A Short Synthesis and Biological Evaluation of Potent and Nontoxic Antimalarial Bridged Bicyclic β-Sulfonyl-Endoperoxides

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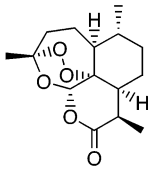
The syntheses and in vitro antimalarial screening of 50 bridged, bicyclic endoperoxides of types **9**−**13** are reported. In contrast to antimalarial trioxanes of the artemisinin family, but like yingzhaosu A and arteflene, the peroxide function of compounds **9**−**13** is contained in a 2,3-dioxabicyclo[3.3.1]nonane system **6**. Peroxides **9** and **10** (R^1 = OH) are readily available through a multicomponent, sequential, free-radical reaction involving thiol-monoterpenes co-oxygenation (a TOCO reaction). β-Sulfenyl peroxides **9** and **10** (R^1 = OH) are converted into β-sulfinyl and β-sulfonyl peroxides of types **11**−**13** by controlled *S*-oxidation and manipulation of the *tert*-hydroxyl group through acylation, alkylation, or dehydration followed by selective hydrogenation. Ten enantiopure β-sulfonyl peroxides of types **12** and **13** exhibit in vitro antimalarial activity comparable to that of artemisinin (IC_{50} = 6−24 nM against *Plasmodium falciparum* NF54). In vivo testing of a few selected peroxides against *Plasmodium berghei* N indicates that the antimalarial efficacies of β-sulfonyl peroxides **39a**, **46a**, **46b**, and **50a** are comparable to those of some of the best antimalarial drugs and are higher than artemisinin against chloroquine-resistant *Plasmodium yoelii* ssp. NS. In view of the nontoxicity of β-sulfonyl peroxides **39a**, **46a**, and **46b** in mice, at high dosing, these compounds are regarded as promising antimalarial drug candidates.

Introduction

Although a variety of new approaches for fighting malaria are being investigated,[1,2] chemotherapy is still the most common method for treating malaria.[3−11] The continuing spread of malaria parasite strains resistant to customary drugs is motivating a worldwide quest for new, effective, and inexpensive therapeutic agents.[2,3] Various organic endoperoxides have been found to exhibit antimalarial activity. The natural product artemisinin (**1**), and its semisynthetic C(10) acetal derivatives artemether (**2b**), arteether (**2c**), artesunic acid (**2d**), and artelinic acid (**2e**) have already been used for treatment of malaria in endemic countries.[3−11] No serious side effects have been reported for the clinical trials with artemisinin (**1**) and its acetal derivatives **2b**−**e** in malaria-endemic areas. However, some indications of serious neurotoxicity and cardiac abnormalities have been found in animal studies at high doses of **1** and its lactols **2b**,**c**.[12] This neurotoxicity is very likely to be associated with the nature of acetals **2b**,**c**, which are rapidly metabolized, hydrolyzed, or both to yield the highly neurotoxic dihydroartemisinin (**2a**) as a major metabolite.[13] Thus, the data on adverse pharmacokinetic and clinical properties, as well as the potentially harmful biological side effects, have deferred approval of this first generation of antimalarial artemisinin derivatives **2** in nonendemic countries.[3,4,14] The first and so far the only antimalarial peroxide to reach the market in those countries is arteether (**2c**), which was registered in the year 2000 in The Netherlands for treatment of severe malaria.[15]

The identification of the trioxane system **5** as the pharmacophore of the natural product **1** and its semisynthetic derivatives **2** led to the development of a variety of structurally simplified racemic trioxanes such as tricyclic compounds **3**[10,11,16] and spirocyclic trioxanes such as fenozan (**4**).[9,17,18] The antimalarial potency against chloroquine-resistant *Plasmodium* strains of some of the synthetic compounds **3** and **4** was found to be considerably higher than that of artemisinin (**1**) and comparable to its derivatives **2b**−**e**.



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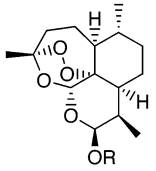
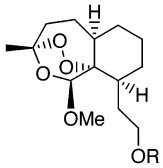


2a: OR = α/β-OH
2b: R = Me
2c: R = Et
2d: R = $C(O)CH_2CH_2CO_2H$
2e: R = $CH_2C_6H_4(CO_2H)$-*p*



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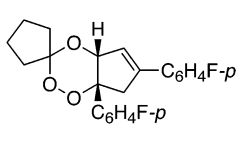

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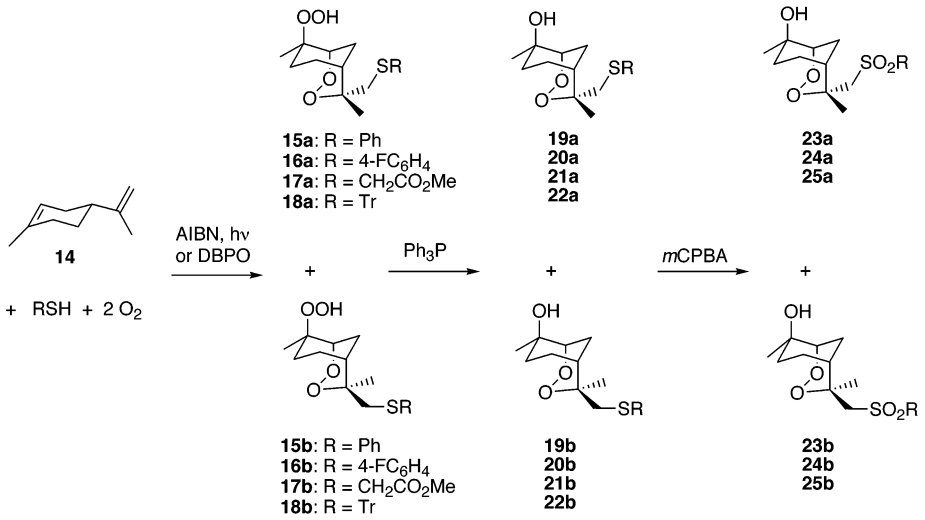
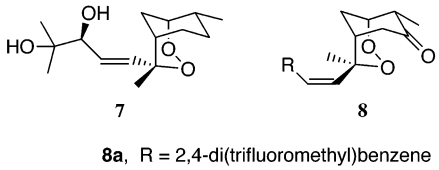
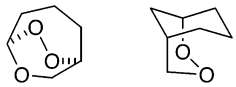
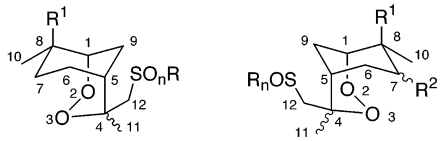
Scheme 1



Another, although a much less studied, group of promising antimalarial peroxides consists of compounds containing the 2,3-dioxabicyclo[3.3.1]nonane pharmacophore (**6**) in their molecular backbone. System **6** was originally identified in yingzhaosu A (**7**), a natural product isolated from a traditional Chinese herbal antimalarial medicament[19] and subsequently obtained by total syntheses.[20−22] Although no data on the antimalarial activity of yingzhaosu A (**7**) was ever reported,[19] it inspired a few research groups to design and synthesize some simplified endoperoxides containing the 2,3-dioxabicyclo[3.3.1]nonane framework (**6**) and screen them for antimalarial activity. In a pioneering work it was shown that synthetic endoperoxides of type **8** do exhibit potent antimalarial activity.[23] Arteflene (**8a**) was identified as a lead drug candidate.[23,24] It exhibits a rapid onset of drug action, long-lasting high antimalarial effect against drug-resistant strains of *P. falciparum*, and a very low toxicity.[24] Essentially no side effects were found for the treatment with arteflene (**8a**) in preclinical and phase 2 clinical studies.[3,25,26] The reported procedure[23] for the synthesis of antimalarials of type **8** is laborious, and their further development as drugs seems to have been interrupted.[6,14]





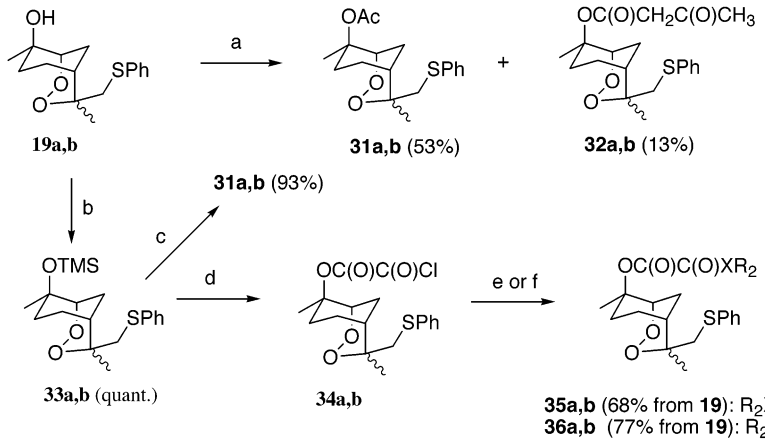


Recently, we reported on an expedient synthesis of endoperoxides of types **9**−**13** (R^1 = OH)[27−29] and on a novel and efficient total synthesis of yingzhaosu A (**5**).[21] In a preliminary screening, we found that some β-sulfonyl-endoperoxides of types **12** and **13** exhibit high antimalarial activity.[29,30] Moderate antimalarial activity was observed also in synthetic acetal derivatives of 2,3-dioxabicyclo[3.3.1]nonane,[31] whereas some similar β-iodo-endoperoxides showed significant antimalarial activities.[32]

In this paper, we give a detailed report on a short and efficient synthesis of numerous β-sulfinyl- and β-sulfonyl-endoperoxides of types **11**−**13**, as well as on their in vitro and in vivo antimalarial evaluation and preliminary toxicological studies. β-Sulfonyl-bridged bicyclic endoperoxides **39a**, **46a**, and **46b** (type **12**), which were synthesized in 3 to 4 steps from readily available starting materials, were found to be highly potent and nontoxic antimalarial agents.

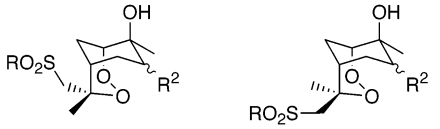
Chemistry: Synthesis of Polysubstituted 2,3-Dioxabicyclo[3.3.1]nonanes 9−13. On the basis of the methodology reported in our previous papers, endoperoxides of types **9**−**13** were prepared in a few synthetic steps from inexpensive, commercially available reagents.[27,28] The first stage, leading to 4-sulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols of type **9**, involves the application of a free-radical sequential thiol-olefins co-oxygenation (TOCO) reaction to monoterpenes, as exemplified using *R*-(+)-limonene (**14**) in Scheme 1. The TOCO reactions were initiated by AIBN and UV irradiation or by di-*tert*-butylperoxalate (DBPO). In this multicomponent reaction, five new bonds are formed in one sequential, free-radical process. Upon completion of the free-radical TOCO reaction, the hydroperoxide function of the resulting hydroperoxide endoperoxides **15**−**18** is chemoselectively reduced in the same vessel, yielding the corresponding β-sulfenyl-endoperoxides **19**−**22**.[28] β-Sulfenyl-endoperoxides **19**−**21** were easily oxidized to the corresponding β-sulfonyl-endoperoxides **23**−**25**.[28] These compounds, which were obtained as mixture of C(4) epimers, as well as additional compounds obtained by further structural modifications, are distinguished throughout this paper by subscripts **a** and **b** in accordance with their absolute configuration on

Scheme 2[a]



[a] Reagents and conditions: (a) AcCl, DMAP, pyridine, CH_2Cl_2, 0 °C to rt; (b) TMSOTf, 2,6-lutidine, CH_2Cl_2, 5 °C; (c) AcCl, rt; (d) oxalyl chloride, rt; (e) EtOH, 2,6-lutidine, CH_2Cl_2, 4 °C; (f) Bn_2NH, 2,6-lutidine, CH_2Cl_2, 0 °C.

stereogenic center C(4). Application of the same procedure to the co-oxygenation of *S*-(−)-limonene or *R*-(−)-carveol derivatives yielded endoperoxides **26**−**30** having the opposite absolute configuration.

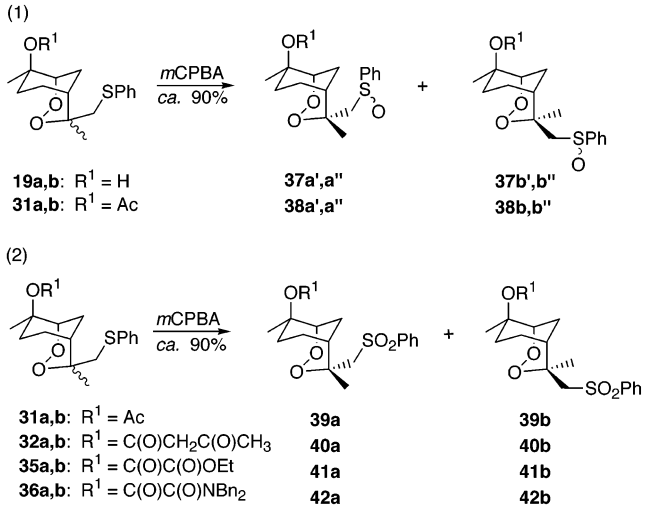


26a: R = Ph, R^2 = H — **26b**
27a: R = Ph, R^2 = β-OBz — **27b**
28a: R = *n*-Bu, R^2 = β-OBz — **28b**
29a: R = Ph, R^2 = α-OBz — **29b**
30a: R = Ph, R^2 = α-OH

At an early stage of this research, it was recognized that the potent and stable *β*-sulfonyl-endoperoxides **12** are more expedient candidates for further development of antimalarials than their sulfenyl precursors, **9**.[30] Additionally, chromatographic separation of *β*-sulfonyl-endoperoxides **12** and **13** to their individual diastereomers is more efficient.[27,28] Therefore, our standard protocol involves the isolation of the *β*-sulfenyl-endoperoxides **19**−**22** as a diastereomeric mixture of the C(4) epimers **a** and **b**. Subsequent oxidation to the corresponding *β*-sulfonyl-endoperoxides **23**−**25**, followed by their separation, affords individual epimers of *β*-sulfonyl-endoperoxides of series **a** and series **b**. A few *β*-sulfinyl-endoperoxides of type **11** were obtained by controlled partial oxidation of the corresponding *β*-sulfenyl-endoperoxides **9**. This protocol allows the preparation of a variety of endoperoxides of types **9**−**13** (R^1 = OH) in which the nature of substituents R and R^2 is predetermined by selection of the thiol and monoterpene used in the TOCO reaction. Additional structural modifications are feasible through manipulations with the 8-hydroxyl group such as acylation, alkylation, and deoxygenation.

Direct acylation with acyl chlorides and DMAP of the sterically hindered hydroxyl group in peroxides **9**, **10**, **12**, and **13** is slow and therefore subject to competitive secondary reactions. Indeed, treatment of *β*-sulfenyl-endoperoxide **19** with acetyl chloride and DMAP (Scheme 2) afforded, in addition to acetoxy derivative **31** (53%), the diacetylated derivative acetoacetate **32** (13%).[30] A more expedient method for mono-acylation involves silylation of hydroxy compound **19** with TMSOTf to give the TMS derivative **33** (quantitative), followed by treatment with excess acetyl chloride to give the acetoxy derivative **31** (93%). A similar procedure was applied for the preparation of oxalyl chloride derivative **34**, which on treatment with ethanol afforded ester **35** and, with dibenzylamine, amide **36** in good yield. The 8-hydroxy- and 8-acetoxy-*β*-sulfenyl-endoperoxides **19** and **31** were oxidized with one equivalent of *m*CPBA to the corresponding *β*-sulfinyl-endoperoxides **37** and **38** (Scheme 3.1). Oxidation of the 8-acyloxy-*β*-sulfenyl-endoperoxides **31**, **32**, **35**, and **36** with an excess of *m*CPBA afforded the corresponding *β*-sulfonyl-endoperoxides **39**−**42** (Scheme 3.2).

Scheme 3



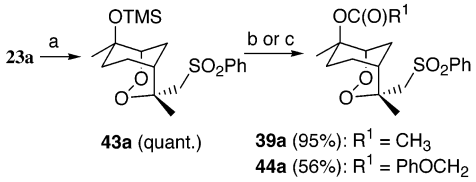
Stereochemistry assignment at stereogenic center C(4) of *β*-sulfonyl-endoperoxides **39a**, **42a**, and **39b**−**42b** was based on their ^{1}H NMR spectra. It was observed that a strong through-space deshielding effect of electronegative O(2) atom on the *syn*-positioned C(12) *HH′* fragment in series **a** and the Me(11) group in series **b**, induces a significant downfield shift in the ^{1}H NMR spectra of all *β*-sulfonyl-endoperoxides **39**−**42**. This effect was previously[27,28] formulated as an empirical rule that holds also for other structurally related bicyclic peroxides. Similarly, the configuration at C(4) in *β*-sulfi-

Table 1. Selected ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR Data for 8-Acetoxy-4,8-dimethyl-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]nonanes **38** in $CDCl_3$[a]

	38a′		**38a″**		**38b′**		**38b″**	
position	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	4.42 (m)	77.58 d	4.47 (br d, 3.6)	77.75 d	4.47 (br dd, 3.8, 1.8)	78.02 d	4.49 (br d, 3.3)	78.34 d
5	~2.20 (m)	29.09 d	~1.85 (m)	30.90 d	2.02 (br dddd)	30.55 d	1.90 (br dddd)	31.60 d
7	2.31 (ddd, *ax*)	32.98 t	2.30 (ddd, *ax*)	33.20 t	2.18−2.29 (m)	32.77 t	2.07 (ddd, *ax*)	32.92 t
	~2.20 (m, *eq*)		2.20 (br dd, 14.8, 6.2 *eq*)		2.18−2.29 (m)		2.14 (br dd, 14.8, 6.6 *eq*)	
10	1.65 (s)	22.43 q	1.68 (s)	22.53 q	1.65 (s)	22.45 q	1.62 (s)	22.59 q
11	1.44 (br s)	23.55 q	1.56 (br s)	22.23 q	1.80 (d, 0.6)	22.88 q	1.89 (br s)	22.05 q
12	3.08 (d, 13.8)	64.54 t	3.31 (AB quartet, 14.0)	66.04 t	2.77 (dd, 13.4. 0.6)	65.45 t	2.67 (br d, 13.6)	65.82 t
	3.61 (dd, 13.8, 0.6)		3.36 (AB quartet, 14.0)		2.92 (br d, 13.4)		3.10 (br d, 13.6)	

[a] For complete NMR data see Experimental Section. The values in brackets refer to a multiplicity of the signal and a coupling constant *J* in Hz.

