Sulfogriseofulvin Derivatives. Synthesis by [4+2]Cycloaddition, Structure, Properties, Crystal Structure Analysis, and Antifungal Activity of Spiro[1,3-benzoxathiole-2,1′-cyclohex-2′-en]-4′-one 3,3-Dioxides ☆

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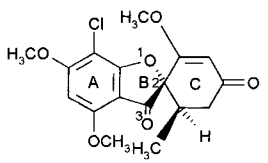
Summary

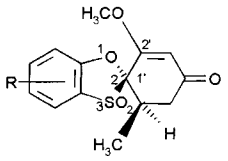
Syntheses of substituted, especially of fluoro substituted benzoxathiole 1,1-dioxides, are described. These derivatives were transformed via the *Peterson* olefination into substituted 2-alkylidene derivatives **27**. *Diels-Alder* reactions of **27** with 1,1-dimethoxy- and 1-methoxy-3-trimethylsiloxy-1,3-butadiene (**30**, **32**) gave sulfone analogues **31** of griseofulvin (named sulfogriseofulvins). From *Z*-**27**, a number of cis-isomers with the relative stereochemistry of griseofulvin (*cis*-**31**) was prepared, and from *E*-isomers of **27**, compounds (*trans*-**31**) with relative stereochemistry of epigriseofulvin were obtained. Some related compounds (**33**, **38**) are synthesized by slight modifications. The stereochemistry is established by spectroscopic methods and crystal structure analyses. The compounds **31** were tested against three species of dermatophytes. The biological activities were all significantly lower than that of griseofulvin.

Introduction

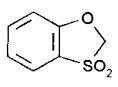
The antibiotic griseofulvin (**A**) is a useful antimycotic for the systemic treatment of infections with dermatophytes[1], but it shows a number of shortcomings, *e.g.* difficult bioavailability, fungistatic instead of fungicide action, and a narrow spectrum of activity. The first total synthesis is reported in 1960[2], and since that time a large number of synthetic variations has been carried out to improve the properties, but could not achieve any real success[3].



Griseofulvin (A)



Sulfogriseofulvins



(B)

We have used the concept of the replacement of the carbonyl group by the bioisosteric sulfonyl group in the field of β-lactams[4]. Until now, the modifications of griseofulvin involved either exchange of the ring-oxygen by other heteroatoms or modifications of the substituents connected with the skeleton. Therefore, it seemed being interestingly to replace the carbonyl group of **A** by SO_2. Now we report about the syntheses, the physico-chemical and stereochemical properties, and antifungal activity of a number of such bioisosteric modified griseofulvins, denoted as sulfogriseofulvins by us.

The synthetic concept for sulfogriseofulvins consists of two steps. The first part is the synthesis of the ring system A/B, which is represented by the benzoxathiole 3,3-dioxide (**B**). This system by itself seems to be a very potent starting compound for fungistatic and bacteriostatic drugs[5]. From the appropriate substituted derivatives of **B** the complete system finally is obtained by addition of the ring C. Fluoro substituents at ring A should improve the lipophilicity and thereby enlarge the biological potency[6] of the sulfogriseofulvins. As the trifluoro group at position 6′ of griseofulvin has a strong influence on the activity[7], this group is included in our studies. Therefore, we synthesized those fluoro-substituted derivatives of **1** and used them as starting materials in the *Peterson* reaction followed by a cyclisation to sulfogriseofulvins.

In recent papers we have described the silylation of 5-methoxy-1,3-benzoxathiole 3,3-dioxide (**1**)[8,9]. Silyl groups on the aromatic part of the molecule can be replaced by electrophiles via *ipso*-reaction, while silyl groups of the cycloaliphatic part may serve as components in the *Peterson* olefination[6].

Results

All attempts to introduce fluoro atoms into the molecule by direct fluorination of **1** or derivatives thereof with N-fluoro-*N*-alkylsulfonamides[10] or *N*-fluoropyridinium triflate[11] completely failed. From **1** the dinitro derivatives **2** and **3** were prepared, but the replacement of a nitro group by F using tetrabutylammonium fluoride (TBAF) in THF[12] was not successful. From **2** we obtained in most experiments products of decomposition, while from **3** the 4-hydroxy-7-nitro deriva-

