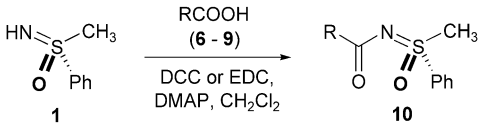


Figure 1. Molecular structure of **11** in the solid state as determined by X-ray crystal structure analysis (ORTEP plot; the ellipsoids are plotted at the 30% propability level).[25]

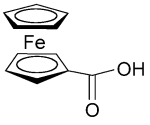
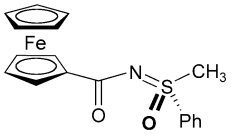
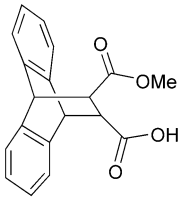
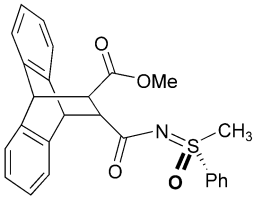
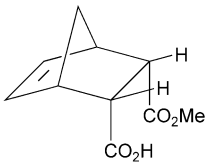
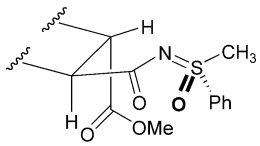
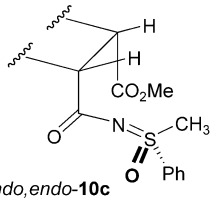
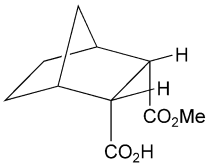
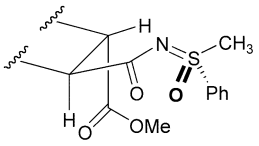
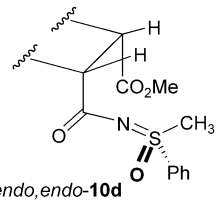
Under basic conditions the hydrolysis of **2c** is slow (Table 4, entries 5–9). Remarkably, higher concentrations of NaOH retard the N–C(O) cleavage. For example, treatment of **2c** with 1 N NaOH at 25 °C results in complete hydrolysis after 139 h (Table 4, entry 5). However, only 11% of **2c** is destroyed when 10 N NaOH is used under otherwise identical conditions (Table 4, entry 7). We attribute the unexpected behavior to deprotonation of the sulfoximine methyl group, which appears to protect the neighboring sulfoximidoyl moiety from being cleaved. Evidence for this hypothesis was gained from experiments performed in D_2O: the methyl hydrogen atoms of **2c** were exchanged by deuterium, and recovered **2c** bore a CD_3 group.

To gain deeper insight into the electronic structure of acylated sulfoximines and to evaluate their reactivity in comparison with that of simple amides, we performed ab initio

Table 3. Synthesis of sulfoximidoyl derivatives **6** by DCC- or EDC-mediated coupling.



1 **10**

Entry	Acid[a]	Carbodiimide	Product	Yield [%]	$\delta(^{13}C)$ for N–C(O) [ppm]
1	 **6**	DCC	 **10a**	84	179.8
2	 **7**	DCC	 **10b**	77	180.3/180.9[b]
3	 **8**	EDC	 *endo,exo*-**10c**	82	183.0
			 *endo,endo*-**10c**	5	180.5
4	 **9**	EDC	 *endo,exo*-**10d**	51	183.2
			 *endo,endo*-**10d**	6	181.1

[a] Hemiester **7** was racemic; hemiesters **8** and **9** were enantiopure. [b] Obtained as a 1:1 mixture of diastereomers.

calculations (ε_0+MP2/6-311++G**) on several model compounds shown in Figure 2.

Compound **12a** $[(CH_3)_2S^1(=O)(=N^2C^3(=O^4)CH_3)]$ was used as a model for acylated sulfoximines, and acetamide **16a** ($H_3C-C(=O)NH_2$) as a representative amide. To check the influence of conjugation between the $C^3=O^4$ and the $S^1=N^2$ bonds on bond lengths and atomic charges, further calculations were performed on **12b**, in which, in contrast to **12a** with a planar $S^1(=O)(=N^2C^3(=O^4))C$ backbone, the $S^1=N^2C^3=O^4$ dihedral angle is 90°. Additional calculations were performed on **13** $[(CH_3)_2S^1(=O)(=N^2C^3(=O^4)CH_2^-)]$, derived from **12a** by abstraction of one of the acetylic methyl protons, on **14** $[(CH_3)_2S^1(=O)(=N^2C^3(O^4)(OH)CH_3)^-]$, obtained from **12a** by addition of an OH^- anion to the carbonyl group, and on cation **15a** $[(CH_3)_2S^1(=O)(=NH^2C^3(=O^4)-CH_3)^+]$ resulting from protonation of N^2 of **12a**. To determine which of the three basic centers of the model sulfoximidoyl is the preferred site of protonation we also per-

Table 4. Cleavage studies on sulfoximidoyl derivative **2c** under aqueous acidic or basic conditions.

Entry	Base or acid	Conditions	Reaction time [h]	Cleavage [%]
1	1 N HCl	CH_2Cl_2/25 °C	1	2
			16	17
			65	100
2	10 N HCl	CH_2Cl_2/25 °C	0.1	100
3	TFA	CH_2Cl_2/25 °C	65	0
4	TFA	CH_2Cl_2/60 °C	12	6
5	1 N NaOH	CH_2Cl_2/25 °C	19	18
			139	100
6	1 N NaOH	CH_2Cl_2/60 °C	19	42
7	10 N NaOH	CH_2Cl_2/25 °C	19	0
			139	11
8	10 N NaOH	CH_2Cl_2/60 °C	19	19
9	10 N NaOH	CH_2Cl_2/D_2O/25 °C	139	18[a]

[a] Compound **2c** with a CD_3 group was isolated.

formed calculations on some cations (**15b**–**15e**) derived from **12a** by protonation of the oxygen atoms. Furthermore, for reasons of comparison, the corresponding structures derived from acetamide were calculated: **16b**, **17** [$H_2C^-C(=O)NH_2$], **18** [$H_3C{-}C(O)(OH)NH_2^-$], and the cations **19a**–**19d** obtained from **16a** by protonation of the nitrogen [**19c**; $H_3C(C{=}O)NH_3^+$] or the oxygen atom [**19a**, **19b**, **19d**; $[H_3C(C{=}OH^+)NH_2]$.

Discussion

The results of the spectroscopic and structural studies as well as the chemical behavior of the acylated sulfoximines suggest that the sulfoximidoyl carbonyl group is highly electron deficient. In contrast to amide carbonyl groups it lacks conjugative electron donation by the adjacent nitrogen lone pair through the N–C(O) bond. Scheme 2 presents possible resonance structures. Canonical form **B** corresponds to the situation in a peptide group with a partial double bond between the amide nitrogen atom and the adjacent carbonyl group. In the case of sulfoximidoyls, however, allene-like structure **B** would correspond to an excited state and will not significantly contribute to the resonance hybrid of the ground state (vide infra). The ideal structure for a conjugative interaction as in **B** would have a linear S-N-C moiety. However, the S-N-C angle is 117.7° in **12a**, and linearization of this segment requires about 19 kcal mol^{-1} at the MP2/6-311++6** level. The electronic nature of the sulfoximine moiety is much better represented by resonance structure **C**. There, the lone pair of electrons on the sulfoximine nitrogen atom is attracted by the formally positively charged sulfur atom, and the bond order between the nitrogen and the carbonyl carbon atoms remains almost unchanged.