Scheme 4[a]



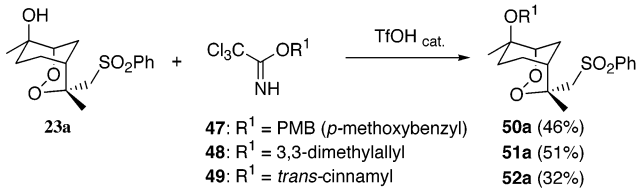
[a] Reagents and conditions: (a) TMSOTf, 2,6-lutidine; (b) AcCl; (c) $PhOCH_2C(O)Cl$, CsF.

nyl-endoperoxides **37a**, **38a** and **37b**, **38b** was determined using 2D NMR techniques (COSY and HMQC) and corroborated by NOE difference experiments. The couples of sulfoxides **a′** and **a″** as well as **b′** and **b″** differ only in the absolute configuration at the sulfur atom, which was not determined in this work. Representative 1D NMR data, relevant for the structural differentiation of all the C(4) diastereomers of 8-acetoxy-*β*-sulfinyl-endoperoxides **38a′**, **38a″**, **38b′**, and **38b″**, are summarized in Table 1.

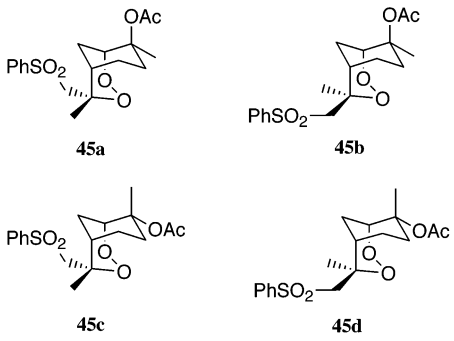
As shown in Table 1, all four isomeric *β*-sulfinyl-endoperoxides **38** reveal very similar NMR patterns for atoms and groups attached to the C(8) stereogenic center and different patterns for atoms and groups juxtaposed to the C(4) stereogenic center. This indicates that all the diastereomers have the same configuration at C(8) and differ in their configurations at only C(4) (series **a** and **b**) and on the sulfur atom. Stereochemical assignment of *β*-sulfinyl-endoperoxides **38** was based on their ^{1}H NMR spectra. Structures **38a′** and **38a″** were assigned to the isomers in which the C(12) *HH′*SO group is more deshielded and the Me(11) group is more shielded relative to the other two isomers to which were assigned structures **38b′** and **38b″**.[28] Indeed, separate oxidation of both individual sulfoxides **38a′** and **38a″** with *m*CPBA (1.5 equiv) gave the same sulfone **39a** (>90%). As we reported previously, the **b** series of 4-sulfonylmethyl- and 4-sulfenylmethyl-2,3-dioxabicyclo-[3.3.1]nonanes is characterized by the higher values of the C(5) chemical shift in ^{13}C NMR spectra ($\Delta_{\mathbf{b}-\mathbf{a}}\delta_C$ ca. 1.5 ppm) than the **a** series.[28] Comparison of the δ_C values within the diastereomeric pairs **a′/b′** and **a″/b″** indicates that this rule is applicable also for the sulfoxides **38** (Table 1) and **37** (Experimental Section).

8-Acylated-*β*-sulfonyl-endoperoxides **39a** and **44a** were prepared from the 8-hydroxy-*β*-sulfonyl-endoperoxides **23a** via its TMS derivative **43a** (Scheme 4). This procedure was used also in gram-scale preparations of compound **39a** (95% yield in two steps). The preparation and characterization of all four individual 8-acetoxy-*β*-sulfonyl-endoperoxides **45a**−**d** from *S*-(−)-limonene and

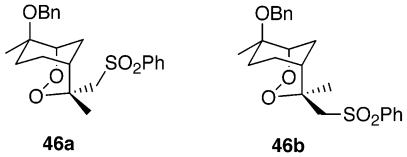
Scheme 5



PhSH using the sequence of transformations displayed in Schemes 1, 2, and 3.2 was reported earlier.[28] The



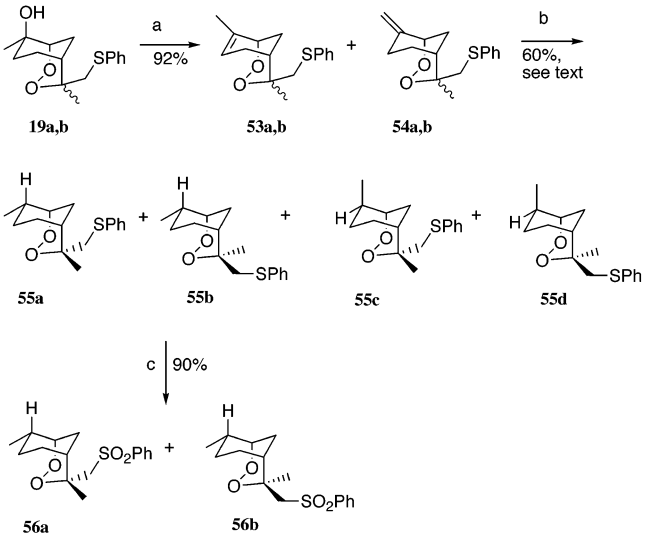
major diastereomers **45a** and **45b** are enantiomeric to **39a** and **39b**, respectively. Alkylation of the tertiary C(8) hydroxyl group in *β*-sulfonyl-endoperoxides **23** with alkyl halides under basic conditions failed because of a competitively fast Kornblum−De La Mare degradation of the peroxidic function.[33,34] Alkylation was therefore performed with strong electrophiles under acidic conditions. The *O*-benzylated derivatives **46a** and **46b** were obtained in 85% yield by treatment of **23a** and **23b**, respectively, with phenyldiazomethane in the presence of a catalytic amount of TfOH.[35] The trichloroacetimi-



dates **47**−**49**, which were obtained from the corresponding benzylic or allylic alcohols and trichloroacetonitrile,[36] were found to be suitable alkylating agents.[36,37] Thus, treatment of 8-hydroxy sulfone **23a** with trichloroacetimidates **49**−**51** and TfOH afforded the corresponding *O*-alkylated products **50a**−**52a**. (Scheme 5).

8-Deoxygenated sulfone-endoperoxide **56** was obtained from 8-hydroxysulfide-peroxide **19**. The latter was readily dehydrated with thionyl chloride and py-

Scheme 6[a]



[a] Reagents and conditions: (a) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C to rt; (b) Potassium azodicarboxilate, AcOH, MeOH, CH_2Cl_2, 0 °C to rt; (c) *m*CPBA, EtOAc, rt.

ridine to give a mixture of cyclohexene-endoperoxide **53** and methylenecyclohexanes-endoperoxide **54** (ca. 85:15) (Scheme 6). Treatment of this mixture with excess of diimide (generated in situ from potassium azodicarboxylate, >10 equiv)[38] resulted in the selective hydrogenation of methylenecyclohexanes **54a**,**b** to give a mixture of the four saturated sulfides **55a**−**d**. The less reactive endocyclic C═C bond in sulfides **53a**,**b** remained unchanged. Attempts to hydrogenate the cyclohexene-sulfide **53** with additional diimide or by catalytic hydrogenation using PtO_2,[39a] Pd/C, and Rh/Al_2O_3 catalysts failed. Likewise unsuccessful were attempts to hydrogenate sulfide **53** using a homogeneous Wilkinson[39b] and Crabtree[39c] catalyst. The pairs of saturated sulfide-endoperoxides **55a**,**b** with an *equatorially* positioned Me(10) group were separated by MPLC from the pair **55c**,**d** having an *axial* Me(10) group. Diastereomers **55a**,**b** were oxidized with *m*CPBA to give a mixture of sulfone-endoperoxides **56a** and **56b** (Scheme 6), which was separated using semipreparative HPLC. The failure of the above-mentioned catalytic hydrogenations was probably due to the poisoning of the catalysts by the divalent sulfur. To circumvent this obstacle, sulfone-endoperoxides **56a** and **56b** were prepared by the hydrogenolysis of unsaturated sulfones **57** and **58** as described in Scheme 7. Thus, dehydration of the 8-hydroxysulfone **23a** afforded a mixture of unsaturated sulfone-endoperoxides **57a** and **58a**. This mixture of unsaturated endoperoxides was hydrogenated over a PtO_2 catalyst at low temperature (−10 °C), giving chemo- and diastereoselectively a single-saturated sulfone **56a** in excellent yield (Scheme 7.1).[40] Following the same protocol, hydroxysulfone **23b** was converted into saturated sulfone **56b** (Scheme 7.2). Additionally, unsaturated sulfone **57a** was diastereoselectively epoxidized from the less-hindered side of the carbocycle to give the epoxy endoperoxide **59a** as a single diastereomer (Scheme 8). The transformations described in this section indicate that the endoperoxide function in compounds of types **9**−**13** is compatible with a wide range of reaction conditions including strong acids, electrophiles, oxidants, and some reducing agents. However, these peroxides are highly sensitive to strong bases and iron salts.[34] It is noted that working with peroxides requires appropriate safety precautions.[41]

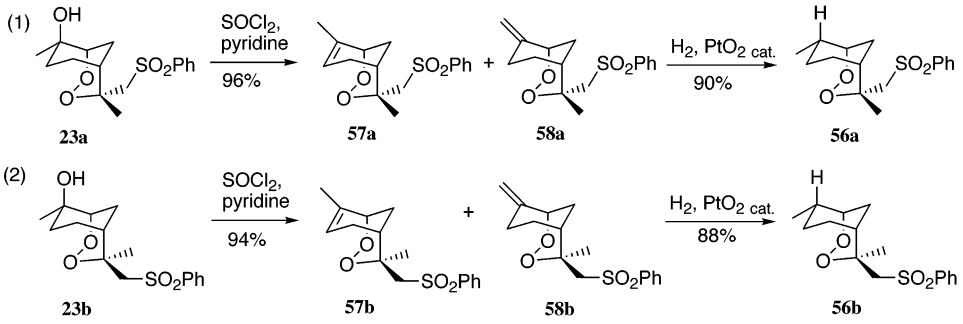
Biology

In Vitro Antimalarial Activity. In vitro antimalarial activity of more than 50 2,3-dioxabicyclo[3.3.1]-nonanes of types **9**−**13** were determined by modification[42] of the methods of Desjardins[43] and Milhous.[44] Tables 2 and 3 summarize the IC_{50} values of these compounds against a chloroquine-sensitive NF54 strain of *P. falciparum* relative to the activity of artemisinin (**1**). At an early stage of the screening, it was observed that the carveol derivatives **27**−**30** (Table 2) possessing substituents X at C(7) are less active than the corresponding C(7)-unfunctionalized analogue **26**, which is readily obtained from *S*-limonene. Therefore, the study was focused on C(7)-unsubstituted endoperoxides deriving from enantiomeric *R*-(+)- and *S*-(−)-limonenes. Assessment of the possible influence of the sulfur-containing appendages Y and Z on antimalarial activity indicated that no difference in antimalarial activity was detected by replacement of the standard phenyl group in **27** with the *n*-Bu substituent as in **28** (Table 2). Also, comparison of the antimalarial activity of *p*-fluorophenyl sulfone **24** with that of the parent phenyl derivative **23** (Table 3) indicates that the frequently beneficial influence of fluorine is rather small in this case. The carbmethoxymethyl derivative **25** is inactive.

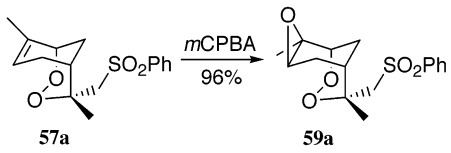
The *β*-sulfonyl-endoperoxides **23** and **26**, themselves in vitro moderately active antimalarial agents, served as intermediates for the preparation of a variety of much more active *β*-sulfonyl-endoperoxides through structural modifications on the C(8) hydroxyl group (Table 3, compounds of the type A). Increasing lipophilicity of a series of antimalarial trioxanes is usually accompanied by enhancement of activity.[45] Such an effect was obtained by acetylation of C(8) hydroxyl in *β*-sulfonyl-endoperoxides **26a** and **26b** to the more liphophilic and active derivatives **45a** and **45b** (Table 2). It is noted that the minor isomeric 8-acetoxy-*β*-sulfonyl-endoperoxides **45c** and **45d** are practically inactive. All the 8-acylated-*β*-sulfonyl-endoperoxides **39**−**42** and **44a** (Table 3) are much less polar than the parent hydroxysulfones **23**, but only half of them are significantly more potent. The moderate activity of peroxides **40a** and **40b** bearing a distal acetoacetate group may be associated with the ability of this function to effectively bind the free iron ions, thus neutralizing the trigger for the activation of endoperoxides.[46,47] In contrast, the relatively polar acetoxysulfoxide **38** showed significant antimalarial activity. This may be due to the ability of its sulfoxide function to ligate metal ions in proximity to the endoperoxide function. One of these sulfoxides, namely **38b″** (IC_{50} = 14 nM), is similar in potency to corresponding sulfones **39a** and **39b** (IC_{50} = 17 nM).

Further increase of lipophilicity was obtained by *O*-benzylation to compounds **46** and **50a**, by *O*-allylation to **51a** and **52a**, as well as by C(8) deoxygenation to *β*-sulfonyl-endoperoxide **56**. All these compounds were found to exhibit in vitro antimalarial activity, close to that of artemisinin (**1**). The most potent of them, namely 8-benzyloxy derivative **46a**, is 140% as active as **1**. The

Scheme 7



Scheme 8



pronounced decrease in antimalarial activity of unsaturated sulfones **57a** and **58a** (Table 3, types B and C), as compared to that of the parent hydroxysulfone **23a**, may derive from the particular chemical properties of the allylic peroxy system. A similar, but more moderate, adverse influence was observed in the case of epoxide **59a**.

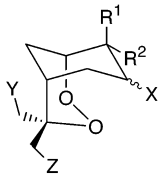
In Vivo Antimalarial Activity. In vitro antimalarial assays have provided reliable guidelines for selecting peroxides for in vivo antimalarial examination.[48] On this basis, the in vitro, highly active 8-acetoxy derivative **39a**, the two 8-benzyloxy C(4) epimers **46a** and **46b**, and the 8-(*p*-methoxybenzyl)oxy derivative **50a** were selected for in vivo biological evaluation. For comparison, the parent 8-hydroxy-endoperoxide **23a** was also tested. All of these five 4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonanes were evaluated in mice against chloroquine-sensitive *P. berghei* N and chloroquine-resistant *P. yoelii* ssp. NS. In Table 4, the data obtained from this screening are compared to those of the peroxidic antimalarial drugs or drug candidates artemisinin (**1**), artemether (**2b**), arteether (**2c**), artelinic acid (**2e**), and arteflene (**8a**), as well as the widely used chloroquine. The parent compound **23a**, bearing a free hydroxyl group and being moderately active in vitro, showed no significant activity in vivo. The acetoxy derivative **39a** is approximately 50% as active as arteflene (**8a**) and 30% as active as artemisinin (**1**) vs *P. berghei* and *P. yoelii*. It is noteworthy that compound **39a** in subcutaneous (SC) administration is ca. two times more active against *P. berghei* than one of the currently leading antimalarial drug candidates, artelinic acid (**2e**).[49] Aralkylated derivatives **46a**, **46b**, and **50a** were found to exhibit potent in vivo activity. When administrated SC, the antimalarial potency of endoperoxides **46a** and **46b** is ca. 200% that of artemisinin (**1**) vs *P. berghei* and 300% vs chloroquine-resistant *P. yoelii*. The most potent representative in this group, namely benzyloxy derivative **46b**, exhibits in vivo activity similar to that of artemether (**2b**) and arteether (**2c**) and 10 times higher activity than artelinic acid (**2e**). The endoperoxide **46b** is also an efficacious antimalarial on oral administration, being comparable to artemisinin (**1**) and arteflene (**8a**).

Toxicology

The remarkable in vivo antimalarial efficacy of β-phenylsulfonyl-endoperoxides **39a**, **46a**,**b**, and **50a** renders them potential drug candidates. Although no significant neuropathology was observed in the studies on arteflene (**8a**),[24,25] other antimalarial peroxides, namely artemisinin (**1**) and its acetal derivatives **2**, were found to be neurotoxic on repeated administration of high doses.[12] This prompted us to submit β-phenylsulfonyl-endoperoxides **46a**,**b** and **39a** to acute, sub-acute, and neural toxicity tests, as well as to preliminary behavioral observations in rodents. Preliminary in vivo acute toxicity studies of the acetoxy derivative **39a** in rodents showed no toxicity at high dosage.[50] Indeed, in a group of six male CD-1 mice dosed with a single dose of 1140 mg/kg of **39a** (solution in sesame oil) using an intraperitoneal (IP) route of treatment, all the animals survived for at least 8 days after administration. Moreover, this single high dose of **39a** produced neither any treatment-related adverse clinical signs nor any dramatic changes in clinical chemistry and hematology. Only a statistically significant decrease in liver weights of mice treated with 285, 570, and 1140 mg/kg was observed, whereas mice treated with 143 mg/kg had normal mean organ weights. Additionally, histopathology studies revealed some renal tubular regeneration, hepatocellular cytomegaly, and increased mitoses, which are considered responses to toxic effects of the compound **39a** administration. For comparison of toxicity, in the reference artemether (**2b**) groups, only 10 and 4 mice (from 18 in each group) survived being treated IP with a single dose of 500 and 1000 mg/kg, respectively. A single dose of 250 mg/kg of **2b** did not cause mice mortality. Nevertheless, even upon this single dosage of **2b**, specific treatment-related adverse clinical signs were noted, including ruffled fur, hypoactivity, and hunched posture.