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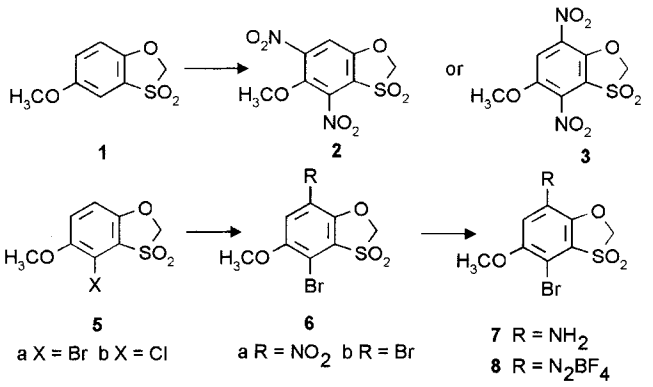
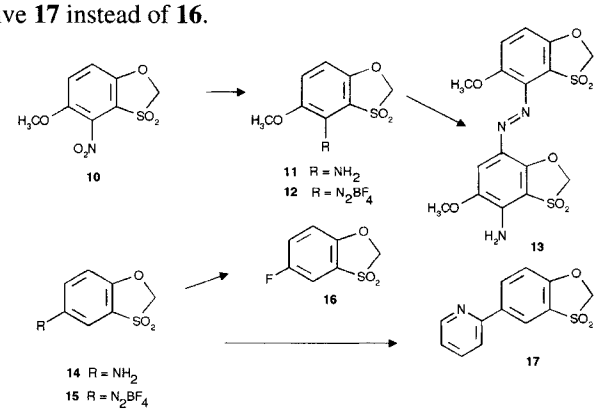
tive **4** was isolated. Attempts to replace Br or Cl by F were also disappointing. Starting with **5** or **6**, the so-called *Halex*-Fluorination[13] using dried KF in an polar solvent (DMSO, sulfolane) was ineffective even with lyophilized KF[14] and tetraphenylphosphonium bromide[15] or the crown ether DC18C6 in acetonitrile[16].

Finally **6a**, prepared from **5a** by nitration, was reduced to **7**, which was diazotised to the stable diazonium salt **8**. Then **8** was heated to 200 °C yielding the first fluoro derivative **9** in a very poor yield (2%!). Application of this sequence to the 4-nitro compound **10** yielded **11** and **12**, but the *Baltz-Schiemann* reaction[17] of **12** led only to traces of the azo compound **13**, probably by coupling of **12** with **11**, which was proven by an independent synthesis.



The results so far suggest that *ortho* substitution inhibits the replacement of the diazo group by a fluoro atom. Therefore, we synthesized **15** from **14**[18], and indeed, heating yielded **16** in acceptable yield. However, when the reaction was performed with pyridine-HF we isolated the pyridino derivative **17** instead of **16**.



The strategy to introduce fluoro atoms by direct fluorination or by replacement of appropriate other functional groups is obviously limited to more or less unsubstituted aromatics. Oligofunctional structures, *e.g.* those with cycloaliphatic parts like derivatives of **1**, either seem to be to sensitive to the drastic reaction conditions, or the replacement is inhibited by other substituents, especially those in *ortho*-positions.

Therefore, the above results suggest another way to fluoro-substituted derivatives: The *de-novo* synthesis starting from fluoro-substituted aromatics.

