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An efficient synthesis of bridged-bicyclic peroxides structurally related to antimalarial yingzhaosu A based on radical co-oxygenation of thiols and monoterpenes

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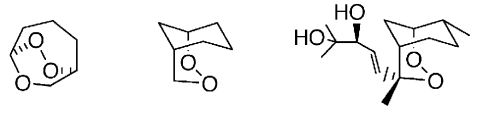
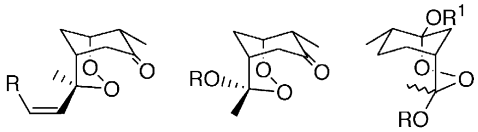
Abstract—Synthesis of β-sulfenyl endoperoxides **9** was achieved by a four component sequential free radical reaction based on the application of the thiol-olefin-co-oxygenation reaction to monoterpenes, followed by in situ treatment with triphenylphosphine. β-Sulfenyl endoperoxides **9** were oxidized with *m*-CPBA to β-sulfonyl endoperoxides **10**. This process provides an efficient method for the preparation of peroxides containing the 2,3-dioxabicyclo[3.3.1]nonane system (**2**) characteristic of antimalarial agents of the yingzhaosu A (**3**) family. A simple NMR diagnostic tool for the identification of stereoisomers is described. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

A promising approach for the treatment of malaria caused by Plasmodia resistant to customary drugs like the quinoline derivatives, chloroquine and mefloquine, involves the use of peroxides.[1,2] Indeed, naturally occurring artemisinin (qinghaosu) and semisynthetic derivatives thereof have been used, on a limited scale, for treating malaria.[3] The development of this first generation of antimalarial peroxide drugs was followed by a world-wide intensive quest for better antimalarial peroxides. Major efforts were directed towards the development of new compounds that, like artemisinin, contain a trioxane system **1** as a pharmacophore.[1,4] Among other investigated cyclic peroxides, particular attention was given to compounds containing, as putative pharmacophore, the 2,3-dioxabicyclo[3.3.1]nonane system **2**. The 2,3-dioxabicyclo[3.3.1]nonane system **2** was first identified in yingzhaosu A (**3**) isolated from an extract of *Artabotrys Uncinatum*s that was used in Chinese folk medicine for treating malaria.[5] Yingzhaosu A was subsequently obtained by a low yield 15-step total synthesis.[6] In this synthesis the bicyclic peroxide system is formed on the sixth step through an intramolecular Michael addition of an hydroperoxide group to a carbonyl-conjugated carbon–carbon double bond.[6] A similar synthetic strategy was applied for the synthesis of more readily accessible endoperoxides of type **4**.[7] While no sufficient data required for evaluation of yingzhaosu A (**3**) as an antimalarial agent were ever reported, the role of the 2,3-dioxabicyclo[3.3.1]-nonane system **2** as a pharmacophore was established through the synthesis and antimalarial screening of synthetic peroxides of type **4**. Compounds of type **4** (R=Ar, Het or long chain alkyl) were found to exhibit high antimalarial activity,[7] and arteflene (**4a**) proved to be a reasonable drug candidate.[1,3e,7,8] It seems that one of the factors that may have halted the further development of natural yingzhaosu A (**3**) and synthetic endoperoxides **4** as antimalarial drug candidates derived from the scant supply of **3** from natural sources and the low-yielding syntheses of **3** and **4**. Recently, syntheses of acetal-peroxides of types **5**[9] and **6**[10] based on the construction of the endoperoxide system **2** by a heterolytic cyclization involving the intermediacy of transient carbonyl-oxide and hydroperoxide derivatives were reported.



1 **2** **3**



4 **5** **6**

4a, R = 2,4-di(trifluoromethyl)benzene

Keywords: antimalarial peroxides; free radicals; multi-component reaction; sequential reactions; thiol olefin co-oxygenation reaction.

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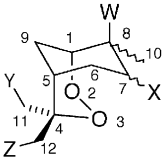
In the mid 1990's we initiated a research project directed towards the design, synthesis, and antimalarial screening of new endoperoxides **7**, **8** containing the 2,3-dioxabicyclo-[3.3.1]nonane system **2**.[11,12] This was followed by the elaboration of a new total synthesis of yingzhaosu A (**3**).[13] We now present a full account on the synthesis and structure determination of β-sulfenyl- and β-sulfonyl-endoperoxides **9** and **10**, which served as precursors in the synthesis of potent antimalarial agents.[12,14,15] Additionally, we showed that 4-sulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonanes **9″** (n=0, R=Ph, R^1=R^2=H) can function as a key intermediate in a total synthesis of yingzhaosu A (**3**).[13]



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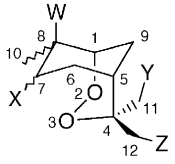

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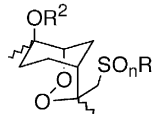
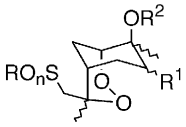


9', n = 0
10', n = 2

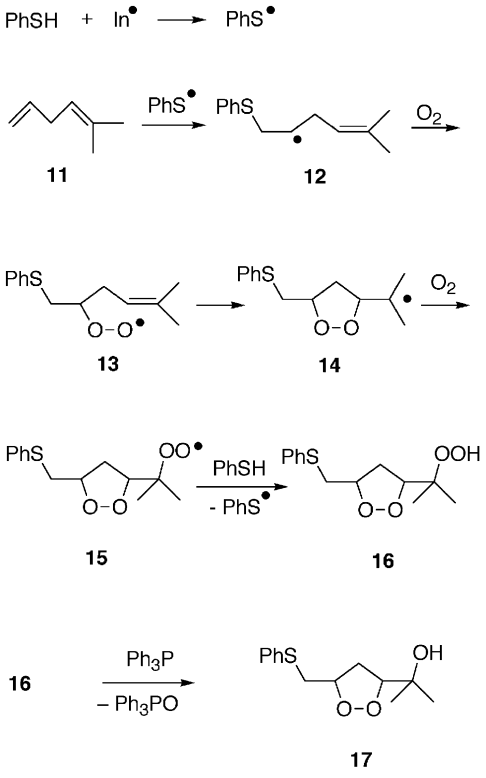


9'', n = 0
10'', n = 2

2. Synthesis design

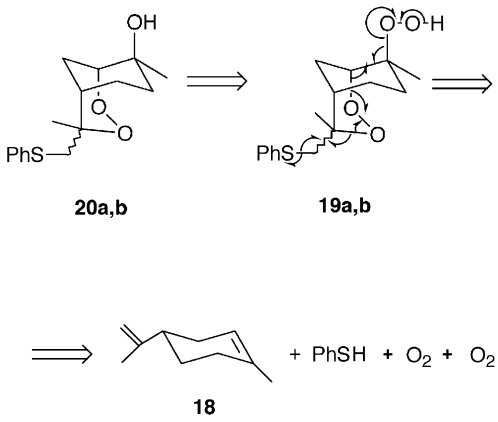
Enantiomeric 2,3-dioxabicyclo[3.3.1]nonanes of type **7** and **8** were defined as synthetic targets in which X, Y, Z and W represent a hydrogen atom, or functional groups that can be modified as deemed necessary from structure–activity studies. Following the development of reactions based on thiol-mediated free radical cyclizations, useful for the synthesis of nitrogen-containing heterocycles,[16] we examined the application of a similar strategy to the synthesis of the dioxygen-containing heterocycles of type **7** and **8**.[11,12] Additional support for using a methodology based on free radical reactions came from two directions: (1) studies by Porter on the synthesis of monocyclic peroxides by a method involving a 6-*exo* intramolecular addition of peroxyradicals to carbon–carbon double bonds;[17] (2) studies by Beckwith on the application of Thiol Olefin Co-Oxygenation (TOCO reaction) to 1,4-dienes for the synthesis of 1,2-dioxolanes like **16**, **17** (Scheme 1).[19,20]

As exemplified in Scheme 1, monocyclic peroxides like **16** were obtained through a highly favored 5-*exo-trig* addition of a peroxy radical intermediate **13**. Application of the TOCO reaction to the synthesis of bridged bicyclic peroxides of type **7** and **8** posed a few questions that required careful consideration. Scheme 2 represents a retro-synthesis of the prototypic β-phenylsulfenyl-endoperoxides **20a**,**b** which leads to endoperoxide–hydroperoxide **19a**,**b** and then, through homolytic bond cleavage to limonene

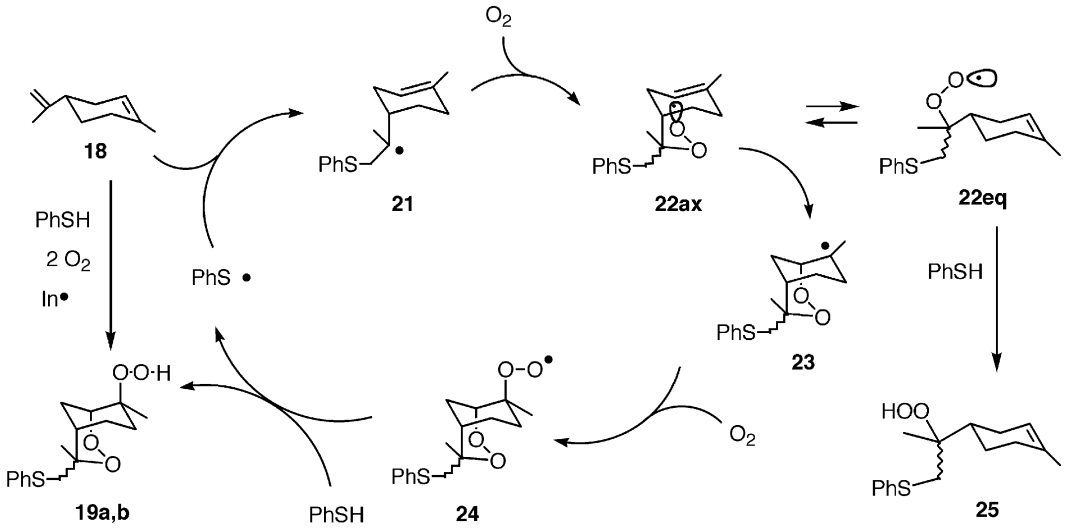


Scheme 1.

18, phenylthiol and two equivalents of molecular oxygen. A straightforward approach to the synthesis of 2,3-dioxabicyclo[3.3.1]nonane **20a**,**b** would thus require a one operation process by which these four components would interact through a sequential free-radical reaction following the pattern described in Scheme 3. This would require that $PhS^{\bullet}$, obtained in the initiation step from PhSH and the radical initiator ($In^{\bullet}$), would add regioselectively to the terminal end of the isopropenyl double bond of limonene **18**. The emerging carbon centered radicals **21** should be rapidly trapped by molecular oxygen to give peroxy-radicals **22**, which should undergo a 6-*exo* intramolecular addition to endocyclic double bond generating tertiary carbon-centered radicals **23**. Radicals **23** should be trapped by a second equivalent of oxygen, thus giving peroxy radicals **24**. In turn, peroxy-radicals **24** should abstract a hydrogen atom



Scheme 2.



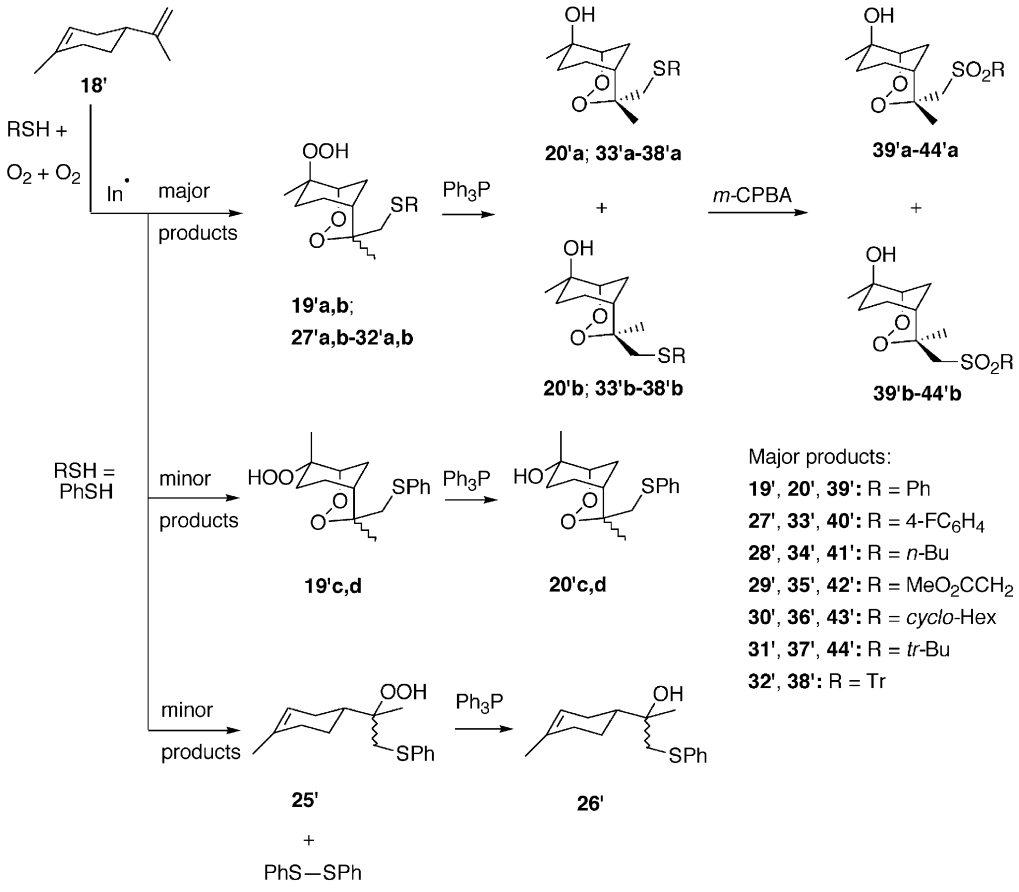
Scheme 3.

from PhSH, giving the target bicyclic hydroperoxides **19a**,**b** and PhS$^{\bullet}$ that continues the chain reaction. In this sequential process every step, except the last one, is reversible. The viability of such a process depends on a particular series of rate constants.[21–26] A major concern during the planning stage derived from the notion that 6-*exo* addition of peroxy radical **22** requires an axial conformation as in **22ax**. The predominance of the equatorial conformation **22eq** could result in an excessive reduction in the rate of cyclization of **22**, e.g. in comparison to the 5-*exo*-cyclization of **13** to the corresponding dioxolanyl-radicals **14** (Scheme 1). Under such circumstances radical **22** (Scheme 3) could take undesired reaction paths resulting from intramolecular hydrogen atom abstraction from allylic positions, and premature intermolecular hydrogen atom abstraction from phenylthiol leading to monocyclic hydroperoxide **25**.

3. Synthesis of 4-sulfenylmethyl- and 4-sulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols 9 and 10

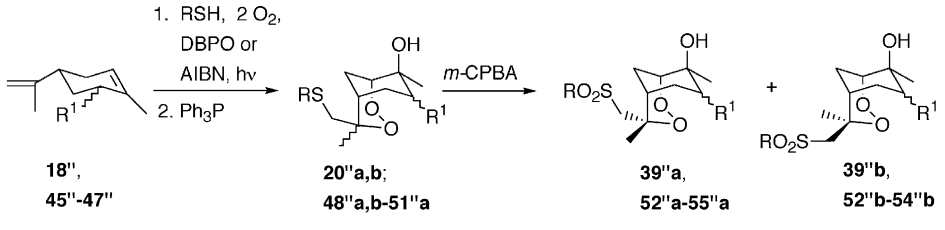
Due to the interest in the antimalarial properties of target compounds **9** and **10**,[12,14,15] some of the experiments described in this paper were performed with *R*-(+)-limonene (**18′**), some with *S*-(−)-limonene (**18″**), and some individually with both of them. To avoid unnecessary repetitions, where discussions are accompanied by 3-dimensional formulas as in Schemes 2 and 3, the structures of *S*-(−)-limonene **18″** and reaction products of it are drawn. Numbering of compounds originating from, or relating, to both *S*-(−)- and *R*-(+)-limonene (**18**) are denoted **mn**, while compounds originating from experiments in which only *R*-(+)-limonene (**18′**) was used are denoted **mn′** and those from experiments in which only *S*-(−)-limonene (**18″**) was used are denoted **mn″**.

Following the synthetic plan shown in Scheme 3, the thiol–limonene co-oxygenation was studied under a variety of conditions and with a number of different thiols. The products of the designed four-component sequential free radical reaction of limonene **18**, a thiol and two equivalents of molecular oxygen are described in Scheme 4 (see also Scheme 5). In this scheme the major reaction products, which were obtained in all the studied reactions, are separated from the minor reaction products that were deliberately sought, isolated and characterized only in a few experiments with limonene **18** and phenylthiol. Due to the instability of the hydroperoxide function in compounds **19′**, **27′**–**32′** and **25′** the crude reaction mixture was treated, in the same vessel, with PPh_3 to give a mixture of the bicyclic 8-hydroxy-endoperoxides **20′**, **33′**–**38′** and monocyclic β-hydroxysulfides of type **26′**. Trapping of the carbon-centered radical **21** by molecular oxygen (Scheme 3) was found to be non-diastereoselective. Indeed, diastereomeric mixtures of endoperoxides **20′a**, **33′a**–**38′a** and **20′b**, **33′b**–**38′b** were isolated and characterized as the two major peroxides (Scheme 4). The ratios of the isomers **a/b** in most experiments and in all the high-yielding experiments (>40%) described in Table 1 and detailed in Section 6, are 55:45 (±3%). A slightly higher, though still insignificant diastereoselectivity was observed in some of the low-yielding experiments. In contrast trapping of the carbon-centered radical **23** (Scheme 3) is highly diastereoselective. Molecular oxygen adds preferentially from the less hindered side of radical **23** to form the *axially*-oriented peroxy-radical **24**, and after subsequent reduction the major hydroxy peroxides **20′a**, **33′a**–**38′a** and **20′b**, **33′b**–**38′b** (Scheme 4). In some large-scale experiments with limonene and PhSH, a few percent of *equatorially* positioned hydroxy peroxides **20c** and **20d** were isolated and characterized by derivatization as shown in Scheme 6. Since preliminary screening indicated that β-sulfonyl-endoperoxides **39′** are much better antimalarial agents than the corresponding β-sulfenyl-endoperoxides **20′**,[12,14] and since they are also more amenable to chromatographic separation into individual diastereomers of types **a** and **b**, diastereomeric mixtures of sulfides **20′**, **33′**–**38′** were usually oxidized to the corresponding sulfones **39′**–**44′** and then separated into individual diastereomers (Scheme 4). Exceptions are the β-sulfenyl-endoperoxides **35′a**,**b**; **38′a**,**b** which were separated to their individual two diastereomers **35′a**, **38′a** and **35′b**, **38′b**, respectively.



Scheme 4.

The data related to the optimization of the TOCO reaction when applied to the co-oxygenation of limonene **18** and phenylthiol are summarized in Table 1 along with a few examples of co-oxygenation involving other representative thiols. The feasibility of the reaction described in Scheme 4 was first examined with PhSH, under conditions (method 1A) similar to those reported[19a] (Scheme 1) for the preparation of 1,2-dioxolane **17** from 1,4-diene **11**. Thus, limonene **18′**, PhSH (equimolar amount) and free radical initiator [di-*tert*-butylperoxalate (DBPO),[27] catalytic amount] were dissolved in benzene, and oxygen gas was bubbled through the solution for 15 h. After flushing with argon to remove excess oxygen, the resulting endoperoxide–hydroperoxide **19′a,b** (R=Ph) was chemoselectively reduced with PPh_3 to give hydroxy-endoperoxides **20′a,b** (14%) as a mixture of two diastereomers (**a/b**, 55:45), PhS–SPh (25%) and hydroxysulfide **26′** (32%). These results (Scheme 4 and Table 1, entry 1; see also Scheme 3) indicated that: (a) PhS• dimerization competes with PhS• addition to limonene; (b) intermolecular hydrogen atom transfer from PhSH to peroxyradical **22** to give hydroperoxy-sulfide **25** (and, after PPh_3 reduction, hydroxy-sulfide **26**) competes with the intramolecular 6-*exo*-addition of peroxy radical **22** to the trisubstituted endocyclic C=C bond. The first problem was handled by increasing the limonene/thiol ratio. Indeed, at a 3:1 ratio (Table 1, entry 2) the yield of endoperoxide



18'': R^1 = H
45'': R^1 = β–OBz
46'': R^1 = α–OBz
47'': R^1 = α–OH

20'' (54%), **39''** (94%): R = Ph, R^1 = H
48'' (22%), **52''** (93%): R = Ph, R^1 = β-OBz
49'' (6.5%), **53''** (91%): R = *n*-Bu, R^1 = β-OBz
50'' (6%), **54''** (89%): R = Ph, R^1 = α-OBz
51'' (13.5%), **55''** (92%): R = Ph, R^1 = α-OH

Scheme 5.