The different properties of the N–C(O) bonds in amides and acylated sulfoximines are also reflected by the structural and energetic changes that occur upon torsion of this bond.[26] Thus, if the structure

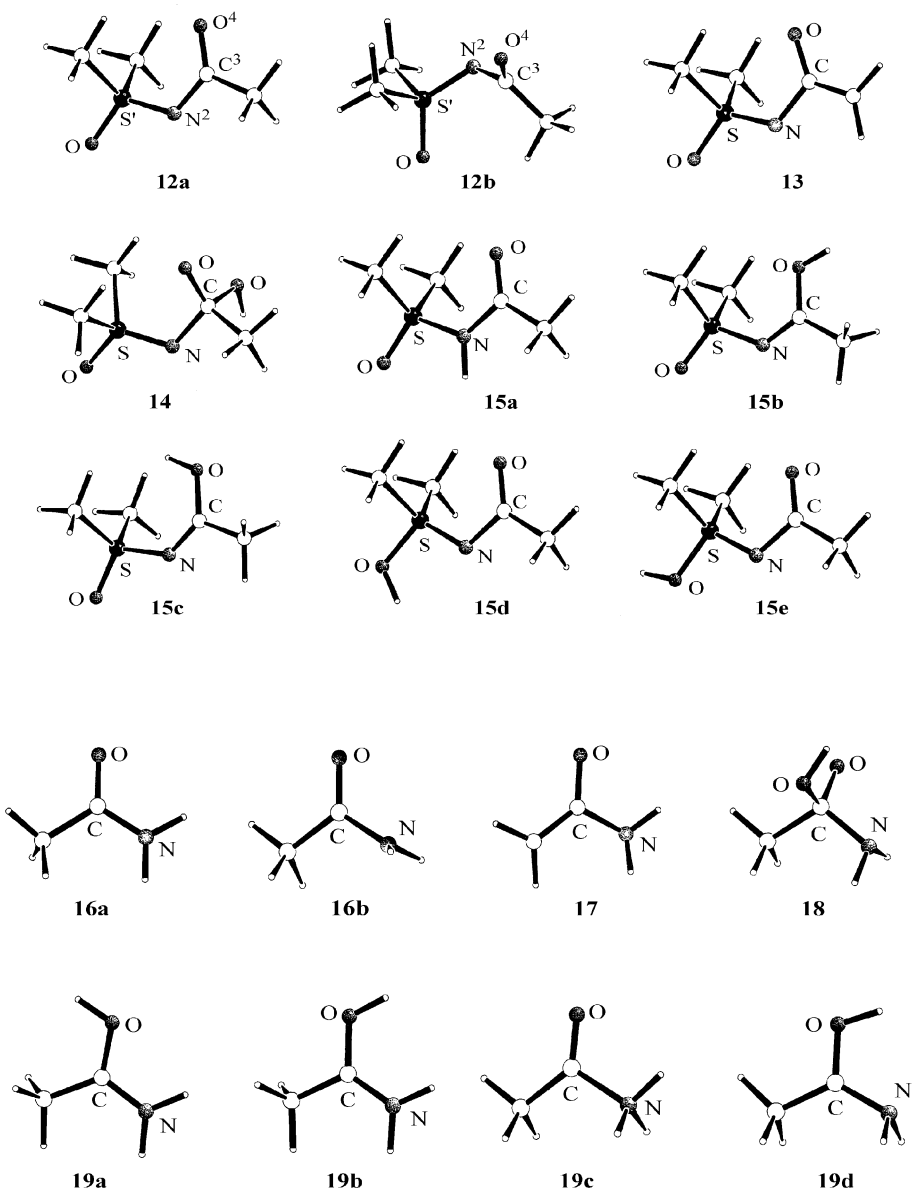
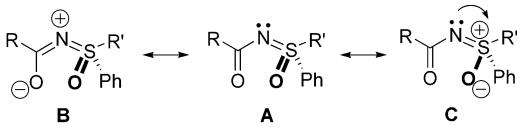


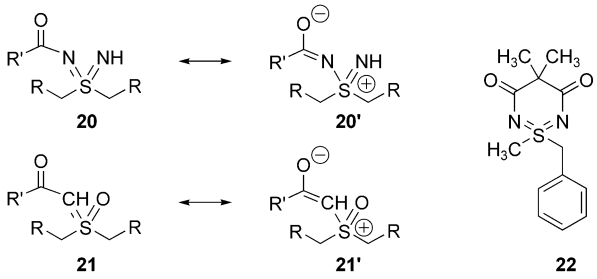
Figure 2. Structures of the model compounds for acylated sulfoximines (**12a, 12b**), simple amides (**16a**, **16b**), and some derived species (**13**–**15** and **17**–**19**), optimized at the HF/6-311++G** level. The structures obtained upon further optimization at the MP2/6-311++G** level are visually indistinguishable from those given in this figure.



Scheme 2. Resonance structures of sulfoximidoyl derivatives.

of acetamide is reoptimized under the constraint that the NH_2 and the CCO planes are orthogonal to each other (**16b**), conjugative interaction between the nitrogen lone pair and the carbonyl group is lost. Consequently, the N–C(O) bond length increases (+0.051 Å), while the length of the C=O bond decreases compared with the values for fully optimized **16a**. The total energy increases and the energy of **16b** is 21.8 kcal mol^{-1} higher than that of **16a**. If the SNC and OCC planes of **12** are fixed in mutually orthogonal positions as in **12b** and the rest of the structure is optimized, the increase in energy is only 8.6 kcal mol^{-1} relative to **12a**. Again, this torsion leads to an increased N–C(O) (+0.044 Å) and decreased C=O bond length (**12b**). Both the increase in energy and the changes in bond lengths might be explained by loss of a butadiene-like conjugation between the S=N and the C=O bonds in **12b**. However, the results of an experimental study on the electron density in methane(triimido)sulfonic acid[27] strongly suggest that, at least in those compounds, the S–N bond should be described as an ylidelike moiety $S^+–N^-$ (shortened relative to an ordinary S–N single bond by strong electrostatic contributions) rather than as a S=N double bond.

Support for the hypothesis that in sulfoximidoyls resonance structure **C** dominates the resonance hybrid of the ground state and therefore determines the electronic nature of the N–C(O) bond stems from spectroscopic studies. As mentioned before the ^{13}C NMR signals for the carbonyl groups of *N*-acylated sulfoximines (Tables 1–3) appear at about 180 ppm. These values are high compared to the corresponding signals of carbonyl groups in peptidic amide bonds, and the significant downfield shift reveals the electron deficiency at the sulfoximidoyl C(O) units. Infrared spectroscopy provides further evidence. Compound **2c** has a single strong band in the carbamide region at 1638 cm^{-1} in $CHCl_3$. Only in KBr two peaks appeared: a strong one at 1635 cm^{-1} and a very weak one at 1581 cm^{-1}. This is in contrast to the situation described for sulfodiimines **20** and sulfur ylides **21**. The former are aza analogues of sulfoximines, which are accessible by double imination of sulfides followed by acylation reactions. They are well-studied compounds,[28] and the chemical behavior of acylated derivatives has intensively been investigated by Haake et al..[29] For these compounds two regions of intensive IR signals were found, one at 1610–1640 cm^{-1} and another around 1565 cm^{-1}. Whereas the former is attributed to amide-like carbonyl bonds, the latter indicates a significant participation of a polar resonance structure such as **20′** (Scheme 3).[29] Analogous data were obtained for the isoelectronic sulfur ylides, which can be described by **21** and **21′**.[30] Because in the case of *N*-acylated sulfoximines the IR band at about 1565 cm^{-1} is absent (or too weak to be observed under the conditions of the experiment) we conclude that the polar



Scheme 3. Resonance structures of sulfodiimines **20**/**20′**, sulfur ylides **21**/**21′**, and thiadiazindione **22**.

structure **B** depicted in Scheme 2 has, if at all, only a minor contribution to the electronic nature of the sulfoximidoyl moiety.