More detailed toxicity tests were performed on 8-benzyloxy derivatives **46a** and **46b** in a mouse model (see Experimental Section). At the first stage of the study, four groups of mice ($\geq$4 mice in each group) were treated intramuscularly (IM) with a single dose of the test articles **46a**,**b**, arteether (**2c**) as a reference, and sesame oil as a vehicle. Solutions (5%) or suspensions of the test articles **46a**,**b** and reference **2c** in sesame oil were used for injections. The test compounds **46a**,**b** and the reference **2c** were injected into one or more sites of the musculature of the rear limb assembly so that the volume injected per site did not exceed 0.05 mL. The doses varied from 85 to about 400 mg/kg. After 14 days, all the mice (from the four groups) treated with 380 $\pm$

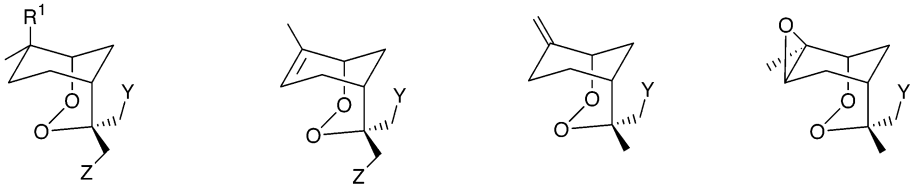
Table 2. In Vitro Antimalarial Activity of (1*S*,5*S*)-4-(*R*-Sulfonyl)methyl-2,3-dioxabicyclo[3.3.1]nonanes Against Chloroquine-Sensitive NF54 Strain of *P. falciparum*



compd	Y	Z	R^1	R^2	X	IC_{50} (nM) [a]
26a	$PhSO_2$	H	OH	Me	H	120
26b	H	$PhSO_2$	OH	Me	H	95
27a	$PhSO_2$	H	OH	Me	*β*-OBz	170
27b	H	$PhSO_2$	OH	Me	*β*-OBz	>2500
28a	*n*-$BuSO_2$	H	OH	Me	*β*-OBz	100−500
28b	H	*n*-$BuSO_2$	OH	Me	*β*-OBz	500−2500
29a	$PhSO_2$	H	OH	Me	α-OBz	815
29b	H	$PhSO_2$	OH	Me	α-OBz	500−2500
30a	$PhSO_2$	H	OH	Me	α-OH	>2500
45a	$PhSO_2$	H	OAc	Me	H	20
45b	H	$PhSO_2$	OAc	Me	H	18
45c[b]	$PhSO_2$	H	Me	OAc	H	270
45d[b]	H	$PhSO_2$	Me	OAc	H	220
Artemisinin**(1)**	8.7 ± 0.7					

[a] Antimalarial activity was determined as described in ref 42. The standard deviation for each set of quadruplicates was an average of 8% (≤38%) of the mean. R^2 values for the fitted curves were ≥0.985. Artemisinin **(1)** activity is mean ± standard deviation of concurrent control (n = 13). [b] Ca. 93% pure.

Table 3. In Vitro Antimalarial Activity of (1*R*,5*R*)-4-(*R*-Sulfenyl)methyl-, (*R*-Sulfinyl)methyl-, and (*R*-Sulfonyl)methyl-2,3-dioxabicyclo[3.3.1]nonanes Against Chloroquine-Sensitive *P. falciparum* (NF 54)



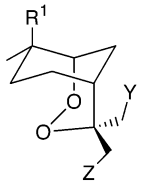
compd	type	Y	Z	R^1	IC_{50} (nM) [a]	compd	type	Y	Z	R^1	IC_{50} (nM)[a]
22a	A	TrS	H	OH	150	**40a**	A	$PhSO_2$	H	$O_2CCH_2C(O)Me$	46[b]
22b	A	H	TrS	OH	72	**40b**	A	H	$PhSO_2$	$O_2CCH_2C(O)Me$	73[b]
23a	A	$PhSO_2$	H	OH	55[b]	**41a**	A	$PhSO_2$	H	O_2CCO_2Et	170[b]
23b	A	H	$PhSO_2$	OH	89[b]	**41b**	A	H	$PhSO_2$	O_2CCO_2Et	140[b]
24a	A	4-$FC_6H_4SO_2$	H	OH	49	**42a**	A	$PhSO_2$	H	$O_2CCONBn_2$	21[b]
24b	A	H	4-$FC_6H_4SO_2$	OH	52	**42b**	A	H	$PhSO_2$	$O_2CCONBn_2$	81[b]
25a	A	$MeO_2CCH_2SO_2$	H	OH	>2500	**44a**	A	$PhSO_2$	H	O_2CCH_2OPh	37
25b	A	H	$MeO_2CCH_2SO_2$	OH	>2500	**46a**	A	$PhSO_2$	H	OBn	6.5
37a″	A	PhSO	H	OH	150	**46b**	A	H	$PhSO_2$	OBn	9.4
37b′	A	H	PhSO	OH	820	**50a**	A	$PhSO_2$	H	$OCH_2C_6H_4OMe$-4	14[b]
38a′	A	PhSO	H	OAc	62	**51a**	A	$PhSO_2$	H	$OCH_2CH{=}CMe_2$	35
38a″	A	PhSO	H	OAc	54	**52a**	A	$PhSO_2$	H	$OCH_2CH{=}CHPh$-*E*	32
38b′	A	H	PhSO	OAc	40	**56a**	A	$PhSO_2$	H	H	17
38b″	A	H	PhSO	OAc	14	**56b**	A	H	$PhSO_2$	H	24
39a	A	$PhSO_2$	H	OAc	17[b]	**53a**	B	PhS	H		940
39b	A	H	$PhSO_2$	OAc	17[b]	**57a**	B	$PhSO_2$	H		360
Artemisinin(**1**)					8.9 ± 1.6	**58a**[c]	C	$PhSO_2$	H		<3220
Arteflene(**8a**)					71	**59a**	D	$PhSO_2$	H		92

[a] Antimalarial activity was determined as reported in ref 42. The standard deviation for each set of quadruplicates was an average of 10% (≤53%) of the mean. R^2 values for the fitted curves were ≥0.975. Artemisinin **(1)** activity is mean ± standard deviation of concurrent control (n = 36). [b] Data reported in ref 30. [c] A mixture containing 80% of **58a** and 20% of **57a**.

20 mg/kg of the test compounds **46a**,**b** or with 360 ± 10 mg/kg of the reference **2c** (two animals) demonstrated 100% survival and normal expected body weight gain. No gross pathological or behavioral findings were noted in any of the treated animals.

In the next stage of the trial, the 7-day repeated IM toxicity test in mice (five animals in each group) was performed (see Experimental Section). The test articles **46a** and **46b** were administered IM daily in two different doses (50 and 200 mg/kg/day). In the reference group, the reference **2c** was administered at the lower dose (50 mg/kg/day), whereas in the control group, only the vehicle sesame oil was injected. No animal mortality occurred prior to the scheduled sacrifice at the 9th day. Body weight determined on days 1, 5, and 8 failed to reveal any significant differences between treated and concurrent reference and control groups. Clinical signs examined daily throughout the study period did not

Table 4. In Vivo Antimalarial Activity of (*1R,5R,8R*)-4-Phenylsulfonyl-2,3-dioxabicyclo[3.3.1]nonane Against Chloroquine-Sensitive *Plasmodium berghei* N and Chloroquine-Resistant *Plasmodium yoelii* ssp. NS in mg/kg/day × 4[a]



				P. berghei N		*P. yoelii* ssp. NS	
compd	Y	Z	R^1	ED_{50}	ED_{90}	ED_{50}	ED_{90}
23a	$PhSO_2$	H	OH	>30	>30	inactive at 30	
39a	$PhSO_2$	H	OAc	3.7	7.3	12.5	28.0
46a	$PhSO_2$	H	OBn	0.8 (10.5)	1.7 (115)	1.3	3.8
46b	H	$PhSO_2$	OBn	0.43 (4.2)	1.3 (23.5)	1.0	3.1
50a	$PhSO_2$	H	OPMB	1.3	2.3	4.8	8.3
Artemisinin **(1)**[b]				0.95 (5.0)	2.5 (14.0)	5.8[c]	10.0[c]
Artemether **(2b)**[b]				0.5 (3.1)	1.1 (5.0)		
Arteether **(2c)**				0.9	1.4		
Artelinic acid **(2e)**				6.6	14.0		
Arteflene **(8a)**[b]				2.7 (10.4)	3.9 (18.0)		
Chloroquine (base)[b]				1.0 (1.9)	1.2 (2.3)	2.4[c]	56.0[c]

[a] Substances were administered to mice subcutaneously. Data in brackets correspond to oral administration. Protocols of these tests were previously described in ref 17a. [b] These data were taken from ref 24. [c] The values were taken from ref 18b.

reveal any abnormalities in any of the groups. The only gross abnormality evident at sacrifice was an enlargement of the spleen observed in all animals of the reference **2c** group, high-dose **46b** test group, and in three of five animals in the **46a** high-dose group. Microscopic examination showed no toxicity-related lesions in any of the examined organs. On the basis of the reported information indicating a loss of neurons and gliosis in rats treated with the 25 mg/kg/day of arteether (**2c**),[12] particular attention was paid to any potential treatment-related lesions in the brain section of the cerebellum, the medulla oblongata nuclei, such as the neuron of the trapezoid body. The microscopically described enlarged spleens were found to consist of a mild degree of extramedullary hematopoesis, but at this stage of the study it was not possible to conclude that splenomegaly is a treatment-related effect. Examination of hematology and clinical chemistry parameters at study termination did not reveal any differences among test and control groups of animals.

Thus, on the basis of the experimental results, the 7-day, daily-repeated IM treatment of mice with 50 and 200 mg/kg of 8-benzyloxy-endoperoxides **46a** and **46b** was well tolerated without any evidence of toxic effects.

Conclusion

As shown in Tables 2 and 3, there are minor differences in the in vitro activity between 2,3-dioxabicyclo-[3.3.1]nonanes of the **a** series and those of the **b** series. These differences are not significant, particularly in view of the fact that the relative activities can be inverted in the in vivo test, as in the case of the β-sulfonyl-endoperoxides **46a** and **46b**. Also, there are no significant differences in potency between the acetoxy-sulfone **45** (Table 2) and its enantiomer **39** (Table 3). Noteworthy exceptions are the enantiomeric hydroxy-sulfones **23a** and **26a**. Similar slight variations in the antimalarial potency were reported for enantiomeric fenozanes (**4**) derivatives.[18b]

More than 50 compounds of types **9**−**13** were screened in vitro. Ten of the β-sulfonyl-endoperoxides of types **12** and **13** and one β-sulfinyl-endoperoxides of type **11** have IC_{50} values lower than 25 nM against *P. falciparum* (NF 54). Upon subcutaneous administration, four β-sulfonyl-endoperoxides, namely **46a**, **46b**, **50a**, and **39a** are highly active in vivo antimalarials against *P. yoelii* and *P. berghei* strains of malaria parasites. Relative to artemisinin (**1**), the most potent compounds **46a** and **46b** are about two times more efficacious against chloroquine-sensitive *P. berghei* and 3−5 times more efficacious against chloroquine-resistant *P. yoelii*. Thus, the potency of the endoperoxides **46a** and **46b** is comparable to those of some of the best currently used antimalarial drugs, including artemether (**2b**) and arteether (**2c**). The benzyloxy derivative **46b** exhibits also a reasonable oral antimalarial efficacy. β-Sulfonyl-endoperoxides **46a** and **46b** were found to be nontoxic and easily tolerable at high doses. Considering also the ready accessibility by chemical synthesis (three to four steps) from inexpensive starting materials, as well as their high chemical stability (compounds **39** and **46** are stable for at least 2 years at 4 °C), β-sulfonyl-endoperoxides **39a**, **46a**, and **46b** constitute promising antimalarial drug candidates.

Experimental Section

Chemistry. General.[28] The compounds **19**−**30** and **45** were synthesized and purified as described earlier.[28] Arteether (**2c**) was prepared according to the reported procedure[51] and thoroughly purified using 3-times-repeated, low-temperature (−20 °C) recrystallization from hexane shortly before testing. Unless otherwise stated, the purity of all the in vitro-tested compounds was judged to be ≥95% by 400 MHz ^{1}H NMR and analytical HPLC determination. The purity of the in vivo-tested compounds was ≥97% according to the same criteria.

Direct Acetylation of Hydroxysulfides 19a,b. To a solution of sulfides **19a**,**b** (1.15 g, 3.91 mmol, a/b ca. 55:45), pyridine (1.54 g, 19.5 mmol), and DMAP (49 mg, 0.4 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added a solution of AcCl (1.22 g, 15.6 mmol) in CH_2Cl_2 (5 mL). After stirring for 12 h at rt, the reaction mixture was poured into water (100 mL), extracted with hexanes−EtOAc (7:3, 3 × 100 mL), dried (Na_2SO_4 + $NaHCO_3$), and evaporated. The residue was subjected to flash chromatography (FC) on silica gel (gradient elution, hexanes−EtOAc, from 9:1 to 7:3) to recover the unreacted hydroxysulfides **19a**,**b** (292 mg, 0.99 mmol, 25.5%) and to give

a mixture of diastereomeric acetoxy derivatives **31a**,**b** (518 mg, 1.54 mmol, 53% yield, **a**/**b** ca. 55:45) and a mixture of diastereomeric acetoacetates **32a**,**b** (152 mg, 13%, **a**/**b** ca. 54:46).

Acetylation of Hydroxysulfides 19a,b via TMS Derivatives 33a,b. (a) To a cold (5 °C) solution of hydroxysulfides **19a**,**b** (305 mg, 1.04 mmol) and 2,6-lutidine (277 mg, 2.60 mmol) in dry CH_2Cl_2 (5 mL) was added neat TfOTMS (491 mg, 2.08 mmol). The reaction mixture was stirred at 5 °C for 40 min, poured into a cold water (50 mL), extracted with EtOAc−hexane (1:4, 2 × 50 mL), washed with cold saturated $NaHCO_3$ (25 mL) and brine (25 mL), and dried over Na_2SO_4. Evaporation, followed by vacuumization overnight at 0.3 mmHg, afforded the crude TMS derivatives **33a**,**b** (377 mg, quantitative yield) as colorless mobile oil, which was used in the next steps without further purification.

(b) A mixture of crude TMS derivatives **33a**,**b** (377 mg) was treated with a freshly distilled AcCl (2.5 mL). The mixture was stirred for 50 h at rt and evaporated. The residue was dissolved in EtOAc−hexane (1:4, 80 mL), washed with water (2 × 20 mL), and dried over Na_2SO_4. Evaporation, followed by FC (10% of EtOAc in hexane), afforded the acetoxysulfides **31a**,**b** (323 mg, 93% in two steps from **19a**,**b**).

(1*R*,4*R*/*S*,5*R*,8*R*)-8-Acetoxy-4,8-dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonane (31a,b): a colorless mobile oil, $R_f = 0.67$ (30% of EtOAc in hexane); IR (neat): 2935, 1732, 1453, 1371, 1254, 1223, 1204, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (br s, **a**), 1.56 (br s, Me(11), **b**), total 3H; 1.65 (s, **b**), 1.66 (s, Me(10), **a**), total 3H; 1.67−1.89 (m, 3H); 1.74 (m, **b**), 1.90 (br dddd, $J = 6.6, 6.6, 3.3, 3.3$ Hz, H(5), **a**), total 1H; 2.00 (s, 3H, *Me*C(O)); 2.07 (br ddd, $J = 14.1, 6.6, 3.4$ Hz, **a**), 2.27 (m, H(9)*eq*, **b**), total 1H; 2.12−2.20 (m, 1H, H(7)*eq*); 2.25 (ddd, $J = 15.0, 13.2, 6.0$ Hz, **b**), 2.28 (ddd, $J = 14.3, 13.3, 6.0$ Hz, H(7)*ax*, **a**), total 1H; 2.95 (d) and 3.02 (dd, $J = 0.4$ Hz) (AB quartet, $J = 12.0$ Hz, HH′(12), **b**), 3.30 (d, $J = 12.8$ Hz, H(12), a), 3.72 (dd, $J = 12.8, 0.5$ Hz, H′(12), **a**), total 2H; 4.40 (br dd, $J = 3.4, 1.0$ Hz, **a**), 4.44 (br dd, $J = 3.4, 0.8$ Hz, H(1), **b**), total 1H; 7.17−7.23 (m, 1H), 7.29 (m, 2H), 7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.03 (Me(11)), 22.42 (Me(10)), 22.55 (*Me*C(O)), 23.50 (CH_2), 23.97 (CH_2), 28.52 (C(5)H), 32.88 (CH_2), 40.71 (C(12)H_2), 77.46 (C(1)H), 82.76 (C), 83.85 (C), 126.24 (CH), 128.91 (2CH), 129.76 (2CH), 136.73 (C), 170.13 (C=O) (isomer **31a**); 21.77 (Me(11)), 22.53 (Me(10)), 22.55 (*Me*C(O)), 23.22 (CH_2), 24.09 (CH_2), 29.89 (C(5)H), 33.20 (CH_2), 40.81 (C(12)H_2), 77.91 (C(1)H), 82.67 (C), 83.73 (C), 126.43 (CH), 128.96 (2CH), 129.73 (2CH), 136.29 (C), 170.13 (C=O) (isomer **31b**).

(1*R*,4*R*/*S*,5*R*,8*R*)-8-Acetylacetoxy-4,8-dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonane (32a,b): a colorless oil, $R_f = 0.40$ (hexanes−EtOAc, 7:3); ^1H NMR (400 MHz, $CDCl_3$) (keto−enol ca. 91:9): δ 1.23 (br s, **a**), 1.55 (br s, Me(11), **b**), total 3H; 1.68 (s, **b**), 1.69 (s, Me(10), **a**), total 3H; 1.70−1.93 (m, 4H); 2.08 (br ddd, $J = 14.0, 6.5, 3.5$ Hz, H(9)*eq*, **a**), 2.15−2.33 (m), total 3H; 2.25 (s, **a**), 2.26 (s, *Me*C(O)CH_2, **b**), total 3H; 2.95 and 3.00 (AB quartet, $J = 12.6$ Hz, HH′(12), **b**), 3.31 (d, $J = 12.8$ Hz, H(12), **a**), 3.69 (br d, $J = 12.8$ Hz, H′(12), **a**), total 2H; 3.40 (s, **a**), 3.41 (s, MeC(O)CH_2, **b**), total 2H; 4.37 (br d, $J = 3.5$ Hz, **a**−keto), 4.41 (br d, $J = 3.6$ Hz, **b**−keto), 4.45 (br d, $J = 3.5$ Hz, **a**−enol), 4.49 (br d, $J = 3.5$ Hz, H(1), **b**−enol), total 1H; 4.92 (br s, **a**), 4.94 (br s, CH=, **b**−enol), total ca. 0.09 H; 7.26−7.42 (m, 5H); 12.05 (br s, ca. 0.09 H, HO−enol); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.89 (Me(11)), 22.48 (Me(10)), 23.28 (CH_2), 23.74 (CH_2), 28.43 (C(5)H), 30.15 (*Me*C(O)), 32.67 (CH_2), 40.59 (C(12)H_2), 51.18 (MeC(O)-CH_2), 77.30 (C(1)H), 83.76 (C), 84.25 (C), 90.60 (HC=, enol), 126.16 (CH), 128.83 (2CH), 129.65 (2CH), 136.62 (C), 165.83 (OC=O), 200.57 (C=O) (isomer **32a**); 21.64 (Me(11)), 22.49 (Me(10)), 22.98 (CH_2), 23.85 (CH_2), 29.74 (C(5)H), 30.15 (*Me*C(O)), 33.02 (CH_2), 40.75 (C(12)H_2), 77.72 (C(1)H), 83.82 (C), 84.17 (C), 90.60 (HC=, enol), 126.37 (CH), 128.88 (2CH), 129.68 (2CH), 136.18 (C), 165.84 (OC=O), 200.57 (C=O) (isomer **32b**).