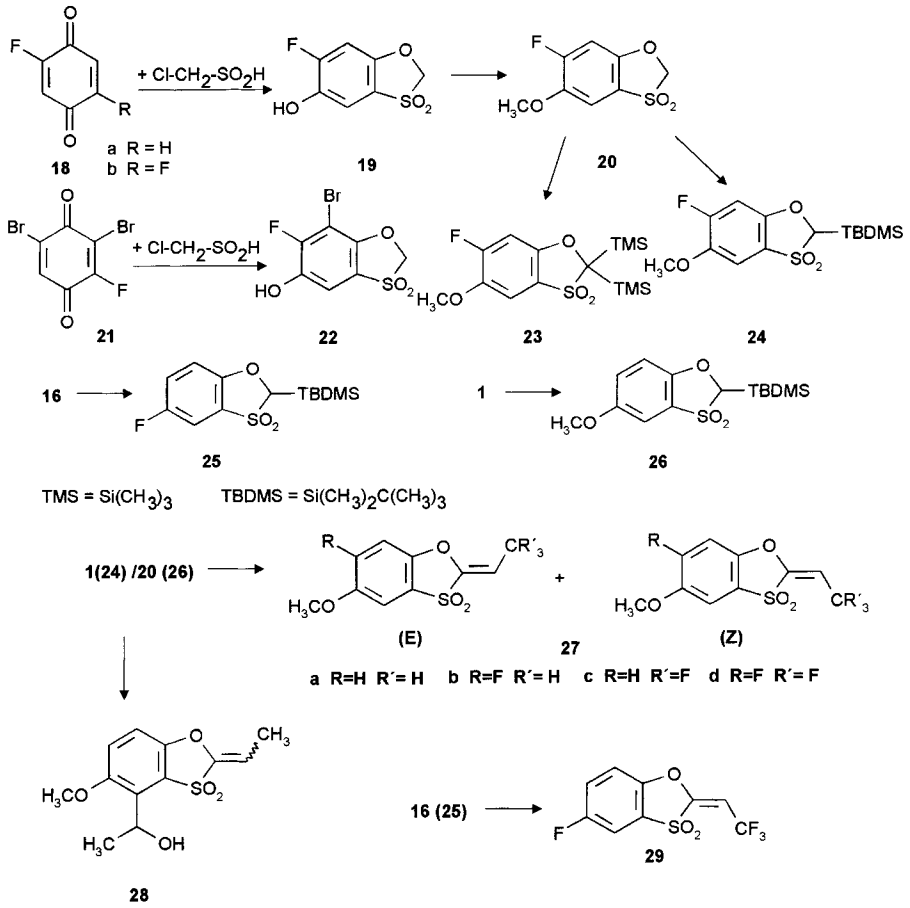
Reaction of the fluoroquinones **18a** or **18b**[19] with chloromethanesulfinic acid resulted in **19**, which was methylated with dimethyl sulfate to **20**. The cyclisation of **18a** with chloromethanesulfinic acid could lead to 3 isomeric compounds[20]. TLC detects only one product, whose structure **19** is proven by the NMR spectrum showing two doublets at δ = 7.04 ppm with J_{HF} = 11 Hz (H-7) and δ = 7.28 ppm with J_{HF} = 9 Hz (H-4). From **18b** we expected the 4,7-difluoro compound, but only product **19** was isolated. The situation was more complicated, when we used the 2,6-dibromo-3-fluoroquinone **21**[21], which was prepared from 3-fluorophenol. The cyclisation could lead to 4 isomers[20], but we obtained after purification by CC only one crystalline product **22**, whose structure was elucidated mainly by comparing the calculated[22] shift values for the ^{13}C-NMR spectrum with the measured values, and by the mass spectrum. To understand the results of these experiments we have to consider that the first step is a 1,4-addition of the sulfinic acid to the quinone[23] occurring always at the *para* position of the fluoro atom.

The silylation was done in the usual way as described earlier[2]. The disilylated product **23** was obtained using chlorotrimethylsilane (CTMS), while with *tert*-butylchloro-dimethylsilane the mono-silylated compounds **24**–**26** were accessible. The silylation always occurred at C-2, no silylation of the aromatic part was observed, and although the deprotonation was done with LDA, no exchange of halogen versus lithium was noticed.

All silylated compounds are stable and crystalline. Their analytical data are in agreement with the postulated structures.

The *Peterson* olefination of **24** with acetaldehyde yielded an *E/Z* mixture of **27b**, which we could not separate by CC. From **26** we obtained *E/Z*-**27a** as described earlier[6]. As a by-product we found in the reaction of **24** the product **28**, which is probably formed from **27** by addition of acetaldehyde to C-4. The reaction with trifluoroacetaldehyde[24] is more convenient without isolation of the silylated products. When we started from **1** or **20**, we obtained after silylation and *Peterson* reaction with the aldehyde an *E/Z* mixture of **27c** or **27d**, showing a large excess of the *Z*-isomers. As the geometry of the olefin depends on the stereochemistry of the intermediate β-hydroxysilane, which is directed by the volume of the silyl group[25], the use of *tert*-butylchlorodimethylsilane explains the favored *Z*-isomers. The 5-fluoro compound **29** was best prepared by starting from **16**. We obtained only the *Z*-isomer and a small amount of **25**.

Although the ^{1}H-NMR spectra of the isomers of **27** show some analogue shifts, it is difficult to determine the geometrical structure of these trisubstituted olefins from their NMR data. Therefore we performed a crystal structure analysis of *Z*-**27d** (Figure 1), which clearly showed the *Z*-orientation of the sulfonyl and the trifluoro group.