Table 1. Co-oxygenation of limonene **18** and thiols (Schemes 4 and 5).

Entry	Procedure[a]	Scheme	RSH	Ratio of limonene/thiol	T (°C)	Initiator (mol %)[b]	Solvent[c]	Reaction time (h)[d]	Product	Yield (%)
1	1A	4	PhSH	1:1	rt	DBPO (5)	Benzene	15	**20′a,b**	14
2	1A	4	PhSH	3:1	rt	DBPO (3)	HP–BN	12	**20′a,b**	29
3	1B	4	PhSH	1:1	rt	DBPO (3)	HP–BN	10+10	**20′a,b**	31
4	1B	4	PhSH	3:1	rt	DBPO (3)	HP–BN	10+10	**20′a,b**	55
5	1B	4, 5	PhSH	3:1	rt	DBPO (3)	HP–BN	10	**20a,b**	54
6[e]	1B	4	PhSH	3:1	rt	DBPO (3)	HP–BN	10+10	**20′a,b**	26
7	1B	4	4-FC_6H_4SH	3:1	rt	DBPO (3)	HP–BN	10	**33′a,b**	47
8	1C	4, 5	PhSH	3:1	rt	DBPO (3)	HP–BN	10	**20a,b**	47
9[e]	1C	5	PhSH	3:1	rt	DBPO (3)	HP–BN	10	**20″a,b**	18
10	1D	4	PhSH	3:1	65	AIBN (3+3)	MeCN	10	**20′a,b**	47
11	1D	4	PhSH	3:1	40	AIBN (3+3)	MeCN	10	**20′a,b**	16
12[e]	1D	4	PhSH	3:1	40	AIBN (3+3)	MeCN	10	**20′a,b**	7
13	1E	4	PhSH	3:1	40	AIBN (3+3)	MeCN	10	**20′a,b**	50
14	1E	5	PhSH	3:1	rt	AIBN (3)	MeCN	10	**20″a,b**	42
15	1E	4, 5	PhSH	3:1	rt	AIBN (3+3)	MeCN	10	**20a,b**	52
16	1E	4, 5	PhSH	3:1	4	AIBN (3+3)	MeCN	10	**20a,b**	49
17	1E	4	PhSH	3:1	4	AIBN (3+3)	MeOH	10	**20′a,b**	31
18	1E	4	PhSH	3:1	4	AIBN (6+6)	MeCN	10	**20′a,b**	48
19	1E	4	PhSH	1:1	4	AIBN (4+4)	MeCN	10	**20′a,b**	34
20	1E	5	PhSH	3:1	4	AIBN (6+6)	MeCN	18	**20″a,b**	44
21	1E	4	PhSH	3:1	−10	AIBN (3+15)	MeCN	36	**20′a,b**	34
22	1E	4	*n*-BuSH	3:1	4	AIBN (3+3)	MeCN	12	**34′a,b**	18
23	1E	4	*n*-BuSH	3:1	4	AIBN (6+6)	MeCN	30	**34′a,b**	25
24	1E	4	MeO_2CCH_2SH	3:1	4	AIBN (3+3)	MeCN	18	**35′a,b**	18
25	1E	4	Cyclo-HexSH	3:1	4	AIBN (6+6)	MeCN	25	**36′a,b**	16
26	1E	4	*tr*-BuSH	3:1	4	AIBN (6+6)	MeCN	48	**37′a,b**	29
27	1E	4	TrSH	3:1	4	AIBN (6+6)	MeCN	30	**38′a,b**	41

[a] Procedures are recorded in the text and detailed in Section 6.
[b] DBPO is an abbreviation for di-*tert*-butylperoxalate. The first value in brackets refers to the portion of initiator initially placed into the reaction mixture; the second value refers to the portion of initiator, which was slowly added simultaneously with the thiol.
[c] HP–BN refers to a mixture of *n*-heptane–benzene (ca. 2.5:1).
[d] The first value refers to the time of the thiol addition, the second value refers to additional exposure to oxygen.
[e] Air was used instead of oxygen.

20′a,b was doubled while the yield of PhS–SPh was reduced to 10%. A corollary to increasing the rate of generation of radicals **21** and consequently **22**, is the increase in the yield of formation of hydroperoxide **25′**, and consequently of hydroxy-sulfide **26′** (46%). To decrease the rate of hydroxy-sulfide **26′** formation, the concentration of PhSH should be decreased throughout the duration of the reaction. Indeed, by adding PhSH to the reaction mixture through a syringe pump over 10 h (method 1B) the yield of hydroxy-endoperoxide **20** was doubled (compare entries 1 and 3, Table 1). When the two modifications which are described in entries 2 and 3, were employed at once, the yield of the endoperoxide **20** was augmented to 55% (entries 4 and 5, method B). No difference was observed between reactions that were terminated immediately after completion of thiol addition and those in which oxygen was bubbled through the reaction mixture for an additional 10 h (compare entries 4 and 5). Substitution of pure oxygen by air resulted in a significant yield diminution (compare entries 4–6, and 8–9). Usually, experiments were directed towards the preparation of endoperoxides like **20a,b**, while by-products were not examined. However, when the overall mass balance was examined (Table 1, entry 5) the following compounds were accounted for: (i) excess of limonene **18** (72%); (ii) β-phenylsulfenyl-endoperoxides **20a–d** (ca. 57%, **a/b/c/d**, ca. 52:42:3:3)[28]; (iii) hydroxy-endoperoxides **26** (25%); and (iv) PhS–SPh (10%), thus accounting for a mass balance of 90% of sulfur-containing products. Fluorophenylsulphenyl-endoperoxides **33′a,b** were obtained in similar yield (entry 7) using 4-fluorothiophenol instead of thiophenol.

Procedure 1B, under the conditions specified in entry 5, was found to be highly reproducible and was used in our laboratory for the preparation of endoperoxides **20a,b** on 2–4 g scale. (See Ref. 29 for SAFETY PRECAUTIONS). In order to minimize the generation of hazardous mixtures of oxygen and organic solvents vapors, and in order to allow testing reactions in a wider range of temperature, the procedure of bubbling oxygen through the reaction mixture (methods 1A and 1B) was substituted by vigorous stirring of the reaction mixtures under a measured volume of pure oxygen (methods 1C–1E). An additional advantage of this modification is the possibility of monitoring oxygen consumption. Applying method 1C did not result in a significant decrease in yield (compare entries 5 and 8). Also, for safety reasons, the hazardous DBPO initiator was substituted by AIBN and the heptane–benzene solvent was substituted by acetonitrile. In these experiments one portion of AIBN initiator was added at the start of the reaction and a second portion was introduced through a syringe pump simultaneously with the thiol. Following this procedure (method 1D) endoperoxides **20′a,b** were obtained in a good yield at 65°C (entry 10) and in a modest yield at 40°C (entry 11), substitution of oxygen by air reduced the yield even further (entry 12). To allow an effective use of AIBN at moderate temperatures the reaction mixture was irradiated (λ=310–400 nm; λ_{max}=365 nm; Pyrex glassware) (method 1E). Indeed at 40°C (entry 13), at room temperature (entries 14

and 15), as well as at 4°C (entry 16) endoperoxides **20a**,**b** were obtained in good yields. Further decrease of reaction temperature (entry 21), increase in amount of initiator (entry 18), prolongation of reaction time (entry 20), and using methanol as a solvent (entry 17) were counterproductive.

Due to safety considerations[29] we recommend the use of method 1E, at 4°C, (entry 16) for the synthesis of β-phenylsulfenyl-endoperoxides **20a**,**b**, although method 1B (entry 5) affords the same products in slightly higher yield. Procedure 1E was repeatedly used for the preparation of endoperoxides **20a**,**b** in up to 5 g scale.

Co-oxygenation of *R*-(+)-limonene (**18′**) with aliphatic thiols, namely *n*-butylthiol, methylthioglycolate, cyclohexylthiol, *tert*-butylthiol,and tritylthiol afforded the corresponding β-sulfenyl-endoperoxides **34′**–**38′** (Table 1, entries 22–27).[30] The tested primary and secondary alkylthiols were found to be considerably less effective than thiophenol (entries 22–25). A modest increase in yield was observed for *tert*-butylthiol (entry 26), and a considerable improvement for the bulky tritylthiol (entry 27). An improvement in the yields of the target endoperoxide in the TOCO reactions with aliphatic thiols was obtained by a prolonging the thiol addition time and by increasing the amount of AIBN (compare the entries 22 and 23). These factors partially compensate for the decreased reactivity of aliphatic thiyl radicals and the lower hydrogen donation ability of alkylthiols as compared to phenylthiol.

In Scheme 5 the co-oxygenation (procedure 1B) of phenylthiol with *S*-(−)-limonene (**18″**) is compared to that of O-benzoylcarveols **45″**, **46″** and *cis*-carveol (**47″**). It was found that the reaction yields significantly decrease with the introduction of substituents at position 7. An atypical high diastereoselectivity at C(4) was observed in the TOCO reaction with carveol **47″** which afforded exclusively isomer **51″a**.

Each mixture of diastereomeric sulfides **20′a**,**b**; **33′a**,**b**–**37′a**,**b**; **20″a**,**b** and **48″a**,**b**–**51″a** was oxidized with *m*-CPBA at rt to give, after chromatographic separation, the corresponding individual sulfones **39′a**–**44′a** and **39′b**–**44′b** (Scheme 4), **39″a**, **52″a**–**55″a** and **39″b**, **52″b**–**54″b** (Scheme 5).[31] Sterically hindered tritylsulfides **38′** couldn't be oxidized under these conditions.

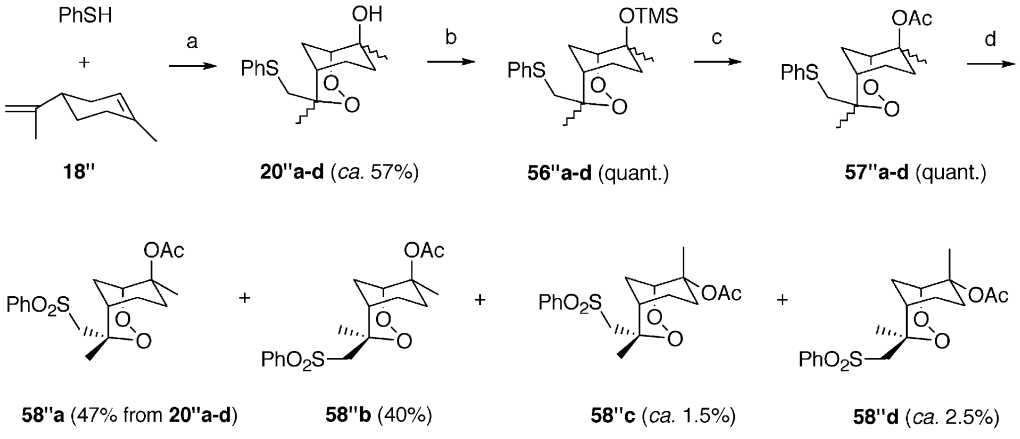
For structural determination (next section) and for preliminary biological screening[12,14,15] a mixture of diastereomeric 8-hydroxy-β-phenylsulfenyl-endoperoxides **20″a**–**d** was converted into 8-acetoxy-β-sulfonylendoperoxides **58″a**–**d** (Scheme 6). Our best procedure involves O-silylation of hydroxyl function in **20″a**–**d** to give the TMS-derivatives **56″a**–**d**, followed by acetylation with neat AcCl to the corresponding 8-acetoxy-β-phenylsulfenyl-endoperoxides **57″a**–**d**.[32] The resulting crude mixture of β-phenylsulfenyl-endoperoxides **57″a**–**d** was oxidized with *m*-CPBA to yield, after repeated chromatography, the four individual diastereomeric 8-acetoxy-β-phenylsulfonyl-endoperoxides **58″a** (47% from **20″a**–**d**), **58″b** (40%), **58″c** (ca. 1.5%), and **58″d** (ca. 2.5%). The major isomers **58a** and **58b** were also prepared from the single hydroxysulfones **39a** and **39b** respectively.[12,15]

Pure endoperoxides of type **10** are highly stable. For example, no change was observed in the NMR spectra of the samples **39″a** (crystals) and **39″b** (oil) that were kept for four years at room temperature.

4. Structure determination

In the thiol–terpene co-oxygenation reaction, described in the previous section, the three new stereogenic centers at C(1), C(4) and C(8) are generated in a single operation. The fourth, stereocenter at C(5), originating from the unaltered stereocenter at C(4) of the parent monoterpenes **18**, **45**–**47**, was used as a reference for the determination of the absolute configuration of all the other stereocenters.

Single crystal X-ray analysis of 4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol **39″a** provided the 3D-structure shown in Fig. 1. The absolute configuration of stereocenters 1*S*, 4*S*, and 5*S* in the bicyclic system is the same as that reported for the corresponding stereocenters in yingzhaosu A (**3**).[6a] Also, the methyl(10)



Scheme 6. *Reagents and conditions*: (a) (i) O_2, DBPO, heptane–benzene (general procedure 1B); (ii) Ph_3P; (b) TMSOTf, 2-6-lutidine, CH_2Cl_2, 0°C, 1 h; (c) AcCl (neat), rt, 48 h; (d) (i) *m*-CPBA, EtOAc, rt, 6 h; (ii) FC and HPLC separation.

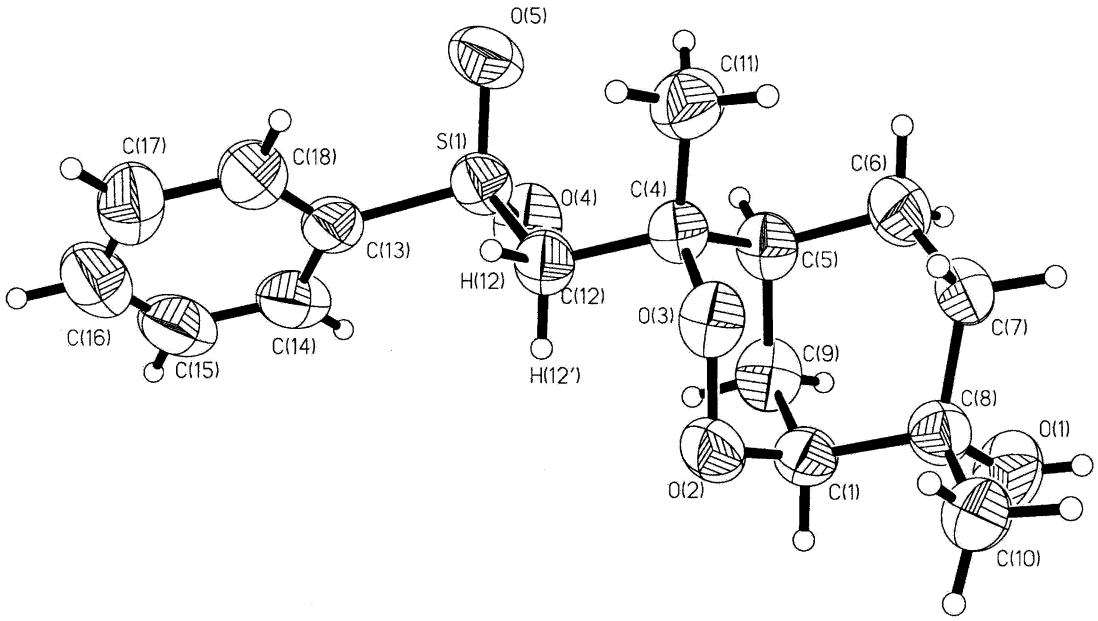
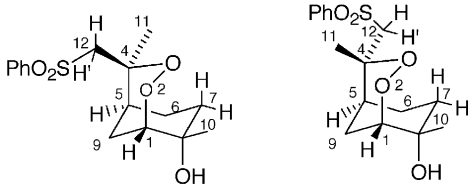


Figure 1. The X-ray crystal structure of the bicyclic endoperoxide **39″a** (ORTEP).[43]

group on the 8*S*-carbon is *equatorially* positioned as the analogous methyl group in **3**.[6a] Both of the 1,2-dioxane and the cyclohexane rings adopt chair conformations, forming a low energy 2,3-dioxabicyclo[3.3.1]nonane system. A chair conformation of the endoperoxide ring has been previously reported for other 2,3-dioxabicyclo[3.3.1]nonane systems[6a,9] as well as for monocyclic 1,2-dioxanes.[33] In contrast to that, the 1,2-dioxane fragment in the peroxide–acetals of type **6** adopts a boat-like conformation.[10a]

Since no simple method for the determination of configuration at the quaternary C(4) and C(8)-stereocenters of 2,3-dioxabicyclo[3.3.1]nonanes has been reported, a thorough NMR study on the new 4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane derivatives was performed, and is detailed herein. β-Sulfonyl-endoperoxides **39a** as well as other diastereomers of series **a** are characterized by a *syn*-arrangement of the O(2)–O(3)–C(4)–C(12) bonds, while β-sulfonyl-endoperoxides **39b** as well as the other diastereomers of series **b** are characterized by an *anti*-arrangement of the O(2)–O(3)–C(4)–C(12) bonds. Analysis of the X-ray data of β-sulfonyl-endoperoxides **39″a** revealed a significant difference in the through space distances between the nonequivalent hydrogen atoms of the C(12)HH′ moiety and the oxygen atoms. For the C(12)H-proton the calculated through space distances are 3.175 Å for H(12)–O(2) and 2.528 Å for H(12)–O(3), while for the C(12)H′-proton the corresponding distances are shorter and almost identical, namely 2.431 Å for H′(12)–O(2) and 2.491 Å for H′(12)–O(3). The difference in through space distances between the diastereotopic C(12)HH′ protons and the electronegative O(2)-atom is bound to be reflected in the ^{1}H NMR spectra. The additional deshielding effect of O(2)-atom should be stronger on the H′(12)-proton than on its geminal H(12)-proton. In contrast, due to the *anti*-arrangement between O(2) and C(12)HH′ in diastereomeric β-sulfonyl-endoperoxide **39b** both protons of the C(12)HH′ group are more remote through space from O(2) than in diastereomer **39a** and therefore should be less deshielded. Accordingly, in isomer **39b**, that has a *syn*-arrangement of the O(2) and Me(11), the protons of the Me(11) group are closer to the O(2)-atom than Me(11)-protons in the isomer **39a**. Consequently, the effect of additional deshielding by O(2)-atom on Me(11) group should be inverted between the isomers **39a** and **39b**. The viability of this analysis was corroborated, as described below by NMR studies on β-sulfonyl-endoperoxides **39**–**44** and **52**–**55** as well as β-sulfenyl-endoperoxides **20**, **33**–**38**, and **48**–**51**, thus providing a simple NMR method for differentiation between diastereomers of series **a** and **b**.