Assuming that the bond length is related to the bond order, comparison of the solid-state structure of **11** with structural data of acylated sulfodiimines and related compounds confirms the weak double-bond character of the nitrogen–carbon bond in the N–C(O) unit of **11**. With a length of 1.402(8) Å in the solid state, this bond is significantly longer than the corresponding bonds in thiadiazindione **22** (1.363(3) Å with a double bond character of 25%, as determined by Debeardermeaker and Allmann[31]), peptides (1.333(13) Å,[32a] 60% double bond character)[32] and imines (1.26 Å).[31] (The N–CO bond lengths calculated for our model compounds in the gas phase are 1.382 Å for **12a** and 1.378 Å for acetamide **16a** (MP2/6-311++G**). The fact that the experimentally determined N–CO bond length in **11** exceeds that calculated for **12a** is attributed to the bulky substituents in the former compound.)

Moreover, in contrast to amides, in which the nitrogen lone pair is approximately perpendicular to the N–C=O plane and can therefore conjugatively interact with the C=O bond, this is not the case for acylated sulfoximines. Here the lone pair lies not only in this plane but is further polarized towards the sulfur atom and is therefore not available to significantly reduce the positive charge of the carbonyl carbon atom. Calculation of the Merz–Singh–Kollman charges[33,34] resulted in a value of 0.97 e_0 for the carbonyl carbon atom of **12a**, while the corresponding charge is 0.91 e_0 for acetamide.

The electron-withdrawing capability of the sulfoximine group and its effect on the entire sulfoximdoyl fragment is further reflected by the ease of epimerization at the α-carbon atom. Apparently, the hydrogen atoms next to the N–C(O) carbonyl group in compounds such as **10c** and **10d** are more acidic than in comparable esters and amides, and even weak bases such as DMAP lead to a significant epimerization at this position.

The experimental finding that a C–H bond in the α position to the carbonyl group in an acylated sulfoximine such as **12a** can more easily be cleaved heterolytically than, for example, a C–H bond in acetamide is also reflected by the difference between their energies of deprotonation. Thus, at the ε_0+MP2/6-311++G** level we calculated the change in energy associated with the reaction **12a**→**13**+H^+ as 370.4 kcal mol^{-1}, while the reaction $H_2N–C(=O)CH_3$→

$H_2N{-}C(=O)CH_2^- + H^+$ requires a higher energy of 376.7 kcal mol^{-1}. Both values are significantly lower than the energy of deprotonation of methane, which is 415.4 kcal mol^{-1} at the same level of theory.

In the light of the structural data and their interpretation, it is not surprising that both acidic and basic conditions can be used to cleave the N–C(O) bond in **2c**. As revealed by Table 4, various concentrations of HCl in dichloromethane and dilute aqueous solutions of NaOH were effective in such bond-breaking processes. In contrast, **2c** was stable to treatment with TFA in CH_2Cl_2 or NaOH at high concentration. This behavior is particularly important because it allows the selective conversion of acylated sulfoximines. If desired the N–C(O) bond can easily be cleaved to liberate both fragments (sulfoximine and acyl units). Alternatively, the entire sulfoximidoyl unit can be retained while other parts of the molecule react. The latter behavior already proved synthetically relevant in conversions of functionalized sulfoximidoyl-containing pseudopeptides. There, *tert*-butoxycarbonyl(Boc)-protected nitrogen atoms were readily converted to free amino groups by treatment of the pseudopeptides with TFA in CH_2Cl_2.[15,18]

The cleavage reactions were also studied theoretically. Since acidic cleavage of the N–C(O) bond in amides and acylated sulfoximines is initiated by protonation of their basic centers, we calculated the proton affinities (PAs)[35] of **12a** and **16a** at 298 K. The energetically more favorable site of protonation of acetamide is the carbonyl oxygen atom (PA = 205.3 kcal mol^{-1}) to yield cation **19a**, while the proton affinity of the nitrogen atom is 12.5 kcal mol^{-1} lower. Protonation of **12a** occurs at the nitrogen atom with a proton affinity of 219.6 kcal mol^{-1}, comparable to that of pyridine (220.9 kcal mol^{-1}) at the same level of theory (ε_0+MP2/6-311++G**). The most stable oxygen-protonated structure is **15b** (PA = 213.8 kcal mol^{-1}), while protonation of the sulfur-bonded oxygen atom is about 16 kcal mol^{-1} less favorable. The more than 14 kcal mol^{-1} higher PA of **12a** might indicate a higher reactivity of acylated sulfoximines under acidic conditions as compared with simple amides.

The initial step in the cleavage of the N–C(O) bond under basic conditions in both amides and the acylated sulfoximines is addition of an OH^- anion to the carbonyl group. A possible competitive reaction is the abstraction of a proton from the α-carbon atom. The energetics of these two reactions are shown in Figure 3. In accordance with the experimentally observed higher reactivity of the acylated sulfoximine as compared with simple amides, both reactions are energetically more favorable for model compound **12a** than for **16a**. However, for both the acylated sulfoximine and acetamide the reaction energy associated with the addition of the OH^- anion to the C=O group is more negative (−29.1 and −19.8 kcal mol^{-1}) than that for the abstraction of a proton (−19.7 and −13.3 kcal mol^{-1}).

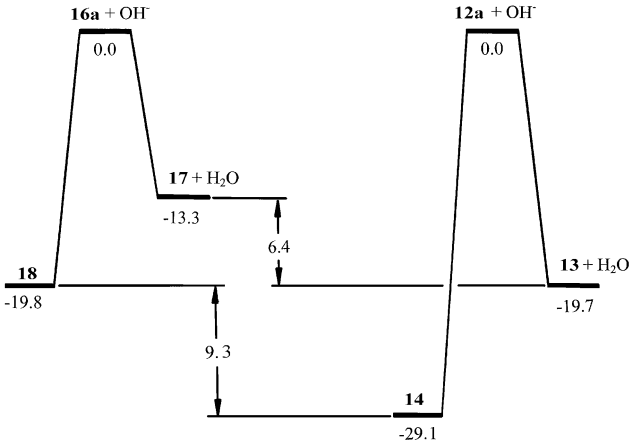


Figure 3. Energetics of the reactions of **12a** and **16a** with OH^- obtained at the ε_0+MP2/6-311++G** level. All values in kcal mol^{-1}.