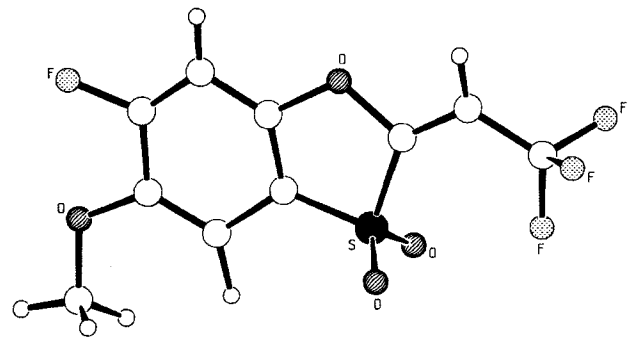


Figure 1: Crystal structure of *Z*-**27d**

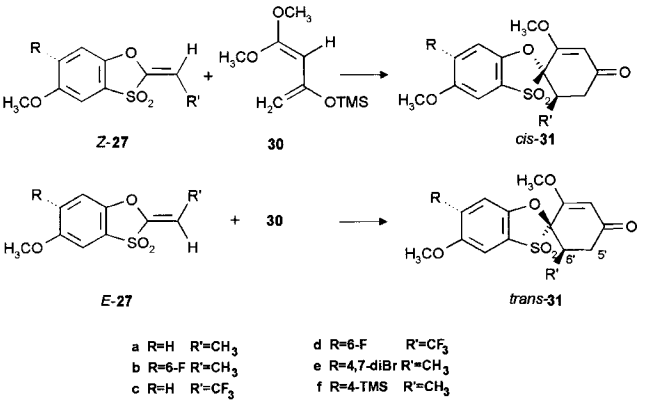


Table 1: ^{1}H-NMR data of the 3 proton systems in *cis*- and *trans*-**31b** [300 MHz, D_6-benzene].

No.	proton	δ (ppm)	type	J_{ea}	J_{aa}	J_{gem}
cis-**31b**	5′-H_e	2.42	dd	4.4	–	17.6
	5′-H_a	3.14	dd	–	13.4	17.6
	6′-H	2.61	dd	4.4	13.4	–
trans-**31b**	5′-H_e	2.48	dd	2.0	–	17.4
	5′-H_a	3.03	dd	–	4.9	17.4
	6′-H	3.12	dd	2.0	4.9	–Fig.

The final step of the sequence is the *Diels-Alder* reaction[26] with the dimethoxylated diene **30**[27]. Although some of our experiments were done in xylene, the best results were obtained, when the olefin was dissolved in an excess of the diene, and when the solution with a trace of hydroquinone was stirred at room temperature for about 36 h. The yields were low in all cases, but even the use of Lewis acids[28] was not successful. From the reaction of **30** with *E/Z*-**27b** we isolated a mixture of two isomeric sulfogriseofulvins **31**. As shown by ^{1}H-NMR spectroscopy, these two isomers show either *cis* or *trans* configuration at C-1′ and C-6′. The *cis* configuration is the griseofulvin stereochemistry, while the *trans* form represents the epigriseofulvin structure.

The ^{1}H-NMR spectra (300 MHz) of *cis*-**31** and *trans*-**31** show a very poor resolution when recorded in $CDCl_3$, but a good resolution in D_6-benzene. The differences in the structures refer to the 3 proton system 5′-H_e, 5′-H_a, and 6′-H. The values for this system in **31b** are summarized in Table 1.

When the ^{1}H-NMR spectra of **31** are recorded in deuterochloroform the signals of the methoxy groups are found between δ = 3.65 and 3.93 ppm, but when the spectra are recorded in [D_6]benzene the signals are found between δ = 2.73 and 2.91 ppm. This effect is probably caused by the influence of the aromatic solvent (ASIS effect).

Furthermore, the spectrum of *trans*-**31b** is characterized by ^4J = 1Hz between 5′-H_e and 3′-H, and both spectra show J = 6.8 Hz for the coupling between 6′-H and the methyl group. These results are strongly supported by ^{1}H,^{13}C-Hector diagrams[29]. To establish the interpretation of these NMR data we simulated the 3 proton part of the spectrum of *trans*-**31b** (Figure 2).