39″a **39″b**

A detailed analysis of the ^{1}H and ^{13}C/DEPT NMR spectra of all the β-sulfonyl-endoperoxides **39**–**44**, **52**–**55**, **58** and β-sulfenyl-endoperoxides **20**, **33**–**38** and **48**–**51**, supported by the COSY, HMQC and NOE difference experiments for the key compounds **20**, **35**, **38**, **39**, **51**–**55** and **58** enabled a full assignment of the resonance signals (see Section 5). Representative signals in the ^{1}H and ^{13}C spectra required for structural discrimination between diastereomers **a** and **b** are given in Table 2 for the β-sulfenyl-endoperoxides **20a**,**b** and β-sulfonyl-endoperoxides **39a**,**b**. Diastereomers **a** and **b** exhibit very similar NMR patterns for stereocenter C(8) and adjacent atoms. In contrast, the NMR patterns related to atoms adjacent to the stereocenter C(4) are significantly different for the **a** and **b** diastereomers. Therefore, diastereomers **a** and **b** differ in their configuration at C(4), but not at C(8). Thus, a typical AB quartet attributed to the C(12)HH′ group appears in the ^{1}H NMR spectra of

Table 2. Selected ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data for 4-phenylsulfenylmethyl- **20a**,**b** and 4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols **39a**,**b** in $CDCl_3$

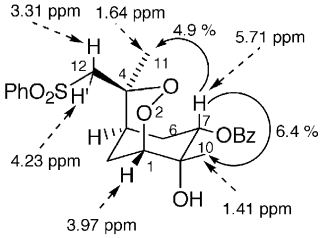
Position	**20a**		**20b**		**39a**		**39b**	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	3.68 m	81.57 d	3.71 m	82.02 d	3.67 br dd (3.5, 2.5)	81.96 d	3.68 br dd (3.3, 1.8)	82.35 d
4		83.77 s		83.83 s		82.71 s		82.84 s
5	1.91 br dddd	29.23 d	1.81 m	30.50 d	2.30 m	30.05 d	2.09 br dddd	31.53 d
10	1.40 s	28.04 q	1.39 s	28.04 q	1.35 s	27.97 q	1.29 s	27.83 q
11	1.25 br s	21.89 q	1.56 d (0.6)	21.76 q	1.51 br s	22.87 q	1.80 br s	21.71 q
12	3.35 d (12.8) 3.71 dd (12.8, 0.5)	40.68 t	2.96 d (12.0) 3.03 dd (12.0, 0.6)	40.73 t	3.27 d (14.3) 4.23 dd (14.3, 0.5)	61.02 t	3.14 d (14.0) 3.33 br d (14.0)	60.55 t

Chemical shifts (ppm), multiplicity of the signal and coupling constants (Hz) are recorded. For the full record of the NMR data see Section 6.

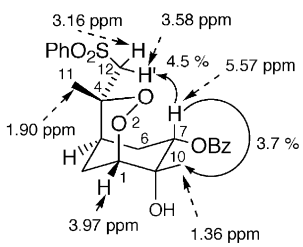
β-sulfonyl-endoperoxide **39a** at δ 3.27 and 4.23 ppm (^{2}J=14.3 Hz), the low field component of the quartet is additionally split (^{4}J=0.5 Hz) by the Me(11) protons. In the spectra of the diastereomeric β-sulfonyl-endoperoxides **39b** the corresponding AB quartet was observed at δ 3.14 and 3.33 ppm (^{2}J=14.0 Hz), the low field signal is broadened by a long-range coupling with the Me(11)-protons. The difference in the chemical shifts $\Delta(\delta H'-\delta H)$ is about 1.0 ppm for **39a** and about 0.2 ppm for its diastereomer **39b**. This conforms with the differences in deshielding magnitude of diastereotopic C(12)HH′ protons, by O(2) in the isomers **a** and **b**, discussed above. A long-range coupling was always observed as a cross-peak of the H′(12)-proton and Me(11) in the COSY spectra in all the examined 2,3-dioxabicyclo[3.3.1]nonanes. This interaction usually results in the broadening of the Me(11) singlet and the downfield component of the C(12)HH′ pattern. In many cases a splitting of the signals with ^{4}J=0.3–0.7 Hz could be directly detected in ^{1}H NMR spectra. The broadened singlet or doublet of Me(11) is clearly distinguished from the narrow singlet of Me(10). The chemical shift values of Me(10) are always very similar for both **a** and **b** diastereomers and are not influenced by the oxidation state of a sulfur atom.

As expected, a low field shift of Me(11) at δ 1.80 was observed in the ^{1}H NMR spectra of β-sulfonyl-endoperoxide **39b** as compared to δ 1.51 in its C(4)-isomer **39a**. The same tendency in the chemical shifts of C(12)HH′ and Me(11) were noticed in the ^{1}H NMR spectra of the diastereomeric β-sulfenyl-endoperoxides **20a**,**b** (Table 2) and all the other bicyclic endoperoxides studied in this work (see Section 5). Thus, downfield chemical shifts for C(12)HH′ AB quartet of $\Delta(\delta$ H′–H) values of about 1.0 ppm for β-sulfonyl-endoperoxides and 0.4 ppm for β-sulfenyl-endoperoxides, as well as a chemical shift of Me(11) at δ 1.5 ppm for β-sulfonyl-endoperoxides and 1.25 ppm for β-sulfenyl-endoperoxides are distinctive ^{1}H NMR features for endoperoxides of the **a** series. For the **b** series the usual chemical shifts difference for C(12)HH′ AB quartet $\Delta(\delta$ H′–H) is about 0.2 ppm for β-sulfonyl-endoperoxides and 0.1 ppm for β-sulfenyl-endoperoxides. Typically, a low field signal at about 1.8 ppm is observed for the Me(11) of β-sulfonyl-endoperoxides and at ca. 1.55 ppm for β-sulfenyl-endoperoxides. Additional diagnostic indications for the a and b series of 2,3-dioxabicyclo[3.3.1]nonanes were found in the ^{13}C NMR spectra. In all the examined compounds the values of δ_C for C(1) and C(5) were always higher by ca. 0.4 and 1.5 ppm respectively in the **b** series than in the corresponding **a** diastereomers (see Table 2 and Section 5). These empirical rules for the quick determination of the configuration at C(4)-stereocenter in 2,3-dioxabicyclo[3.3.1]nonanes by NMR were proved to be valid not only for the β-sulfonyl-endoperoxides and β-sulfenyl-endoperoxides,[11] but also for the corresponding β-sulfinyl-endoperoxides.[15]

The configuration of the substituents on the stereogenic atoms C(4) and C(8) of the 2,3-dioxabicyclo[3.3.1]nonane system was corroborated by the ^{1}H NOE difference experiments. Upon irradiation of H(1) at 3.68 ppm in **39′b** a NOE enhancement of the signals Me(10) 4.2%, Me(11) 0.8%, H(9)*eq* 7.4% and H(9)*ax* 3.2% was detected. The magnitude of the NOE correlation between the *equatorial* H(1) and Me(11) is in accordance with the *axial* orientation of the latter. Irradiation of the distinctively situated H(7)*ax* signal of both β-benzoates **52″a** and **52″b** provided a simple unambiguous elucidation of the configurations at C(4) and C(8)-stereocenters (Fig. 2). Irradiation of H(7) in **52″a** resulted in a strong NOE response for both the Me(10) and Me(11) signals, indicating that H(7) and the two methyl groups are situated in spatial proximity on the same side of both the 1,2-dioxane and of the carbocyclic rings. In contrast, irradiation of the H(7) signal in **52″b** resulted in



52''a



52''b

Figure 2. Distinctive ^{1}H NMR and NOE difference data for **52″a** and **52″b**.

a significant NOE enhancement of the Me(10) and H′(12) patterns and no response at the Me(11) signal.

Analysis of the coupling constants indicated the conservation of the chair conformation for both 1,2-dioxane and cyclohexane rings of the 2,3-dioxabicyclo[3.3.1]nonane system in $CDCl_3$ solutions.[34,35] In agreement with the chair conformation, the splitting pattern of H(7) in the β-benzoates **52″**, **53″** corresponds to the *axial* orientation of the proton ($J_{7ax,6ax}$=11.8 Hz, $J_{7ax,6eq}$=6.2 Hz), whereas in the α-benzoates **54″a**,**b** the H(7) is *equatorial* ($J_{7eq,6eq}$=6.5 Hz, $J_{7eq,6ax}$=1.6 Hz). In the ^{1}H NMR spectra of the related 7α-hydroxy-β-sulfonyl-endoperoxides **55″a** the H(7)*eq* pattern was observed as a doublet with 2 coupling constants similar to the previous ones ($J_{7eq,6eq}$=5.4 Hz, $J_{7eq,6ax}$=0.9 Hz), and the third, larger one (J=13.2 Hz). Similar values of coupling constants (J=13.2 Hz and $J_{7eq,6eq}$=5.5 Hz, $J_{7eq,6ax}\approx$0 Hz) were observed for H(7)*eq* in β-sulfenyl-endoperoxides **51″a**. COSY experiments revealed a strong interrelationship of H(7)*eq* and the doublets (J=13.2 Hz) at δ 4.09 and 3.89 ppm in **51″a** and **55″a** respectively. These doublets lack the cross-peaks in the HMQC-spectra. The doublets disappeared in the ^{1}H NMR spectra upon deuteration with excess of CD_3CO_2D, but not with CD_3OD or D_2O. Thus, the doublets at δ 4.09 and 3.89 ppm were attributed to the secondary OH protons at C(7), coupled with the H(7)*eq*. The unusually high value of the vicinal coupling $^3J_{OH,7eq}$=13.2 Hz is consonant with the nearly 180° dihedral angle between H–C(7)–O and H–O–C(7) planes.[36] This angle could be stabilized by the intramolecular hydrogen bonding of C(7)–OH with O(3) of the endoperoxide bridge.[37,38] Presumably, the rigid 3D structure of compounds **51″a** and **55″a** sustains this particular intramolecular hydrogen bonding through two bridged 7-membered rings (Fig. 3).

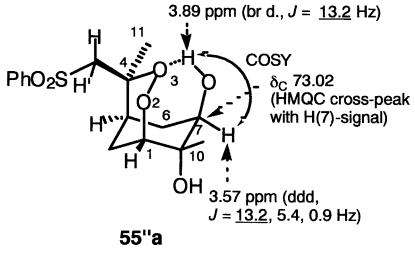


Figure 3. Selected NMR data, evidence for intramolecular hydrogen bonding in **55″a**.

Representative NMR data for the four diastereomeric 8-acetoxy-β-sulfonyl-endoperoxides **58″a–d** (Scheme 6) are summarized in the Table 3. The NMR spectra of the minor diastereomers **58″c** and **58″d** differ extensively from the spectra of the major diastereomers **58″a** and **58″b** in the pattern attributed to the C(8)-stereocenter fragment, but not of the C(4)-stereocenter moiety. This indicates that in these two pairs the C(8)-stereocenter has the opposite configuration. Thus, the acetoxy-group at C(8) occupies an *equatorial* position in the minor diastereomers **58″c**,**d**. Indeed, the bridgehead H(1) protons were observed at δ 4.7 ppm in the diastereomers **58″c,d** and at 4.45 ppm in the diastereomers **58″a**,**b**. The *axial* H(7) protons in the minor diastereomers **58″c**,**d** shifted downfield by 0.3–0.4 ppm because of the deshielding effect of the neighboring acetoxy-group, while for the *equatorial* H(7) the opposite, albeit less pronounced effect, was observed. In the ^{1}H NMR spectra of both minor diastereomers **58″c**,**d** the Me(10) signal appeared as two singlets of about equal intensity (total 3H), which indicated a restricted rotation of the acetoxy group with two energetically favored conformations of similar population. A marked difference in the ^{13}C NMR spectra of the minor diastereomers **58″c**,**d** with respect to those of major diastereomers **58″a**,**b** is the downfield shift of C(7) and Me(10) signals by ca. 1.7 and 0.8–1.0 ppm respectively. The similarity of the NMR patterns attributed to the C(4)-stereocenter in the pairs of diastereomers **58″a** and **58″c** as well as diastereomers **58″b** and **58″d** proves that the configuration at C(4) is identical for each of these couples. The criteria described above for the differentiation between a and b series of 2,3-dioxabicyclo[3.3.1]-nonanes can be applied also for the differentiation between **c** and **d** series of endoperoxides.

5. Conclusion

New hydroperoxide–endoperoxides of type **9** (R^2=OH), containing the 2,3-dioxabicyclo[3.3.1]nonane system were obtained from monoterpenes by a 4-component, one operation free radical process, in which five new bonds are sequentially formed. These compounds were

Table 3. Selected ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data for 8-acetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonanes **58″a–d** in $CDCl_3$

Position	**58″a**		**58″b**		**58″c**		**58″d**	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	4.45 br dd (3.2, 1.2)	77.80 d	4.42 br dd (3.6, 1.4)	78.45 d	4.71 br d (4.2)	77.96 d	4.68 br dd (4.3)	78.52 d
4		82.72 s		82.97 s		82.61 s		82.82 s
5	2.30 br dddd	29.42 d	2.10 br dddd	30.92 d	2.35 br dddd	29.73 d	2.14–2.23 m	31.14 d
7 *ax*	2.19 m	33.26 t	2.04 m	32.92 t	2.56 br ddd	34.99 t	2.39–2.47 m	34.74 t
7 *eq*	2.14 m		2.16 br dd (14.5, 6.0)		1.92 br dd (13.8, 6.7)		1.94 br dd (13.7, 5.8)	
8		82.54 s		82.35 s		82.61 s		81.65 s
10	1.62 s	22.49 q	1.56 s	22.53 q	1.602, 1.604 (2×s)	23.58 q	1.584, 1.586 (2×s)	23.25 q
11	1.51 br s	23.09 q	1.80 br s	21.94 q	1.54 d (0.6)	23.06 q	1.80 br s	22.00 q
12H	3.25 d (14.3)	60.98 t	3.12 d (14.0)	60.50 t	3.21 d (14.3)	61.06 t	3.12 d (14.0)	60.29 t
12H′	4.22 dd (14.3, 0.4)		3.32 br d (14.0)		4.27 dd (14.3, 0.6)		3.39 br d (14.0)	

Chemical shifts (ppm), multiplicity of the signal and coupling constants (Hz) are recorded. For the full record of the NMR data see Section 6.

selectively reduced (PPh_3) in the same vessel to give 4,8-dimethyl-4-sulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols **9** (R^2=H) and, after oxidation, 4,8-dimethyl-4-sulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols **10** (R^2=H). Compounds **9** and **10** served as precursors for the preparation of new potent antimalarial agents[39] and in the total synthesis of natural antimalarial endoperoxide yingzhaosu A (**3**).[13] Compounds of type **9**, **10** share with naturally occurring yingzhaosu A (**3**) and synthetic arteflene (**4a**) the 2,3-dioxabicyclo[3.3.1]nonane system **2**, which is considered to account for the antimalarial activity of these compounds. The present study opens an avenue for the preparation of an expanding class of antimalarial peroxide agents and provides a comprehensive NMR analysis, that allows a simple determination of the configuration at the four stereogenic centers of compounds **9** and **10**.

6. Experimental

6.1. General

^{1}H, COSY, NOE-difference, ^{13}C, DEPT and 2D-HMQC NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer or on a Bruker Avance DPX-250 spectrometer (^{1}H and ^{13}C/DEPT only) in $CDCl_3$. Residual $CHCl_3$ (7.26 ppm for ^{1}H NMR) and $CDCl_3$ (77.00 ppm for ^{13}C NMR) peaks were used as internal standards. IR spectra were obtained with a Protégé 460 FT-IR instrument. Specific rotations were determined on a Perkin–Elmer 341 polarimeter using a microaperture mode. HRMS was recorded on an AutoSpec mass-spectrometer at 70 eV with direct probe insertion unit using a DCI (desorption chemical ionization) technique (Bar Ilan University, Ramat Gan). Microanalyses were conducted by Microanalysis Laboratory of Hebrew University (Jerusalem). Melting points were determined on a Büchi apparatus and are uncorrected. For UV irradiation was used a 100 W BLAK-RAY® UV lamp B-100AP (UVP), λ=310–400 nm (λ_{max}=365 nm) and a Pyrex glassware. TLC analysis was performed on E. Merck 0.25 mm precoated silica gel 60 F-254 plates (UV detection) followed by charring with either alkaline $KMnO_4$ (stain 1) or *N*,*N*-dimethyl-*p*-phenylenediamine dihydrochloride in water–MeOH–AcOH (stain 2, specific for peroxides),[40] stabilized by 2–3 mL of conc. HCl per 150 mL of the stain solution. Such stabilization provides stability of the stain solution for at least 2–3 months at rt without a significant decrease in effectiveness. Flash column chromatography (FC) was performed on silica gel 60 (230–400 mesh ASTM) from Merck. Medium pressure liquid chromatography (MPLC) was performed on glass columns (Büchi-B-685, *l*=460 mm, *d*=26 or 43 mm, filled with LiChroprep silica gel (15–25 μm particle size). For analytical and semipreparative HPLC a LaChrom HPLC instrument (Merck-Hitachi) with UV detector was used. DP refers to direct-phase HPLC [semipreparative using LiChrospher Si-60 (10 μm), 250×10 mm^2 column, flow rate: 2.5–3 mL/min; analytical—LiChrospher Si-60 (5 μm), 250×4 mm^2 column, 1 mL/min]. RP refers to reversed-phase HPLC [semipreparative—LiChrospher 100 RP-18 (5 μm), 250×10 mm^2 column, flow rate 2–2.5 mL/min; analytical—LiChrospher 100 RP-18 (5 μm), 250×4 mm^2 column, 1 mL/min]. Retention times τ_R are given for analytical HPLC, eluents are specified in the single examples.

(*R*)-(+)-Limonene (Aldrich, # 18,316-4) (**18′**) and (*S*)-(−)-Limonene (Aldrich, # 21,836-7) (**18″**) were used as starting materials. Di-*tert*-butyl peroxalate (DBPO)[27a] (*Caution*!—a potentially explosive compound),[29] *trans*-carveol benzoate **45″**,[41] and *cis*-carveol **47″**[42] were prepared according to the reported procedures. Other reagents are available from Aldrich and Merck, and were purified if necessary by conventional methods. The following commercial solvents were used for the TOCO reactions: *n*-heptane (99+%, Aldrich), benzene (puriss, Merck), acetonitrile and methanol (HPLC grade, BioLab, Israel); for oxidations—dichloromethane (puriss, Merck) and ethyl acetate (analytical, BDH or BioLab). For silylation and benzoylation commercial CH_2Cl_2 was distilled over CaH_2 or P_2O_5, pyridine was distilled over KOH pellets.

Unless otherwise stated the purity of all the title compounds was estimated to be ≥95% by ^{1}H NMR and analytical HPLC determination. The ratios of diastereomers were determined by integration of the relevant separated signals in ^{1}H NMR spectra.

6.1.1. *R-cis*-Carveol benzoate (46″). A solution of *cis*-carveol **47″** (480 mg, 3.15 mmol) in dry pyridine (8 mL) at 0°C was treated with BzCl (496 mg, 3.53 mmol). The mixture was stirred at 0°C for 5 h and at rt overnight, poured into a cold 10% H_2SO_4 (100 mL), extracted with EtOAc–hexane (1:9, 2×100 mL), dried (Na_2SO_4+Na_2CO_3) and concentrated under reduced pressure. FC (EtOAc–hexane, 1:24) afforded the benzoate **46″** (656 mg, 81%) as a colorless oil: R_f 0.48 (EtOAc–hexane 7:93); IR (neat): 2970, 2920, 1717 (vs), 1452, 1315, 1270 (s), 1112 (s), 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (ddd, 1H, *J*=12.3, 12.3, 10.0 Hz), 1.72 (m, 3H, Me), 1.74 (br s, 3H, Me), 2.05 (m, 1H), 2.16 (m, 1H), 2.30–2.43 (m, 2H), 4.74 (br s, 2H), 5.67 (m, 1H), 5.70 (m, 1H), 7.45 (ddd, 2H, *J*=7.9, 1.2, 1.2 Hz), 7.56 (m, 1H), 8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.00, 20.51, 30.79, 33.99, 40.25, 73.80, 109.38, 125.99, 128.34, 129.59, 132.85, 133.08, 148.26, 166.40.

6.2. General procedures for the synthesis of 2,3-dioxabicyclo[3.3.1]nonanes by the TOCO reactions.[29] Preparation of (1*R*,4*R*/*S*,5*R*,8*R*)- and (1*S*,4*S*/*R*,5*S*,8*S*)-4,8-dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo-[3.3.1]nonan-8-ols (20a,b)

6.2.1. Procedure 1A[19a] **(entry 1, Table 1).** Through a vigorously stirred solution of *R*-(+)-limonene (**18′**) (409 mg, 3.0 mmol, 1 equiv.), PhSH (330 mg, 3 mmol, 1 equiv.) and DBPO (35 mg, 0.15 mmol, 0.05 equiv.) in benzene (100 mL) at rt is passed a slow stream of oxygen gas for 15 h. Reaction mixture is cooled to 5°C, flushed with argon, diluted with CH_2Cl_2 (20 mL), and Ph_3P (786 mg, 3 mmol, 1 equiv.) is added. The mixture is stirred for an additional 1 h at 5°C and for 1 h at rt. Evaporation in vacuum at rt (*Caution*!—Safety screen is commonly recommended to use for evaporation of peroxide-containing solutions)[29] followed by FC (gradient elution, EtOAc–hexane, from 1:49 to 3:7) affords the (1*R*,4*R*/*S*,5*R*,8*R*)-endo-

peroxides **20′a**,**b** (123 mg, 0.42 mmol, 14%, **a**/**b** ca. 55:45), and unsaturated hydroxysulfides **26′a**,**b** (233 g, 0.96 mmol, 32%, **a**/**b** ca. 60:40). Evaporation of the least polar fraction from FC followed by treatment of the residue with hexane, filtration and recrystallization from MeOH gives diphenyl disulfide (82 mg, 0.376 mmol, 25%), mp 60°C.