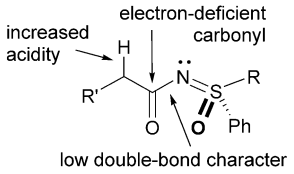


Figure 4. Characteristic features of the sulfoximidoyl fragment in acyl sulfoximines.

Conclusion

The characteristic features of the sulfoximidoyl moiety, which determine the reactivity of acylated sulfoximines, are summarized in Figure 4. Due to the strongly electron-withdrawing sulfur atom, the carbonyl carbon atom in an acylated sulfoximine is a highly electrophilic center which is prone to attack by nucleophiles. In contrast to the situation in amides, the lone pair of electrons at the neighboring nitrogen atom does not reduce this electron deficiency at the carbonyl group. The unusual downfield shift of the ^{13}C NMR signal for the carbonyl group and IR and X-ray crystal structure data, which reveal a low bond order of the N–C(O) bond, support this interpretation. Further evidence stems from theoretical studies. As a consequence of the electronic nature of the sulfoximine carbonyl group the α-hydrogen atoms in the acyl part of sulfoximidoyls are more acidic than those of simple amides. Upon treatment with base, compounds having stereogenic centers at this position tend to epimerize, as was observed in the phenylglycine derivatives (*R*)- and (*S*)-**5g** and bicyclic compounds **10c** and **10d**. In reactions with nucleophiles the high electrophilicity of the sulfoximine carbonyl group explains the reactivity of acylated sulfoximines. For example, under appropriate (acidic and basic) conditions they can readily be hydrolyzed, and enzymes recognize the N–C(O) bond as their preferred cleavage site. Experiments utilizing this highly activated carbonyl moiety in other chemical transformations are ongoing.

Experimental Section

General: All reactions employing anhydrous conditions were performed under argon by using standard Schlenk techniques. *S*-Methyl-*S*-phenyl sulfoximines (*S*)-**1** and (*R*)-**1** were synthesized according to the literature

procedure.[8] Compounds **2** were prepared by acylation with acyl halides according to the published protocol,[9b,15b] and compounds **8** and **9** were synthesized according to general procedure GP1. CH_2Cl_2 was dried with lithium aluminum hydride and distilled prior to use under an inert atmosphere. Unless otherwise specified all starting materials were purchased from commercial suppliers and were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded with TMS as internal standard. Mass spectra were obtained with a Finnigan SSQ 7000 and with a Varian MAT 212 S spectrometer. FTIR spectra were recorded on a Perkin-Elmer PE-1760 FT. Elemental analyses were carried out on a Heraeus CHNO-Rapid instrument. Melting points were measured with a Büchi B-540 and are uncorrected. Optical rotations were obtained with a Perkin-Elmer PE-241. Flash chromatography was performed with Merck silica gel 60, mesh 37–70 μm. EE = diethyl ether, PE = petroleum ether.

The structures of all molecules shown in Figure 2 were preoptimized at the Hartree–Fock (HF) level with the 6-311++G** basis set (HF/6-311++G**). The obtained stationary points were characterized by calculation and diagonalization of their force-constant matrices, and all completely optimized structures (**12a**, **13**, **14**, **15a–e**, **16a**, **17**, **18**, and **19a–c**) shown in Figure 2 turned out to be local minima. Starting from these points further optimizations were carried out using the same basis set and including correlation energy by means of Møller–Plesset perturbation theory to the second order (MP2[36]). The zero-point energies ε_0 obtained at the HF level were scaled by a factor of 0.95 and added to the correlated total energies. The resulting values (ε_0+MP2/6-311++G**) were then used to calculate the relative energies discussed in the text and used in Figure 3. Total energies (ε_0+MP2/6-311++G** in Hartrees, 1 Hartree = 627.5095 kcal mol^{-1}): **12a**: −759.610974, **13**: −759.020755, **14**: −835.288742, **15a**: −759.958501, **15b**: −759.949345, **15c**: −759.931316, **15d**: −759.923713, **15e**: −759.913044, **16a**: −208.635391, **17**: −208.035057, **18**: −284.298293, **19a**: −208.960154, **19b**: −208.955562, **19c**: −208.940239, H_2O: −76.253031, OH^-: −75.631426. All calculations were performed with the Gaussian 98[37] suite of quantum-chemical routines running on the computational facilities of the computing center of the RWTH Aachen.

General procedure GP1 for the carbodiimide-mediated coupling of *N*-protected amino acids and other acid derivatives with sulfoximines:

a) DCC coupling (GP1a): In a Schlenk flask *N*-protected amino acid (1 equiv), sulfoximine (*S*)-**1** or (*R*)-**1** (1 equiv), hydroxybenzotriazole (HOBt, 1 equiv), and 4-dimethylaminopyridine (DMAP, 0.1 equiv) were dissolved in CH_2Cl_2 (10 mL mmol^{-1}) and cooled to 0 °C, and dicyclohexylcarbodiimide (DCC, 1.1 equiv) in CH_2Cl_2 (5 mL mmol^{-1}) was added. When a simple carboxylic acid was coupled, HOBt was omitted. Alternatively, a 1 M solution of DCC in CH_2Cl_2 was used. After the mixture had been stirred for 1 h at 0 °C and 12 h at room temperature, the solvent was evaporated under reduced pressure. The product was dissolved in ethyl acetate (ca. 15 mL mmol^{-1}), and the precipitate was filtered off. After column chromatography the product was obtained as colorless solid or liquid.

b) EDC Coupling (GP1b): Coupling with *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC) was performed in the same manner as DCC coupling by using 1 equiv of EDC or 1.1 equiv of EDC·HCl in the presence of triethylamine (1.1 equiv). The reaction mixture was extracted with 1 N HCl, a 10% aqueous solution of $NaHCO_3$, and brine (for a 1 mmol scale: 3 × ca. 15 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The product was purified by column chromatography.

General procedure GP2 for the hydrolysis of 2c under aqueous acidic or basic conditions: Sulfoximine **2c** (42 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (2 mL) and a 1 N aqueous solution of NaOH (5 equiv), 1 N HCl (1 mL, 1 mmol) or a 10 N aqueous solution of NaOH (25 equiv), or 10 N HCl (0.5 mL, 5 mmol) was added. When TFA was used, 65 equiv (1 mL, 13 mmol) were used. After the mixture had been stirred at the indicated temperature (Table 4), the reaction was stopped by adjusting the pH to slightly basic (pH 8). The aqueous phase was extracted with CH_2Cl_2 (2 mL), and the organic layer was dried ($MgSO_4$) and concentrated. Analysis of the crude product by ^{1}H NMR spectroscopy allowed the determination of the percentage cleavage.

(*S*)-*N*-Propionyl-*S*-methyl-*S*-phenylsulfoximine (2c): $[\alpha]_D^{25} = +19.0$ (c = 0.79 in acetone); m.p. 50 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.06 (dt, J_1 = 1.3 Hz, J_2 = 7.4 Hz, 3H), 2.36 (dq, J_1 = 1.2 Hz, J_2 = 7.4 Hz, 2H), 3.27 (s, 3H), 7.50–7.64 (m, 3H), 7.89–7.93 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.0, 33.1, 44.5, 127.3, 129.8, 133.9, 139.1, 183.7 ppm; IR (KBr): $\tilde{\nu}$ = 3056, 3023, 2977, 2924, 1635, 1581, 1445, 1354, 1284, 1213, 1092, 1073, 980, 839, 751 cm^{-1}; IR ($CHCl_3$): $\tilde{\nu}$ = 3017, 2936, 1638, 1449, 1354, 1323, 1278, 1197, 1099, 1075, 976, 733 cm^{-1}; MS (EI, DIP, 70 eV): *m/z* (%): 184 (6), 183 (11), 182 (100, [M^+−CH_2CH_3]), 156 (21), 125 (7), 77 (20), 65 (15); elemental analysis (%) calcd for $C_{10}H_{13}NO_2S$: C 56.85, H 6.20, N 6.63; found: C 56.85, H 6.63, N 6.62.