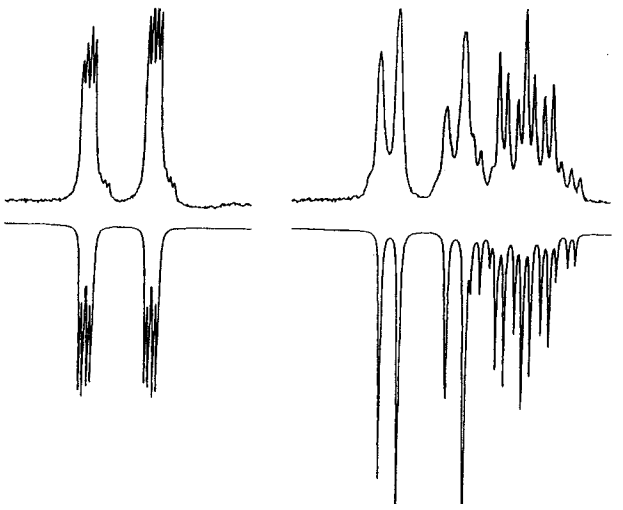


Figure 2: Recorded (above) and simulated (down) ABX-part (5′-H_e, 5′-H_a, and 6′-H) of the ^{1}H-NMR spectrum of *trans*-**31b**

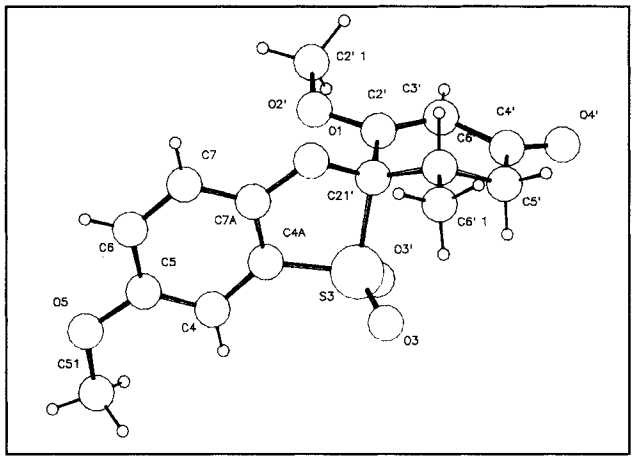


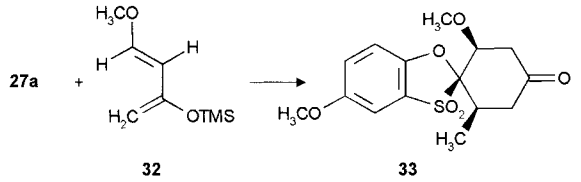
Figure 3: Crystal structure of *cis*-**31a**

Finally, we performed a crystal structure analysis of *cis*-**31a** (Figure 3), clearly showing the *cis* orientation of the sulfonyl and the methyl group. Comparing of the NMR spectra of *cis*-**31a** with the spectra of the other sulfogriseofulvins very beautifully supports our structure elucidation.

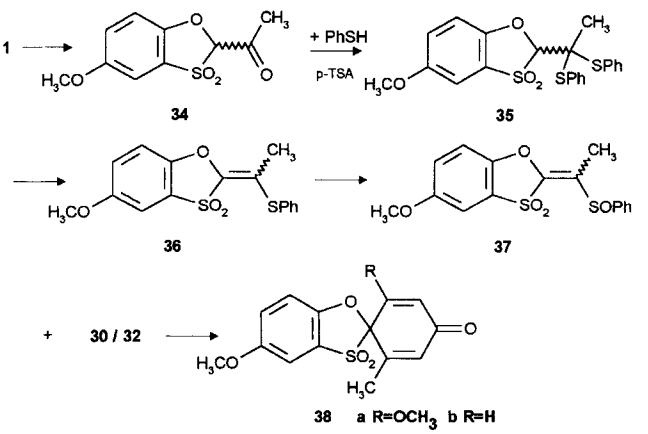
The relative configurations of all compounds establish, that the (*Z*)-isomers of the 2-alkylidene benzoxathiole 1,1-dioxides yield stereoselectively the *cis* orientation (griseofulvin structure) when reacted with **30**, while the *trans* orientation (epigriseofulvin) is isolated from the reactions with the (*E*)-isomers. This is in agreement with the predictions made by frontier orbital theory[30]. Obviously, the (*Z*)-isomers are the more stable isomers. From the reactions of the pure (*E*)-isomers **27a** and **27e** we always obtained a *cis*/*trans* mixture of the parent sulfogriseofulvin. This is best explained by a thermal isomerisation of the (*E*)-isomers, which was proven by a separate experiment.

The purity of **31** was proven by HPLC, and using an analytical ChiraSpher column we were able to resolve *cis*-**31d** into the enantiomers[31].