6.2.2. General procedure 1B (entry 5, Table 1). Oxygen gas is bubbled at rt through a vigorously stirred solution of *R*-(+)-limonene (**18′**) (6.13 g, 45 mmol, 3 equiv.) and DBPO (105 mg, 0.45 mmol, 0.03 equiv.) in *n*-heptane–benzene mixture (500 mL/200 mL) with simultaneous addition of thiophenol (1.65 g, 15 mmol, 1 equiv.) in heptane (20 mL) over a period of 10 h (syringe pump). After the addition of thiol is completed, the mixture is cooled to 0–5°C, flushed with argon, diluted with CH_2Cl_2 (100 mL), and powdered Ph_3P (3.93 g, 15 mmol, 1 equiv.) is added. The mixture is stirred for an additional 2 h at 0–5°C, for 1 h at rt and evaporated at rt. FC (gradient elution, EtOAc–hexane, from 1:49 to 3:7) affords the title (1*R*,4*R*/*S*,5*R*,8*R*)-endoperoxides **20′a**,**b** (2.41 g, 8.20 mmol, 54%) as a mixture of diastereomers (**a**/**b** ca. 55:45), and unsaturated hydroxysulfides **26′a**,**b** (0.975 g, 4.03 mmol, 25%, **a**/**b** ca. 60:40). Evaporation of the least polar fraction from FC followed by dilution with hexane, cooling (−20°C) and filtration gives $(PhS)_2$ (162 mg, 0.743 mmol, 10%). Evaporation of the filtrate followed by distillation affords (2.93 g, 21.5 mmol, 72% recovery) of *R*-(+)-limonene (**18′**), bp 175–176°C.

6.2.3. General procedure 1C (entry 8, Table 1). A solution of *R*-(+)-limonene (**18′**) (6.13 g, 45 mmol, 3 equiv.) and DBPO (105 mg, 0.45 mmol, 0.03 equiv.) in *n*-heptane–benzene mixture (500 mL/200 mL) is placed into 2 L 3-necked round-bottomed flask, equipped with an efficient egg-shaped magnetic stirring bar. A central neck of the reaction flask is connected to a big (2 L) external graduated reservoir filled with oxygen and joined from its bottom through a flexible tube to a leveling bulb (2 L) filled with brine. The two side necks of the reaction flask are equipped with septums. The reaction vessel is thoroughly flashed with pure oxygen and oxygen pressure is adjusted to 15–20 cm of brine. To a vigorously stirred under oxygen at rt reaction mixture, a solution of thiophenol (1.65 g, 15 mmol, 1 equiv.) in heptane (20 mL) is added over a period of 10 h (syringe pump). Since no additional consumption of oxygen occurs after completion of thiol addition (up to 10 h monitoring), the reaction mixture is worked-up as described in the procedure 1B to give the endoperoxides **20′a**,**b** (2.09 g, 7.11 mmol, 47%) as a mixture of diastereomers (ca. 55:45).

6.2.4. Procedure 1D (entry 10, Table 1). In this procedure the same equipment is used as in the procedure 1C, except that oxygen filled external reservoir was connected with the reaction flask via a bulb type vertically positioned condenser. To a vigorously stirred under oxygen solution of *R*-(+)-limonene (**18′**) (409 mg, 3.0 mmol, 3 equiv.) and AIBN (5.0 mg, 0.03 mmol, 0.03 equiv.) in acetonitrile (120 mL) at 65°C solutions of thiophenol (110 mg, 1.0 mmol, 1 equiv.) in MeCN (10 mL) and AIBN (5.0 mg, 0.03 mmol, 0.03 equiv.) in MeCN (10 mL) are added simultaneously over 10 h (syringe pump). After completion of thiol addition the reaction mixture is cooled and worked-up as described above to give the endoperoxides **20′a**,**b** (137 mg, 0.47 mmol, 47%) as a mixture of diastereomers (ca. 58:42).

6.2.5. General procedure 1E (entry 16, Table 1). A solution of *R*-(+)-limonene (**18′**) (6.13 g, 45 mmol, 3 equiv.) and AIBN (77 mg, 0.45 mmol, 0.03 equiv.) in acetonitrile (700 mL) is placed into a Pyrex 3-necked round-bottom flask equipped as described above for the procedure 1C and kept under small positive pressure of pure oxygen. The reaction mixture is vigorously stirred and UV irradiated (from a distance ca. 5–7 cm) at 4°C with simultaneous addition of solutions of thiophenol (1.65 g, 15 mmol, 1 equiv.) and AIBN (77 mg, 0.45 mmol, 0.03 equiv.) in acetonitrile (10 mL each) over a period of 10 h (syringe pump). After completion of the addition, the reaction mixture is worked-up as described above to yield endoperoxides **20′a**,**b** (2.17 g, 7.38 mmol, 49%) as a mixture of diastereomers (ca. 55:45).

Procedures 1B, 1C and 1E gave essentially the same results when applied to the preparation of (1*S*,4*S*/*R*,5*S*,8*S*)-4,8-dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]-nonan-8-ols (**20″a**,**b**) from *S*-(−)-limonene (**18″**). NMR and IR spectra of **20′a**,**b** and **20″a**,**b** coincided. Three-fold scaling up of these TOCO reactions according to the procedures 1C and 1E does not significantly affect yields and purity of endoperoxides **20**.

6.2.6. Endoperoxides 20a,b. A colorless oil, R_f 0.29 (EtOAc–hexane, 3:7); IR (neat): 3420, 2964, 2928, 1584, 1480, 1454, 1440, 1373, 1055, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (br s, Me(11), **a**), 1.56 (d, J=0.6 Hz, Me(11), **b**), total 3H; 1.39 (s, Me(10), **b**), 1.40 (s, Me(10), **a**), total 3H; 1.58 (m, 1H, H(7)*eq*, **a**+**b**); 1.76–1.85 (m, 2H, H(6)*ax*+*eq*, **a**+**b**); 1.81 (m, H(5), **b**), 1.91 (dddd, J=6.4, 6.4, 3.2, 3.2 Hz, H(5), **a**), total 1H; 1.98 (ddd, J=13.6, 3.2, 2.0 Hz, H(9)*ax*, **a**), 2.01 (ddd, J=14.2, 3.2, 1.9 Hz, H(9)*ax*, **b**), total 1H; 2.10 (ddd, J=13.6, 5.5, 3.2 Hz, H(9)*eq*, **a**), 2.26 (ddd, J=14.2, 4.4, 3.0 Hz, H(9)*eq*, **b**), total 1H; 2.31–2.41 (m, 1H, H(7)*ax*, **a**+**b**); 2.96 (d, J=12.0 Hz, H(12), b), 3.35 (d, J=12.8 Hz, H(12), **a**), total 1H; 3.03 (dd, J=12.0, 0.6 Hz, H′(12), **b**), 3.71 (dd, J=12.8, 0.5 Hz, H′(12), **a**), total 1H; 3.68 (m, H(1), **a**), 3.71 (m, H(1), **b**), total 1H; 7.17–7.23 (m, 1H), 7.27–7.33 (m, 2H), 7.36–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.89 (Me(11)), 23.58 ($C(6)H_2$), 24.17 ($C(9)H_2$), 28.04 (Me(10)), 29.23 (C(5)H), 35.51 ($C(7)H_2$), 40.68 ($C(12)H_2$), 71.40 (C(8)), 81.57 (C(1)H), 83.77 (C(4)), 126.14 (CH), 128.87 (2CH), 129.63 (2CH), 136.84 (C) (isomer **20a**); 21.76 (Me(11)), 23.30 ($C(6)H_2$), 24.26 ($C(9)H_2$), 28.04 (Me(10)), 30.50 (C(5)H), 35.84 ($C(7)H_2$), 40.73 ($C(12)H_2$), 71.35 (C(8)), 82.02 (C(1)H), 83.83 (C(4)), 126.33 (CH), 128.93 (2CH), 129.63 (2CH), 136.42 (C) (isomer **20b**).

Unsaturated hydroxysulfides **26′a**,**b**: a colorless oil, R_f 0.53 (EtOAc–hexane, 1:4); IR (neat): 3420, 2977, 2935, 1584, 1480, 1438, 1377, 1089, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, Me, **a**), 1.20 (s, Me, **b**), total 3H; 1.20–1.33 (m, 1H); 1.64 (br s, MeC═, **b**), 1.65 (br s, MeC═, **a**), total 3H; 1.68–1.83 (m, 2H), 1.87–1.93 (m, 1H), 1.94–2.19

(m, 3H); 3.11 and 3.20 (AB quartet, J=13.1 Hz, CHH′S, **a**), 3.13 and 3.24 (AB quartet, J=13.4 Hz, CHH′S, **b**), total 2H; 5.33–5.37 (m, HC═, **a**), 5.37–5.41 (m, HC═, **b**), total 1H; 7.15–7.21 (m, 1H), 7.24–7.30 (m, 2H), 7.38–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.58 (Me), 23.26 (CH_2), 23.29 (Me), 27.00 (CH_2), 30.75 (CH_2), 42.79 (CH), 46.27 (CH_2), 74.02 (C), 119.95 (HC═), 126.11 (CH), 128.88 (2CH), 129.50 (2CH), 134.20 (Me*C*═), 137.01 (C) (isomer **26′a**); 22.58 (Me), 23.50 (Me), 24.25 (CH_2), 26.04 (CH_2), 30.71 (CH_2), 42.63 (CH), 45.62 (CH_2), 74.02 (C), 120.43 (HC═), 126.14 (CH), 128.88 (2CH), 129.54 (2CH), 133.70 (Me*C*═), 137.01 (C) (isomer **26′b**).

6.2.7. (1*R*,4*R*/*S*,5*R*,8*R*)-4,8-Dimethyl-4-(4-fluorophenyl)-sulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols (33′a,b). A mixture of endoperoxides **33′a**,**b** (248.5 mg, 47%, **a/b** ca. 52:48) was prepared from *R*-(+)-limonene (**18′**) (695 mg, 5.10 mmol) and 4-FC_6H_4SH (217 mg, 1.69 mmol) according to the general procedure 1B (thiol addition time 10 h). A pale yellow oil, R_f 0.23 (EtOAc–hexane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (br s, Me(11), **a**), 1.53 (br s, Me(11), **b**), total 3H; 1.36 (s, Me(10), **b**), 1.38 (s, Me(10), **a**), total 3H; 1.55–1.67 (m, 1H, H(7)*eq*, **a**+**b**), 1.72–1.86 (m, 3H); 1.96 (ddd, J=13.5, 3.2, 2.0 Hz, H(9)*ax*, **a**), 2.04 (ddd, J=14.0, 3.2, 1.8 Hz, H(9)*ax*, **b**), total 1H; 2.03–2.07 (m, H(9)*eq*, **a**), 2.22–2.38 (m), total 2H; 2.89 (d, J=12.2 Hz, H(12), **b**), 3.31 (d, J=12.9 Hz, H(12), **a**), total 1H; 2.97 (br d, J=12.2 Hz, H′(12), **b**), 3.60 (br d, J=12.9 Hz, H′(12), **a**), total 1H; 3.66 (m, H(1), **a**), 3.69 (m, H(1), **b**), total 1H; 6.97–7.01 (m, 2H), 7.36–7.43 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.78, 21.91 (Me(11)); 23.37, 23.67 (C(6)H_2); 24.24, 24.34 (C(9)H_2); 28.12 (Me(10)), 29.35 (C(5)H, **a**), 30.57 (C(5)H, **b**); 35.59, 35.89 (C(7)H_2); 42.12, 42.24 (C(12)H_2); 71.45, 71.50 (C(8)); 81.62, 82.06 (C(1)H); 83.78, 83.89 (C(4)); 116.08 (J_{C-F}=21.9 Hz), 116.15 (J_{C-F}=22.1 Hz)(2CH); 131.33 (J_{C-F}=3.6 Hz), 131.77 (J_{C-F}=3.1 Hz)(C); 132.60 (J_{C-F}=8.3 Hz), 132.73 (J_{C-F}=8.4 Hz)(2CH); 161.78 (J_{C-F}=246.6 Hz), 161.91 (J_{C-F}=246.8 Hz)(C–F).

6.2.8. (1*R*,4*R*/*S*,5*R*,8*R*)-4-*n*-Butylsulfenylmethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (34′a,b). A diastereomeric mixture **34′a**,**b** (229 mg, 25%, **a/b** ca. 60:40) was prepared from *R*-limonene **18′** (1.36 g, 10 mmol), *n*-BuSH (300 mg, 3.33 mmol) and AIBN (68 mg, 0.40 mmol) according to the general procedure 1E (thiol addition time 30 h). A pale yellow oil, R_f 0.23 (EtOAc–hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 t, J=7.3 Hz, *Me*$CH_2CH_2CH_2$S, **a**), 0.91 (t, J=7.3 Hz, *Me*$CH_2CH_2CH_2$S, **b**), total 3H; 1.23 (br s, Me(11), **a**), 1.56 (d, J=0.3 Hz, Me(11), **b**), total 3H; 1.36 (s, Me(10), **b**), 1.37 (s, Me(10), **a**), total 3H; 1.38–1.46 (m, 2H), 1.54–1.63 (m, 3H), 1.70–1.85 (m, 4H), 1.99–2.04 (m, 2H), 2.13–2.26 (m, 2H), 2.28–2.42 (m, 2H); 2.47 (d, J=12.2 Hz, H(12), **b**), 2.95 (d, J=13.0 Hz, H(12), **a**), total 1H; 2.54 (br t, J=7.2 Hz, $C_3H_7CH_2$S, **b**), 2.59 (br t, J=7.2 Hz, $C_3H_7CH_2$S, **a**), total 2H; 2.62 (br d, J=12.0 Hz, H′(12), **b**), 3.14 (br d, J=13.0 Hz, H′(12), **a**), total 1H; 3.67 (m, 1H, H(1), **a**+**b**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.67 (*Me*$CH_2CH_2CH_2$S), 21.76 (Me(11)), 21.87 (CH_2), 23.80 (C(6)H_2), 24.40 (C(9)H_2), 28.12 (Me(10)), 29.59 (C(5)H), 31.89 (CH_2), 33.46 (CH_2), 35.66 (C(7)H_2), 38.60 (C(12)H_2), 71.54 (C(8)), 81.63 (C(1)H), 83.90 (C(4)) (isomer **34′a**); 13.63 (*Me*$CH_2CH_2CH_2$S), 21.66 (Me(11)), 21.92 (CH_2), 23.43 (C(6)H_2), 24.44 (C(9)H_2), 28.12 (Me(10)), 30.61 (C(5)H), 31.68 (CH_2), 33.74 (CH_2), 35.99 (C(7)H_2), 38.93 (C(12)H_2), 71.48 (C(8)), 82.01 (C(1)H), 84.17 (C(4)) (isomer **34′b**).

6.2.9. (1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-4-(methoxycarbonylmethylsulfenyl)methyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (35′a) and (1*R*,4*S*,5*R*,8*R*)-4,8-dimethyl-4-(methoxycarbonylmethylsulfenyl)methyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (35′b). A mixture of diastereomers **35″a**,**b** (178.5 mg, 18%, **a/b** ca. 50:50) was prepared from *R*-limonene **18′** (1.36 g, 10 mmol), methyl thioglycolate (353 mg, 3.33 mmol) and AIBN (34 mg, 0.20 mmol) according to the general procedure 1E (thiol addition time 18 h). The diastereomers were separated by additional MPLC (EtOAc–hexane, 1:2). More polar isomer **35′a**: a colorless oil, R_f 0.20 (EtOAc–hexane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (br s, 3H, Me(11)), 1.38 (s, 3H, Me(10)), 1.57–1.61 (m, 1H, H(7)*eq*), 1.70 (br dddd, 1H, J=6.4, 6.4, 3.2, 3.2 Hz, H(5)), 1.81–1.88 (m, 2H), 2.04 (ddd, 1H, J=13.6, 3.2, 2.0 Hz, H(9)*ax*), 2.22 (br ddd, 1H, J=13.6, 6.4, 3.6 Hz, H(9)*eq*), 2.36 (ddd, 1H, J=14.2, 12.7, 7.6 Hz, H(7)*ax*), 2.99 (d, 1H, J=13.4 Hz, H(12)), 3.29 (d, 1H, J=14.9 Hz, SC*H*H′CO_2Me), 3.37 (br d, 1H, J=13.4 Hz, H′(12)), 3.44 (d, 1H, J=14.9 Hz, SCH*H*′CO_2Me), 3.69 (br d, 1H, J=3.6 Hz, H(1)), 3.74 (s, 3H, MeO); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.32 (Me(11)), 23.80 (C(6)H_2), 24.26 (C(9)H_2), 27.95 (Me(10)), 30.29 (C(5)H), 34.28 (CH_2), 35.45 (C(7)H_2), 38.46 (C(12)H_2), 52.32 (MeO), 71.35 (C(8)), 81.61 (C(1)H), 83.34 (C(4)), 171.05 (C═O).

Less polar isomer **35′b**: a colorless oil, R_f 0.23 (EtOAc–hexane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H, Me(10)), 1.57 (br s, 3H, Me(11)), 1.58–1.62 (m, 1H, H(7)*eq*), 1.66 (br dddd, 1H, J=6.4, 6.4, 3.2, 3.2 Hz, H(5)), 1.77–1.88 (m, 2H), 2.04 (ddd, 1H, J=13.4, 3.2, 1.8 Hz, H(9)*ax*), 2.24 (br ddd, 1H, J=13.4, 6.4, 3.2 Hz, H(9)*eq*), 2.34 (ddd, 1H, J=14.0, 14.0, 7.0 Hz, H(7)*ax*), 2.68 (br d, 1H, J=12.7 Hz, H(12)), 2.81 (d, 1H, J=12.7 Hz, H′(12)), 3.23 and 3.32 (AB quartet, 2H, J=14.8 Hz, SC*HH*′CO_2Me), 3.69 (br d, 1H, J=3.2 Hz, H(1)), 3.74 (s, 3H, MeO); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.19 (Me(11)), 23.23 (C(6)H_2), 24.41 (C(9)H_2), 28.01 (Me(10)), 31.14 (C(5)H), 34.74 (CH_2), 35.64 (C(7)H_2), 39.17 (C(12)H_2), 52.38 (MeO), 71.32 (C(8)), 81.92 (C(1)H), 83.98 (C(4)), 170.65 (C═O).

6.2.10. (1*R*,4*R*/*S*,5*R*,8*R*)-4-Cyclohexylsulfenylmethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (36′a,b). A mixture of diastereomers **36′a**,**b** (200 mg of ca. 75% purity, ca. 16% yield, **a/b** ca. 55:45) was prepared from *R*-limonene **18′** (1.36 g, 10 mmol), cyclohexylthiol (387 mg, 3.33 mmol) and AIBN (68 mg, 0.40 mmol) according to the general procedure 1E (addition time 25 h). A pale-yellow oil, R_f 0.24 (EtOAc–hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 br s, Me(11), **a**), 1.54 (br s, Me(11), **b**), total 3H; 1.21–1.39 (m, 6H); 1.36 (s, Me(10)), 1.37 (s, Me(10)), total 3H; 1.58–1.68 (m, 1H), 1.70–1.90 (m, 4H), 1.91–2.07 (m, 2H), 2.16–2.26 (m, 1H), 2.27–2.39 (m, 1H); 2.47 (d, J=11.8 Hz), 2.62 (br d, J=11.8 Hz), 2.90 (d, J=12.6 Hz), 3.16 (d, J=13.4 Hz), 3.23

(br d, J=12.6 Hz), 3.52 (d, J=13.4 Hz), (C(12)HH′S) total 2H; 3.67 (br s, 1H, H(1)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.74, 21.82 (Me(11)); 23.44, 23.72, 24.39, 24.43, 25.78, 25.84, 25.97, 26.04 (CH_2); 28.13 (Me(10)); 29.42 (C(5)H, **a**), 30.52 (C(5)H, **b**); 33.56, 33.65, 33.73, 33.81, 35.69, 36.10, 36.31, 36.50 (CH_2); 44.66, 44.93 (CH); 71.48, 71.55 (C(8)); 81.63 (C(1)H, **a**), 82.07 (C(1)H, **b**), 83.83 (C(4), **a**), 84.03 (C(4), **b**).