(*S*)-*N*-Propionyl-*S*-trideuteromethyl-*S*-phenylsulfoximine (2c-CD$_3$): **2c-CD$_3$** was isolated (together with remaining (*S*)-**1**) from a reaction mixture obtained by following GP2. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.13 (t, J = 7.7 Hz, 3H), 2.44 (q, J = 7.7 Hz, 2H), 7.52–7.69 (m, 3H), 7.81–8.05 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.7, 32.8, 127.1, 129.3, 133.7, 139.3, 183.6 ppm; IR (KBr): $\tilde{\nu}$ = 3063, 2973, 1640, 1447, 1278, 1215, 1097, 1076, 858, 785, 759, 711, 686 cm^{-1}; MS (EI, DIP, 70 eV): *m/z* (%): 215 (1, [M^++H]), 185 (100, [M^+−CH_2CH_3]), 140 (31), 92 (55), 77 (79); HRMS calcd for $C_{10}H_{10}NO_2SD_3$−C_2H_5: 185.0464; found: 185.0464.

(*S*)-*N*-Trifluoracetyl-*S*-methyl-*S*-phenylsulfoximine (2h): $[\alpha]_D^{25} = +46.2$ (c = 1.00 in $CHCl_3$); m.p. 79 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.38 (s, 3H), 7.55–7.62 (m, 2H), 7.68 (tt, J_1 = 1.4 Hz, J_2 = 7.4 Hz, 1H), 7.90–7.94 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 44.6, 116.1 (d, J = 286 Hz), 127.3, 130.3, 135.1, 136.8, 164.3 ppm (d, J = 37.9 Hz); ^{19}F NMR (375 MHz, $CDCl_3$, 25 °C): δ = −76.4 ppm (s, 3F); IR (KBr): $\tilde{\nu}$ = 3437, 3063, 3033, 3015, 2932, 1661, 1451, 1386, 1241, 1199, 1134, 1090 cm^{-1}; MS (EI, 70 eV): *m/z* = 182 (100, [M^+−F_3C]), 94 (24), 77 (48), 65 (24), 51 (38); elemental analysis (%) calcd for $C_9H_8F_3NO_2S$: C 43.03, H 3.21, N 5.58; found: C 43.01, H 3.41, N 5.51.

L-Boc-Tyr-Bn-(*S*)-Sulf (5a): $[\alpha]_D^{25} = +57.0$ (c = 0.50 in acetone); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.14 (s, 9H), 3.13 (d, J = 5.8 Hz, 2H), 2.15 (s, 3H), 4.54 (q, J = 6.3 Hz, 1H), 5.02 (s, 2H), 5.16 (d, J = 7.2 Hz, 1H), 6.88 (td, J = 1.1, 8.5 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.27–7.43 (m, 5H), 7.55 (t, J = 8.3 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.84 ppm (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 28.7, 38.4, 44.3, 58.0, 70.3, 79.5, 114.9, 127.4, 127.7, 127.7, 128.1, 128.8, 129.7, 129.8, 130.8, 134.1, 137.3, 138.5, 155.4, 157.8, 180.3 ppm; IR (KBr): $\tilde{\nu}$ = 3382, 2934, 1697, 1638, 1247 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 391 (69, [M^+−BocHN$^+$+H]), 182 (92), 91 (100); elemental analysis (%) calcd for $C_{28}H_{32}N_2O_5S$: C 66.12, H 6.34, N 5.51; found: C 66.43, H 6.36, N 5.62.

L-Boc-Lys-Cbz-(*S*)-Sulf (5b): $[\alpha]_D^{25} = -68.1$ (c = 0.50 in acetone); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.34 (s, 9H), 1.40–1.54 (m, 2H), 1.55–1.70 (m, 2H), 1.77–1.94 (m, 2H), 3.08–3.14 (m, 2H), 3.22 (s, 3H), 4.20 (q, J = 5.2 Hz, 1H), 4.94 (brs, 1H), 5.00 (s, 2H), 5.17 (d, J = 7.1 Hz, 1H), 7.21–7.28 (m, 5H), 7.52 (t, J = 8.0 Hz, 2H), 7.60 (tt, J = 1.1, 7.4 Hz, 1H), 7.87 ppm (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.5, 28.6, 29.6, 33.2, 41.0, 44.4, 56.6, 66.7, 79.5, 127.4, 128.3, 128.3, 128.7, 130.0, 134.2, 136.9, 138.5, 155.9, 156.7, 181.3 ppm; IR (KBr): $\tilde{\nu}$ = 3376, 2927, 1714, 1690, 1641, 1261, 1212 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 517 (1, [M^+]), 182 (100); elemental analysis (%) calcd for $C_{26}H_{35}N_3O_6S$: C 60.33, H 6.82, N 8.12; found: 60.36, H 6.66, N 7.93.

L-Boc-Lys-Boc-(*S*)-Sulf (5c): $[\alpha]_D^{25} = -70.1$ (c = 0.51 in acetone); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.35 (s, 9H), 1.36 (s, 9H), 1.23–1.48 (m, 4H), 1.58–1.69 (m, 1H), 1.79–1.90 (m, 1H), 3.00 (brs, 2H), 3.26 (s, 3H), 4.21 (q, J = 7.1 Hz, 1H), 4.61 (brs, 1H), 5.16 (d, J = 7.4 Hz, 1H), 7.54 (t, J = 7.9 Hz, 2H), 7.62 (tt, J = 1.1, 7.4 Hz, 1H), 7.90 ppm (tt, J = 1.1, 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 22.8, 28.7, 28.8, 29.9, 33.3, 40.7, 44.6, 56.8, 79.2, 79.5, 127.3, 129.9, 134.1, 138.5, 155.8, 156.1, 181.2 ppm; IR (KBr): $\tilde{\nu}$ = 3392, 2978, 2932, 1698, 1654, 1223, 1170 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 483 (3, [M^+−H]); 184 (100); elemental analysis (%) calcd for $C_{23}H_{37}N_3O_6S$: C 57.12, H 7.71, N 8.69; found: C 57.04, H 7.43, N 8.60.