(1*R*,4*R*/*S*,5*R*,8*R*)-4,8-Dimethyl-4-phenylsulfenylmethyl-8-trimethylsilyloxy-2,3-dioxabicyclo[3.3.1]nonanes (33a,b): a mobile pale yellow oil, $R_f = 0.55$ (5% of EtOAc in hexane); IR (neat): 2954, 2928, 1453, 1446, 1372, 1250, 1125, 1060, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.108 and 0.111 (2 × s, Me_3Si), total 9H; 1.22 (br s, **a**), 1.53 (d, $J = 0.5$ Hz, Me-(11), **b**), total 3H; 1.38 (s, **b**), 1.39 (s, Me(10), **a**), total 3H; 1.58−1.65 (m, 1H, H(7)*eq*), 1.67−1.82 (m, 3H), 1.84 (br dddd, $J = 6.0, 6.0, 3.0, 3.0$ Hz, H(5), **a**), 1.97−1.99 (m, 1H); 2.06 (ddd, $J = 13.0, 3.0, 2.5$ Hz, H(9)*ax*, **a**), 2.13−2.25 (m), total 2H; 2.94 (d) and 3.02 (dd, $J = 0.5$ Hz) (AB quartet, $J = 12.0$ Hz, HH′-(12), **b**), 3.32 (d, $J = 12.7$ Hz, H(12), **a**), 3.68 (dd, $J = 12.7, 0.6$ Hz, H′(12), **a**), total 2H; 3.59 (br dd, $J = 2.5, 2.5$ Hz, **a**), 3.63 (m, H(1), **b**), total 1H; 7.26−7.42 (m, 5H).

Oxalylation of Hydroxysulfides 19a,b via TMS Derivatives 33a,b. (1) (a) A mixture of TMS derivatives **33a**,**b** (193 mg, ca. 0.52 mmol), prepared from hydroxysulfides **19a**,**b** (153 mg, 0.52 mmol) as described above, was treated with a freshly distilled oxalyl chloride (3 mL). The mixture was stirred at rt for 18 h and evaporated and vacuumized at 0.2 mmHg for 3 h to yield the crude chloride **34a**,**b** (205 mg, **a**/**b** ca. 56:44), which was used in the next steps without additional purification.

(b) To a solution of chloride **34a**,**b** in dry CH_2Cl_2 (3 mL) at 0 °C was added a solution of dry EtOH (79 mg, 1.7 mmol) and 2,6-lutidine (214 mg, 2.0 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at 4 °C overnight and poured into cold water (50 mL), extracted with EtOAc−hexane (1:4, 2 × 50 mL), dried (Na_2SO_4), and evaporated. FC (hexanes−EtOAc, 85:15) of the residue gave the esters **35a**,**b** (140 mg, 68% in three steps from **19a**,**b**; **a**/**b** ca. 57:43).

(2) To a solution of chloride **34a**,**b**, prepared from hydroxysulfide **19a**,**b** (112 mg, 0.38 mmol) as described above, in CH_2Cl_2 (3 mL) at 0 °C was added a solution of dibenzylamine (156 mg, 0.8 mmol) and 2,6-lutidine (160 mg, 1.5 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at 0°C for 8 h and poured into cold water (50 mL). Extraction with hexanes−EtOAc (3:1, 2 × 50 mL), washing with saturated $KHSO_4$ (15 mL) and $NaHCO_3$ (15 mL), drying over Na_2SO_4, and evaporation followed by FC (hexanes−EtOAc, 85:15) gave the amides **36a**,**b** (**a**/**b** ca. 59:41) (160 mg, 77% in three steps from **19a**,**b**; **a**/**b** ca. 59:41).

(1*R*,4*R*/*S*,5*R*,8*R*)-8-Chlorooxalyloxy-4,8-dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo [3.3.1]nonane (34a,b): a pale brown immobile oil; IR (neat): 2965, 2937, 1796, 1754, 1481, 1452, 1441, 1376, 1275, 1224, 1118, 1053, 1015 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.26 (br s, **a**), 1.58 (br s, Me-(11), **b**), total 3H; 1.78 (s, **b**), 1.79 (s, Me(10), **a**), total 3H; 1.68−2.02 (m, 4H); 2.15 (br ddd, $J = 13.8, 6.6, 3.4$ Hz, H(9)*eq*, **a**), 2.30−2.44 (m), total 3H; 2.965 and 3.02 (br) (AB quartet, $J = 12.1$ Hz, HH′(12), **b**), 3.33 (d, $J = 13.0$ Hz, H(12), **a**), 3.70 (dd, $J = 13.0, 0.5$ Hz, H′(12), **a**), total 2H; 4.28 (br dd, $J = 3.4, 1.0$ Hz, **a**), 4.44 (br dd, $J = 3.4, 1.0$ Hz, H(1), **b**), total 1H; 7.18−7.45 (m, 5H).

(1*R*,4*R*/*S*,5*R*,8*R*)-4,8-Dimethyl-8-ethoxyoxalyloxy-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonane (35a,b): a pale yellow oil, $R_f = 0.41$ (hexanes−EtOAc, 4:1); IR (neat): 2984, 2938, 1765, 1742, 1451, 1441, 1374, 1320, 1185, 1090, 1053, 1013 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.26 (br s, **a**), 1.57 (br s, Me(11), **b**), total 3H; 1.373 and 1.378 (2 × t, 3H, $J = 7.1$ Hz, *Me*CH_2O); 1.75 (s, **b**), 1.76 (s, Me(10), a), total 3H; 1.68−1.96 (m, 4H); 2.11 (br ddd, $J = 13.6, 6.4, 3.4$ Hz, H(9)*eq*, **a**), 2.27−2.39 (m), total 3H; 2.96 and 3.02 (br) (AB quartet, $J = 12.1$ Hz, HH′(12), **b**), 3.32 (d, $J = 12.9$ Hz, H(12), **a**), 3.71 (br d, $J = 12.9$ Hz, H′(12), **a**), total 2H; 4.325 and 4.331 (2 × q, 2H, $J = 7.1$ Hz, MeCH_2O); 4.34 (m, **a**), 4.38 (m, H(1), **b**), total 1H; 7.17−7.44 (m, 5H).

(1*R*,4*R*/*S*,5*R*,8*R*)-8-Dibenzylaminooxalyloxy-4,8-dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonane (36a,b): a colorless immobile oil, $R_f = 0.38$ (hexanes−EtOAc, 4:1); IR (neat): 2988, 2936, 1728, 1661, 1452, 1440, 1374, 1287, 1265, 1170, 1081, 1053, 1014 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.24 (br s, **a**), 1.57 (br s, Me(11), **b**), total 3H; 1.62−1.90 (m, 4H), 1.71 (br s, 3H, Me(10)); 2.06 (br ddd, $J = 13.4, 6.2, 3.4$ Hz, H(9)*eq*, **a**), 2.18−2.42 (m), total 3H; 2.95 and 3.00 (br) (AB quartet, $J = 12.1$ Hz, HH′(12), **b**), 3.32 (d, $J = 13.0$ Hz, H(12), **a**), 3.68 (br d, $J = 13.0$ Hz, H′(12), **a**), total

2H; 4.33 (br d, J = 3.4 Hz, **a**), 4.39 (m, H(1), **b**), total 1H; 4.38 (br s, 2H) and 4.52 (br s, 2H, PhCH_2N), 7.22−7.41 (m, 15H).

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols (37a′, 37a″) and (1*R*,4*S*,-5*R*,8*R*)-4,8-Dimethyl-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols (37b′, 37b″). To a solution of sulfides **19a**,**b** (468 mg, 1.59 mmol, ratio **a**/**b** ca. 55:45) in EtOAc (25 mL) at −50 °C was added a solution of *m*CPBA (478 mg of ca. 60%, ca. 1.65 mmol) in EtOAc (20 mL). The mixture was stirred at −30 °C for 1 h (TLC monitoring), poured into saturated $NaHCO_3$ (75 mL), extracted with EtOAc (3 × 60 mL), dried (Na_2SO_4 + $NaHCO_3$), and evaporated. The residue was purified by FC (hexanes−EtOAc, 1:4) to give the diastereomeric sulfoxides **37a**′,**a**″,**b**′,**b**″ (438 mg, total yield 89%, ratio **a**′/**a**″/**b**′/**b**″ ca. 21:32:20: 27). The individual diastereomers of the sulfoxides **37** were isolated by sequential medium-pressure liquid chromatography (MPLC) on silica gel (hexanes−EtOAc, 22:78).

The isomer 37a′: a colorless solid, mp 131−133 °C dec; R_f = 0.35 (hexanes−EtOAc, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 3H, Me(10)), 1.45 (br s, 3H, Me(11)), 1.63 (br dd, 1H, J = 13.8, 5.3 Hz, H(7*eq*), 1.65 (br s, 1H, OH), 1.88−2.02 (m, 2H), 2.16−2.21 (m, 3H), 2.39 (ddd, 1H, J = 13.8, 13.8, 6.9 Hz, H(7*ax*), 3.12 (d, 1H, J = 13.9 Hz, H(12)), 3.59 (br d, 1H, J = 13.9 Hz, H′(12)), 3.73 (br s, 1H, H(1)), 7.48−7.57 (m, 3H), 7.65−7.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.53 (Me(11)), 23.60 (C(6)H_2), 24.47 (C(9)H_2), 28.11 (Me(10)), 29.88 (C(5)H), 35.75 (C(7)H_2), 64.87 (C(12)H_2), 71.43 (C(8)), 81.89 (C(1)H), 82.53 (C(4)), 123.83 (2CH), 129.42 (2CH), 131.13 (CH), 144.76 (C).

The most polar isomer 37a″: a colorless solid, mp 153−155 °C; R_f = 0.32 (hexanes−EtOAc, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H, Me(10)), 1.55 (br s, 3H, Me(11)), 1.63 (br dd, 1H, J = 14.0, 5.6 Hz, H(7*eq*), 1.83 (br dddd, 1H, J = 6.4, 6.4, 3.0, 3.0 Hz, H(5)), 1.86 (dddd, 1H, J = 14.0, 14.0, 5.9, 3.4 Hz, H(6*ax*), 1.91−1.99 (m, 1H, H(6*eq*), 2.06 (ddd, 1H, J = 13.8, 3.0, 2.0 Hz, H(9*ax*), 2.18 (ddd, 1H, J = 13.8, 6.4, 3.6 Hz, H(9*eq*), 2.37 (br ddd, 1H, J = 14.0, 14.0, 6.5 Hz, H(7*ax*), 3.31 and 3.35 (AB quartet, 2H, J = 14.0 Hz, HH′(12)), 3.70 (m, 1H, H(1)), 7.47−7.56 (m, 3H), 7.64−7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.08 (Me(11)), 23.47 (C(6)H_2), 24.37 (C(9)H_2), 28.06 (Me(10)), 31.56 (C(5)H), 35.77 (C(7)H_2), 66.08 (C(12)H_2), 71.42 (C(8)), 81.94 (C(1)H), 82.25 (C(4)), 123.83 (2CH), 129.32 (2CH), 130.87 (CH), 144.91 (C).

The least polar isomer 37b′: a white foam; R_f = 0.38 (hexanes−EtOAc, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 3H, Me(10)), 1.62 (br dd, 1H, J = 13.9, 5.8 Hz, H(7*eq*), 1.78−1.85 (m, 1H, H(6*eq*), 1.79 (br s, 3H, Me(11)), 1.96 (dddd, 1H, J = 13.9, 13.9, 6.0, 3.5 Hz, H(6*ax*), 2.00 (br dddd, 1H, J = 6.4, 6.4, 3.0, 3.0 Hz, H(5)), 2.13 (ddd, 1H, J = 13.5, 3.0, 2.0 Hz, H(9*ax*), 2.29 (br ddd, 1H, J = 13.9, 13.9, 6.2 Hz, H(7*ax*), 2.35 (ddd, 1H, J = 13.5, 6.4, 3.6 Hz, H(9*eq*), 2.77 (dd, 1H, J = 13.5. 0.6 Hz, H(12)), 2.91 (br d, 1H, J = 13.5 Hz, H′(12)), 3.73 (m, 1H, H(1)), 7.50−7.56 (m, 3H), 7.63−7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.93 (Me(11)), 23.70 (C(6)H_2), 24.00 (C(9)H_2), 28.04 (Me(10)), 31.21 (C(5)H), 35.47 (C(7)H_2), 65.57 (C(12)H_2), 71.32 (C(8)), 82.20 (C(1)H), 82.61 (C(4)), 123.77 (2CH), 129.49 (2CH), 131.34 (CH), 144.73 (C).

The isomer 37b″: a colorless solid, mp 138−140 °C dec; R_f = 0.34 (hexanes−EtOAc, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H, Me(10)), 1.55 (br dd, 1H, J = 14.0, 5.7 Hz, H(7)-*eq*), 1.83 (br dddd, 1H, J = 14.2, 14.2, 5.8, 3.4 Hz, H(6*ax*), 1.85−1.98 (m, 3H), 1.87 (br s, 3H, Me(11)), 2.06 (ddd, 1H, J = 13.5, 3.0, 1.9 Hz, H(9*ax*), 2.15 (br ddd, 1H, J = 14.2, 14.0, 6.2 Hz H(7*ax*), 2.32 (ddd, 1H, J = 13.5, 6.8, 3.3 Hz, H(9*eq*), 2.70 (br d, 1H, J = 13.7 Hz, H(12)), 3.09 (br d, 1H, J = 13.7 Hz, H′(12)), 3.73 (m, 1H, H(1)), 7.47−7.55 (m, 3H), 7.63−7.66 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.97 (Me(11)), 23.48 (C(6)-H_2), 23.94 (C(9)H_2), 28.04 (Me(10)), 32.16 (C(5)H), 35.46 (C(7)-H_2), 65.93 (C(12)H_2), 71.37 (C(8)), 82.35 (C(1)H), 82.73 (C(4)), 123.82 (2CH), 129.39 (2CH), 131.12 (CH), 144.84 (C).

(1*R*,4*R*,5*R*,8*R*)-8-Acetoxy-4,8-dimethyl-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]nonanes (38a′, 38a″) and (1*R*,4*S*,5*R*,8*R*)-8-Acetoxy-4,8-dimethyl-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]nonanes (38b′,b″). A mixture of title diastereomeric sulfoxides **38** (total 364 mg, 1.02 mmol, 91%) was prepared by oxidation of sulfides **31a**,**b** (376 mg, 1.12 mmol) according to the procedure described above and completely separated by MPLC (hexanes−EtOAc, 1:1).

The isomer 38a′ (78 mg, 0.221 mmol)**:** a colorless oil, R_f = 0.40 (hexanes−EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (br s, 3H, Me(11)), 1.65 (s, 3H, Me(10)), 1.86 (br dddd, 1H, J = 14.0, 14.0, 6.0, 3.5 Hz, H(6*ax*), 1.94−2.00 (m, 1H, H(6*eq*), 1.96 (ddd, 1H, J = 14.0, 4.0, 1.7 Hz, H(9*ax*), 2.01 (s, 3H, MeC-(O)), 2.18−2.25 (m, 3H), 2.31 (ddd, 1H, J = 14.0, 14.0, 6.0 Hz, H(7*ax*), 3.08 (d, 1H, J = 13.8 Hz, H(12)), 3.61 (dd, 1H, J = 13.8, 0.6 Hz, H′(12)), 4.52 (m, 1H, H(1)), 7.50−7.58 (m, 3H), 7.65−7.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.36 (*Me*C-(O)), 22.43 (Me(10)), 23.36 (C(6)H_2), 23.55 (Me(11)), 24.16 (C(9)-H_2), 29.09 (C(5)H), 32.98 (C(7)H_2), 64.54 (C(12)H_2), 77.58 (C(1)H), 82.37 (C(4)), 82.53 (C(8)), 123.65 (2CH), 129.35 (2CH), 131.10 (CH), 144.38 (C), 170.10 (C═O).

The most polar isomer 38a″ (122 mg, 0.346 mmol)**:** a colorless solid, mp 98−100 °C; R_f = 0.29 (hexanes−EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (br s, 3H, Me(11)), 1.68 (s, 3H, Me(10)), 1.78 (br dddd, 1H, J = 14.0, 14.0, 6.0, 3.2 Hz, H(6*ax*), 1.80−1.88 (m, 2H), 1.92−1.98 (m, 1H, H(6*eq*), 2.01 (s, 3H, *Me*C(O)), 2.17−2.24 (m, 1H, H(9*eq*), 2.20 (br dd, 1H, J = 14.8, 6.2 Hz, H(7*eq*), 2.30 (ddd, 1H, J = 14.8, 14.0, 5.9 Hz, H(7*ax*), 3.31 and 3.36 (AB quartet, 2H, J = 14.0 Hz, HH′-(12)), 4.47 (br d, 1H, J = 3.6 Hz, H(1)), 7.48−7.57 (m, 3H), 7.66−7.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.23 (Me-(11)), 22.48 (*Me*C(O)), 22.53 (Me(10)), 23.42 (C(6)H_2), 24.17 (C(9)H_2), 30.90 (C(5)H), 33.20 (C(7)H_2), 66.04 (C(12)H_2), 77.75 (C(1)H), 82.25 (C(4)), 82.67 (C(8)), 123.82 (2CH), 129.35 (2CH), 130.92 (CH), 144.86 (C), 170.22 (C═O).