We studied the possibilities of using the olefins **27** in some other *Diels-Alder* reactions. These experiments mostly failed. For example, when *Z*-**27a** was refluxed with cyclopentadiene no addition product was obtained. But from **27a** we obtained the cycloadduct **33** when using the Danishefsky diene[32] **32**, although the yield was only 5%. The structure is elucidated by the spectroscopic data.



Finally, we tried to transfer the method used by Danishefsky and Walker[33] for the synthesis of griseofulvin to the sulfogriseofulvins. From **1** we obtained the 2-acetyl derivative **34**, which reacted with thiophenol to **35**. Depending on the conditions we either obtained a mixture of **35** and the isomers of **36** or the pure products. **35** was transformed to **36** by refluxing with *p*-toluenesulfonic acid. Oxidation with *m*-chloroperbenzoic acid made the isomers of **37** accessible, and the cycloaddition products **38** were isolated from the reaction with **30** or **32**. The formation of **38** includes a number of interesting observations. The regiochemistry of the addition is controlled by the carbonyl group in β-sulfinyl ketones[34].



To our knowledge, the formation of **38** is the first reported example of a sulfone group in a β-sulfinyl sulfone controlling the regiochemistry. **38** is the *ortho* regiomer referred to the sulfone group and the methoxy groups. After cycloaddition, benzene sulfenic acid is *cis*-stereoselectively eliminated[35] catalyzing the cleavage of the intermediate ketal and of the siloxy group leading to **38a**, or the elimination of methanol to **38b**. The stereochemistry of **37** does not influence on that of **38**, which is obtained as (*RS*)-**38**.

Antifungal Activity

The antifungal activity of *cis*-**31b**, *trans*-**31b**, *cis*-**31c**, *cis*-**31d** and *trans*-**31d** measured by the minimum inhibition

concentration (MIC) against the dermatophytes *Trichophyton mentagrophytes*, *Trichophyton rubrum* and *Microsporum canis* was compared with that of griseofulvin[36]. The antifungal activity of other compounds was not tested. Compared to griseofulvin, the biological activities of the tested derivatives were significantly lower. The MIC values were higher than the tested maximum concentrations of 12.5 or 50 μg/ml (see Table 2).

Table 2: Antifungal activity of some sulfogriseofulvins **31** [MIC (μg/ml)].

Cpd.	*Trichoph. mentagrophytes*	*Trichoph. rubrum*	*Microsporum canis*
Griseofulvin	6.25	6.25	3.13
cis-**31b**	>50.0	>50.0	>50.0
trans-**31b**	>12.5	>12.5	>52.5
cis-**31c**	>50.0	>50.0	>50.0
cis-**31d**	>50.0	>50.0	>50.0
trans-**31d**	>50.0	>50.0	50.0

The results of this work show that, at least in the compounds studied, the sulfonyl group seems to be not a good bioisoster to the ketone functional group.

Acknowledgments

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Experimental

General

Mp: not corrected; Linström apparatus. IR Spectra[29]: Perkin-Elmer IR 841, IR 1310, Beckman IR 4240; in KBr, if not noted otherwise. NMR Spectra[29]: Varian T60, Bruker WP80, WH90, WM250, Varian Unity 300 for ^{1}H; Bruker WP80 (20.15 MHz), Varian Unity 300 (gated, dec., 75.43 MHz) for ^{13}C, $J = J_{CH}$; δ in ppm rel. to Me_4Si as internal standard; values from 80-MHz spectra in $CDCl_3$, if not noted otherwise; Varian Unity 300 for ^{19}F; δ in ppm rel. to $CFCl_3$. MS (70 eV): Finnigan GC MS 4000, MAT 312, at 220°. Elemental analyses were performed at the Pharmazeutisches Institut or Chemisches Laboratorium der Universität Freiburg i. Br. Abbreviations: CTMS = chlorotrimethylsilane, mCPBA = *meta*-chloroperbenzoic acid, THF = tetrahydrofuran, dried with $MgSO_4$, distilled from sodium/benzophenone, and stored over molecular sieve. LDA = lithium diisopropylamide, freshly prepared by mixing equimolar amounts of diisopropylamine and *n*-butyllithium (1.6 molar in *n*-hexane) in THF at –78 °C. Other solvents were purified and dried according to standard procedures. CC with silica gel 60 (Merck No. 7734, 0.063-0.0200 mm). TLC with "PSC-Fertigplatten Kieselgel 60 F_{254}" (Merck No. 13792) or "DC-Fertigplatten Kieselgel 60 F_{254}" (Merck No. 5715).