***N*-[*N*-*tert*-Butyloxycarbonyl-4-acetyl-L-prolinyl]-(*S*)-*S*-methyl-*S*-phenylsulfoximine (L,(*S*)-5d)**: $[\alpha]_D^{25} = -3.5$ (c = 0.10 in $CHCl_3$); R_f = 0.46 (EE); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.42–1.47 (m, 9H), 2.05–2.07 (m, 3H), 2.35–2.46 (m, 2H), 3.35–3.40 (m, 3H), 3.71–3.79 (m, 2H), 4.32–4.48 (m, 1H), 5.20–5.30 (m, 1H), 7.54–7.74 (m, 3H), 7.95–7.99 (m, 1H), 8.02–8.06 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.0, 28.4, 28.4, 35.9, 37.0, 44.0, 44.1, 52.0, 52.5, 61.3, 61.6, 72.0, 72.9, 79.7, 80.0, 126.9, 127.4, 129.3, 129.5, 133.6, 133.8, 138.3, 138.4, 154.0,

154.1, 170.3, 181.1, 181.2 ppm; IR (KBr): $\tilde{\nu}$ = 2978, 2931, 1741, 1697, 1653, 1404, 1368, 1225, 1162, 1130, 754, 514 cm^{-1}; MS (EI, DIP): *m/z* (%): 410 (1, [*M*$^+$]), 350 (4), 337 (5), 228 (29), 182 (100), 172 (25), 141 (68), 112 (28), 68 (51), 57 (92); HRMS calcd for $C_{19}H_{26}N_2O_6S-OC_4H_9$: 337.0858; found: 337.0857.

***N*-[*N*-*tert*-Butyloxycarbonyl-4-acetyl-L-prolinyl]-(*R*)-*S*-methyl-*S*-phenylsulfoximine (L,(*R*)-5d)**: $[\alpha]_D^{25} = -2.9$ (c = 0.10 in $CHCl_3$); R_f = 0.46 (EE); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.43–1.51 (m, 9H), 2.06–2.08 (m, 3H), 2.35–2.48 (m, 2H), 3.36–3.40 (m, 3H), 3.74–3.81 (m, 2H), 4.34–4.50 (m, 1H), 5.26–5.32 (m, 1H), 7.58–7.65 (m, 2H), 7.66–7.74 (m, 1H), 7.94–8.00 (m, 1H), 8.03–8.10 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.0, 28.3, 28.4, 35.9, 37.0, 44.2, 52.0, 52.5, 61.1, 61.4, 72.0, 72.9, 79.8, 80.1, 126.3, 126.8, 127.3, 129.4, 129.5, 133.7, 133.8, 138.2, 138.4, 153.9, 154.3, 170.3, 180.8, 180.9 ppm; IR (KBr): $\tilde{\nu}$ = 2978, 2932, 1740, 1696, 1654, 1405, 1367, 1226, 1162, 734 cm^{-1}; MS (EI, DIP): *m/z* (%): 410 (1, [*M*$^+$]), 350 (8), 337 (6), 308 (6), 228 (34), 182 (100), 172 (26), 141 (67), 112 (23), 68 (40), 57 (47); HRMS calcd for $C_{19}H_{26}N_2O_6S-OC_4H_9$: 337.0858; found: 337.0858.

***N*-[*N*-*tert*-Butyloxycarbonyl-*O*-acetyl-L-serinyl]-(*S*)-*S*-methyl-*S*-phenylsulfoximine (5e)**: $[\alpha]_D^{25} = +2.8$ (c = 0.10 in $CHCl_3$); m.p. 88 °C; R_f = 0.45 (EE/EtOH 8:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.43–1.45 (s, 9H), 2.04–2.06 (m, 3H), 3.37 (s, 3H), 4.40 (dd, J_1 = 3.0 Hz, J_2 = 13.0 Hz, 1H), 4.51–4.57 (m, 1H), 4.68 (dd, J_1 = 3.0 Hz, J_2 = 13.0 Hz, 1H), 5.45 (d, J = 6.1 Hz, 1H), 7.58–7.65 (m, 2H), 7.67–7.73 (m, 1H), 7.95–8.05 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 20.8, 28.3, 43.9, 56.0, 65.0, 79.6, 127.0, 129.6, 133.9, 138.0, 155.1, 170.6, 177.2 ppm; IR (KBr): $\tilde{\nu}$ = 3382, 2986, 2936, 1742, 1696, 1655, 1503, 1365, 1221, 1164, 1032, 748 cm^{-1}; MS (EI, DIP): *m/z* (%): 324 (1, [*M*$^+$ $-CH_3COO$+H]), 311 (3), 269 (1), 182 (100), 57 (8); elemental analysis (%) calcd for $C_{17}H_{24}N_2O_6S$: C 53.11, H 6.49, N 7.29; found: C 53.17, H 6.80, N 7.60.

Boc-L-His-Bn-(*S*)-Sulf (5f): $[\alpha]_D^{25} = -2.7$ (c = 0.26 in $CHCl_3$); R_f = 0.50 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.41 (s, 9H), 3.19 (dAB system, J_1 = 4.9 Hz, J_2 = 14.3 Hz, 2H), 3.36 (s, 3H), 4.51–4.56 (m, 1H), 5.03 (s, 2H), 5.74 (d, J = 7.4 Hz, 1H), 6.74 (s, 1H), 7.12–7.15 (m, 2H), 7.28–7.35 (m, 3H), 7.39 (s, 1H), 7.54–7.68 (m, 3H), 8.01–8.03 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 28.8, 31.5, 44.0, 51.1, 56.9, 79.3, 117.6, 127.5, 127.7, 128.4, 129.2, 129.7, 134.0, 136.4, 136.7, 138.5, 139.0, 155.7, 180.7 ppm; IR (KBr): $\tilde{\nu}$ = 3424, 3004, 2928, 1706, 1647, 1498, 1450, 1365, 1220, 1166, 1099, 1023, 861, 515 cm^{-1}; MS (EI, DIP): *m/z* (%): 483 (3, [*M*$^+$+H]), 482 (9, [*M*$^+$+H]), 409 (10, [*M*$^+$−Boc]), 301 (13), 300 (60), 182 (60), 139 (60), 91 (100); elemental analysis (%) calcd for $C_{25}H_{30}N_4O_4S\cdot H_2O$: C 59.98, H 6.44, N 11.19; found: C 60.04, H 6.73, N 10.95.

Boc-D/L-Phg-(*R*)-Sulf [D/L,(*R*)-5g]: Starting from D-Phg, a mixture of diastereomers was obtained. R_f = 0.55 (EE/PE 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (main isomer) = 1.42 (brs, 9H), 3.25 (s, 3H), 5.32 (d, J = 7.2 Hz, 1H), 5.91–5.93 (m, 1H), 7.30–7.79 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ (main isomer) = 28.4, 43.8, 60.8, 79.5, 126.9, 127.2, 127.5, 127.7, 128.5, 129.7, 134.0, 137.7, 155.0, 178.4 ppm; IR (KBr): $\tilde{\nu}$ = 3423, 3028, 2979, 1708, 1654, 1624, 1492, 1450, 1357, 1326, 1217, 1172, 980, 855, 807 cm^{-1}; MS (EI, DIP): *m/z* (%): 315 (2, [*M*$^+$−OC(CH$_3$)$_3$]), 184 (11), 182 (70), 124 (42), 110 (31), 76 (30), 57 (100); HRMS calcd for $C_{20}H_{24}N_2O_4S-OC_4H_9$: 315.0803; found: 315.0803.