6.2.11. (1*R*,4*R*/*S*,5*R*,8*R*)-4-*tert*-Butylsulfenylmethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (37′a,b). A mixture of diastereomers **37′a**,**b** (264 mg, 29%, **a**/**b** ca. 52:48) was prepared from *R*-limonene **18′** (1.36 g, 10 mmol), *tert*-BuSH (300 mg, 3.33 mmol) and AIBN (68 mg, 0.40 mmol) according to the general procedure 1E (thiol addition time 48 h). A colorless oil, R_f 0.42 (EtOAc–hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (br s, Me(11), **a**), 1.55 (br s, Me(11), **b**), total 3H; 1.31 (s, Me_3C, **b**), 1.34 (s, Me_3C, **a**), total 9H; 1.369 (s, Me(10), **b**), 1.373 (s, Me(10), **a**), total 3H; 1.53–1.91 (m, 4H); 1.97–1.99 (m, H(5), **b**), 2.00–2.03 (m, H(5), **a**), total 1H; 2.16–2.25 (m, 1H, H(9)*eq*, **a**+**b**), 2.30–2.41 (m, 1H, H(7)*ax*, **a**+**b**); 2.39 (d, J=10.7 Hz, H(12), **b**), 2.63 (br d, J=10.7 Hz, H′(12), **b**), 2.76 (d, J=11.5 Hz, H(12), **a**), 3.36 (br d, J=11.5 Hz, H′(12), **a**), total 2H; 3.67–3.68 (m, 1H, H(1), **a**+**b**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.98, 22.04 (Me(11)); 23.37, 23.59 ($C(6)H_2$,); 24.25 ($C(9)H_2$), 28.12 (Me(10)), 29.34 (C(5)H, **a**), 30.52 (C(5)H, **b**); 30.67, 30.84 (*Me*$_3$CS); 34.42, 34.45 ($C(12)H_2$); 35.67, 36.17 ($C(7)H_2$); 41.95, 41.99 (Me_3*C*S); 71.47, 71.55 (C(8)); 81.61, 82.15 (C(1)H); 83.57, 83.72 (C(4).

6.2.12. (1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-4-(triphenylmethylsulfenyl)methyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (38′a) and (1*R*,4*S*,5*R*,8*R*)-4,8-dimethyl-4-(triphenylmethylsulfenyl)methyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (38′b). A mixture of diastereomers **38′a**,**b** (630 mg, 41%, **a**/**b** ca. 57:43) was prepared from *R*-limonene **18′** (1.36 g, 10 mmol), TrSH (919 mg, 3.33 mmol) and AIBN (68 mg, 0.40 mmol) according to the general procedure 1E (thiol addition time 30 h). The diastereomers were separated by MPLC (hexane–EtOAc, 7:3) and purified by semipreparative DP HPLC (hexane–EtOAc, 7:3). Less polar isomer **38′a**: a pale yellow oil, R_f 0.23 (EtOAc–hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (br s, 3H, Me(11)), 1.32 (s, 3H, Me(10)), 1.49–1.54 (m, 1H, H(7)*eq*), 1.68–1.87 (m, 5H), 2.27 (ddd, 1H, J=14.8, 11.8, 8.4 Hz, H(7)*ax*), 2.52 (d, 1H, J=11.5 Hz, H(12)), 2.88 (br d, 1H, J=11.5 Hz, H′(12)), 3.57 (br s, 1H, H(1)), 7.19–7.22 (m, 3H), 7.26–7.30 (m, 6H), 7.45–7.48 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.85 (Me(11)), 23.44 ($C(6)H_2$), 24.15 ($C(9)H_2$), 28.04 (Me(10)), 29.54 (C(5)H), 35.56 ($C(7)H_2$), 37.74 ($C(12)H_2$), 66.54 (Ph_3*C*S), 71.42 (C(8)), 81.40 (C(1)H), 83.45 (C(4)), 126.63 (3CH), 127.83 (6CH), 129.59 (6CH), 144.59 (3C). DCI (CH_4) HRMS: obsd 461.2090, calcd for $C_{29}H_{33}O_3S$ (MH^+) 461.2150. More polar isomer **38′b**: a pale yellow oil, R_f 0.21 (EtOAc–hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H, Me(10)), 1.42 (dd, 1H, J=14.0, 5.7 Hz, H(7)*eq*), 1.47 br s, 3H, Me(11)), 1.49–1.65 (m, 3H), 1.93 (ddd, 1H, J=13.4, 3.2, 1.9 Hz, H(9)*ax*), 2.04 (ddd, 1H, J=14.0, 14.0, 6.4 Hz, H(7)*ax*), 2.12 and 2.13 (AB quartet, 2H, J=11.4 Hz, C(12)HH′), 2.16 (ddd, 1H, J=13.4, 6.5, 3.4 Hz, H(9)*eq*), 3.62 (br d, 1H, J=3.4 Hz, H(1)), 7.18–7.23 (m, 3H), 7.26–7.30 (m, 6H), 7.42–7.46 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.80 (Me(11)), 23.26 ($C(6)H_2$), 24.11 ($C(9)H_2$), 28.01 (Me(10)), 30.98 (C(5)H), 35.76 ($C(7)H_2$), 37.98 ($C(12)H_2$), 66.45 (Ph_3*C*S), 71.36 (C(8)), 82.04 (C(1)H), 83.53 (C(4)), 126.69 (3CH), 127.87 (6CH), 129.50 (6CH), 144.28 (3C).

6.2.13. (1*S*,4*S*,5*S*,7*S*,8*S*)-7-Benzoyloxy-4,8-dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols (48″a) and (1*S*,4*R*,5*S*,7*S*,8*S*)-7-benzoyloxy-4,8-dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols (48″b). A mixture of endoperoxides **48″a**,**b** (42 mg, 22%, **a**/**b** ca. 1:1) was synthesized from β-benzoate **45″** (350 mg, 1.36 mmol) and PhSH (50 mg, 0.45 mmol) according to the general procedure 1B (thiol addition time 12 h). A colorless waxy solid, R_f 0.25–0.26 (EtOAc–hexane, 1:3); IR (neat): 3547, 1713,1271, 711 cm^{-1}. Additional FC (EtOAc–hexane, 1:4) afforded a sample of a solid **48″a** (less polar isomer): mp 139–140°C; R_f 0.26 (EtOAc–hexane, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 br s, 3H, Me(11)), 1.44 (s, 3H, Me(10)), 1.83 (ddd, 1H, J=13.1, 11.6, 3.3 Hz, H(6)*ax*), 2.08 (m, 2H, H(9)*ax*+*eq*), 2.20 (m, 1H, H(5)), 2.37 (m, 1H, H(6)*eq*), 3.35 (d, 1H, J=12.9 Hz, H(12)), 3.73 (br d, 1H, J=12.9 Hz, H′(12)), 3.96 (dd, 1H, J=2.4, 2.4 Hz, H(1)), 5.76 (dd, 1H, J=11.6, 6.3 Hz, H(7)*ax*), 7.20 (m, 1H), 7.30 (m, 2H), 7.42 (m, 2H), 7.48 (m, 2H), 7.60 (m, 1H), 8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.30 (Me(11)), 23.68 ($C(9)H_2$), 24.46 (Me(10)), 29.23 ($C(6)H_2$), 31.31 (C(5)H), 40.54 ($C(12)H_2$), 72.81 (C(8)), 74.75 (C(7)H), 82.75 (C(1)H), 83.79 (C(4)), 126.43 (CH), 128.54 (2CH), 129.03 (2CH), 129.48 (2CH), 129.94 (2CH), 130.07 (C), 133.24 (CH), 136.56 (C), 165.69 (C=O). More polar isomer **48″b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H, Me(10)), 1.58 br s, 3H, Me(11)), 1.77 (ddd, 1H, J=12.8, 11.2, 3.4 Hz, H(6)*ax*), 2.07–2.36 (m, 4H), 3.03 (d, 1H, J=12.3 Hz, H(12)), 3.24 (br d, 1H, J=12.3 Hz, H′(12)), 3.99 (m, 1H, H(1)), 5.78 (dd, 1H, J=11.2, 6.3 Hz, H(7)*ax*), 7.21 (m, 1H), 7.30 (m, 2H), 7.42 (m, 2H), 7.48 (m, 2H), 7.59 (m, 1H), 8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.40 (Me(11)), 23.80 ($C(9)H_2$), 24.46 (Me(10)), 28.99 ($C(6)H_2$), 32.53 (C(5)H), 40.70 ($C(12)H_2$), 72.83 (C(8)), 74.81 (C(7)H), 83.23 (C(1)H), 83.88 (C(4)), 126.51 (CH), 128.52 (2CH), 129.03 (2CH), 129.48 (2CH), 129.90 (2CH), 130.08 (C), 133.20 (CH), 135.99 (C), 165.52 (C=O).

6.2.14. (1*S*,4*S*/*R*,5*S*,7*S*,8*S*)-7-Benzoyloxy-4-*n*-butylsulfenylmethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols (49″a,b). A mixture of endoperoxides **49″a**,**b** (59 mg of ca. 85% purity, ca. 6.5% yield, **a**/**b** ca. 55:45) was prepared from β-benzoate **45″** (993 mg, 3.87 mmol) and *n*-BuSH (180 mg, 2.0 mmol) according to the general procedure 1B (thiol addition time 12 h). A pale yellow oil: R_f 0.26 (EtOAc–hexane, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 t, J=7.3 Hz, *Me*$CH_2CH_2CH_2$S, **b**), 0.92 (t, J=7.3 Hz, *Me*$CH_2CH_2CH_2$S, **a**), total 3H;?1.36 (s, Me(11), **a**), 1.58 (s, Me(11), **b**), total 3H; 1.42 (m, 2H), 1.43 (s, Me(10), **b**), 1.44 (s, Me(10), **b**), total 3H; 1.60 (m, 2H), 1.78 (ddd, J=13.3, 11.6, 3.4 Hz, H(6)*ax,* **b**), 1.82 (ddd, J=13.2, 11.8, 3.5 Hz, H(6)*ax,* **a**), total 1H; 1.96–2.52 (m, 4H); 2.59 (br t, J=7.3 Hz, C_3H_7*CH*$_2$S, **a**), 2.61 (br t, J=7.3 Hz,

$C_3H_7CH_2S$, **b**), total 2H; 2.60 (br d, J=12.2 Hz, H(12), **b**), 2.80 (br d, J=12.2 Hz, H′(12), **b**), 2.96 (br d, J=13.2 Hz, H(12), **a**), 3.20 (br d, J=13.2 Hz, H′(12), **a**), total 2H; 3.97 (m, 1H, H(1), **a**+**b**), 5.76 (m, 1H, H(7)*ax*, **a**+**b**), 7.46 (m, 2H), 7.59 (m, 1H), 8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.67 ($MeCH_2CH_2CH_2S$), 21.89 (CH_2), 22.09 (Me(11)), 23.79 (C(9)H_2), 24.44 (Me(10)), 29.33 (C(6)H_2), 31.58 (C(5)H), 31.82 (CH_2), 33.47 (CH_2), 38.16 (C(12)H_2), 72.81 (C(8)), 74.79 (C(7)H), 82.73 (C(1)H), 83.81 (C(4)), 128.50 (2CH), 129.46 (2CH), 130.05 (C), 133.20 (CH), 165.58 (C=O) (isomer **49″a**); 13.62 ($MeCH_2CH_2CH_2S$), 20.66 (Me(11)), 21.85 (CH_2), 23.89 (C(9)H_2), 24.44 (Me(10)), 28.99 (C(6)H_2), 31.54 (CH_2), 32.59 (C(5)H), 33.67 (CH_2), 38.88 (C(12)H_2), 72.80 (C(8)), 74.96 (C(7)H), 83.15 (C(1)H), 83.92 (C(4)), 128.50 (2CH), 129.46 (2CH), 130.09 (C), 133.17 (CH), 165.58 (C=O) (isomer **49″b**).

6.2.15. (1*S*,4*S*/*R*,5*S*,7*R*,8*S*)-7-Benzoyloxy-4,8-dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols (50″a,b). A mixture of endoperoxides **50″a**,**b** (24 mg, 6%, **a/b** ca. 65:35) was prepared from α-benzoate **46″** (690 mg, 2.70 mmol) and PhSH (99 mg, 0.90 mmol) according to the general procedure 1B (thiol addition time 12 h). A pale yellow oil, R_f 0.42 (EtOAc–hexane, 35:65); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 br s, Me(11), **a**), 1.59 br s, Me(11), **b**), total 3H; 1.41 (s, Me(10), **b**), 1.42 (s, Me(10), **a**), total 3H; 1.91–2.37 (m, 5H); 3.00 (d, J=12.1 Hz, H(12), **b**), 3.14 (br d, J=12.1 Hz, H′(12), **b**), 3.39 (d, J=12.8 Hz, H(12), **a**), 3.80 (br d, J=12.8 Hz, H′(12), **a**), total 2H; 3.82 (m, H(1), **a**), 3.88 (dd, J=4.1, 1.5 Hz, H(1), **b**), total 1H; 5.26 (dd, J=5.0, 1.7 Hz, H(7)*eq*, **b**), 5.27 (dd, J=5.0, 1.5 Hz, H(7)*eq*, **a**), total 1H; 7.09 (m, 1H); 7.22 (m, **b**), 7.29 (m, **a**), total 2H; 7.41–7.47 (m), 7.54–7.58 (m), total 5H; 8.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.30 (Me(11)), 23.42 (C(9)H_2), 23.47 (Me(10)), 28.81 (C(6)H_2), 29.36 (C(5)H), 40.78 (C(12)H_2), 73.83 (C(8)), 74.36 (C(7)H), 80.85 (C(1)H), 82.74 (C(4)), 126.36 (CH), 128.48 (2CH), 129.00 (2CH), 129.81 (2CH), 129.90 (2CH), 130.15 (C), 133.11 (CH), 136.71 (C), 166.33 (C=O) (isomer **50″a**); 21.68 (Me(11)), 23.35 (Me(10)), 23.56 (C(9)H_2), 28.68 (C(6)H_2), 30.86 (C(5)H), 40.37 (C(12)H_2), 73.68 (C(8)), 74.51 (C(7)H), 81.38 (C(1)H), 82.83 (C(4)), 126.12 (CH), 128.52 (2CH), 128.88 (2CH), 129.06 (2CH), 129.81 (C), 129.90 (2CH), 133.18 (CH), 136.25 (C), 166.25 (C=O) (isomer **50″b**).

6.2.16. (1*S*,4*S*,5*S*,7*R*,8*S*)-4,8-Dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1] nonan-7,8-diol (51″a). The endoperoxide **51″a** (222 mg, 13.5%, a single isomer) was synthesized from *cis*-carveol **47″** (2.284 g, 15 mmol) and PhSH (550 mg, 5 mmol) according to general procedure 1B (thiol addition time 12 h) and isolated as a monohydrate. A colorless solid (needles), mp 108–109°C (EtOAc–hexane), R_f 0.20 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}$=+177.2 (c=0.5, $CHCl_3$); IR ($CHCl_3$): 3490 (br, s), 3006, 2957, 2930, 1602, 1480, 1458, 1439, 1418, 1378, 1229, 1075 (s), 1041 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 br s, 3H, Me(11)), 1.45 (s, 3H, Me(10)), 1.96–2.06 (m, 3H), 2.09 (ddd, 1H, J=16.0, 3.7, 1.4 Hz, H(6)*ax*), 2.18 (ddd, 1H, J=16.0, 5.5, 4.4 Hz, H(6)*eq*), 3.37 (d, 1H, J=12.9 Hz, H(12)), 3.55 (br dd, 1H, J=13.2, 5.5 Hz, H(7)*eq*), 3.76 (dd, 1H, J=12.9, 0.6 Hz, H′(12)), 3.76 (m, 1H, H(1)), 4.09 (d, 1H, J=13.2 Hz, C(7)OH, exch. with CD_3CO_2D), 7.22 (m, 1H), 7.32 (m, 2H), 7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.22 (Me(11)), 22.91 (C(9)H_2), 24.57 (Me(10)), 29.95 (C(5)H), 30.92 (C(6)H_2), 40.55 (C(12)H_2), 72.98 (C(7)H), 74.21 (C(8)), 82.19 (C(1)H), 83.86 (C(4)), 126.56 (CH), 129.03 (2CH), 130.07 (2CH), 136.35 (C). Anal. Calcd for $C_{16}H_{22}O_4S\cdot H_2O$: C, 58.51; H, 7.36; S, 9.76. Found: C, 58.48; H, 7.34; S, 9.27.

6.3. General procedure 2 for oxidation of sulfides to sulfones by *m*-CPBA

A solution of sulfides (0.3 mmol, 1 equiv., a mixture of diastereomers or single isomer) and *m*-CPBA (0.75–0.9 mmol, 2.5–3.0 equiv.) in 5 mL of EtOAc (procedure 2A) or CH_2Cl_2 (procedure 2B) is stirred for 4–6 h at rt. After consumption of the more polar intermediate sulfoxide (TLC monitoring), the mixture is poured into a saturated solution of $NaHCO_3$ (2A) or cold 5% K_2CO_3 (2B), extracted with EtOAc–hexane (2A) or CH_2Cl_2 (2B), dried (Na_2SO_4 and $NaHCO_3$) and evaporated. FC of the residue affords the title compounds as a mixture of diastereomers. The mixture of diastereomeric sulfones is separated by additional FC, MPLC or HPLC. The reactions can be scaled up by a factor of 20 without significant affect on the yields.

6.3.1. (1*S*,4*S*,5*S*,8*S*)-4,8-Dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (39″a) and (1*S*,4*R*,5*S*,8*S*)-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (39″b). A mixture of diastereomers **39″a**,**b** (877 mg, 94%) was prepared from the sulfides **20″a**,**b** (840 mg, 2.85 mmol) and *m*-CPBA (ca. 60%, 2.05 g, 7.12 mmol) according to the general procedure 2A (reaction time 5 h). The diastereomers were separated by MPLC (EtOAc–hexane, 1:1). Less polar sulfone **39″a**: a colorless solid (plates), mp 112–113°C (EtOAc–hexane, 1:5); R_f 0.38 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}$=+236.7 (c=1.0, $CHCl_3$); IR ($CHCl_3$): 3300–3500, 2960, 2928, 1602, 1448, 1318 (s), 1308 (s), 1228, 1151 (s), 1086, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3H, Me(10)), 1.51 (br s, 3H, Me(11)), 1.60 (br dd, 1H, J=14.2, 5.6 Hz, H(7)*eq*), 1.86 (br dddd, 1H, J=14.2, 14.2, 6.0, 3.6 Hz, H(6)*ax*), 1.93 (m, 1H, H(6)*eq*), 2.11 (ddd, 1H, J=13.9, 3.0, 2.0 Hz, H(9)*ax*), 2.23 (br ddd, 1H, J=13.9, 6.0, 3.5 Hz, H(9)*eq*), 2.30 (m, 1H, H(5)), 2.30 (ddd, 1H, J=14.2, 14.2, 6.7 Hz, H(7)*ax*), 3.27 (d, 1H, J=14.3 Hz, H(12)), 3.67 (br dd, 1H, J=3.5, 2.5 Hz, H(1)), 4.23 (dd, 1H, J=14.3, 0.5 Hz, H′(12)), 7.58 (m, 2H), 7.67 (m, 1H), 7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.87 (Me(11)), 23.45 (C(6)H_2), 24.64 (C(9)H_2), 27.97 (Me(10)), 30.05 (C(5)H), 35.70 (C(7)H_2), 61.02 (C(12)H_2), 71.30 (C(8)), 81.96 (C(1)H), 82.71 (C(4)), 127.51 (2CH), 129.33 (2CH), 133.71 (CH), 141.08 (C). DCI (CH_4) HRMS: obsd 327.1255, calcd for $C_{16}H_{23}O_5S$ (MH^+) 327.1266. Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.87; H, 6.79; S, 9.82. Found: C, 58.94; H, 6.86; S, 9.75. The molecular structure of **39″a** was confirmed by single crystal X-ray analysis.