5-Methoxy-1,3-benzoxathiole 3,3-Dioxide (**1**), *4,6-Dinitro-5-methoxy-1,3-benzoxathiol 3,3-Dioxide* (**2**), *and 4,7-Dinitro-5-methoxy-1,3-benzoxathiole 3,3-Dioxide* (**3**). *See*[8a]

4-Hydroxy-5-methoxy-7-nitro-1,3-benzoxathiol 3,3-Dioxide (**4**)

Under N_2, **3** (0.4 g, 1.4 mmol) is suspended in THF (80 ml), TBAF (7 mmol) [freshly prepared from TBAF × $3H_2O$ at 60 °C, 133 Pa, 24 h, r.t.] is added, the mixture is stirred for 2 h at r.t., water (50 ml) is added, then it is 3 times extracted with Et_2O (150 ml each), the combined org. layers are twice washed with 80–100 ml of water each, dried (Na_2SO_4), and evaporated: 80 mg (22%). Yellow powder, mp = 234 °C (MeOH). IR: ν = 3327 cm^{-1} (OH), 1503 (NO_2), 1440 (CH_2), 1312, 1144 (SO_2).– ^{1}H-NMR ([D$_6$]DMSO, 90 MHz): δ= 3.94 (*s*, 3H, OMe), 5.48 (*s*, 2H, CH_2), 5.78 (*s*, 1H, OH), 7.85 (*s*, 1H, aromatic H).– MS (70 eV); *m/z* (%) = 261 (27) [M$^+$], 197 (17), 137 (28), 124 (27), 94 (26), 77 (100).– Anal. ($C_8H_7NO_7S$).

4-Bromo-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**5a**) *and 4-Chloro-5-methoxy-1,3-benzoxathiole 3,3-Dioxide* (**5b**). *See*[8a].

4-Bromo-5-methoxy-7-nitro-1,3-benzoxathiole 3,3-Dioxide (**6a**)

With stirring at 0 °C, **5a** (2.0 g, 7.2 mmol) is added to a mixture of conc. H_2SO_4 (20 ml) and conc. HNO_3 (20 ml), stirring is continued for 3 h, while the mixture is warmed to r.t.; then it is poured into an ice–water mixture (100 ml), the precipitate is separated, and washed with water and MeOH: 2.2 g (94%). Yellow powder, mp = 237 °C (dec., acetone/THF 5:1). IR: ν = 1532 cm^{-1} (NO_2), 1469 (CH_2), 1317, 1155 (SO_2).– ^{1}H-NMR ([D$_6$]DMSO, 90 MHz): δ = 4.00 (*s*, 3H, OMe), 5.65 (*s*, 2H, CH_2), 8.03 (*s*, 1H, aromatic H).– Anal. ($C_8H_6BrNO_6S$).

4,7-Dibromo-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**6b**). *See*[8b].

7-Amino-4-bromo-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**7**)

6a (1.0 g, 11 mmol) in 50 ml of glacial acetic acid is reduced by H_2 [ca. 300 ml, r.t., 1 atm, 400 mg of Pd-C (10%), 40 min]. After separation of the catalyst, the solvent is evaporated (max. temp. 35 °C!): 860 mg (93%). Yellow powder, mp = 185 °C (dec., CH_2Cl_2/Et_2O 5:1). IR: ν = 3450, 3369 cm^{-1} (NH_2), 1485 (CH_2), 1317, 1146 (SO_2).– ^{1}H-NMR ([D$_6$]DMSO, 80 MHz): δ = 3.75 (*s*, 3H, OMe), 5.1–5.6 (br.*s*, 2H, NH_2), 5.36 (*s*, 2H, CH_2), 6.70 (*s*, 1H, aromatic H).– Anal. ($C_8H_8BrNO_4S$).

4-Bromo-5-methoxy-3,3-doxo-1,3-benzoxathiole-7-diazonium Tetrafluoroborate (**8**)

Under N_2 at –20 °C, **7** (860 mg, 3 mmol) in THF (60 ml) is added to BF_3 etherate (0.8 ml, 5 mmol), then *tert*-butyl nitrite (0.6 ml, 6 mmol) is injected in small portions, and the mixture is stirred for 15 min. After warming to 5 °C (20 min), *n*-pentane (30 ml) is added, the precipitate is separated, washed with cold Et_2O (20-30 ml), and then purified by refluxing (5–10 min) in Et_2O (30-50 ml): 1.0 g (90%). Violet crystalline powder, mp = 161 °C (dec.). IR: ν = 2265 cm^{-1} (N_2^+), 1474 (CH_2), 1342, 1157 (SO_2).– ^{1}H-NMR (CD_3CN, 80 MHz): δ = 4.02 (*s*, 3H, OMe), 5.52 (*s*, 2H, CH_2), 7.99 (*s*, 1H, aromatic H).– Anal. ($C_8H_7BF_4N_2O_4S$).