Boc-D/L-Phg-(*S*)-Sulf [D/L,(*S*)-5g]: Starting from D-Phg, a mixture of diastereomers was obtained. R_f = 0.55 (EE/PE 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (main isomer) = 1.40 (brs, 9H), 3.21 (s, 3H), 5.34 (d, J = 6.9 Hz, 1H), 5.83–5.85 (m, 1H), 7.30–7.79 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ (main isomer) = 28.3, 44.5, 60.9, 79.5, 127.3, 128.4, 128.5, 129.6, 129.8, 134.0, 138.2, 139.1, 154.9, 178.4 ppm; IR (KBr): $\tilde{\nu}$ = 3393, 3033, 2979, 2931, 1700, 1650, 1620, 1500, 1449, 1363, 1323, 1305, 1224, 1167, 853, 803 cm^{-1}; MS (EI, DIP): *m/z* (%): 315 (2, [*M*$^+$−OC(CH$_3$)$_3$]), 184 (10), 182 (100), 124 (47), 110 (29), 57 (90); HRMS calcd for $C_{20}H_{24}N_2O_4S-OC_4H_9$: 315.0803; found: 315.0803.

(*S*)-*N*-Ferrocenoyl-*S*-methyl-*S*-phenylsulfoximine (10a): $[\alpha]_D^{25} = +65.1$ (c = 0.50 in $CHCl_3$); m.p. 143 °C; R_f = 0.70 (EE/PE 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.43 (s, 3H), 4.21 (brs, 5H), 4.38 (brs, 2H), 4.87 (brs, 1H), 4.89–4.91 (m, 1H), 7.60–7.72 (m, 3H), 8.05 ppm (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 44.8, 70.1, 70.8, 71.4, 127.4, 129.8, 133.8, 139.7, 179.8 ppm; IR (KBr): $\tilde{\nu}$ = 2925, 1596, 1453, 1374, 1289, 1209, 1157, 1088, 975, 946, 823, 779, 744, 683, 609, 574, 539, 498; MS (EI, 70 eV): m/z (%): 367 (M$^+$, 7), 299 (1), 257 (1), 230 (7), 224 (17), 218 (11), 182 (6), 167 (20), 148 (81), 105 (16), 98 (48), 85 (64), 83 (100), 57 (94); HRMS calcd for $C_{18}H_{17}NSFeO_2$: 367.0329; found: 367.0330.

Coupling of *rac*-anthracene acid methyl ester with (*S*)-*S*-methyl-*S*-phenylsulfoximine to give 10b: $[\alpha]_D^{25} = -2.7$ (c = 1.00 in $CHCl_3$); m.p. 84 °C; R_f = 0.37 (EE:PE 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.23 (s, 3H), 3.26 (s, 3H), 3.43 (dd, J_1 = 2.8 Hz, J_2 = 4.6 Hz, 1H), 3.47 (dd, J_1 = 2.8 Hz, J_2 = 4.6 Hz, 1H), 3.58–3.62 (m, 8H), 4.72 (m, 2H), 4.88 (m, 2H), 7.00–7.38 (m, 16H), 7.48–7.70 (m, 8H), 7.83 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 43.9, 44.1, 47.0, 47.7, 48.0, 51.9, 52.2, 123.8, 124.5, 124.6, 124.7, 124.8, 125.9, 126.1, 126.1, 126.2, 126.2, 126.3, 127.0, 127.2, 129.4, 129.6, 133.8, 133.8, 138.5, 138.7, 140.8, 140.8, 141.2, 142.5, 142.7, 173.3, 173.4, 180.3, 180.9 ppm; IR (KBr): $\tilde{\nu}$ = 3444, 3066, 3021, 2950, 2928, 2847, 2251, 1731, 1635, 1584, 1462, 1368, 1309, 1265, 1219, 1096, 1022, 971, 910, 848, 803, 732, 684, 584 cm^{-1}; MS (EI, DIP): *m/z* (%): 445 (5, [*M*$^+$]), 203 (7), 202 (6), 182 (27), 179 (15), 178 (100), 99 (5), 99 (4), 98 (4), 86 (7), 84 (11), 77 (4), 56 (8), 47 (3); HRMS calcd for $C_{26}H_{23}NO_4S$: 445.1348; found: 445.1348.

(2*S*,3*S*)-3-*exo*-[(*S*)-*S*-Methyl-*S*-phenylsulfoximidoyl)bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid methyl ester (*endo*,*exo*-10c): $[\alpha]_D^{25} = +83.1$ (c = 0.63 in acetone); m.p. 124 °C; R_f = 0.50 (EE/PE 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.40 (ddd, J_1 = 1.3 Hz, J_2 = 1.8 Hz, J_3 = 17.6 Hz, 1H), 1.62 (d, J = 7.6 Hz, 1H), 2.79 (dd, J_1 = 1.7 Hz, J_2 = 4.5 Hz, 1H), 3.20–3.22 (m, 2H), 3.36 (s, 3H), 3.50 (dd, J_1 = 3.6 Hz, J_2 = 4.2 Hz, 1H), 3.64 (s, 3H), 6.08 (dd, J_1 = 2.9 Hz, J_2 = 5.7 Hz, 1H), 6.28 (dd, J_1 = 3.4 Hz, J_2 = 5.7 Hz, 1H), 7.60–7.63 (m, 2H), 7.66–7.75 (m, 1H), 7.97–8.00 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 44.6, 46.1, 47.4, 47.9, 48.8, 51.9, 52.3, 127.3, 129.9, 133.9, 135.4, 138.2, 139.0, 174.6, 183.0 ppm; IR (KBr): $\tilde{\nu}$ = 3426, 3011, 2997, 2974, 2920, 1723, 1639, 1582, 1447, 1315, 1274, 1242, 1214, 1189, 1112, 1092, 1022, 975, 869, 846, 830, 751, 738, 685, 498 cm^{-1}; MS (EI, DIP): *m/z* (%): 333 (10, [*M*$^+$]), 302 (8), 274 (6), 269 (8), 268 (45), 236 (12), 194 (5), 184 (6), 182 (100), 156 (38), 125 (8), 119 (10), 91 (12), 77 (13); elemental analysis (%) calcd for $C_{17}H_{19}NO_4S$ (333.2): C 61.24, H 5.74, N 4.20; found: C 61.16, H 5.82, N 4.32.

(2*S*,3*R*)-3-*endo*-[(*S*)-S-Methyl-*S*-phenylsulfoximidoyl)bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid methyl ester (*endo*,*endo*-10c): $[\alpha]_D^{25} = +27.2$ (c = 0.57 in acetone); m.p. 118 °C; R_f = 0.45 (EE/PE 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.32 (d, J = 8.2 Hz, 1H), 1.45 (td, J_1 = 1.6 Hz, J_2 = 8.2 Hz, 1H), 3.11–3.13 (m, 1H), 3.22–3.24 (m, 2H), 3.34 (s, 3H), 3.48 (s, 3H), 3.49–3.51 (m, 1H), 6.18 (dd, J_1 = 3.0 Hz, J_2 = 5.5 Hz, 1H), 6.36 (dd, J_1 = 3.0 Hz, J_2 = 5.7 Hz, 1H), 7.55–7.70 (m, 3H), 7.97–8.00 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 43.8, 45.9, 47.3, 48.6, 48.9, 51.3, 53.3, 127.1, 129.4, 133.5, 134.2, 135.2, 138.7, 173.7, 180.5 ppm.