More polar sulfone **39″b**: a colorless oil, R_f 0.34 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}$=+107.8 (c=1.0, $CHCl_3$); IR ($CHCl_3$): 3300–3500, 2962, 2929, 1602, 1448, 1321 (s), 1310, 1154 (s), 1086, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H, Me(10)), 1.58 (br dd, 1H, J=14.2, 5.4 Hz, H(7)*eq*),

1.80 (br s, 3H, Me(11)), 1.86–2.00 (m, 2H, H(6)*ax*+*eq*), 2.03 (ddd, 1H, *J*=13.6, 3.2, 1.8 Hz, H(9)*ax*), 2.09 (br dddd, 1H, *J*=6.4, 6.4, 3.2, 3.2 Hz, H(5)), 2.14 (br ddd, 1H, *J*=14.0, 14.0, 6.6 Hz, H(7)*ax*), 2.27 (br ddd, 1H, *J*=13.6, 6.4, 3.3 Hz, H(9)*eq*), 3.14 (d, 1H, *J*=14.0 Hz, H(12)), 3.33 (br d, 1H, *J*=14.0 Hz, H′(12)), 3.68 (br dd, 1H, *J*=3.3, 1.8 Hz, H(1)), 7.58 (m, 2H), 7.67 (m, 1H), 7.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.71 (Me(11)), 23.46 ($C(9)H_2$), 23.72 ($C(6)H_2$), 27.83 (Me(10)), 31.53 (C(5)H), 35.35 ($C(7)H_2$), 60.55 ($C(12)H_2$), 71.02 (C(8)), 82.35 (C(1)H), 82.84 (C(4)), 127.52 (2CH), 129.25 (2CH), 133.76 (CH), 141.13 (C). DCI (CH_4) HRMS: obsd 327.1247, calcd for $C_{16}H_{23}O_5S$ (MH^+) 327.1266.

6.3.2. (1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (39′a) and (1*R*,4*S*,5*R*,8*R*)-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (39′b). A mixture of diastereomers **39′a**,**b** (2.128 g, 91%) was prepared by oxidation of sulfides **20′a**,**b** (2.10 g, 7.13 mmol) according to procedure 2A. The diastereomers were separated by MPLC (hexane–EtOAc, 1:1). Less polar isomer **39′a**: a colorless solid (plates), mp 112–113°C (hexane–EtOAc, 5:1); R_f 0.38 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}=-247.5$ (*c*=1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.87; H, 6.79; S, 9.82. Found: C, 58.87; H, 6.84; S, 9.73. More polar isomer **39′b**: a colorless oil, R_f 0.34 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}=-111.9$ (*c*=1.0, $CHCl_3$). DCI (CH_4) HRMS: obsd 327.1258, calcd for $C_{16}H_{23}O_5S$ (MH^+) 327.1266. The NMR spectra of sulfones **39′a** and **39′b** coincide with that of enantiomers **39″a** and **39″b** respectively (see above).

6.3.3. (1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-4-(4-fluorophenylsulfonyl)methyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (40′a) and (1*R*,4*S*,5*R*,8*R*)-4,8-dimethyl-4-(4-fluorophenylsulfonyl)methyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (40′b). A 56:44 mixture of diastereomers **40′a**,**b** (177 mg, 90%) was prepared by oxidation of sulfides **33′a**,**b** (179.5 mg, 0.57 mmol) according to procedure 2B (reaction time 6 h) and isolated by FC (hexane–EtOAc, 1:1). The diastereomers were separated by MPLC (hexane–EtOAc, 3:2). Less polar isomer **40′a**: a colorless oil, R_f 0.44 (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, Me(10)), 1.50 br s, 3H, Me(11)), 1.58 (br dd, 1H, *J*=14.0, 5.5 Hz, H(7)*eq*), 1.81–1.93 (m, 2H, H(6)*ax*+*eq*), 2.11 (ddd, 1H, *J*=13.0, 2.4, 2.4 Hz, H(9)*ax*), 2.20 (br ddd, 1H, *J*=13.0, 6.0, 3.4 Hz, H(9)*eq*), 2.22 (m, 1H, H(5)), 2.27 (ddd, 1H, *J*=14.0, 14.0, 6.8 Hz, H(7)*ax*), 3.30 (d, 1H, *J*=14.3 Hz, H(12)), 3.66 (br d, 1H, *J*=3.4 Hz, H(1)), 4.15 (br d, 1H, *J*=14.3 Hz, H′(12)), 7.22–7.27 (m, 2H), 7.92–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.76 (Me(11)), 23.47 ($C(6)H_2$), 24.68 ($C(9)H_2$), 27.97 (Me(10)), 30.25 (C(5)H), 35.72 ($C(7)H_2$), 61.20 ($C(12)H_2$), 71.31 (C(8)), 81.98 (C(1)H), 82.64 (C(4)), 116.60 (2CH, J_{C-F}=22.7 Hz), 130.51 (2CH, J_{C-F}=9.6 Hz), 133.27 (C, J_{C-F}=2.7 Hz), 165.77 (C–F, J_{C-F}=256.5 Hz). DCI (CH_4) HRMS: obsd 345.1154, calcd for $C_{14}H_{21}FO_5S$ (MH^+) 345.1172.

More polar isomer **40′b**: a colorless oil, R_f 0.41 (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 3H, Me(10)), 1.57 (ddd, 1H, *J*=14.0, 3.3, 3.3 Hz, H(7)*eq*), 1.79 (d, 3H, *J*=0.3 Hz, Me(11)), 1.88–1.95 (m, 2H, H(6)*ax*+*eq*), 2.01–2.13 (m, 3H, H(5)+H(7)*ax*+H(9)*ax*), 2.26 (br ddd, 1H, *J*=14.0, 4.0, 4.0 Hz, H(9)*eq*), 3.16 (d, 1H, *J*=14.0 Hz, H(12)), 3.31 (br d, 1H, *J*=14.0 Hz, H′(12)), 3.68 (br d, 1H, *J*=4.0 Hz, H(1)), 7.21–7.27 (m, 2H), 7.91–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.76 (Me(11)), 23.54 ($C(9)H_2$), 23.80 ($C(6)H_2$), 28.00 (Me(10)), 31.73 (C(5)H), 35.49 ($C(7)H_2$), 60.91 ($C(12)H_2$), 71.13 (C(8)), 82.40 (C(1)H), 82.85 (C(4)), 116.58 (2CH, J_{C-F}=22.7 Hz), 130.62 (2CH, J_{C-F}=9.6 Hz), 133.37 (C, J_{C-F}=2.8 Hz), 165.82 (C–F, J_{C-F}=256.8 Hz). DCI (CH_4) HRMS: obsd 345.1167, calcd for $C_{14}H_{21}FO_5S$ (MH^+) 345.1172.

6.3.4. (1*R*,4*R*,5*R*,8*R*)-4-(*n*-Butylsulfonyl)methyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (41′a) and (1*R*,4*S*,5*R*,8*R*)-4-(*n*-butylsulfonyl)methyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (41′b). A mixture of diastereomers **41′a**,**b** (34.2 mg, 88% yield, **a/b** ca. 63:37) was prepared by oxidation of sulfides **34′a**,**b** (34.7 mg, 0.127 mmol, **a/b** ca. 60:40) according to procedure 2B and purified by FC (hexane–EtOAc, 1:1) to give a colorless oil, R_f 0.23 (EtOAc–hexane, 1:1). A single more polar isomer **41′a** (ca. 95% purity, containing 5% of **41′b**) was isolated by semipreparative DP HPLC (hexane–EtOAc, 3:2). A colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, 3H, *J*=7.4 Hz, *Me*$CH_2CH_2CHH'SO_2$), 1.36 (s, 3H, Me(10)), 1.48 (tq, 3H, *J*=7.4, 7.4 Hz, Me*CH*$_2CH_2CHH'SO_2$), 1.50 (br s, 3H, Me(11)), 1.60 (br dd, 1H, *J*=14.2, 5.4 Hz, H(7)*eq*), 1.78–1.96 (m, 5H, $MeCH_2$*CH*$_2CHH'SO_2$+H(5)+H(6)*ax*+*eq*), 2.13 (ddd, 1H, *J*=13.9, 2.4, 2.4 Hz, H(9)*ax*), 2.25 (br ddd, 1H, *J*=13.9, 6.8, 3.3 Hz, H(9)*eq*), 2.31 (ddd, 1H, *J*=14.2, 14.2, 6.4 Hz, H(7)*ax*), 3.01–3.13 (m, 2H, $MeCH_2CH_2$*CHH*′SO_2), 3.56 and 3.62 (AB quartet, 2H, *J*=14.4 Hz, C(12)HH′), 3.67 (br s, 1H, H(1)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.54 (*Me*$CH_2CH_2CH_2SO_2$), 21.73 (Me*CH*$_2CH_2CH_2SO_2$), 21.96 (Me(11)), 23.48 ($C(6)H_2$), 23.86 ($MeCH_2$*CH*$_2CH_2SO_2$), 24.69 ($C(9)H_2$), 28.06 (Me(10)), 31.05 (C(5)H), 35.74 ($C(7)H_2$), 55.36 ($MeCH_2CH_2$*CH*$_2SO_2$), 57.00 ($C(12)H_2$), 71.40 (C(8)), 82.04 (C(1)H), 82.09 (C(4)). DCI (CH_4) HRMS: obsd 307.1543, calcd for $C_{14}H_{27}O_5S$ (MH^+) 307.1579. Selected NMR data for the sulfon **41′b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, Me(10)), 1.76 br s, 3H, Me(11)), 3.04 (d, 1H, *J*=14.1 Hz, H(12)), 3.23 (br d, 1H, *J*=14.1 Hz, H′(12)), 3.71 (br d, 1H, *J*=3.8 Hz, H(1)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.54 (*Me*$CH_2CH_2CH_2SO_2$), 21.07 (Me(11)), 21.59 (Me*CH*$_2CH_2CH_2SO_2$), 23.41 (CH_2), 23.49 (CH_2), 24.05 (CH_2), 28.08 (Me(10)), 32.48 (C(5)H), 35.38 ($C(7)H_2$), 55.77 ($MeCH_2CH_2$*CH*$_2SO_2$), 57.58 ($C(12)H_2$), 70.98 (C(8)), 81.97 (C(4)), 82.27 (C(1)H).

6.3.5. (1*R*,4*R*,5*R*,8*R*)-4,8-Dimethyl-4-(methoxycarbonylmethylsulfonyl)methyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (42′a) and (1*R*,4*S*,5*R*,8*R*)-4,8-dimethyl-4-(methoxycarbonylmethylsulfonyl)methyl-2,3-dioxabicyclo[3.3.1]-nonan-8-ol (42′b). Oxidation of sulfide **35′a** (42.4 mg, 0.146 mmol) according to procedure 2B afforded after FC purification (hexane–EtOAc, 1:1) the title sulfone **42′a** (41.5 mg, 88%). A colorless oil, R_f 0.11 (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, Me(10)), 1.53 br s, 3H, Me(11)), 1.58–1.64 (m, 1H, H(7)*eq*), 1.79–1.96 (m, 3H, H(5)+H(6)*ax*+*eq*), 2.14 (ddd, 1H, *J*=13.8, 2.2, 2.2 Hz, H(9)*ax*), 2.25–2.30 (m, 1H, H(9)*eq*), 2.30 (ddd, 1H, *J*=13.5, 13.5, 6.6 Hz, H(7)*ax*), 3.65 (br d, 1H,

J=14.7 Hz, H(12)), 3.73 (br d, 1H, J=3.5 Hz, H(1)), 3.82 (s, 3H, MeO), 3.98 (br d, 1H, J=15.2 Hz, $MeO_2CCH'H'SO_2$), 4.21 (d, 1H, J=14.7 Hz, H′(12)), 4.31 (d, 1H, J=15.2 Hz, $MeO_2CCH\mathit{H}'SO_2$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.96 (Me(11)), 23.23 ($C(6)H_2$), 24.31 ($C(9)H_2$), 27.92 (Me(10)), 31.11 (C(5)H), 35.44 ($C(7)H_2$), 53.14 (MeO), 57.38 ($C(12)H_2$), 59.06 ($MeO_2C\mathit{CH_2}SO_2$), 71.24 (C(8)), 81.94 (C(1)H), 81.99 (C(4)), 163.79 (C═O). DCI (CH_4) HRMS: obsd 323.1187, calcd for $C_{13}H_{23}O_7S$ (MH^+) 323.1165.

Similarly, oxidation of the sulfide **35′b** (60.0 mg, 0.207 mmol) (procedure 2B) afforded the sulfone **42′b** (59.4 mg, 89%). A colorless oil, R_f 0.13 (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, Me(10)), 1.59–1.66 (m, 1H, H(7) *eq*), 1.78 br s, 3H, Me(11)), 1.79–1.93 (m, 3H, H(5)+H(6)*ax*+*eq*), 2.08 (ddd, 1H, J=13.6, 3.3, 1.7 Hz, H(9)*ax*), 2.26–2.35 (m, 2H, H(7)*ax*+H(9)*eq*), 3.21 (dd, 1H, J=14.6, 1.6 Hz, H(12)), 3.78 (br d, 1H, J=4.2 Hz, H(1)), 3.81 (s, 3H, MeO), 3.89 (br d, 1H, J=14.6 Hz, H′(12)), 3.94 (dd, 1H, J=15.3, 1.8 Hz, $MeO_2CC\mathit{H}H'SO_2$), 4.31 (d, 1H, J=15.3 Hz, $MeO_2CCH\mathit{H}'SO_2$); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.07 (Me(11)), 23.24 ($C(6)H_2$), 23.41 ($C(9)H_2$), 28.11 (Me(10)), 32.89 (C(5)H), 34.83 ($C(7)H_2$), 53.19 (MeO), 58.02 ($C(12)H_2$), 59.57 ($MeO_2C\mathit{CH_2}SO_2$), 71.00 (C(8)), 82.22 (C(1)H), 81.42 (C(4)), 163.74 (C═O). DCI (CH_4) HRMS: obsd 323.1158, calcd for $C_{13}H_{23}O_7S$ (MH^+) 323.1165.

6.3.6. (1*R*,4*R*/*S*,5*R*,8*R*)-4-Cyclohexylsulfonylmethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols (43′a,b). A mixture of diastereomeric sulfones **43′a**,**b** (70.5 mg, ca. 85% yield, **a**/**b** ca. 60:40) was prepared by oxidation of sulfides **36′a**,**b** (100 mg of ca. 75% purity, ca. 0.25 mmol) (procedure 2B) and isolated by FC (hexane–EtOAc, 1:1). A colorless oil, R_f 0.24 (EtOAc–hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20–1.35 (m, 2H); 1.35 (s, Me(10), **b**), 1.37 (s, Me(10), **a**), total 3H; 1.49 br s, Me(11), **a**), 1.79 br s, Me(11), **a**), total 3H; 1.50–1.75 (m, 6H); 1.83–1.98 (m, ca. 5H), 1.99 (br dddd, J=6.4, 6.4, 3.2, 3.2 Hz, H(5)), 2.04 (ddd, 1H, J=13.5, 3.2, 1.8 Hz, H(9)*ax*), total 7H; 2.10–2.30 (m, ca. 5H), 2.31 (ddd, 1H, J=114.0, 114.0, 6.5 Hz, H(7)*ax*), total 6H; 2.86–2.98 (m, 1H, $CHSO_2$); 3.03 and 3.10 (AB quartet, J=13.9 Hz, C(12)HH′, **b**), 3.27 (d, J=14.0 Hz, H(12), **a**), 3.83 (d, 1H, J=14.0 Hz, H′(12)), total 2H; 3.71 (br d, J=3.3 Hz, H(1), **a**), 3.74 (br d, J=4.0 Hz, H(1), **b**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.56 (Me(11), **b**), 22.51 (Me(11), **a**); 23.44, 23.55, 23.60, 24.26, 24.55, 24.67, 24.94, 24.99, 25.03, 25.09, 25.66, 25.91 (CH_2); 27.98 (Me(10), **a**), 28.10 (Me(10), **b**); 30.43 (C(5)H, **a**), 32.01 (C(5)H, **b**); 35.58 ($C(7)H_2$, **b**), 35.71 ($C(7)H_2$, **a**); 53.29 ($C(12)H_2$, **a**), 53.58 ($C(12)H_2$, **a**); 63.45 (*CH*SO_2, **a**), 63.76 (*CH*SO_2, **b**); 71.08 (C(8), **b**), 71.32 (C(8), **a**); 82.00 (C(1)H, **a**), 82.41 (C(1)H, **b**); 82.47 (C(4), **a**), 82.83 (C(4), **b**). DCI (CH_4) HRMS: obsd 333.1752, calcd for $C_{16}H_{29}O_5S$ (MH^+) 333.1736.

6.3.7. (1*R*,4*R*,5*R*,8*R*)-4-(*tert*-Butylsulfonyl)methyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (44′a) and (1*R*,4*S*,5*R*,8*R*)-4-(*tert*-butylsulfonyl)methyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (44′b). Oxidation of sulfides **37′a**,**b** (180 mg, 0.66 mmol) according to procedure 2B followed by FC (hexane–EtOAc, 1:1) afforded a mixture of diastereomeric sulfones **44′a**,**b** (149 mg, 74% yield, **a**/**b** ca. 58:42) as a colorless oil: R_f 0.22 (EtOAc–hexane, 1:1). Recrystallization from EtOAc–hexane (1:9) gave a single isomer **44′a**: a colorless solid, mp 89–91°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, Me(10)), 1.44 (s, 9H, $\mathit{Me_3}$CS), 1.49 br s, 3H, Me(11)), 1.68 (br dd, 1H, J=13.8, 6.0 Hz, H(7)*eq*), 1.84 (dddd, 1H, J=14.3, 14.3, 5.8, 3.5 Hz, H(6)*ax*), 1.89–1.95 (m, 1H, H(6)*eq*), 2.12 (ddd, 1H, J=13.8, 3.1, 1.9 Hz, H(9)*ax*), 2.24–2.36 (m, 3H, H(5)+H(7)*ax*+H(9)*eq*), 3.05 (d, 1H, J=13.6 Hz, H(12)), 3.72 (br s, 1H, H(1)), 4.14 (br d, 1H, J=13.6 Hz, H′(12)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.99 (Me(11)), 23.29 ($\mathit{Me_3}$CS), 23.54 ($C(6)H_2$), 24.80 ($C(9)H_2$), 28.08 (Me(10)), 29.74 (C(5)H), 35.89 ($C(7)H_2$), 49.50 ($C(12)H_2$), 60.33 ($Me_3\mathit{C}S$), 71.42 (C(8)), 82.15 (C(1)H), 83.05 (C(4)). DCI (CH_4) HRMS: obsd 307.1615, calcd for $C_{14}H_{27}O_5S$ (MH^+) 307.1579. Sulfon **44′b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 3H, Me(10)), 1.42 (s, 9H, $\mathit{Me_3}$CS), 1.57–1.66 (m, 1H, H(7)*eq*), 1.81 br s, 3H, Me(11)), 1.86–1.98 (m, 2H, H(6)*ax*+*eq*), 2.02 (ddd, 1H, J=13.8, 3.2, 1.9 Hz, H(9)*ax*), 2.15 (br dddd, 1H, J=6.4, 6.4, 3.2, 3.2 Hz, H(5)), 2.19–2.29 (m, 2H, H(7)*ax*+H(9)*eq*), 2.83 (d, 1H, J=13.0 Hz, H(12)), 3.18 (br d, 1H, J=13.0 Hz, H′(12)), 3.72 (br s, 1H, H(1)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.18 (Me(11)), 23.29 ($\mathit{Me_3}$CS), 23.61 ($C(6)H_2$), 23.85 ($C(9)H_2$), 28.10 (Me(10)), 31.18 (C(5)H), 35.73 ($C(7)H_2$), 49.02 ($C(12)H_2$), 60.83 ($Me_3\mathit{C}S$), 71.20 (C(8)), 82.73 (C(1)H), 83.46 (C(4)).