The least polar isomer 38b′ (68 mg, 0.193 mmol)**:** a colorless solid, mp 116−118 °C; R_f = 0.41 (hexanes−EtOAc, 1:1); IR (neat): 2980, 2929, 1734, 1445, 1372, 1257, 1232, 1186, 1153, 1086, 1056, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (s, 3H, Me(10)), 1.80 (d, 3H, J = 0.6 Hz, Me(11)), 1.82−1.89 (m, 2H), 1.89 (ddd, 1H, J = 13.6, 3.2, 1.8 Hz, H(9*ax*), 2.02 (br dddd, 1H, J = 6.0, 6.0, 3.2, 3.2 Hz, H(5)), 2.03 (s, 3H, *Me*C(O)), 2.18−2.29 (m, 2H), 2.39 (br ddd, 1H, J = 13.6, 6.0, 3.8 Hz, H(9*eq*), 2.77 (dd, 1H, J = 13.4, 0.6 Hz, H(12)), 2.92 (br d, 1H, J = 13.4 Hz, H′(12)), 4.47 (br dd, 1H, J = 3.8, 1.8 Hz, H(1)), 7.52−7.57 (m, 3H), 7.64−7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.38 (MeC(O)), 22.45 (Me(10)), 22.88 (Me(11)), 23.52 (C(6)H_2), 23.76 (C(9)H_2), 30.55 (C(5)H), 32.77 (C(7)H_2), 65.45 (C(12)H_2), 78.02 (C(1)H), 82.50 (C(8)), 82.57 (C(4)), 123.69 (2CH), 129.45 (2CH), 131.33 (CH), 144.57 (C), 170.08 (C═O).

The isomer 38b″ (96 mg, 0.272 mmol)**:** a colorless solid, mp 105−107 °C; R_f = 0.36 (hexanes−EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (s, 3H, Me(10)), 1.76 (dddd, 1H, J = 14.2, 12.5, 7.2, 3.3 Hz, H(6*ax*), 1.83 (ddd, 1H, J = 13.6, 3.3, 1.8 Hz, H(9*ax*), 1.89 (br s, 3H, Me(11)), 1.90 (br dddd, 1H, J = 6.4, 6.4, 3.3, 3.3 Hz, H(5)), 1.93−2.01 (m, 1H, H(6*eq*), 2.02 (s, 3H, *Me*C(O)), 2.07 (ddd, 1H, J = 14.8, 14.2, 5.6 Hz, H(7)-*ax*), 2.14 (br dd, 1H, J = 14.8, 6.6 Hz, H(7*eq*), 2.35 (br ddd, 1H, J = 13.6, 6.4, 3.3 Hz, H(9*eq*), 2.67 (br d, 1H, J = 13.6 Hz, H(12)), 3.10 (br d, 1H, J = 13.6 Hz, H′(12)), 4.49 (br d, 1H, J = 3.3 Hz, H(1)), 7.48−7.57 (m, 3H), 7.63−7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.05 (Me(11)), 22.47 (*Me*C(O)), 22.59 (Me(10)), 23.46 (C(6)H_2), 23.80 (C(9)H_2), 31.60 (C(5)H), 32.92 (C(7)H_2), 65.82 (C(12)H_2), 78.34 (C(1)H), 82.64 (C(8)), 82.81 (C(4)), 123.81 (2CH), 129.42 (2CH), 131.16 (CH), 144.90 (C), 170.22 (C═O).

Oxidation of Sulfides to Sulfones (General Procedure 1). A solution of sulfides (0.3 mmol, 1 equiv, a mixture of diastereomers) and *m*CPBA (0.75−0.9 mmol, 2.5−3.0 equiv) in EtOAc (5 mL) was stirred for 4−6 h at rt. After consumption of the more polar intermediate sulfoxide (TLC monitoring), the mixture was poured into a saturated solution of $NaHCO_3$, extracted with EtOAc/hexane, dried over Na_2SO_4, and evaporated. FC (hexanes−EtOAc) of the residue afforded the title compounds as a mixture of diastereomers. An additional FC,

MPLC, or HPLC provided a separation of a mixture of diastereomers.

(1*R*,4*R*,5*R*,8*R*)-8-Acetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonanes (39a) and (1*R*,4*S*,5*R*,8*R*)-8-Acetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonanes (39b). The sulfones **39a** (31 mg) and **39b** (26 mg) (total yield 97%) were prepared by oxidation of a mixture of diastereomeric sulfides **31a**,**b** (55 mg, 0.163 mmol, **a**/**b** ca. 55:45) and separated by MPLC (hexanes−EtOAc, 7:3).

The less polar isomer 39a: a colorless solid, mp 97−98 °C; R_f = 0.37 (hexane−benzene−EtOAc, 11:6:3); $[\alpha]^{20}_D$ −259.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (br s, 3H, Me(11)), 1.62 (s, 3H, Me(10)), 1.78 (br dddd, 1H, *J* = 14.5, 13.4, 6.8, 3.4 Hz, H(6)*ax*), 1.88 (ddd, 1H, *J* = 14.0, 3.4, 1.2 Hz, H(9)*ax*), 1.90 (dddd, 1H, *J* = 14.5, 6.8, 2.8, 2.8 Hz, H(6)-*eq*), 2.01 (s, 3H, *Me*C(O)), 2.14 (m, 1H, H(7)*eq*), 2.19 (m, 1H, H(7)*ax*), 2.26 (ddd, 1H, *J* = 14.0, 6.6, 3.2 Hz, H(9)*eq*), 2.30 (br dddd, 1H, *J* = 6.8, 6.8, 3.4, 3.4 Hz, H(5)), 3.25 (d, 1H, *J* = 14.3 Hz, H(12)), 4.22 (dd, 1H, *J* = 14.3, 0.4 Hz, H′(12)), 4.45 (br dd, 1H, *J* = 3.2, 1.2 Hz, H(1)), 7.58 (m, 2H), 7.66 (m, 1H), 7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.42 (*Me*C(O)), 22.49 (Me-(10)), 23.09 (Me(11)), 23.39 (C(6)H_2), 24.52 (C(9)H_2), 29.42 (C(5)H), 33.26 (C(7)H_2), 60.98 (C(12)H_2), 77.80 (C(1)H), 82.54 (C(8)), 82.72 (C(4)), 127.52 (2CH), 129.35 (2CH), 133.75 (CH), 141.08 (C), 170.20 (C═O); DCI (CH_4) HRMS: obsd 369.1354, calcd for $C_{18}H_{25}O_6S$ (MH^+), 369.1372. Anal. Calcd for $C_{18}H_{24}O_6S$: C, 58.68; H, 6.56; S, 8.70. Found: C, 58.64; H, 6.55; S, 8.34.

The more polar acetoxysulfone 39b: a colorless solid, mp 101−102 °C; R_f = 0.32 (hexane−benzene−EtOAc, 11:6:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 3H, Me(10)), 1.79 (ddd, 1H, *J* = 13.6, 3.4, 1.4 Hz, H(9)*ax*), 1.80 (br s, 3H, Me(11)), 1.84 (br dddd, 1H, *J* = 14.0, 14.0, 6.0, 3.4 Hz, H(6)*ax*), 1.96 (m, 1H, H(6)*eq*), 2.00 (s, 3H, *Me*C(O)), 2.04 (m, 1H, H(7)*ax*), 2.10 (br dddd, 1H, *J* = 6.8, 6.8, 3.4, 3.4 Hz, H(5)), 2.16 (br dd, 1H, *J* = 14.5, 6.0 Hz, H(7)*eq*), 2.29 (ddd, 1H, *J* = 13.6, 6.8, 3.6 Hz, H(9)-*eq*), 3.12 (d, 1H, *J* = 14.0 Hz, H(12)), 3.32 (br d, 1H, *J* = 14.0 Hz, H′(12)), 4.42 (br dd, 1H, *J* = 3.6, 1.4 Hz, H(1)), 7.57 (m, 2H), 7.66 (m, 1H), 7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.94 (Me(11)), 22.43 (*Me*C(O)), 22.53 (Me(10)), 23.40 (C(9)-H_2), 23.78 (C(6)H_2), 30.92 (C(5)H), 32.92 (C(7)H_2), 60.50 (C(12)-H_2), 78.45 (C(1)H), 82.35 (C(8)), 82.97 (C(4)), 127.61 (2CH), 129.37 (2CH), 133.89 (CH), 141.15 (C), 170.16 (C═O). Anal. Calcd for $C_{18}H_{24}O_6S$: C, 58.68; H, 6.56; S, 8.70. Found: C, 58.72; H, 6.57; S, 8.51.

(1*R*,4*R*,5*R*,8*R*)-8-Acetylacetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (40a) and (1*R*,4*S*,5*R*,8*R*)-8-Acetylacetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo [3.3.1]nonane (40b). A mixture of diastereomeric sulfones **40a**,**b** (94 mg, 67%, **a**/**b** ca. 55:45) was prepared by oxidation of a mixture of sulfides **32a**,**b** (130 mg, 0.34 mmol) according to general procedure 1 and separated by MPLC (hexanes−EtOAc, 3:2).

The less polar isomer 40a: a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (keto−enol ca. 93:7): δ 1.52 (br s, 3H, Me(11)), 1.66 (s, 3H, Me(10)), 1.80 (br dddd, 1H, *J* = 14.0, 13.7, 6.5, 3.4 Hz, H(6)*ax*), 1.87−1.97 (m, 2H), 2.15−2.25 (m, 2H), 2.26 (s, 3H, *Me*C(O)CH_2), 2.28 (ddd, 1H, *J* = 13.0, 6.4, 3.6 Hz, H(9)-*eq*), 2.31 (br dddd, 1H, *J* = 6.4, 6.4, 3.2, 3.2 Hz, H(5)), 3.27 (d, 1H, *J* = 14.4 Hz, H(12)), 3.42 (s, 2H, MeC(O)*CH*$_2$); 4.20 (br d, *J* = 14.4 Hz, H′(12)−keto), 4.23 (br d, *J* = 14.0 Hz, H′(12)−enol), total 1H; 4.43 (br d, *J* = 3.6 Hz, H(1)−keto), 4.50 (br d, *J* = 4.0 Hz, H(1)−enol), total 1H; 4.94 (br s, HC═enol), 7.58 (m, 2H), 7.67 (m, 1H), 7.94 (m, 2H), 12.05 (br s, HO−enol); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.53 (Me(10)), 23.01 (Me(11)), 23.27 (C(6)H_2), 24.39 (C(9)H_2), 29.39 (C(5)H), 30.28 (*Me*C(O)-CH_2), 33.13 (C(7)H_2), 51.29 (MeC(O)*CH*$_2$), 60.95 (C(12)H_2), 77.73 (C(1)H), 82.75 (C(8)), 84.17 (C(4)), 127.53 (2CH), 129.36 (2CH), 133.76 (CH), 141.05 (C), 165.99 (OC═O), 200.48 (C═O); DCI (CH_4) HRMS: obsd 411.1507, calcd for $C_{20}H_{27}O_7S$ (MH^+), 411.1478.

The more polar isomer 40b: 40b was finally purified by semipreparative DP HPLC (hexanes−EtOAc, 65:35): a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (keto−enol ca. 95:5): δ 1.60 (s, 3H, Me(10)), 1.80 (br s, 3H, Me(11)), 1.81−1.88 (m, 2H) 1.91−1.98 (m, 1H), 1.93 (d, ca. 0.15H, *J* = 0.4 Hz, MeC═enol), 2.07 (br ddd, 1H, *J* = 14.5, 14.5, 6.0 Hz, H(7)*ax*), 2.10 (br dddd, 1H, *J* = 6.8, 6.8, 3.4, 3.4 Hz, H(5)), 2.18 (br dd, 1H, *J* = 14.5, 6.0 Hz, H(7)*eq*), 2.25 (s, 3H, *Me*C(O)CH_2), 2.30 (br ddd, 1H, *J* = 13.8, 6.8, 3.6 Hz, H(9)*eq*), 3.13 (d, 1H, *J* = 14.0 Hz, H(12)); 3.32 (dd, *J* = 14.0, 0.3 Hz, H′(12)−keto), 3.33 (br d, *J* = 14.0 Hz, H′(12)−enol), total 1H; 3.41 (s, 2H, MeC(O)-*CH*$_2$); 4.39 (br d, *J* = 3.6 Hz, H(1)−keto), 4.49 (br d, *J* = 3.8 Hz, H(1)−enol), total 1H; 4.93 (br s, HC═enol), 7.58 (m, 2H), 7.66 (m, 1H), 7.92 (m, 2H), 12.04 (br s, HO−enol); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.89 (Me(11)), 22.56 (Me(10)), 23.25 (C(9)H_2), 23.65 (C(6)H_2), 30.30 (*Me*C(O)CH_2), 30.84 (C(5)H), 32.82 (C(7)H_2), 51.29 (MeC(O)*CH*$_2$), 60.51 (C(12)H_2), 78.35 (C(1)H), 83.03 (C(8)), 83.97 (C(4)), 127.62 (2CH), 129.38 (2CH), 133.91 (CH), 141.12 (C), 165.95 (OC═O), 200.58 (C═O); DCI (CH_4) HRMS: obsd 411.1421, calcd for $C_{20}H_{27}O_7S$ (MH^+), 411.1478.

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-8-ethoxyoxalyloxy-4-phenylsulfonylmethyl-2,3-dioxabicyclo [3.3.1]nonane (41a) and (1*R*,4*S*,5*R*,8*R*)-4,8-Dimethyl-8-ethoxyoxalyloxy-4-phenylsulfonylmethyl-2,3-dioxabicyclo [3.3.1]nonane (41b). A mixture of diastereomeric sulfones **41a**,**b** (120 mg, 94%, **a**/**b** ca. 57:43) was prepared by oxidation of a mixture of sulfides **35a**,**b** (118 mg, 0.30 mmol) according to general procedure 1 and separated by MPLC (hexanes−EtOAc, 3:1).

The less polar isomer 41a: a colorless oil; IR (neat): 2987, 2940, 1767, 1737, 1448, 1376, 1310, 1187, 1152, 1095, 1086, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, 3H, *J* = 7.1 Hz, *Me*CH_2O), 1.53 (br s, 3H, Me(11)), 1.72 (s, 3H, Me(10)), 1.82 (dddd, 1H, *J* = 14.2, 13.2, 6.8, 3.5 Hz, H(6)*ax*), 1.94 (ddddd, 1H, *J* = 14.2, 5.2, 2.6, 2.6, 2.6 Hz, H(6)*eq*), 1.97 (ddd, 1H, *J* = 14.0, 2.6, 1.4 Hz, H(9)*ax*), 2.24−2.37 (m, 4H), 3.27 (d, 1H, *J* = 14.3 Hz, H(12)), 4.21 (br d, 1H, *J* = 14.3 Hz, H′(12)), 4.33 (q, 2H, *J* = 7.1 Hz, CH_2O), 4.36 (br dd, 1H, *J* = 3.6, 1.4 Hz, H(1)), 7.59 (m, 2H), 7.67 (m, 1H), 7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.92 (*Me*CH_2O), 22.34 (Me(10)),23.05 (Me(11)), 23.23 (C(6)H_2), 24.46 (C(9)H_2), 29.32 (C(5)H), 32.49 (C(7)H_2), 60.96 (C(12)H_2), 63.03 (CH_2O), 77.74 (C(1)H), 82.91 (C(4)), 86.58 (C(8)), 127.57 (2CH), 129.41 (2CH), 133.83 (CH), 141.03 (C), 156.66 (OC═O), 158.08 (OC═O); DCI (CH_4) HRMS: obsd 427.1407, calcd for $C_{20}H_{27}O_8S$ (MH^+), 427.1427.

The more polar isomer 41b: a colorless oil; IR (neat): 2986, 2942, 1763, 1740, 1448, 1376, 1322, 1197, 1181, 1154, 1087, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, 3H, *J* = 7.1 Hz, *Me*CH_2O), 1.66 (s, 3H, Me(10)), 1.80−1.89 (m, 1H, H(6)*ax*), 1.82 (br s, 3H, Me(11)), 1.88 (ddd, 1H, *J* = 14.2, 3.4, 1.8 Hz, H(9)*ax*), 1.94−2.02 (m, 1H, H(6)*eq*), 2.11−2.15 (m, 1H, H(5)), 2.14 (ddd, 1H, *J* = 14.5, 14.5, 6.0 Hz, H(7)*ax*), 2.33 (br dd, 1H, *J* = 14.5, 6.2 Hz, H(7)*eq*), 2.34 (ddd, 1H, *J* = 14.2, 6.4, 3.6 Hz, H(9)*eq*), 3.12 (d, 1H, *J* = 14.0 Hz, H(12)), 3.32 (br d, 1H, *J* = 14.0 Hz, H′(12)), 4.32 (q, 2H, *J* = 7.1 Hz, CH_2O), 4.35 (m, 1H, H(1)), 7.57 (m, 2H), 7.67 (m, 1H), 7.92 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 13.87 (*Me*CH_2O), 21.87 (Me(11)), 22.29 (Me(10)), 23.30 (C(9)H_2), 23.53 (C(6)H_2), 30.70 (C(5)H), 32.14 (C(7)H_2), 60.41 (C(12)H_2), 63.01 (CH_2O), 78.26 (C(1)H), 83.12 (C(4)), 86.31 (C(8)), 127.58 (2CH), 129.37 (2CH), 133.92 (CH), 141.02 (C), 156.56 (OC═O), 158.00 (OC═O).

(1*R*,4*R*,5*R*,8*R*)-8-Dibenzylaminooxalyloxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (42a) and (1*R*,4*S*,5*R*,8*R*)-Dibenzylaminooxalyloxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]-nonane (42b). A mixture of diastereomeric sulfones **42a**,**b** (143.5 mg, 99%, **a**/**b** ca. 60:40) was prepared by oxidation of sulfides **36a**,**b** (137 mg, 0.25 mmol) according to general procedure 1 and separated by MPLC (hexanes−EtOAc, 7:3).