(2*S*,3*S*)-3-*exo*-[(*S*)-*S*-Methyl-*S*-phenylsulfoximidoyl]bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid methyl ester (*endo*,*exo*-10d): $[\alpha]_D^{25} = +62.9$ (c = 0.45 in acetone); m.p. 133 °C; R_f = 0.30 (EE/PE 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.38–1.34 (m, 2H), 1.51–1.53 (m, 1H), 1.54–1.56 (m, 1H), 1.56–1.64 (m, 2H), 2.59–2.61 (m, 1H), 2.66 (d, J = 3.9 Hz, 1H), 2.91 (dd, J_1 = 1.5 Hz, J_2 = 5.2 Hz, 1H), 3.30–3.35 (m, 1H), 3.33 (s, 3H), 3.69 (s, 3H), 7.58–7.63 (m, 2H), 7.66–7.70 (m, 1H), 7.96–7.98 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 24.7, 29.2, 40.0, 40.5, 42.5, 44.4, 49.1, 51.7, 53.3, 127.1, 129.6, 133.7, 138.9, 174.6, 183.2 ppm; IR (KBr): $\tilde{\nu}$ = 3421, 3011, 2972, 1720, 1635, 1476, 1449, 1330, 1308, 1252, 1219, 1189, 1119, 1092, 1016, 977, 751 cm^{-1}; MS (EI, DIP): *m/z* (%): 335 (7, [*M*$^+$]), 306 (3), 183 (9), 182 (100); elemental analysis (%) calcd for $C_{17}H_{21}NO_4S$: C 60.87, H 6.31, N 4.18; found: C 60.76, H 6.53, N 4.06.

(2*S*,3*R*)-3-*endo*-[(*S*)-*S*-Methyl-*S*-phenylsulfoximidoyl)bicyclo[2.2.1]-heptane-2-*endo*-carboxylic acid methyl ester (*endo*,*endo*-10d): $[\alpha]_D^{25} = +19.8$ (c = 0.65 in acetone); m.p. 122 °C; R_f = 0.27 (EE/PE 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.41–1.49 (m, 4H), 1.58–1.60 (m, 2H), 1.70–1.76 (m, 1H), 1.99–2.03 (m, 1H), 2.49–2.51 (m, 1H), 2.63–2.64 (m, 1H), 2.83 (ddd, J_1 = 1.6 Hz, J_2 = 3.7 Hz, J_1 = 11.6 Hz, 1H), 3.22 (ddd, J_1 = 1.6 Hz, J_2 = 4.6 Hz, J_1 = 11.6 Hz, 1H), 3.33 (s, 3H), 3.45 (s, 3H), 7.58–7.63 (m, 2H), 7.65–7.67 (m, 1H), 7.99–8.01 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 23.6, 24.8, 40.1, 40.2, 41.4, 44.0, 46.9, 51.0, 51.5, 127.2, 129.5, 133.5, 139.5, 173.6, 181.1 ppm.

(2*S*,3*S*)-3-*exo*-(*S*)-*S*-Methyl-*S*-phenylsulfoximidoylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (*endo*,*exo*-11): Sulfoximine *endo*,*exo*-**10c** (200 mg, 0.60 mmol) was dissolved in methanol (3 mL) and 1N NaOH (1.80 mL, 3 equiv) was slowly added. After stirring for 4 h at room temperature the reaction mixture was extracted with 10 mL of ethyl acetate, and the aqueous phase was acidified (pH 3) and additionally extracted with ethyl acetate (3×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Finally, the product was recrystallized from ethanol to yield 163 mg (0.51 mmol, 85%) of **11** as colorless crystals that were suitable for X-ray crystal structure analysis. $[\alpha]_D^{25} = +102.0$ ($c = 1.00$ in DMSO); m.p. 183°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25°C): $\delta = 1.26$ (dd, $J_1 = 1.4$ Hz, $J_2 = 1.5$ Hz, $J_3 = 7.6$ Hz, 1H), 1.38 (d, $J = 7.6$ Hz, 1H), 2.53 (dd, $J_1 = 1.9$ Hz, $J_2 = 4.8$ Hz, 1H), 3.10–3.12 (m, 2H), 3.21–3.23 (m, 1H), 3.47 (s, 3H), 6.06 (dd, $J_1 = 2.8$ Hz, $J_2 = 5.6$ Hz, 1H), 6.31 (dd, $J_1 = 3.1$ Hz, $J_2 = 5.6$ Hz, 1H), 7.66–7.70 (m, 2H), 7.74–7.78 (m, 1H), 7.94–7.98 (m, 2H), 11.90 ppm (br s, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25°C): $\delta = 44.0$, 45.8, 47.5, 47.9, 48.6, 51.9, 127.6, 130.1, 134.2, 135.8, 138.3, 139.3, 175.1, 181.8 ppm; IR (KBr): $\tilde{\nu} = 3060$, 2998, 2937, 2913, 1726, 1649, 1450, 1334, 1108, 1092, 992, 868, 839, 749, 684, 663, 501 cm^{-1}; MS (EI, DIP): *m*/*z* (%): 319 (2, [M^+]), 301 (2), 274 (1), 254 (30), 236 (1), 210 (1), 183 (10), 182 (100), 156 (53), 140 (10), 125 (9), 119 (6), 109 (1), 99 (3), 97 (3), 93 (6), 92 (2), 91 (11), 77 (15), 66 (10), 65 (12), 51 (5); elemental analysis (%) calcd for $C_{16}H_{17}NO_4S$: C 60.17, H 5.37, N 4.39; found: C 60.14, H 5.61, N 4.25.

X-ray crystallographic study on *endo*,*exo*-11: The compound ($C_{16}H_{17}NO_4S$, $M_r = 319.38$) crystallizes in monoclinic space group $P2_1$ (No. 4) with cell dimensions $a = 5.995(2)$, $b = 11.963(2)$, $c = 10.637(5)$ Å, and $\beta = 97.42(3)°$. A cell volume of $V = 756.5(5)$ Å^3 and $Z = 2$ result in a calculated density of $\rho_{calcd} = 1.402$ g cm^{-3}. A total number of 3262 reflections were collected in the $\omega/2\Theta$ mode at $T = 150$ K on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated $Cu_{K\alpha}$ radiation ($\lambda = 1.54179$ Å). Data collection (Friedel pairs) covered the range $-7 \le h \le 6$, $-14 \le k \le 14$, and $-13 \le l \le 13$ up to $\Theta_{max} = 72.8°$. Lorentzian and polarization corrections were applied to the diffraction data, but no correction was made for absorption effects ($\mu = 2.064$ mm^{-1}) The structure was solved by direct methods as implemented in the Xtal3.7 suite of crystallographic routines;[38] GENSIN was used to generate the structure-invariant relationships, and GENTAN for the general tangent phasing procedure. 2927 observed reflections ($I > 2\sigma(I)$) were included in the final full-matrix least-squares refinement on F involving 266 parameters and converging at $R(R_w) = 0.037$ (0.052, $w = 1/[12.0\,\sigma^2(F)]$, a final shift/error < 0.0006, $S = 1.062$, and a residual electron density of $-0.63/0.32$e Å^{-3}. $X_{abs} = -0.001(34)$[39] for the structure shown in Figure 1. The positions of hydrogen atoms could be located in a difference Fourier map and were refined isotropically.

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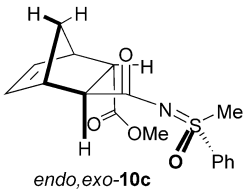

endo,exo-**10c**

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