6.3.8. (1*S*,4*S*,5*S*,7*S*,8*S*)-7-Benzoyloxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (52″a) and (1*S*,4*R*,5*S*,7*S*,8*S*)-7-benzoyloxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (52″b). A diastereomeric mixture of sulfones **52″a**,**b** (80.5 mg, 93%) was prepared by oxidation of sulfides **48″a**,**b** (80 mg, 0.193 mmol) (protocol 2A) and purified by FC (hexane–EtOAc, 65:35). The diastereomers were separated by MPLC (hexane–EtOAc, 3:2). More polar isomer **52″a**: a colorless solid, mp 182–183°C; R_f 0.36 (hexane–EtOAc, 3:2); $[\alpha]_D^{20}$=+164 (c=0.25, $CHCl_3$); IR ($CHCl_3$): 3400–3550, 2989, 2973, 2934, 1717 (s), 1448, 1316 (s), 1310, 1270 (s), 1151 (s), 1087, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 3H, Me(10)), 1.64 br s, 3H, Me(11)), 1.88 (ddd, 1H, J=13.3, 11.8, 3.6 Hz, H(6)*ax*), 2.25 (ddd, 1H, J=14.0, 2.8, 2.8 Hz, H(9)*ax*), 2.28 (dddd, 1H, J=14.0, 3.2, 2.8, 2.2 Hz, H(9)*eq*), 2.38 (br s, 1H, OH), 2.39 (dddd, 1H, J=13.3, 6.2, 3.2, 2.2 Hz, H(6)*eq*), 2.61 (br dddd, 1H, J=6.2, 6.2, 3.6, 3.2 Hz, H(5)), 3.31 (d, 1H, J=14.3 Hz, H(12)), 3.97 (br dd, 1H, J=2.8, 2.8 Hz, H(1)), 4.23 (br d, 1H, J=14.3 Hz, H′(12)), 5.71 (dd, 1H, J=11.8, 6.2 Hz, H(7)*ax*), 7.48 (m, 2H), 7.58–7.62 (m, 3H), 7.68 (m, 1H), 7.96 (m, 2H), 8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.28 (Me(11)), 24.19 ($C(9)H_2$), 24.41 (Me(10)), 29.13 ($C(6)H_2$), 32.10 (C(5)H), 60.87 ($C(12)H_2$), 72.71 (C(8)), 74.51 (C(7)H), 82.51 (C(4)), 83.14 (C(1)H), 127.59 (2CH), 128.56 (2CH), 129.42 (2CH), 129.51 (2CH), 129.93 (C), 133.31 (CH), 133.87 (CH), 140.96 (C), 165.61 (C═O). Anal. Calcd for $C_{23}H_{26}O_7S$: C, 61.87; H, 5.87; S 7.18. Found: C, 61.60; H 5.81; S 6.87.

Less polar isomer **52″b**: a colorless solid, mp 132–133°C; R_f 0.42 (hexane–EtOAc, 3:2); $[\alpha]_D^{20}$=+57.2 (c=0.5, $CHCl_3$);

IR ($CHCl_3$): 3300–3550, 3013, 2986, 2973, 2933, 1716 (s), 1602, 1448, 1321 (s), 1270 (s), 1154 (s), 1105, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 3H, Me(10)), 1.90 br s, 3H, Me(11)), 1.93 (ddd, 1H, J=13.8, 12.0, 3.5 Hz, H(6)*ax*), 2.16 (ddd, 1H, J=13.8, 3.3, 2.0 Hz, H(9)*ax*), 2.30 (dddd, 1H, J=13.8, 3.6, 3.6, 2.9 Hz, H(9)*eq*), 2.34 (br s, 1H, OH), 2.43 (m, 1H, H(5)), 2.57 (dddd, 1H, J=13.8, 6.1, 2.9, 2.9 Hz, H(6)*eq*), 3.16 (d, 1H, J=13.9 Hz, H(12)), 3.58 (br d, 1H, J=14.3 Hz, H′(12)), 3.97 (ddd, 1H, J=3.6, 2.0, 1.5 Hz, H(1)), 5.57 (dd, 1H, J=12.0, 6.1 Hz, H(7)*ax*), 7.50 (m, 2H), 7.58–7.63 (m, 3H), 7.67 (m, 1H), 7.97–8.05 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.71 (Me(11)), 23.27 ($C(9)H_2$), 24.31 (Me(10)), 29.49 ($C(6)H_2$), 33.61 (C(5)H), 60.24 ($C(12)H_2$), 72.70 (C(8)), 74.58 (C(7)H), 82.91 (C(4)), 83.80 (C(1)H), 127.79 (2CH), 128.55 (2CH), 129.39 (2CH), 129.49 (2CH), 129.97 (C), 133.30 (CH), 133.91 (CH), 141.02 (C), 165.69 (C=O). Anal. Calcd for $C_{23}H_{26}O_7S$: C, 61.87; H, 5.87; S 7.18. Found: C, 61.60; H 5.91; S 7.43.

6.3.9. (1*S*,4*S*,5*S*,7*S*,8*S*)-7-Benzoyloxy-4-(*n*-butylsulfonyl)-methyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (53″a) and (1*S*,4*R*,5*S*,7*S*,8*S*)-7-benzoyloxy-4-(*n*-butylsulfonyl)methyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (53″b). Oxidation of sulfides **49″a**,**b** (37.5 mg, 0.095 mmol, ca. 55:45) according to protocol 2A (reaction time 5 h) followed by FC (hexane–EtOAc, 7:3) afforded the individual diastereomeric sulfones **53″a** (19.5 mg) and **53″b** (17.2 mg) (total yield 91%). More polar isomer **53″a**: a colorless solid, mp 140–142°C, R_f 0.25 (hexane–EtOAc, 3:2); ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, 3H, J=7.4 Hz, *Me*$CH_2CH_2CHH'SO_2$), 1.43 (s, 3H, Me(10)), 1.49 (tq, 2H, J=7.4, 7.4 Hz, $CH_3CH_2CH_2CHH'SO_2$), 1.64 (br s, 3H, Me(11)), 1.83–1.91 (m, 2H, $CH_3CH_2CH_2CHH'SO_2$), 1.85 (ddd, 1H, J=13.5, 11.7, 3.3 Hz, H(6)ax), 2.25 (m, 2H, H(9)*ax*+*eq*), 2.31 (br dddd, 1H, J=6.4, 6.4, 3.3, 3.3 Hz, H(5)), 2.38 (ddddd, 1H, J=13.5, 6.2, 3.3, 1.6, 1.6 Hz, H(6)*eq*), 2.40 (br s, 1H, OH), 3.08 (m, 2H, $CH_3CH_2CH_2CHH'SO_2$), 3.50 (d, 1H, J=14.2 Hz, H(12)), 3.76 (br d, 1H, J=14.2 Hz, H′(12)), 4.01 (br dd, 1H, J=2.5, 2.5 Hz, H(1)), 5.72 (dd, 1H, J=11.7, 6.2 Hz, H(7)*ax*), 7.48 (m, 2H), 7.60 (m, 1H), 8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.55 (*Me*$CH_2CH_2CH_2SO_2$), 21.70 (Me*CH*$_2CH_2CH_2SO_2$), 22.46 (Me(11)), 23.86 ($MeCH_2CH_2CH_2SO_2$), 24.12 ($C(9)H_2$), 24.40 (Me(10)), 29.06 ($C(6)H_2$), 32.84 (C(5)H), 55.41 ($MeCH_2CH_2CH_2SO_2$), 56.64 ($C(12)H_2$), 72.71 (C(8)), 74.36 (C(7)H), 81.95 (C(4)), 83.12 (C(1)H), 128.57 (2CH), 129.51 (2CH), 129.90 (C), 133.33 (CH), 165.58 (C=O). Anal. Calcd for $C_{21}H_{30}O_7S$: C, 59.14; H, 7.09; S, 7.52. Found: C, 59.34; H, 7.17; S, 7.22.

Less polar isomer **53″b**: a colorless oil, R_f 0.36 (hexane–EtOAc, 3:2); ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, 3H, J=7.4 Hz, *Me*$CH_2CH_2CHH'SO_2$), 1.44 (s, 3H, Me(10)), 1.50 (tq, 2H, J=7.4, 7.4 Hz, $CH_3CH_2CH_2CHH'SO_2$), 1.86–1.95 (m, 3H, H(6)*ax*+$MeCH_2CH_2CHH'SO_2$), 1.88 (br s, 3H, Me(11)), 2.16 (ddd, 1H, J=13.0, 2.5, 1.9 Hz, H(9)*ax*), 2.28 (m, 1H, H(5)), 2.31 (dddd, 1H, J=13.0, 3.5, 3.3, 2.9 Hz, H(9)*eq*), 2.32 (br s, 1H, OH), 2.42 (dddd, 1H, J=13.8, 6.1, 2.9, 2.9 Hz, H(6)*eq*), 3.08 (m, 2H, $MeCH_2CH_2CHH'SO_2$), 3.17 (d, 1H, J=13.8 Hz, H(12)), 3.37 (br d, 1H, J=13.8 Hz, H′(12)), 4.00 (br ddd, 1H, J=3.5, 2.5, 1.8 Hz, H(1)), 5.68 (dd, 1H, J=12.0, 6.1 Hz, H(7)*ax*), 7.48 (m, 2H), 7.61 (m, 1H), 8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.52 (*Me*$CH_2CH_2CH_2SO_2$), 21.16 (Me(11)), 21.68 (Me*CH*$_2CH_2CH_2SO_2$), 23.23 ($C(9)H_2$), 24.13 ($MeCH_2CH_2CH_2SO_2$), 24.36 (Me(10)), 29.33 ($C(6)H_2$), 33.79 (C(5)H), 56.19 ($MeCH_2CH_2CH_2SO_2$), 56.57 ($C(12)H_2$), 72.71 (C(8)), 74.44 (C(7)H), 82.53 (C(4)), 83.73 (C(1)H), 128.60 (2CH), 129.49 (2CH), 129.87 (C), 133.36 (CH), 165.79 (C=O).

6.3.10. (1*S*,4*S*,5*S*,7*R*,8*S*)-7-Benzoyloxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (54″a) and (1*S*,4*R*,5*S*,7*R*,8*S*)-7-benzoyloxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (54″b). A mixture of the title sulfones **54″a**,**b** was prepared by oxidation of the sulfides **50″a**,**b** (19.0 mg, 0.0435 mmol, ca. 65:35) according to protocol 2A. The mixture was separated by MPLC (hexane–EtOAc, 3:2) to give individual sulfones **54″a** (11.0 mg) and **54″b** (6.3 mg) (total yield 89%). More polar isomer **54″a**: a colorless solid, mp 71–73°C; IR ($CHCl_3$): 3504 (br), 3405 (br), 2960, 2930, 1709 (s), 1600, 1448, 1377, 1317 (s), 1308 (s), 1283 (s), 1274 (s), 1149 (s), 1116 (s), 1086, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 3H, Me(10)), 1.51 (br s, 3H, Me(11)), 1.94 (br s, 1H, OH), 2.14 (ddd, 1H, J=14.0, 5.0, 2.4 Hz, H(9)*ax*), 2.15 (ddd, 1H, J=16.0, 4.7, 1.6 Hz, H(6)*ax*), 2.35 (ddd, 1H, J=16.0, 6.5, 5.0 Hz, H(6)*eq*), 2.36 (m, 1H, H(9)*eq*), 2.50 (m, 1H, H(5)), 3.36 (d, 1H, J=14.3 Hz, H(12)), 3.83 (br dd, 1H, J=3.6, 2.4 Hz, H(1)), 4.34 (br d, 1H, J=14.3 Hz, H′(12)), 5.29 (dd, 1H, J=6.5, 1.6 Hz, H(7)*eq*), 7.44 (m, 2H), 7.55–7.62 (m, 3H), 7.68 (m, 1H), 7.97 (m, 2H), 8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.23 (Me(11)), 23.41 (Me(10)), 23.97 ($C(9)H_2$), 28.71 ($C(6)H_2$), 30.15 (C(5)H), 60.89 ($C(12)H_2$), 73.75 (C(8)), 74.14 (C(7)H), 81.21 (C(1)H), 81.71 (C(4)), 127.58 (2CH), 128.48 (2CH), 129.42 (2CH), 129.90 (2CH), 130.11 (C), 133.15 (CH), 133.83 (CH), 141.10 (C), 166.20 (C=O). DCI (CH_4) HRMS: obsd 447.1510, calcd for $C_{23}H_{27}O_7S$ (MH^+) 447.1478.

Less polar isomer **54″b**: a colorless solid, mp 160–162°C (dec.); ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H, Me(10)), 1.86 (br s, 3H, Me(11)), 1.97 (br s, 1H, OH), 2.08 (ddd, 1H, J=13.6, 3.0, 1.6 Hz, H(9)*ax*), 2.21 (ddd, 1H, J=16.0, 4.4, 2.0 Hz, H(6)*ax*), 2.32 (m, 1H, H(5)), 2.34–2.42 (m, 2H, H(6)*eq*+H(9)*eq*), 3.11 (d, 1H, J=14.0 Hz, H(12)), 3.58 (br d, 1H, J=14.0 Hz, H′(12)), 3.94 (br dd, 1H, J=3.6, 1.6 Hz, H(1)), 5.27 (dd, 1H, J=6.3, 2.0 Hz, H(7)*eq*), 7.34 (m, 3H), 7.49 (m, 2H), 7.68 (m, 1H), 7.97 (m, 2H), 8.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.89 (Me(11)), 22.83 ($C(9)H_2$), 23.33 (Me(10)), 29.32 ($C(6)H_2$), 32.20 (C(5)H), 60.85 ($C(12)H_2$), 73.33 (C(8)), 74.80 (C(7)H), 81.87 (C(1)H), 82.04 (C(4)), 127.02 (2CH), 128.48 (2CH), 129.17 (2CH), 129.65 (2CH), 129.83 (C), 133.18 (CH), 133.55 (CH), 140.88 (C), 166.08 (C=O). DCI (CH_4) HRMS: obsd 447.1591, calcd for $C_{23}H_{27}O_7S$ (MH^+) 447.1478.

6.3.11. (1*S*,4*S*,5*S*,7*R*,8*S*)-4,8-Dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-7,8-diol monohydrate (55″a). The title sulfone **55″a** (83 mg, 92% yield) was prepared by oxidation of sulfide **51″a** (82 mg,

0.25 mmol) according to protocol 2A and purified by FC (hexane–EtOAc, 2:3). A colorless solid: mp 132–133°C (needles from hexane–EtOAc, 2:1); R_f 0.20 (EtOAc–hexane, 1: 1); $[\alpha]_D^{20}=+142.8$ (c=0.5, $CHCl_3$); IR ($CHCl_3$): 3510 (br, s), 3300–3550, 3006, 2959, 2930, 1602, 1448, 1381, 1319 (s), 1309 (s), 1151 (s), 1085, 1076, 1042 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H, Me(10)), 1.64 (br s, 3H, Me(11)), 2.16 (ddd, 1H, J=14.0, 3.4, 1.9 Hz, H(9)*ax*), 2.17–2.25 (m, 2H, H(6)*ax*+*eq*), 2.27 (ddd, 1H, J=14.0, 6.8, 3.4 Hz, H(9)*eq*), 2.42 (br dddd, J=6.4, 6.4, 3.4, 3.4 Hz, H(5)), 3.36 (d, 1H, J=14.3 Hz, H(12)), 3.57 (ddd, 1H, J=13.2, 5.4, 0.9 Hz, H(7)*eq*), 3.78 (br dd, 1H, J=3.4, 1.9 Hz, 1H, H(1)), 3.89 (br d, 1H, J=13.2 Hz, C(7)OH, exch. with CD_3CO_2D), 4.25 (dd, 1H, J=14.3, 0.5 Hz, H′(12)), 7.60 (m, 2H), 7.68 (m, 1H), 7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.19 (Me(11)), 23.65 (C(9)H_2), 24.53 (Me(10)), 30.86 (C(5)H), 30.92 (C(6)H_2), 60.70 (C(12)H_2), 73.02 (C(7)H), 74.25 (C(8)), 82.63 (C(1)H), 82.72 (C(4)), 127.63 (2CH), 129.46 (2CH), 133.90 (CH), 141.09 (C). Anal. Calcd for $C_{16}H_{22}O_6S\cdot H_2O$: C, 53.32; H, 6.71; S, 8.90. Found: C, 53.08; H, 6.82; S, 8.54.

6.3.12. (1*S*,4*S*,5*S*,8*S*)-8-Acetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (58″a), (1*S*,4*R*,5*S*,8*S*)-8-acetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (58″b), (1*S*,4*S*,5*S*,8*R*)-8-acetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (58″c), and (1*S*,4*R*,5*S*,8*R*)-8-acetoxy-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonane (58″d). (a) A mixture of hydroxysulfides **20″a–d** (2.657 g, about 57% yield) was prepared applying the TOCO reaction to *S*-limonene **18″** (6.13 g, 45.0 mmol) and PhSH (1.653 g, 15 mmol) according to general procedure 1B. A crude reaction mixture was fractionated by FC (EtOAc–hexane, 3:7) with collection of the peroxidic fractions (TLC monitoring using the stain 2) of R_f 0.23–0.29 (EtOAc–hexane, 3:7). The hydroxysulfides **20″a–d** isolated by this method were contaminated by unidentified nonperoxidic impurities (3–4%). Hydroxysulfides **20″a–d** were used in the next steps without additional purification.

(b) To a cold (0°C) solution of hydroxysulfides **20″a–d** (250 mg, ca. 0.84 mmol) and 2,6-lutidine (250 mg, 2.34 mmol) in dry CH_2Cl_2 (5 mL) was added neat TfOTMS (422 mg, 1.79 mmol) and the reaction mixture was stirred at 0°C for 1 h (TLC monitoring). The mixture was then poured into cold water (50 mL), extracted with EtOAc–hexane (1:4, 2×50 mL), washed with cold saturated $NaHCO_3$ (25 mL), dried (Na_2SO_4), and evaporated to give the crude TMS-derivative **56″a–d** (313 mg, quantitative yield). 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, Me(11), **a**), 1.53 (d, J=0.5 Hz, Me(11), **b**), total 3H; 1.38 (s, Me(10), **b**), 1.39 (s, Me(10), **a**), total 3H; 1.58–1.65 (m, 1H, H(7)*eq*, **a**+**b**), 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; 3.63 (br dd, J=2.5, 2.5 Hz, H(1), **a**), 3.63 (m, H(1), **b**), total 1H; 7.26–7.42 (m, 5H).

(c) A diastereomeric mixture of TMS-derivatives **56″a–d** (313 mg) was treated with freshly distilled AcCl (2.5 mL) and stirred for 48 h at rt. The mixture was evaporated and dried under vacuum (0.05 mm Hg) to give the crude acetoxysulfides **57″a–d** (283 mg). A pale brown 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, Me(11), **a**), 1.56 (br s, Me(11), **b**), total 3H; 1.65 (s, Me(10), **b**), 1.66 (s, Me(10), **a**), total 3H; 1.67–1.89 (m, 3H); 1.74 (m, H(5), **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, H(9)*eq*, **a**), 2.27 (m, H(9)*eq*, **b**), total 1H; 2.12–2.20 (m, 1H, H(7)*eq*, **a**+**b**); 2.25 (ddd, J=15.0, 13.2, 6.0 Hz, H(7)*ax*, **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, H(1), **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 (C(6)H_2), 23.97 (C(9)H_2), 28.52 (C(5)H), 32.88 (C(7)H_2), 40.71 (C(12)H_2), 77.46 (C(1)H), 82.76 (C(8)), 83.85 (C(4)), 126.24 (CH), 128.91 (2CH), 129.76 (2CH), 136.73 (C), 170.13 (C=O) (isomer **57″a**); 21.77 (Me(11)), 22.53 (Me(10)), 22.55 (*Me*C(O)), 23.22 (C(6)H_2), 24.09 (C(9)H_2), 29.89 (C(5)H), 33.20 (C(7)H_2), 40.81 (C(12)H_2), 77.91 (C(1)H), 82.67 (C(8)), 83.73 (C(4)), 126.43 (CH), 128.96 (2CH), 129.73 (2CH), 136.29 (C), 170.13 (C=O) (isomer **57″b**).