The less polar isomer 42a: a colorless oil; IR (neat): 2985, 2928, 1736, 1670, 1653, 1496, 1453, 1377, 1318, 1272, 1181, 1171, 1150, 1083, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (br s, 3H, Me(11)), 1.67 (s, 3H, Me(10)), 1.68−1.75 (m, 1H, H(6)*ax*), 1.82−1.92 (m, 2H), 2.18−2.28 (m, 4H), 3.27 (d, 1H, *J* = 14.3 Hz, H(12)), 4.17 (br d, 1H, *J* = 14.3 Hz, H′(12)), 4.35 (br s, 2H, Ph*CH*$_2$N), 4.36 (m, 1H, H(1)), 4.50 (br s, 2H,

PhCH_2N), 7.19−7.26 (m, 4H), 7.31−7.41 (m, 6H), 7.59 (m, 2H), 7.67 (m, 1H), 7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.46 (Me(10)), 22.93 (Me(11)), 23.12 (C(6)H_2), 24.33 (C(9)H_2), 29.25 (C(5)H), 32.90 (C(7)H_2), 46.22 (PhCH_2N), 50.02 (PhCH_2N), 60.89 (C(12)H_2), 77.60 (C(1)H), 82.78 (C(4)), 86.51 (C(8)), 127.38 (2CH), 127.53 (2CH), 127.87 (CH), 128.25 (CH), 128.46 (2CH), 128.78 (2CH), 128.93 (2CH), 129.36 (2CH), 133.79 (CH), 134.81 (C), 135.34 (C), 140.98 (C), 162.14 (C=O), 162.18 (C=O); DCI (CH_4) HRMS: obsd 578.2187, calcd for $C_{32}H_{36}NO_7S$ (MH^+), 578.2212. Anal. Calcd for $C_{32}H_{35}NO_7S$: N, 2.42; S, 5.55. Found: N, 2.10; S, 5.28.

The more polar isomer 42b: a colorless oil; IR (neat): 2982, 2935, 1733, 1663, 1654, 1450, 1379, 1322, 1312, 1176, 1153, 1084, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 3H, Me(10)), 1.71−1.80 (m, 2H), 1.79 (br s, 3H, Me(11)), 1.87−1.95 (m, 1H, H(6)*eq*), 2.03 (br dddd, 1H, J = 6.4, 6.4, 3.2, 3.2 Hz, H(5)), 2.09 (br ddd, 1H, J = 14.2, 14.2, 6.0 Hz, H(7)*ax*), 2.07 (br dd, 1H, J = 14.2, 5.8 Hz, H(7)*eq*), 2.27 (br ddd, 1H, J = 13.8, 6.4, 3.3 Hz, H(7)*eq*), 3.11 (d, 1H, J = 14.0 Hz, H(12)), 3.29 (br d, 1H, J = 14.3 Hz, H′(12)), 4.34 (m, 1H, H(1)), 4.35 (br s, 2H, PhCH_2N), 4.48 and 4.51 (AB quartet, 2H, J = 14.0 Hz, PhCH_2N), 7.19−7.24 (m, 4H), 7.30−7.40 (m, 6H), 7.57 (m, 2H), 7.66 (m, 1H), 7.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.84 (Me(11)), 22.49 (Me(10)), 23.24 (C(9)H_2), 23.50 (C(6)H_2), 30.71 (C(5)H), 32.71 (C(7)H_2), 46.27 (PhCH_2N), 50.04 (PhCH_2N), 60.49 (C(12)H_2), 78.19 (C(1)H), 83.11 (C(4)), 86.30 (C(8)), 127.36 (2CH), 127.63 (2CH), 127.90 (CH), 128.26 (CH), 128.48 (2CH), 128.80 (2CH), 128.95 (2CH), 129.38 (2CH), 133.93 (CH), 134.84 (C), 135.35 (C), 141.09 (C), 162.10 (C=O), 162.21 (C=O). Anal. Calcd for $C_{32}H_{35}NO_7S$: N, 2.42; S, 5.55. Found: N, 2.23; S, 5.17.

Oxidation of (1*R*,4*R*,5*R*,8*R*)-8-Acetoxy-4,8-dimethyl-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]nonanes (38a′ and 38a″). (i) A mixture of sulfoxide **38a′** (14.2 mg, 0.040 mmol) and *m*CPBA (ca. 60%, 14.4 mg, 0.05 mmol) in EtOAc (0.2 mL) was stirred for 6 h at rt. A workup as above, followed by FC (EtOAc−hexane, 1:4), afforded the sulfone **39a** (13.8 mg, 93%) as a colorless solid, mp 96−98 °C. (ii) Oxidation of sulfoxide **38a″** (15.5 mg, 0.044 mmol) with *m*CPBA (ca. 60%, 15.8 mg, 0.055 mmol) as above yielded the same sulfone **39a** (15.3 mg, 94%).

Synthesis of (1*R*,4*R*,5*R*,8*R*)-8-Acetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonanes (38a) from Hydroxysulfone 25a via TMS Derivative 42a. (a) To a cold (0 °C) solution of hydroxysulfone **23a** (230 mg, 0.705 mmol) and 2,6-lutidine (193 mg, 1.80 mmol) in dry CH_2Cl_2 (5 mL) was added neat TfOTMS (354 mg, 1.50 mmol). The reaction mixture was stirred at 0 °C for 1.5 h, poured into a cold water (50 mL), extracted with EtOAc−hexane (1:4, 2 × 75 mL), washed with cold saturated $NaHCO_3$ (30 mL) and brine (30 mL), and dried over Na_2SO_4. Evaporation, followed by vacuumization overnight at 0.3 mmHg, afforded the crude TMS derivative **43a** (283 mg, quantitative yield) containing traces of 2,6-lutidine. The TMS derivative **43a** was used in the next steps without additional purification.

(b) As prepared in the previous step, TMS derivative **43a** (283 mg) was treated with a freshly distilled AcCl (3.0 mL) and stirred for 50 h at rt. The mixture was evaporated, the residue was dissolved in EtOAc−hexane (1:2, 60 mL), washed with saturated $NaHCO_3$ (30 mL), and dried over $MgSO_4$. Evaporation, followed by FC (EtOAc−hexane, 1:4), afforded the acetoxysulfone **39a** (247 mg, yield 95% in two steps) as a colorless solid, mp 97−98 °C.

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-4-phenylsulfonylmethyl-8-trimethylsilyloxy-2,3-dioxabicyclo[3.3.1]nonane (43a): a mobile colorless oil, R_f = 0.36 (15% of EtOAc in hexane); ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.12 (br s, 9H), 1.37 (s, 3H, Me(10)), 1.51 (br s, 3H, Me(11)), 1.66 (ddd, 1H, J = 13.6, 3.4, 3.4 Hz, H(9)*ax*), 1.79−1.90 (m, 2H), 2.11−2.22 (m, 3H), 2.25 (br dddd, 1H, J = 6.8, 6.8, 3.4, 3.4 Hz, H(5)), 3.27 (d, 1H, J = 14.2 Hz, H(12)), 3.67 (br dd, 1H, J = 3.4, 3.4 Hz, H(1)), 4.24 (br d, 1H, J = 14.3 Hz, H′(12)), 7.59 (m, 2H), 7.68 (m, 1H), 7.96 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 2.46 (Me_3Si), 22.93 (Me(11)), 23.49 (C(6)H_2), 24.33 (C(9)H_2), 27.15 (Me(10)), 30.03 (C(5)H), 35.97 (C(7)H_2), 61.09 (C(12)H_2), 74.40 (C(8)), 82.45 (C(1)H), 82.65 (C(4)), 127.54 (2CH), 129.31 (2CH), 133.65 (CH), 141.22 (C).

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-8-(phenoxy)acetoxy-4-phenylsulfonylmethyl-2,3dioxabicyclo[3.3.1]nonane (44a). A mixture of TMS derivative **43a** (prepared from 72 mg, 0.22 mmol of hydroxysulfone **23a** as described above), phenoxyacetyl chloride (1.0 mL) and freshly oven-dried CsF (152 mg, 1.0 mmol) in dry acetonitrile (2.5 mL) was stirred at rt for a week. The mixture was poured into saturated $NaHCO_3$ (40 mL) and stirred for 2 h at rt. A mixture of hexanes−EtOAc (3:1, 100 mL) was added, and the organic layer was separated and washed with water (2 × 25 mL) and with saturated $NaHCO_3$ (25 mL). The organic extract was dried (Na_2SO_4 + $NaHCO_3$) and evaporated. MPLC (hexanes−EtOAc, 4:1) of the residue gave the title product **44a** (57 mg, 56% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (br s, 3H, Me(11)), 1.58−1.66 (m, 1H, H(6)*ax*), 1.67 (s, 3H, Me(10)), 1.74 (ddd, 1H, J = 14.0, 3.4, 1.4 Hz, H(9)*ax*), 1.82−1.90 (m, 1H, H(6)*eq*), 2.16−2.27 (m, 4H), 3.24 (d, 1H, J = 14.4 Hz, H(12)), 4.19 (br d, 1H, J = 14.4 Hz, H′(12)), 4.36 (br d, 1H, J = 3.2 Hz, H(1)), 6.89 (m, 2H), 7.00 (m, 1H), 7.30 (m, 2H), 7.58 (m, 2H), 7.66 (m, 1H), 7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.60 (Me(10)), 23.02 (Me(11)), 23.18 (C(6)H_2), 24.36 (C(9)H_2), 29.29 (C(5)H), 32.97 (C(7)H_2), 60.93 (C(12)H_2), 65.52 (PhOCH_2), 77.84 (C(1)H), 82.76 (C(4)), 84.47 (C(8)), 114.36 (2CH), 121.73 (CH), 127.53 (2CH), 129.37 (2CH), 129.58 (2CH), 133.78 (CH), 141.02 (C), 157.65 (C), 167.93 (C=O); DCI (CH_4) HRMS: obsd 461.1617, calcd for $C_{24}H_{29}O_7S$ (MH^+), 461.1634.

(1*R*,4*R*,5*R*,8*R*)- 8-Benzyloxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (46a). Phenyldiazomethane was freshly prepared by dry pyrolysis of sodium salt of benzaldehyde tosylhydrazone (11.87 g, 40.1 mmol).[52] To a vigorously stirred cold (−30 °C) solution of hydroxysulfone **23a** (1.26 g, 3.86 mmol) and freshly distilled TfOH (0.1 mL) in dry CH_2Cl_2 (12 mL) was slowly cannulated over 1 h a cold (−40 °C) solution of phenyldiazomethane in CH_2Cl_2 (8 mL). The rate of cannulation was regulated in the way to maintain the reaction mixture colorless or very pale pink. When the reaction mixture became reddish, the cannulation was interrupted, and a new portion of TfOH (0.1 mL) was added, followed by continuation of the cannulation. The cannulation was interrupted five times, and new portions of TfOH (0.1 mL) were added. After completion of the cannulation, the reaction mixture was stirred at −30 °C for an additional 30 min and quenched with pyridine (1 mL). A cold (0 °C) reaction mixture was poured into cold water (100 mL) and extracted with EtOAc−hexane (400 mL, 1:3). The organic extract was washed with water (2 × 100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL) and was dried over Na_2SO_4. Evaporation, followed by FC (from 6% to 25% EtOAc in hexane) and MPLC (EtOAc−hexane, 1:9) afforded the title product **46a** (1.380 g, 86% yield, ≥98.5 purity) as a colorless solid: mp 85−86 °C (*tert*-butyl methyl ether); $[\alpha]^{20}_D$ −237.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 3H, Me(10)), 1.54 (d, 3H, J = 0.5 Hz, Me(11)), 1.83 (dddd, 1H, J = 14.0, 14.0, 5.6, 3.6 Hz, H(6)*ax*), 1.86−1.92 (m, 1H, H(6)*eq*), 1.97 (br dd, 1H, J = 14.7, 5.2 Hz, H(7)*eq*), 2.13 (ddd, 1H, J = 14.7, 14.0, 6.5 Hz, H(7)*ax*), 2.19−2.22 (m, 2H, H(9)*ax* + *eq*), 2.29 (br dddd, 1H, J = 6.4, 6.4, 3.2, 3.2 Hz, H(5)), 3.31 (d, 1H, J = 14.3 Hz, H(12)), 3.85 (br dd, 1H, J = 2.8, 2.8 Hz, H(1)), 4.25 (dd, 1H, J = 14.3, 0.5 Hz, H′(12)), 4.38 (d, 1H, J = 11.2 Hz, PhC*H*H′O), 4.50 (d, 1H, J = 11.2 Hz, PhCH*H*′O), 7.26−7.30 (m, 1H), 7.33−7.38 (m, 4H), 7.57−7.62 (m, 2H), 7.65−7.70 (m, 1H), 7.95−7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.15 (Me(10)), 22.94 (Me(11)), 23.55 (C(6)H_2), 24.61 (C(9)H_2), 29.88 (C(5)H), 30.73 (C(7)H_2), 61.12 (C(12)H_2), 63.23 (PhCH_2O), 76.07 (C(8)), 80.89 (C(1)H), 82.76 (C(4)), 127.19 (2CH), 127.31 (CH), 127.58 (2CH), 128.35 (2CH), 129.35 (2CH), 133.71 (CH), 139.22 (C), 141.19 (C); DCI (CH_4) HRMS: obsd 417.1746, calcd for $C_{23}H_{29}O_5S$ (MH^+), 417.1736. Anal. Calcd for $C_{23}H_{28}O_5S$: C, 66.32; H, 6.78; S, 7.70. Found: C, 66.43; H, 6.78; S, 7.37.

(1*R*,4*S*,5*R*,8*R*)- 8-Benzyloxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo-[3.3.1]nonane (46b). The

benzylated endoperoxide **46b** (1.53 g, 85%, ≥98% purity) was prepared from hydroxy endoperoxide **23b** (1.418 g, 4.345 mmol) according to the procedure for **46a**. A colorless oil, $[\alpha]^{20}_D$ −62.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H, Me-(10)), 1.82 (d, 3H, *J* = 0.3 Hz, Me(11)), 1.86−1.92 (m, 2H), 1.94−1.99 (m, 2H), 2.08 (br dddd, 1H, *J* = 6.2, 6.2, 3.1, 3.1 Hz, H(5)), 2.09−2.13 (m, 1H), 2.23−2.28 (m, 1H), 3.18 (d, 1H, *J* = 14.0 Hz, H(12)), 3.38 (dd, 1H, *J* = 14.0, 0.3 Hz, H′(12)), 3.87 (br dd, 1H, *J* = 3.7, 2.0 Hz, H(1)), 4.37 (d, 1H, *J* = 11.2 Hz, PhC*H*H′O), 4.48 (d, 1H, *J* = 11.2 Hz, PhCH*H*′O), 7.26−7.30 (m, 1H), 7.31−7.37 (m, 4H), 7.57−7.62 (m, 2H), 7.66−7.70 (m, 1H), 7.93−7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.92 (Me(11)), 22.12 (Me(10)), 23.43 (CH_2), 23.88 (CH_2), 30.70 (C(7)H_2), 31.37 (C(5)H), 60.60 (C(12)H_2), 63.27 (Ph*C*H_2O), 75.88 (C(8)), 81.23 (C(1)H), 82.93(C(4)), 127.18 (2CH), 127.31 (CH), 127.66 (2CH), 128.34 (2CH), 129.33 (2CH), 133.82 (CH), 139.19 (C), 141.25 (C); DCI (CH_4) HRMS: obsd 417.1774, calcd for $C_{23}H_{29}O_5S$ (MH^+), 417.1736.

***O*-(3-Methylbut-2-enyl) Trichloroacetimidate (48).** To a suspension of NaH (121 mg of 70% suspension in mineral oil, 3.53 mmol) in dry ether (5 mL) was added dropwise over 10 min a solution of 3-methylbut-2-en-1-ol (3.015 g, 35.0 mmol) in ether (5 mL). After stirring for an additional 20 min at rt, a homogeneous mixture was cooled to −30 °C, and CCl_3CN (4.90 g, 34.0 mmol) was added gradually. The mixture was allowed to warm to rt (1 h) and was stirred at rt for an additional 1 h. Ether and excess of alcohol were evaporated under reduced pressure, and the residue was treated with a solution of MeOH (112 mg, 0.14 mL, 3.5 mmol) in dry pentane (25 mL). The resulting solution was filtered through a short plug of Celite, evaporated, and vacuumized at 0.2 mmHg for 6 h to give the imidate **48** (7.315 g, 93%) as a pale yellow viscous liquid of ca. 95% purity (according to the ^{1}H NMR spectra). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.76 (br s, 3H, Me), 1.81 (br s, 3H, Me), 4.80 (d, 2H, *J* = 6.5 Hz, CH_2O), 5.49 (m, 1H, CH═), 8.27 (br s, 1H, ═NH).

***O*-(3-Phenylprop-2-enyl) Trichloroacetimidate (49).** A treatment of *trans*-cinnamyl alcohol (3.414 g, 25.44 mmol) with CCl_3CN (3.673 g, 25.44 mmol) as described above provided the title imidate **49**[53] (6.719 g, 95%) as a yellow-orange oil of ca. 97% purity (according to the ^{1}H NMR spectra). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.01 (d, 2H, *J* = 6.2 Hz, CH_2O), 6.43 (dt, 1H, *J* = 15.9, 6.5 Hz, CH═), 6.79 (d, 1H, *J* = 15.9 Hz, Ph*CH*═), 7.27−7.47 (m, 5H, Ph), 8.40 (br s, 1H, ═NH). The imidates **48** and **49** were used for allylation without further purification.