(d) A mixture of acetoxysulfides **57″a–d** (283 mg) was dissolved in EtOAc (8 mL) and oxidized by *m*-CPBA (526 mg of ca. 70%, 2.135 mmol) (protocol 2A, 6 h). A conventional work-up followed by FC (hexane–EtOAc, 3:1) afforded a solid mixture of sulfones **58″a**,**b** (265 mg, 84%, **a**/**b** ca. 56:44) and more polar semisolid fraction (44 mg) consisted of the sulfones **58″b–d** and some nonperoxidic impurities. The mixture of sulfones **58″a**,**b** was separated by MPLC (hexane–EtOAc, 3:1) to give the individual diastereomers **58″a** (the least polar component), and **58″b**, both as a colorless solid (see below). The fraction consisted of **58″b–d** was separated by semipreparative DP HPLC (EtOAc–hexane, 40:60) to give the sulfone **58″b** (8 mg), the sulfone **58″d** (8 mg of ca. 93% purity) as a colorless oil (the most polar component), and a fraction containing the sulfone **58″c** (12 mg). The middle fraction containing **58″c** was subjected to semipreparative RP HPLC (methanol–water, 70:30) to afford the sulfone **58″c** (5 mg of ca. 93% purity) as a colorless semisolid. Analytical HPLC data (EtOAc–hexane, 25:75) for **58″a–d**: τ_R 11.9 (**58″a**), 12.8 (**58″b**), 16.1 (**58″c**) and 17.5 (**58″d**) min. Analytical RP HPLC (methanol–water, 70:30, flow rate 0.5 mL/min): τ_R 8.1 min for **58″c**.

The least polar major isomer **58″a**: a colorless solid, mp 97–98°C; R_f 0.37 (hexane–benzene–EtOAc, 11:6:3); ^1H 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, 58.73; H, 6.49; S, 8.41.

The middle major acetoxysulfone **58″b**: 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.

The middle minor acetoxysulfone **58″c**: a colorless waxy solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, 3H, *J*=0.6 Hz, Me(11)), 1.602 and 1.604 (2×s, 3H, Me(10)), 1.63–1.73 (m, 2H, H(6)*ax*+H(9)*ax*), 1.92 (br dd, 1H, *J*=13.8, 6.7 Hz, H(7)*eq*), 2.03 (s, 3H, *Me*C(O)), 2.04–2.12 (m, 1H, H(6)*eq*), 2.35 (br dddd, 1H, *J*=6.4, 6.4, 3.2, 3.2 Hz, H(5)), 2.43 (dddd, 1H, *J*=14.4, 4.3, 3.2, 3.2 Hz, H(9)*eq*), 2.56 (br ddd, 1H, *J*=13.8, 13.8, 6.5 Hz, H(7)*ax*), 3.21 (d, 1H, *J*=14.3 Hz, H(12)), 4.27 (dd, 1H, *J*=14.3, 0.6 Hz, H′(12)), 4.71 (br d, 1H, *J*=4.3 Hz, H(1)), 7.59 (m, 2H), 7.67 (m, 1H), 7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.21 (*Me*C(O)), 23.06 (Me(11)), 23.58 (Me(10)), 24.60 ($C(6)H_2$), 26.33 ($C(9)H_2$), 29.73 (C(5)H), 34.99 ($C(7)H_2$), 61.06 ($C(12)H_2$), 77.96 (C(1)H), 82.61 (C(4)+C(8)), 127.55 (2CH), 129.41 (2CH), 133.78 (CH), 141.42 (C). DCI (CH_4) HRMS: obsd 369.1349, calcd for $C_{18}H_{25}O_6S$ (MH^+) 369.1372.

The most polar minor acetoxysulfone **58″d**: a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.584 and 1.586 (2×s, 3H, Me(10)), 1.56 (ddd, 1H, *J*=13.5, 3.4, 1.6 Hz, H(9)*ax*), 1.68–1.78 (m, 1H, H(6)*ax*), 1.80 br s, 3H, Me(11)), 1.94 (br dd, 1H, *J*=13.7, 5.8 Hz, H(7)*eq*), 1.99 (s, 3H, *Me*C(O)), 2.14–2.23 (m, 2H, H(5)+H(6)*eq*), 2.39–2.47 (m, 2H, H(7)*ax*+H(9)*eq*), 3.12 (d, 1H, *J*=14.0 Hz, H(12)), 3.39 (br d, 1H, *J*=14.0 Hz, H′(12)), 4.68 (br d, 1H, *J*=4.3 Hz, H(1)), 7.58 (m, 2H), 7.67 (m, 1H), 7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.00 (Me(11)), 22.18 (*Me*C(O)), 23.25 (Me(10)), 25.00 ($C(6)H_2$), 25.11 ($C(9)H_2$), 31.14 (C(5)H), 34.74 ($C(7)H_2$), 60.29 ($C(12)H_2$), 78.52 (C(1)H), 81.65 (C(8)), 82.82 (C(4)), 127.57 (2CH), 129.42 (2CH), 133.91 (CH), 141.19 (C), 170.39 (C═O). DCI (CH_4) HRMS: obsd 369.1396, calcd for $C_{18}H_{25}O_6S$ (MH^+) 369.1372.

6.4. X-Ray analysis of the structure of endoperoxide 39″a[43]

Endoperoxide **39″a** was crystallized from hexane–EtOAc (4:1) at room temperature.

Crystal data: $C_{16}H_{22}O_5S$, colorless transparent, prismatic, 0.3×0.3×0.3 mm^3, monoclinic, *P*2(1)/*c* (No. 4), *a*=6.060(1) Å, *b*=14.126(3) Å, *c*=18.844(4) Å, β=92.68(3)° from 25 reflections, *T*=293 K, *V*=1611.3(6) Å^3, *Z*=2, Fw=326.40, D_c=1.345 g/cm^3, μ=0.221 mm^{-1}. Data collection and treatment: AFC5R diffractometer, Mo, graphite monochromator (λ=0.70173 Å), 7798 reflections collected, $1.08° \le \Theta \le 27.51°$, $-7 \le h \le 7$, $0 \le k \le 18$, $-24 \le l \le 24$, ω scan method, scan width=1.2°, scan speed 8°/min, typical half-height width=0.35°, three standards collected 40 times, 2% change in intensity, 3847 independent reflections (R_{int}=0.0243). Solution and refinement: the structure was solved by direct methods with SHELXL-97. Full-matrix least-squares refinement was based on F^2 with SHELXL-97. Hydrogens were calculated and refined in a riding mode, 400 parameters with 0 restraints, final R_1=0.0594 (based on F^2) for all data, goodness-on-fit on F^2=1.065, largest residual electron density=0.351 e/Å^{-3}.

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References

1. Meshnick, S. R.; Jefford, C. W.; Posner, G. H.; Avery, M. A.; Peters, W. *Parasitol. Today* **1996**, *12*, 79–82.
2. (a) Peters, W. *Adv. Parasitol.* **1998**, *41*, 1–62. (b) Newton, P.; White, N. *Ann. Rev. Med.* **1999**, *50*, 179–192. (c) Warhurst, D. C. *Infection* **1999**, *27*, 55–58.
3. (a) Lugt, C. B. *TDR News* **2000**, *63*, 13. (b) van Agtmael, M. A.; Eggelte, T. A.; van Boxtel, C. J. *Trends Pharmacol. Sci.* **1999**, *20*, 199–205. (c) Price, R. N. *Exp. Opin. Investigat. Drugs* **2000**, *9*, 1815–1827. (d) Dhingra, V.; Rao, K. V.; Narasu, M. L. *Life Sci.* **2000**, *66*, 279–300. (e) Ridley, R. G. *Exp. Parasitol.* **1997**, *87*, 293–304.
4. (a) Posner, G. H.; Cumming, J. N.; Krasavin, M. In *Biomedicinal Chemistry*; Torrence, P. F., Ed.; Wiley: New York, 2000; pp 289–309. (b) Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *37*, 253–297. (c) Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301–315. (d) Vroman, J. A.; Alvim-

Gaston, M.; Avery, M. A. *Curr. Pharmacol. Des.* **1999**, *5*, 101–138. (e) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, *51*, 1681–1745.

5. For isolation and structure determination of yingzhaosu A (**3**), see: (a) Liang, X. T.; Yu, D. Q.; Wu, W. L.; Deng, H. C. *Acta Chim. Sinica* **1979**, *37*, 215–230. (b) Liang, X. In *Advances in Chinese Medicinal Materials*; Chang, H. M., Yeung, H. W., Tso, W. W., Koo, A., Eds.; World Scientific: Singapore, 1985; pp 427–432 The only available qualitative information on antimalarial activity of **3** has been mentioned in Ref. 5b.
6. (a) Xu, X. X.; Zhu, J.; Huang, D.-Z.; Zhou, W.-S. *Tetrahedron Lett.* **1991**, *32*, 5785–5788. (b) Zhou, W. S.; Xu, X. X. *Acc. Chem. Res.* **1994**, *27*, 211–216.
7. (a) Hofheinz, W.; Schmid, G.; Stohler, H. Eur. Pat. Appl. 311955, 1989; *Chem. Abstr.* **1990**, *112*, 20999. (b) Hofheinz, W.; Burgin, H.; Gocke, E.; Jaquet, C.; Masciadri, R.; Schmid, G.; Stohler, H.; Urwyler, H. *Trop. Med. Parasitol.* **1994**, *45*, 261–265.
8. (a) Jaquet, C.; Stohler, H. R.; Chollet, J.; Peters, W. *Trop. Med. Parasitol.* **1994**, *45*, 266–271. (b) Weidekamm, E.; Dumont, E.; Jaquet, C. *Trop. Med. Parasitol.* **1994**, *45*, 278–283. (c) Salako, L. A.; Guiguemde, R.; Mittelholzer, M.-L.; Haller, L.; Sorenson, F.; Stürchler, D. *Trop. Med. Parasitol.* **1994**, *45*, 284–287. (d) Somo-Moyou, R.; Mittelholzer, M.-L.; Sorenson, F.; Haller, L.; Stürchler, D. *Trop. Med. Parasitol.* **1994**, *45*, 288–291.
9. O'Neill, P. M.; Searle, N. L.; Raynes, K. J.; Maggs, J. L.; Ward, S. A.; Storr, R. C.; Park, B. K.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 6065–6068.
10. (a) Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Wataya, Y. *Tetrahedron* **2001**, *57*, 5979–5989. (b) Tokuyasu, T.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Wataya, Y. *Tetrahedron Lett.* **2000**, *41*, 3145–3148.
11. Preliminary report: Bachi, M. D.; Korshin, E. E. *Synlett* **1998**, 122–124.
12. Patented in: Bachi, M. D.; Posner, G. H.; Korshin, E. E. PCT Int. Appl. WO 99/12900 A2, 1999; *Chem. Abstr.* **1999**, *130*, 237573.
13. Bachi, M. D.; Korshin, E. E.; Hoos, R.; Szpilman, A. M. *J. Heterocycl. Chem.* **2000**, *37*, 639–646.
14. Preliminary report: Bachi, M. D.; Korshin, E. E.; Ploypradith, P.; Cumming, J. N.; Xie, S. J.; Shapiro, T. A.; Posner, G. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 903–908.
15. Full account on in vivo/in vitro antimalarial activity and toxicology of potent β-sulfonyl-endoperoxides of type **10** will be published soon elsewhere: Bachi, M. D.; Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Cumming, J. N.; Ploypradith, P.; Xie, S. J.; Shapiro, T. A.; Posner, G. H. Manuscript in preparation.
16. See, for example: (a) Bachi, M. D.; Balanov, A.; Bar-Ner, N. *J. Org. Chem.* **1994**, *59*, 7752–7758. (b) Bachi, M. D.; Bar-Ner, N.; Melman, A. *J. Org. Chem.* **1996**, *61*, 7116–7124.
17. (a) Roe, A. N.; McPhail, A. T.; Porter, N. A. *J. Am. Chem. Soc.* **1983**, *105*, 1199–1203. (b) Porter, N. A.; Lehman, L. S.; Weber, B. A.; Smith, K. J. *J. Am. Chem. Soc.* **1981**, *103*, 6447–6455. (c) Porter, N. A.; Roe, A. N.; McPhail, A. T. *J. Am. Chem. Soc.* **1980**, *102*, 7574–7576. (d) Porter, N. A.; Funk, M. O.; Gilmore, D.; Isaac, R.; Nixon, J. *J. Am. Chem. Soc.* **1976**, *98*, 6000–6005. See also Ref. 18.
18. For an application of 6-*exo-trig* cyclization of unsaturated peroxy-radicals in the total synthesis of monocyclic natural endoperoxide yingzhaosu C, see: Boukouvalas, J.; Pouliot, R.; Frechette, Y. *Tetrahedron Lett.* **1995**, *36*, 4167–4170.
19. (a) Beckwith, A. L. J.; Wagner, R. D. *J. Am. Chem. Soc.* **1979**, *101*, 7099–7100. (b) Beckwith, A. L. J.; Wagner, R. D. *J. Chem. Soc., Chem. Commun.* **1980**, 485–486. (c) Barker, P. A.; Beckwith, A. L. J.; Fung, Y. *Tetrahedron Lett.* **1983**, *24*, 97–100 See also Ref. 20.
20. For an elegant application of the TOCO reaction in the synthesis of 1,2-dioxolanes from alkenylcyclopropanes and $(PhSe)_2$ or $(PhS)_2$, see: (a) Feldman, K. S. *Synlett* **1995**, 217–225. (b) Feldman, K. S.; Parvez, M. *J. Am. Chem. Soc.* **1986**, *108*, 1328–1330. (c) Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878–4886. (d) Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985–6988. (e) Feldman, K. S.; Kraebel, C. M. *J. Org. Chem.* **1992**, *57*, 4574–4576. (f) Weinreb, C. K.; Hartsough, D.; Feldman, K. S. *Tetrahedron Lett.* **1995**, *36*, 6859–6862.
21. The reported absolute rate constants k_1 for addition of phenylthiyl-radicals (PhS·) to simple alkenes C=C bond lie in the range 10^4–10^5 M^{-1} s^{-1} while the reverse process is characterized by values k_{-1} ca. 10^8 s^{-1}; see Refs. 22–24. Trapping of molecular oxygen by simple carbon-centered radicals is very fast: $k_2 \approx 10^8$–10^9 M^{-1} s^{-1}, $k_{-2} \approx 10^2$ s^{-1}; see Refs. 17,23–25. The rate of 6-*exo-trig*-cyclization of hex-4-enylperoxy-radicals to form monocyclic 1,2-dioxane system was reported to be $k_3 \approx 10^5$ s^{-1} while the reverse process of the ring opening is much slower, $k_{-3} \approx 10^2$ s^{-1}; see Refs. 17,25. The irreversible hydrogen transfer from thiophenol to peroxy-radical has a value of $k_4 \approx 5 \times 10^3$ M^{-1} s^{-1} (Refs. 23,26).
22. (a) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1979**, *101*, 5732–5735. (b) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1979**, *101*, 1815–1819. (c) Wagner, P. J.; Sedon, J. H.; Lindstrom, M. *J. Am. Chem. Soc.* **1978**, *100*, 2579–2580.
23. Beckwith, A. L. J.; Wagner, R. D. *J. Org. Chem.* **1981**, *46*, 3638–3645.
24. Ito, O. In *S-Centered Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, 1999; pp 193–224.
25. (a) Porter, N. A.; Mills, K. A.; Caldwell, S. E.; Dubay, G. B. *J. Am. Chem. Soc.* **1994**, *116*, 6697–6705. (b) Porter, N. A.; Caldwell, S. E.; Mills, K. A. *Lipids* **1995**, *30*, 277–290.
26. Chenier, J. H. B.; Furimsky, E.; Howard, J. A. *Can. J. Chem.* **1974**, *52*, 3682–3688.
27. (a) Bartlett, P. D.; Benzing, E. P.; Pincock, R. *J. Am. Chem. Soc.* **1960**, *82*, 1762–1768. (b) Boukouvalas, J. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. O., Ed.; Wiley: Chichester, 1995; Vol. 3, pp 1621–1623.
28. While the major isomers **20a**, and **20b** were isolated in pure state by FC, the minor isomers were separated and characterized as their derivatives **58″c** and **58″d** in the experiment described in Scheme 6.
29. *CAUTION*! Although no accidents occurred in this laboratory, it is mandatory to observe appropriate precautions for working with potentially explosive materials. Particular attention should be given to potentially explosive mixtures of oxygen and vapors of organic solvents, to the potentially explosive DBPO as well as to evaporation of peroxide containing solutions. Ph_3P is expected to reduce the most reactive peroxy-component. Reaction mixtures, prior to treatment with PPh_3, may contain unidentified explosive by-products
30. To the best of our knowledge, there are no reports on the use of aliphatic mercaptans in a TOCO reaction yielding cyclic peroxides. For early studies on co-oxygenation of aliphatic mercaptans with 1,3-dienes or with monoolefins leading to open-chain hydroxy-sulfides or sulfoxides, see: Oswald, A. A.; Wallace, T. J. *The Chemistry of Organic Sulfur Compounds*; Kharasch, N., Meyers, C. V., Eds.; Pergamon:

Oxford, 1966; Vol. 2, pp 205–232 and the references cited therein. For more recent applied studies, see e.g.: (a) Muller, U.; Kunze, A.; Herzig, C.; Weis, J. *J. Macromol. Sci., Pure Appl. Chem. A* **1996**, *33*, 439–457.

31. In the case of sulfides **35′a**, **35′b** and **51″a** isolation of individual isomers preceded the oxidation step.
32. Direct acetylation of the sterically hindered tertiary hydroxyl of endoperoxides **20a**,**b** with AcCl in the presence of base was found to be far less effective. See Refs. 12,14,15.
33. The chair conformation of the 1,2-dioxane system has been previously determined by X-ray diffraction analysis and reported in (a) Tanaka, J.; Higa, T.; Suwanborirux, K.; Kokpol, U.; Bernardinelli, G.; Jefford, C. W. *J. Org. Chem.* **1993**, *58*, 2999–3002. (b) Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M.; Albericci, M.; Braekman, J. C.; Daloze, D.; Turch, B. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1523–1526. (c) Jefford, C. W.; Eschenhof, H.; Bernardinelli, G. *Heterocycles* **1998**, *47*, 283–288. (d) Albericci, M.; Collart-Lempereur, M.; Braekman, J. C.; Dalcze, D.; Tursch, B.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Tetrahedron Lett.* **1979**, 2687–2690.
34. For the chair conformation of the 1,2-dioxane ring in solutions determined by the NMR technique, see: (a) Capon, R. J.; Macleod, J. K. *Tetrahedron* **1985**, *41*, 3391–3404. (b) Xu, X. X.; Dong, H. Q. *J. Org. Chem.* **1995**, *60*, 3039–3044. (c) Fontana, A.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1998**, *54*, 2041–2048. (d) Compagnone, R. S.; Pina, I. C.; Rangel, H. R.; Dagger, F.; Suarez, A. I.; Reddy, M. V. R.; Faulkner, D. J. *Tetrahedron* **1998**, *54*, 3057–3068. See also Refs. 17,32a.
35. The conformational studies on the endoperoxides were reviewed in (a) Gougoutas, J. Z. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: Chichester, 1983; pp 375–415. (b) Clennan, E. L.; Foote, C. S. In *Organic Peroxides*; Ando, W., Ed.; Wiley: Chichester, 1992; pp 255–318.
36. Jackman, L. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; 2nd ed.; Pergamon: Oxford, 1969; pp 280–301.
37. Intramolecular hydrogen bonding using oxygen atoms as proton acceptors in endoperoxides was not extensively studied. For the only available data obtained by the IR method, see: (a) Richardson, W. H.; Smith, R. S. *J. Org. Chem.* **1968**, *33*, 3882–3885. (b) Richardson, W. H. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: Chichester, 1983; pp 129–160.
38. Intramolecular hydrogen bonding of the hydroperoxy proton to a dioxolane oxygen in 3-hydroperoxy-1,2-dioxolanes was proposed to influence the oxidative properties of these compounds. See: Baumstark, A.; Chen, Y. X.; Rodriguez, A. *J. Heterocycl. Chem.* **1996**, *33*, 1399–1402.
39. Compounds of type **10**, e.g. **10′** (R=Ph, R^2=*p*-$MeOC_6H_4CH_2$) exhibit antimalarial activity comparable to that of artemisinin. For preliminary communications see Refs. 12,14. Comprehensive results will be published elsewhere (Ref. 15).
40. (a) Mair, R. D.; Hall, R. T. *Organic Peroxides*; Swern, D., Ed.; Wiley: London, 1971; Vol. 2, p 553. (b) Knappe, E.; Peteri, D. *Z. Anal. Chem.* **1962**, *190*, 386–389.
41. Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633–5642.
42. Mascarenas, J. L.; Sarandeses, L. A.; Castedo, L.; Mourino, A. *Tetrahedron* **1991**, *47*, 3485–3498.
43. Crystallographic data (excluding structure factors) for the structure **39″a** have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication number CCDC 172269. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ca.uk).