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-8-(*p*-methoxybenzyl)oxy-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (50a). To a suspension of hydroxysulfone **23a** (280 mg, 0.858 mmol) in dry diethyl ether (3 mL) at 0 °C was added a solution of *O*-*p*-methoxybenzyl trichloroacetimidate **47**[37b] (1.287 g of ca. 93% purity, 4.20 mmol) in dry CH_2Cl_2 (1.5 mL). The mixture was stirred for 10 min until a homogeneous solution was formed, and a solution of TfOH in ether (0.43 mL of 0.1 M TfOH solution in ether, 0.043 mmol) was added. The mixture was stirred for 1.5 h at 0 °C and for 10 h at rt. The second portion of TfOH solution (0.25 mL, 0.025 mmol) was added, and the mixture was stirred for additional 12 h. At that time, the second portion of imidate **47** (772 mg, 2.51 mmol) and the third portion of TfOH solution (0.25 mL, 0.025 mmol) were added, and the resulting mixture was stirred for additional 8 h until consumption of starting alcohol **23a** was detected (TLC monitoring). The mixture was diluted with ether (15 mL) and hexane (15 mL), and $NaHCO_3$ (0.6 g) and Na_2SO_4 (2.0 g) were added. After being stirred overnight the mixture was filtered, evaporated, fractionated by FC (hexanes−EtOAc, 3:1), and purified by MPLC (hexanes−EtOAc, 78:22) to give the title product **50a** (175 mg, 46%) as a pale yellow oil: R_f = 0.40 (hexanes−EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, Me(10)), 1.53 (br s, 3H, Me(11)), 1.81 (br dddd, 1H, *J* = 14.0, 14.0, 6.4, 3.3 Hz, H(6)*ax*), 1.82−1.89 (m, 1H, H(6)*eq*), 1.94 (br dd, 1H, *J* = 14.6, 5.0 Hz, H(7)*eq*), 2.11 (br ddd, 1H, *J* = 14.6, 14.0, 6.4 Hz, H(7)*ax*), 2.15−2.19 (m, 2H, H(9)*ax* + *eq*), 2.27 (br dddd, 1H, *J* = 6.4, 6.4, 3.2, 3.2 Hz, H(5)), 3.29 (d, 1H, *J* = 14.3 Hz, H(12)), 3.81 (s, 3H, MeO), 3.83 (br dd, 1H, *J* = 3.0, 3.0 Hz, H(1)), 4.24 (br d, 1H, *J* = 14.3 Hz, H′(12)), 4.29 (d, 1H, *J* = 10.7 Hz, ArC*H*H′O), 4.41 (d, 1H, *J* = 10.7 Hz, ArCH*H*′O), 6.88 (m, 2H), 7.24 (m, 2H), 7.58 (m, 2H), 7.66 (m, 1H), 7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.16 (Me-(10)), 22.92 (Me(11)), 23.53 (C(6)H_2), 24.57 (C(9)H_2), 29.86 (C(5)H), 30.76 (C(7)H_2), 61.10 (C(12)H_2), 62.91 (Ar*C*H_2O), 75.94 (C(8)), 80.84 (C(1)H), 82.71 (C(4)), 113.78 (2CH), 127.55 (2CH), 128.72 (2CH), 129.33 (2CH), 131.26 (C), 133.68 (CH), 141.17 (C), 158.92 (C); DCI (CH_4) HRMS: obsd 447.1869, calcd for $C_{24}H_{31}O_6S$ (MH^+), 447.1841.

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-8-(3-methylbut-2-enyl)oxy-4-phenylsulfonylmethyl-2,3-dioxabicyclo [3.3.1]nonane (51a). The title compound **51a** (58 mg, 51%) was prepared from hydroxysulfone **23a** (95 mg, 0.32 mmol) and imidate **48** (720 mg, 3.0 mmol) according to the procedure described for **50a** and purified by MPLC (hexanes−EtOAc, 84:16). A colorless oil: R_f = 0.42 (hexanes−EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H, Me(10)), 1.50 (br s, 3H, Me(11)), 1.65 (m, 3H, *Me*Me′C═), 1.73 (m, 3H, Me*Me*′C═),1.78 (dddd, 1H, *J* = 14.0, 14.0, 6.0, 3.5 Hz, H(6)*ax*), 1.79−1.85 (m, 1H, H(6)*eq*), 1.85 (br dd, 1H, *J* = 14.0, 5.5 Hz, H(7)*eq*), 2.06 (br ddd, 1H, *J* = 14.0, 14.0, 6.1 Hz, H(7)*ax*), 2.10−2.18 (m, 2H, H(9)*ax* + *eq*), 2.27 (br dddd, 1H, *J* = 6.0, 6.0, 3.0, 3.0 Hz, H(5)), 3.27 (d, 1H, *J* = 14.3 Hz, H(12)), 3.77 (br s, 1H, H(1)), 3.80 (br dd, 1H, *J* = 10.8, 6.8 Hz, ═CHC*H*H′O), 3.90 (br dd, 1H, *J* = 10.8, 6.8 Hz, ═CHCH*H*′O), 4.22 (dd, 1H, *J* = 14.3, 0.3 Hz, H′(12)), 5.27 (ddqq, 1H, *J* = 6.8, 6.8, 1.4, 1.4 Hz, ═C*H*CHH′O), 7.56 (m, 2H), 7.65 (m, 1H), 7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.94 (*Me*Me′C═), 22.04 (Me(10)), 22.87 (Me(11)), 23.49 (C(6)-H_2), 24.48 (C(9)H_2), 25.81 (Me*Me*′C═), 29.84 (C(5)H), 30.97 (C(7)H_2), 57.58 (═CH*C*H_2O), 61.09 (C(12)H_2), 75.47 (C(8)), 80.70 (C(1)H), 82.63 (C(4)), 121.78 (═*C*HCH$_2$O), 127.53 (2CH), 129.29 (2CH), 133.64 (CH), 135.90 (Me$_2$*C*═), 141.17 (C); DCI (CH_4) HRMS: obsd 395.1859, calcd for $C_{21}H_{31}O_5S$ (MH^+), 395.1892.

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-8-(3-phenylprop-2-enyl)-oxy-4-phenylsulfonylmethyl-2,3-dioxabicyclo [3.3.1]nonane (52a). The title compound **52a** (49 mg, 32%, *E*/*Z* ca. 9:1) was prepared from hydroxysulfone **23a** (113 mg, 0.345 mmol) and imidate **49** (1.218 g, 4.23 mmol) according to the procedure described above and purified by MPLC (hexanes−EtOAc, 4:1). The final purification was achieved using semi-preparative RP HPLC (MeCN−H_2O, 65:35). A pale yellow immobile oil: R_f = 0.46 (hexanes−EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H, Me(10)), 1.53 (br s, 3H, Me(11)), 1.84 (br dddd, 1H, *J* = 14.0, 14.0, 5.6, 3.6 Hz, H(6)*ax*), 1.84−1.93 (m, 2H), 2.10 (br ddd, 1H, *J* = 14.0, 14.0, 6.4 Hz, H(7)*ax*), 2.15−2.22 (m, 2H), 2.27 (br dddd, 1H, *J* = 6.0, 6.0, 3.0, 3.0 Hz, H(5)), 3.29 (d, 1H, *J* = 14.3 Hz, H(12)), 3.82 (br s, 1H, H(1)), 4.01 (ddd, 1H, *J* = 12.6, 5.8, 1.5 Hz, ═CHC*H*H′O), 4.12 (ddd, 1H, *J* = 12.6, 5.8, 1.5 Hz, ═CHCH*H*′O), 4.24 (br d, 1H, *J* = 14.3 Hz, H′(12)), 6.25 (ddd, 1H, *J* = 15.9, 5.8, 5.8 Hz, CH═C*H*CHH′O), 6.60 (br d, 1H, *J* = 15.9 Hz, PhC*H*═CHCHH′O), 7.22−7.40 (m, 5H), 7.56−7.60 (m, 2H), 7.64−7.69 (m, 1H), 7.94−7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.11 (Me-(10)), 22.93 (Me(11)), 23.53 (C(6)H_2), 24.58 (C(9)H_2), 29.90 (C(5)H), 31.00 (C(7)H_2), 61.15 (C(12)H_2), 61.94 (═CH*C*H_2O), 75.96 (C(8)), 80.78 (C(1)H), 82.75 (C(4)), 126.40 (2CH), 127.12 (CH), 127.52 (CH), 127.59 (2CH), 128.52 (2CH), 129.34 (2CH), 130.99 (CH), 133.69 (CH), 136.85 (C), 141.24 (C); DCI (CH_4) HRMS: obsd 443.1915, calcd for $C_{25}H_{31}O_5S$ (MH^+), 443.1892.

Preparation of Unsaturated Sulfides 53a,b and 54a,b. To a solution of $SOCl_2$ (1.90 g, 16.0 mmol) and pyridine (3.165 g, 40.0 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C was added a solution of hydroxysulfides **19a**,**b** (1.10 g, 3.74 mmol, ca. 55:45) in CH_2Cl_2 (30 mL) over 1.5 h. The reaction mixture was allowed to warm to rt and stirred for an additional 2 h. At that time, the mixture was poured into ice-cold 0.1 M HCl (100 mL) and extracted with hexanes−EtOAc (9:1, 2 × 300 mL). The organic extract was washed with saturated $NaHCO_3$ (2 × 80 mL), dried (Na_2SO_4 + $NaHCO_3$), and evaporated. The residue was purified by FC (hexanes−EtOAc, 95:5) to give a mixture of unsaturated sulfides **53a**,**b** and **54a**,**b** (955 mg, total yield 92%; **53a**/**53b**/**54a**/**54b** ca. 47:39:8:6 according to the

integration of the H(1) peaks in ^{1}H NMR spectrum at 400 MHz). A colorless oil: R_f = 0.29 (5% of EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (d, J = 0.7 Hz, **53a**), 1.29 (d, J = 0.6 Hz, **54a**), 1.57 (d, J = 0.5 Hz, **54b**), 1.58 (d, J = 0.8 Hz, Me(11), **53b**), total 3H; 1.55 (ddd, J = 13.1, 3.0, 2.0 Hz, **53a**), 1.63 (dddd, J = 13.0, 2.9, 2.4, 0.5 Hz, H(9)*ax*, **53b**), total ca. 1H; 1.79−1.81 (m, ca. 3H, Me(10), **53a**,**b**); 1.93 (m, **53b**), 2.04 (m, H(5), **53a**), total ca. 1H; 2.15−2.37 (m), 2.48 (dddd, J = 13.0, 3.6, 3.6, 1.6 Hz, H(9)*eq*, **53b**), total 3H; 2.90 (d, J = 11.8 Hz, H(12), **53b**) and 3.03 (dd, J = 11.8, 0.8 Hz, H′(12), **53b**), 3.00 (d, J = 12.0 Hz, H(12), **54b**) and 3.10 (dd, J = 12.0, 0.5 Hz, H′(12), **54b**), 3.30 (d, J = 12.2 Hz, H(12), **54a**), 3.33 (d, J = 12.7 Hz, H(12), **53a**), and 3.79 (dd, J = 12.7, 0.7 Hz, H′-(12), **53a**), total 2H; 4.10 (br dd, J = 3.6, 2.0 Hz, **53a**), 4.13 (br dd, J = 3.6, 2.4 Hz, **53b**), 4.34 (br dd, J = 4.0, 1.4 Hz, **54a**), 4.40 (br dd, J = 4.3, 1.7 Hz, H(1), **54b**), total 1H; 4.89 (m, HH′C(10)=, **54a**,**b**), 5.73 (m, **53b**), 5.75 (m, H(7), **53a**), total ca. 1H; 7.18−7.46 (m, 5H). The mixture of unsaturated sulfides **53a**,**b** and **54a**,**b** was used in the next step without further separation or purification. For the characterization and biological evaluation, the major component **53a** (ca. 97% purity) was isolated by an additional preparative RP HPLC (column LiChrosorb RP-8 (7 μm), 250−25 mm; MeCN−H_2O, 60:40).

(1*R*,4*R*,5*R*)-4,8-Dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]non-7-ene (53a). A colorless waxy solid: mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (d, 3H, J = 0.7 Hz, Me(11)), 1.55 (ddd, 1H, J = 13.1, 3.0, 2.0 Hz, H(9)*ax*), 1.80 (ddd, 3H, J = 2.7, 1.6, 1.6 Hz, Me(10)), 2.04 (m, 1H, H(5)), 2.21 (dddq, 1H, J = 19.0, 5.4, 2.7, 2.7 Hz, H(6)*ax*), 2.30 (dddd, 1H, J = 13.1, 3.6, 3.6, 1.6 Hz, H(9)*eq*), 2.33 (dddq, 1H, J = 19.0, 6.4, 1.6, 1.6 Hz, H(6)*eq*), 3.34 (d, 1H, J = 12.7 Hz, H(12)), 3.79 (d, 1H, J = 12.7, 0.7 Hz, H′(12)), 4.10 (br dd, J = 3.6, 2.0 Hz, H(1)), 5.76 (m, H(7)), 7.19 (m, 1H), 7.29 (m, 2H), 7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.17 (Me(10)), 22.72 (Me-(11)), 26.38 ($C(9)H_2$), 27.56 ($C(6)H_2$), 28.52 (C(5)H), 40.73 ($C(12)H_2$), 76.21 (C(1)H), 83.37 (C(4)), 126.15 (CH), 126.82 (C(7)H), 128.90 (2CH), 129.69 (2CH), 131.26 (C(8)), 136.96 (C); DCI (CH_4) HRMS: obsd 277.1253, calcd for $C_{16}H_{21}O_2S$ (MH^+), 277.1262.

Hydrogenation of Unsaturated Sulfides 53a,b and 54a,b with Diimide.[38] To a mixture of unsaturated sulfides **53a**,**b** and **54a**,**b** (120 mg, total 0.43 mmol; **53a**/**53b**/**54a**/**54b** ca. 54:34: 6.5:5.5) and potassium azodicarboxilate (1.00 g, 5.15 mmol) in MeOH−CH_2Cl_2 (5 mL, 3:2) at 0 °C over 45 min was added a solution of AcOH (620 mg, 10.3 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was allowed to warm to ambient temperature and stirred for an additional 48 h. The mixture was diluted with ether (50 mL), filtered through Celite, and evaporated. The residue was fractionated by sequential MPLC (hexanes−EtOAc, 98: 2) to recover the starting unsaturated sulfides **53a**,**b** (70 mg, 0.25 mmol; **a**/**b** ca. 61: 39), and to give the saturated sulfides **55c** (4 mg) and **55d** (3 mg) (both ca. 95% purity), as well as two fractions consisting of the mixtures of **55a**,**b** with a different ratio of isomers: (4 mg, **a**/**b** ca. 83: 17) and (19 mg, **a**/**b** ca. 53: 47). Total yield of hydrogenated sulfides **55a**−**d**: 30 mg (60% based on consumed, unsaturated sulfides).

(1*R*,4*R*/*S*,5*R*,8*S*)-4,8-Dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonanes (55a,b): a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J = 6.7 Hz, **b**), 1.10 (d, J = 6.7 Hz, Me(10), **a**), total 3H; 1.24 (br s, **a**), 1.55 (d, J = 0.7 Hz, Me(11), **b**), total 3H; 1.41 (ddd, J = 13.3, 3.0, 1.7 Hz, **a**), 1.48 (ddd, J = 13.1, 3.2, 1.7 Hz, H(9)*ax*, **b**), total 1H; 1.58−1.69 (m, 2H, H(6)*ax* + *eq*, **a** + **b**), 1.75−1.85 (m, 1H, H(8)*ax*, **a** + **b**); 1.90−1.94 (m, 1H, H(5), **a** + **b**), 1.94−2.05 (m, 2H, H(7)-*ax* + *eq*, **a** + **b**); 2.28 (dddd, J = 13.3, 4.0, 4.0, 2.6 Hz, **a**), 2.45 (dddd, J = 13.1, 3.8, 3.8, 2.9 Hz, H(9)*eq*, **b**), total 1H; 2.94 (d, J = 11.9 Hz, H(12), **b**), 3.05 (dd, J = 11.9, 0.7 Hz, H′(12), **b**), 3.31 (d, J = 12.7 Hz, H(12), **a**), 3.73 (dd, J = 12.7, 0.7 Hz, H′(12), **a**), total 2H; 3.83 (br dd, J = 4.0, 1.7 Hz, **a**), 3.71 (br dd, J = 3.8, 1.7 Hz, H(1), **b**), total 1H; 7.17−7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.56 (Me(10)), 22.05 (Me(11)), 27.06 (CH_2), 29.19 (C(5)H), 29.56 (CH_2), 29.59 (CH_2), 35.62 (C(8)H), 40.91 ($C(12)H_2$), 79.23 (C(1)H), 83.36 (C(4)), 126.07 (CH), 128.90 (2CH), 129.59 (2CH), 136.90 (C) (isomer **55a**).

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo [3.3.1]nonane (55c): a colorless waxy substance; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (d, 3H, J = 7.4 Hz, Me(10)), 1.25 (d, 3H, J = 0.6 Hz, Me(11)), 1.29 (br dd, 1H, J = 14.0, 5.8 Hz, H(7)*eq*), 1.62 (ddd, 1H, J = 13.6, 3.2, 1.8 Hz, H(9)*ax*), 1.74 (br dddd, 1H, J = 14.0, 14.0, 6.2, 3.4 Hz, H(6)-*ax*), 1.80−1.87 (m, 1H, H(6)*eq*), 1.87 (br dddd, 1H, J = 6.3, 6.3, 3.2, 3.2 Hz, H(5)), 2.02 (dddd, J = 13.6, 6.2, 3.6, 1.3 Hz, H(9)*eq*), 2.38 (br qd, 1H, J = 7.4, 7.2 Hz, H(8)*eq*), 2.55 (br dddd, 1H, J = 14.0, 14.0, 7.2, 7.2 Hz, H(7)*ax*), 3.29 (d, 1H, J = 12.8 Hz, H(12)), 3.75 (br dd, 1H, J = 12.8, 0.7 Hz, H′(12)), 3.83 (br ddd, 1H, J = 3.6, 1.8, 1.8 Hz, H(1)), 7.18 (m, 1H), 7.28 (m, 2H), 7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.18 (Me-(10)), 22.06 (Me(11)), 23.38 ($C(6)H_2$), 24.02 ($C(9)H_2$), 27.17 ($C(7)H_2$), 29.61 (C(5)H), 32.98 (C(8)H), 40.83 ($C(12)H_2$), 80.32 (C(1)H), 83.66 (C(4)), 126.11 (CH), 128.90 (2CH), 129.66 (2CH), 136.92 (C).

(1*R*,4*S*,5*R*,8*R*)-4,8-Dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo [3.3.1]nonane (55d): a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, 3H, J = 7.4 Hz, Me(10)), 1.29 (br dd, 1H, J = 13.6, 6.0 Hz, H(7)*eq*), 1.54 (d, 3H, J = 0.7 Hz, Me(11)), 1.64−1.82 (m, 4H), 2.20 (dddd, J = 13.4, 6.6, 3.9, 1.3 Hz, H(9)*eq*), 2.37 (br qd, 1H, J = 7.4, 6.8 Hz, H(8)*eq*), 2.53 (br dddd, 1H, J = 13.6, 13.6, 6.8, 6.8 Hz, H(7)*ax*), 2.97 (d, 1H, J = 12.0 Hz, H(12)), 3.09 (br dd, 1H, J = 12.0, 0.7 Hz, H′(12)), 3.84 (br ddd, 1H, J = 3.9, 1.8, 1.8 Hz, H(1)), 7.19 (m, 1H), 7.28 (m, 2H), 7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.02 (Me(10)), 21.96 (Me(11)), 23.05 ($C(6)H_2$), 24.05 ($C(9)H_2$), 27.51 ($C(7)H_2$), 31.14 (C(5)H), 32.89 (C(8)H), 40.78 ($C(12)H_2$), 80.76 (C(1)H), 83.65 (C(4)), 126.29 (CH), 128.97 (2CH), 129.62 (2CH), 136.86 (C).

(1*R*,4*R*,5*R*)-4,8-Dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo [3.3.1]non-7-ene (57a) and (1*R*,4*R*,5*R*)-4-Methyl-8-methylidene-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (58a). To a mixture of $SOCl_2$ (395 mg, 3.32 mmol) and pyridine (656 mg, 8.30 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added a solution of hydroxysulfone **23a** (270 mg, 0.827 mmol) in CH_2Cl_2 (15 mL) over 30 min. The mixture was stirred at 0 °C for 2 h and for 4 h at rt, poured into ice-cold 0.2 N HCl (100 mL), and extracted with hexanes−EtOAc (3:1, 2 × 200 mL). The combined organic extract was washed with saturated $NaHCO_3$ (30 mL), dried (Na_2SO_4), filtered, and evaporated. FC (hexanes−EtOAc, 4:1) afforded a colorless solid mixture of **57a** and **58a** (243 mg, 95.5%, **57a**/**58a** ca. **86:14).** More polar isomer **57a** (ca. 97.5% purity) was isolated using sequential MPLC (hexanes−EtOAc, 85:15) as a colorless solid, mp 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, 3H, J = 0.6 Hz, Me(11)), 1.72 (ddd, 1H, J = 13.3, 2.8, 2.0 Hz, H(9)*ax*), 1.78 (ddd, 3H, J = 2.7, 1.7, 1.7 Hz, Me-(10)), 2.26 (dddq, 1H, J = 19.1, 5.4, 1.7, 1.7 Hz, H(6)*ax*), 2.39 (dddq, 1H, J = 19.1, 3.2, 1.7, 1.7 Hz, H(6)*eq*), 2.46 (m, 1H, H(5)), 2.50 (dddd, 1H, J = 13.3, 3.5, 3.5, 1.6 Hz, H(9)*eq*), 3.29 (d, 1H, J = 14.3 Hz, H(12)), 4.12 (m, 1H, H(1)), 4.31 (dd, 1H, J = 14.3, 0.6 Hz, H′(12)), 5.77 (m, 1H, H(7)), 7.58 (m, 2H), 7.66 (m, 1H), 7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.16 (Me(10)), 23.62 (Me(11)), 26.83 ($C(9)H_2$), 27.48 ($C(6)H_2$), 29.54 (C(5)H), 61.23 ($C(12)H_2$), 76.70 (C(1)H), 82.35 (C(4)), 127.28 (C(7)H), 127.55 (2CH), 129.35 (2CH), 131.15 (=C(8)), 133.71 (CH), 141.20 (C). Anal. Calcd for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.54; S, 10.40. Found: C, 62.17; H, 6.57; S, 10.47.

The less polar isomer 58a: 58a (ca. 95% purity) was isolated by semipreparative DP HPLC (i-PrOH−hexane, 2:98) as a colorless waxy substance; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (d, 3H, J = 0.6 Hz, Me(11)), 1.65 (ddd, 1H, J = 13.7, 3.2, 1.7 Hz, H(9)*ax*), 1.73 (dddd, 1H, J = 14.2, 14.2, 6.4, 3.8 Hz, H(6)*ax*), 2.15 (br ddd, 1H, J = 14.2, 6.6, 3.2 Hz, H(6)*eq*), 2.39 (br dd, 1H, J = 14.2, 6.6 Hz, H(7)*eq*), 2.46 (dddd, 1H, J = 6.4, 6.4, 3.2, 3.2 Hz, H(5)), 2.57 (ddd, 1H, J = 13.7, 6.4, 3.6 Hz, H(9)*eq*), 2.99 (m, 1H, H(7)*ax*), 3.29 (d, 1H, J = 14.3 Hz, H(12)), 4.30 (br dd, 1H, J = 14.3, 0.6 Hz, H′(12)), 4.36 (br dd, 1H, J = 3.6, 1.7 Hz, H(1)), 4.92 (br dd, 1H, J = 2.2, 2.2 Hz, =C*H*H′), 4.95 (br ddd, 1H, J = 2.2, 2.2, 0.6 Hz, =CH*H*′),7.59 (m, 2H),

7.67 (m, 1H), 7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.32 (Me(11)), 27.02 (C(6)H_2), 30.39 (C(5)H), 30.50 (C(9)H_2), 30.52 (C(7)H_2), 61.27 (C(12)H_2), 80.77 (C(1)H), 82.96 (C(4)), 113.59 (=C(10)H_2), 127.57 (2CH), 129.36 (2CH), 133.74 (CH), 141.18 (C), 146.21 (=C(8)); DCI (CH_4) HRMS: obsd 309.1193, calcd for $C_{16}H_{21}O_4S$ (MH^+), 309.1161.

(1*R*,4*S*,5*R*)-4,8-Dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo [3.3.1]non-7-ene (57b) and (1*R*,4*S*,5*R*)-4-Methyl-8-methylidene-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (58b). With the same procedure as above, **23b** (780 mg, 2.39 mmol) was transformed into a mixture of **57b** and **58b** (total 692 mg, 94%, **57b**/**58b** ca. 84:16), which was obtained as a colorless solid, mp 121−124 °C. Recrystallization from EtOAc−hexane (5:95) afforded a single isomer **57b** (≥97% purity): a colorless solid, mp 133−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (br ddd, 1H, J = 13.1, 2.8, 2.2 Hz, H(9)*ax*), 1.77 (m, 3H, Me(10)), 1.86 (d, 3H, J = 0.7 Hz, Me(11)), 2.31 (m, 1H, H(5)), 2.34 (ddq, 1H, J = 18.5, 2.6, 2.6 Hz, H(6)*ax*), 2.45 (m, 1H, J = 18.5 Hz, H(6)*eq*), 2.54 (dddd, 1H, J = 13.1, 3.4, 3.4, 1.7 Hz, H(9)*eq*), 3.02 (d, 1H, J = 14.0 Hz, H(12)), 3.37 (br d, 1H, J = 14.0 Hz, H′(12)), 4.14 (m, 1H, H(1)), 5.74 (m, 1H, H(7)), 7.58 (m, 2H), 7.68 (m, 1H), 7.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.11 (Me(10)), 22.30 (Me(11)), 25.97 (CH_2), 28.52 (CH_2), 30.67 (C(5)H), 60.70 (C(12)H_2), 77.43 (C(1)H), 82.70 (C(4)), 126.74 (C(7)H), 127.49 (2CH), 129.41(2CH), 131.17 (=C(8)), 133.88 (CH), 141.20 (C). Anal. Calcd for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.54. Found: C, 62.37; H, 6.58.

Selected NMR data for 58b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (br ddd, 1H, J = 13.6, 3.1, 1.5 Hz, H(9)*ax*), 1.78 (br s, 3H, Me(11)), 2.15−2.25 (m, 3H), 2.52−2.57 (m, 1H), 2.76−2.87 (m, 1H, H(7)*ax*), 3.21 (d, 1H, J = 14.0 Hz, H(12)), 3.41 (br d, 1H, J = 14.0 Hz, H′(12)), 4.37 (br d, 1H, J = 3.4 Hz, H(1)), 4.85−4.90 (m, 2H, =CHH′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.95 (Me(11)), 27.24 (CH_2), 29.23 (CH_2), 30.12 (CH_2), 32.02 (C(5)H), 60.39 (C(12)H_2), 80.96 (C(1)H), 82.96 (C(4)), 112.92 (=C(10)H_2), 145.97 (=C(8)).

Synthesis of (1*R*,4*R*,5*R*,8*S*)-4,8-Dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (56a) by Hydrogenation of Unsaturated Sulfones 57a and 58a. A mixture of unsaturated sulfones **57a** and **58a** (37.0 mg, 0.120 mmol, **57a**/**58a** ca. 86:14) in EtOAc (7 mL) was hydrogenated over PtO_2·H_2O (4.0 mg) at −10 °C ± 2 °C for 40 min (atmospheric pressure of hydrogen). After completion of hydrogenation, excess hydrogen was removed in vacuo. The mixture was filtered through a plug of cotton, washed with EtOAc, and evaporated. FC (EtOAc−hexane, 1:4) of the residue afforded the hydrogenated endoperoxide **56a** (33.2 mg, 90%) as a colorless solid: mp 112−113 °C; $[\alpha]^{20}_D$ −246.7° (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, 3H, J = 6.6 Hz, Me(10)), 1.52 (d, 3H, J = 0.7 Hz, Me(11)), 1.57 (ddd, 1H, J = 13.5, 3.1, 1.7 Hz, H(9)*ax*), 1.64−1.74 (m, 2H), 1.79−1.88 (m, 1H, H(8)*ax*), 1.89−1.98 (m, 1H), 2.04−2.10 (m, 1H), 2.35 (br dddd, 1H, J = 6.0, 6.0, 3.2, 3.2 Hz, H(5)), 2.46 (dddd, 1H, J = 13.5, 6.0, 3.2, 3.2 Hz, H(9)*eq*), 3.24 (d, 1H, J = 14.2 Hz, H(12)), 3.85 (br s, 1H, H(1)), 4.31 (dd, 1H, J = 14.2, 0.7 Hz, H′(12)), 7.59 (m, 2H), 7.67 (m, 1H), 7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.50 (Me(10)), 23.06 (Me(11)), 26.88 (C(9)H_2), 29.69 (C(6)H_2), 30.00 (C(5)H), 30.02 (C(7)H_2), 35.54 (C(8)H), 61.31 (C(12)H_2), 79.78 (C(1)H), 82.42 (C(4)), 127.55 (2CH), 129.34 (2CH), 133.67 (CH), 141.26 (C); DCI (CH_4) HRMS: obsd 311.1294, calcd for $C_{16}H_{23}O_4S$ (MH^+), 311.1317. Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.33. Found: C, 62.20; H, 7.24; S, 9.99.

(1*R*,4*S*,5*R*,8*S*)-4,8-Dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (56b). The saturated endoperoxide **56b** (48.6 mg, 88%) was synthesized from a mixture of unsaturated endoperoxides **57b** and **58b** (55.0 mg, 0.178 mmol; **57b**/**58b** ca. 84:16) according to the procedure described above for **56a.** A colorless solid, mp 134−135 °C (hexane−*tert*-butyl methyl ether); $[\alpha]^{20}_D$ −147.8° (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, 3H, J = 6.4 Hz, Me(10)), 1.46 (ddd, 1H, J = 13.3, 3.1, 2.0 Hz, H(9)*ax*), 1.65 (m, 1H), 1.68−1.82 (m, 3H), 1.80 (d, 3H, J = 0.5 Hz, Me(11)), 2.07−2.14 (m, 2H, H(8)*ax* + H(5)), 2.47 (dddd, 1H, J = 13.3, 4.4, 3.2, 3.2 Hz, H(9)*eq*), 3.14 (d, 1H, J = 14.0 Hz, H(12)), 3.37 (br dd, 1H, J = 14.0, 0.5 Hz, H′(12)), 3.85 (br dd, 1H, J = 4.4, 2.0 Hz, H(1)), 7.57 (m, 2H), 7.66 (m, 1H), 7.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.49 (Me(10)), 22.06 (Me(11)), 27.33 (C(9)H_2), 28.96 (C(6)H_2), 29.61 (C(7)H_2), 31.56 (C(5)H), 35.53 (C(8)H), 60.60 (C(12)H_2), 80.06 (C(1)H), 82.53 (C(4)), 127.64 (2CH), 129.32 (2CH), 133.76 (CH), 141.37 (C); DCI(CH_4) HRMS: obsd 311.1265, calcd for $C_{16}H_{23}O_4S$ (MH^+), 311.1317. Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.33. Found: C, 62.31; H, 7.16; S, 10.58.

Preparation of Saturated Sulfone-Endoperoxides 56a and 56b by Oxidation of Sulfides 55a,b. A mixture of diastereomers **56a**,**b** (18.0 mg, 90%, **a**/**b** ca. 55:45) was prepared by oxidation of sulfides **55 a**,**b** (18.0 mg, 0.065 mmol, **a**/**b** ca. 54:46) according to the general procedure 1 and purified by FC (hexanes−EtOAc, 4:1). The isomers **56a** and **56b** were separated by semipreparative DP HPLC (*i*-PrOH-hexane, 2:98).

(1*R*,4*R*,5*R*,7*R*,8*R*)-4,8-Dimethyl-7,8-epoxy-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (59a). A mixture of unsaturated sulfone **57a** (36.0 mg, 0.114 mmol) and *m*CPBA (38.0 mg of ca. 60%, 0.13 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 12 h. The reaction mixture was diluted with hexanes−EtOAc (40 mL, 3:1), washed with saturated $NaHCO_3$ (2 × 5 mL), and the aqueous washings were extracted with hexanes−EtOAc (20 mL, 3:1). The combined organic extract was dried (Na_2SO_4 + $NaHCO_3$) and evaporated. The residue was purified by FC (hexanes−EtOAc, 4:1) to afford the epoxide **59a** (35.5 mg, 96%) as a colorless solid: mp 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 3H, Me(10)), 1.50 (d, 3H, J = 0.5 Hz, Me(11)), 1.91 (ddd, 1H, J = 14.0, 2.3, 1.8 Hz, H(9)*ax*), 2.01 (br dd, 1H, J = 16.5, 2.3 Hz, H(6)*ax*), 2.15 (ddd, 1H, J = 14.0, 6.6, 3.8 Hz, H(9)*eq*), 2.21−2.32 (m, 2H), 3.19 (br d, 1H, J = 5.5 Hz, H(7)*eq*), 3.29 (d, 1H, J = 14.3 Hz, H(12)), 4.18 (br dd, 1H, J = 3.8, 1.8 Hz, H(1)), 4.22 (dd, 1H, J = 14.3, 0.5 Hz, H′(12)), 7.59 (m, 2H), 7.68 (m, 1H), 7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.64 (Me(10)), 22.57 (C(9)H_2), 23.38 (Me(11)), 25.27 (C(6)H_2), 28.74 (C(5)H), 57.10 (C(8)), 59.00 (C(7)H), 60.93 (C(12)H_2), 78.29 (C(1)H), 82.15 (C(4)), 127.50 (2CH), 129.36 (2CH), 133.79 (CH), 140.99 (C). Anal. Calcd for $C_{16}H_{20}O_5S$: C, 59.24; H, 6.21; S, 9.88. Found: C, 59.54; H, 6.21; S, 9.46.

Biology

In Vitro Antimalarial Activity. Antimalarial activities in vitro were determined in the Department of Medicine, JHU, by a modification[42] of the 48-h sensitivity assay of Desjardins[43] and Milhous,[44] based on a measuring the incorporation of [^{3}H]-hypoxanthine as an assessment of parasite growth.

In Vivo Antimalarial Activity. In vivo antimalarial activity was determined by W. Peters and B. L. Robinson (the Tropical Parasitic Diseases Unit, Northwick Park Institute for Medical Research, U.K.) according to the previously reported 4-d test protocol in a mice model.[17a]

Toxicology. The studies were carried out at Harlan Biotech Israel, Ltd., Rehovot, Israel, in compliance with good laboratory practice (GLP). The potential toxic effects of the test articles **46a** and **46b** were assessed following 7-d repeated intramuscular injections in equally sized groups, comprising 5 male healthy 5-week-old ICR/CD-1 mice. During acclimation and following dosing, the animals were housed within a limited-access rodent facility and kept in groups of five mice per cage. Automatically controlled environmental conditions were set to maintain temperature at 20−24 °C with a relative humidity of 30−70%. Sufficient air changes and 12-h light/12-h dark cycles were provided in the study room. Animals were provided a commercial rodent diet and were allowed free access to drinking water.

Animals were treated by injecting at one or more sites into the musculature of the rear limb assemblies (thigh or leg muscles) the maximal volume of injection, which was limited to 0.05 mL/site. Compound **46b** and arteether (**2c**) were freshly

dissolved daily, while compound **46a** was freshly finely suspended using ultrasound technique in sesame oil (vehicle, Sigma Chemical Co.) at 45−50 °C to prepare 5% (50 mg/mL) stock solutions (suspensions) for injections. The solutions were thermostated at 37 °C before injections. Variable volumes appropriate for the selected dose level were injected. The same dose of vehicle was administered under identical conditions.

Assessment of toxicity was based on a comparison of effects between the test groups, and both a reference and a control group were administered the reference article arteether (**2b**) and the vehicle, respectively. During the 7-d study, careful clinical examinations were carried out daily, including observations of potentially induced changes in the skin, fur, eyes, mucous membranes, respiratory, circulatory, autonomic and CNS, somatomotor activity, and behavior pattern. Particular attention was paid to the possible appearance of tremors, convulsions, salivation, diarrhea, lethargy, sleep, and coma. Changes in gait, posture, and response to handling, as well as stereotypes, such as excessive grooming, repetitive circling, or otherwise bizarre behaviors were also monitored. Morbidity and mortality were monitored and recorded twice every day. Individual body weights of animals were determined just prior to dosing (day 1). Thereafter, the animals were weighed also on day 5 and at study termination prior to sacrifice (day 8). At the end of the study, surviving animals were sacrificed by CO_2 asphyxiation. Hematology and clinical chemistry parameters for all animals of the vehicle control, arteether (**2c**) reference, and the high-dose groups of both test articles **46a** and **46b** were determined in blood samples, collected at the time of the scheduled terminal sacrifice (day 8 of the study).

All animals were subjected to a full necropsy, including examination of the external surface of the body, all orifices, and the cranial, thoracic, and abdominal cavities and their contents. The heart, liver, kidneys, and spleens from the animals were trimmed of any adherent tissue, as appropriate, weighed wet as soon as possible after dissection, and then preserved in 4% formaldehyde solution. The brain was not trimmed but rather excised following in situ perfusion. Perfusion was carried out through the left ventricle and by an appropriate fixative (a mixture of concentrated 37% formaldehyde (100 mL), distilled water (900 mL), $NaHPO_3$ (4 g), and Na_2PO_3 (65 g)). The brains were further preserved in the same medium and submitted as such to further processing. Tissue processing and slide preparations were performed by Pathology International Associates (U.S.A.), a GLP-approved laboratory.

Final assessment of the test articles **46a** and **46b** effects was based on the results of clinical observations, as well as on the body weights, clinical pathology, necropsy findings, organ weights, and histopathology results as compared to those of the vehicle (sesame oil) and the reference article (arteether (**2c**)) treated groups. Where applicable (i.e., the data of body weights, organ weights, and clinical pathology results), statistical analysis of the data was performed (software: GraphPad Instat, version 3.02; Statistical method: One-Way ANOVA-Dunnet Multiple Comparison Test).

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