4-Bromo-7-fluoro-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**9**)

8 (1.0 g, 2.6 mmol) and sea sand (1 g) are mixed together in an Erlenmeyer flask with a reflux condenser, and heated to 200 °C in a silicone bath for 2 h. After cooling to r.t., the mixture is extracted 3 times with CH_2Cl_2 (30 ml each), the combined org. extracts are concentrated, and the residue is purified by preparative tlc (cyclohexane/ethyl acetate 1:1, elut. acetone): R_F 0.65. 15 mg (2%). Colorless crystals, mp = 200 °C. IR: ν = 1480 cm^{-1} (CH_2), 1328, 1148 (SO_2).– ^{1}H-NMR ([D$_6$]acetone, 90 MHz): δ = 3.98 (*s*, 3H, OMe), 5.38 (s, 2H, CH_2), 7.42 (*d*, *J* = 12 Hz, 1H, aromatic H).– ^{19}F-NMR ([D$_6$]acetone): δ = –134 (*d*, 1F, aromatic F). –MS (70 eV); *m/z* (%) = 298 (25) [M$^+$], 296 (25) [M$^+$], 266 (38), 264 (36), 204 (25), 202 (25), 61 (100).– Anal. ($C_8H_6BrFO_4S$).

*4-Nitro-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**10**). See*[8a].

*4-Amino-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**11**)*

From **10** (2.7 g, 11 mmol) in glacial acetic acid (150 ml) as described for **7** (r.t., 1 atm, 1.0 g of Pd-C (10%), 40 min, 1500 ml of H_2): 1.6 g (67%). Colorless crystals, mp = 166 °C (MeOH). IR: ν = 3436, 3353 cm^{-1} (NH_2), 1501 (CH_2), 1329, 1149 (SO_2).– ^{1}H-NMR (80 MHz): δ = 3.83 (*s*, 3H, OMe), 4.65 (*s*, 2H, NH_2), 4.95 (*s*, 2H, CH_2), 6.25 (*d*, *J* = 9 Hz, 1H, aromatic H), 6.87 (*d*, *J* = 9 Hz, 1H, aromatic H).– Anal. ($C_8H_9NO_4S$).

*5-Methoxy-3,3-dioxo-1,3-benzoxathiole-4-diazonium Tetrafluoroborate (**12**)*

From **11** (1.0 g, 5 mmol), BF_3 etherate (1.2 g, 8.5 mmol), and *tert*-butyl nitrite (0.65 g, 6.3 mmol) in CH_2Cl_2 as described for **8**: 0.84 g (54%). Violet crystalline powder, mp = 165 °C (dec.). IR: ν = 2229 cm^{-1} (N_2^+), 1487 (CH_2), 1299, 1166 (SO_2).– ^{1}H-NMR (CD_3CN, 80 MHz): δ = 4.30 (*s*, 3H, OMe), 5.46 (*s*, 2H, CH_2), 7.82 (*d*, *J* = 10 Hz, 1H, aromatic H), 8.10 (*d*, *J* = 10 Hz, 1H, aromatic H).– Anal. ($C_8H_7BF_4N_2O_4S$).

*4-Amino-5-methoxy-7-(5-methoxy-3,3-dioxo-1,3-benzoxathiol-4-ylazo)-1,3-benzoxathiol 3,3-Dioxide (**13**)*

12 (0.2 g, 0.65 mmol) and **11** (0.14 g, 0.65 mmol) are suspended in freon-113 (10 ml), NEt_3/HF (0.3 ml) is added, and the mixture is kept in an ultrasound bath for 20 h at 40 °C. The precipitate is separated, and extracted with boiling acetone (10 ml): 110 mg (38%). Brown powder, mp = 309 °C. IR: ν = 3473, 3369, 1629 cm^{-1} (NH), 1595 (N=N), 1511 (CH_2), 1315, 1142 (SO_2).– ^{1}H-NMR ([D$_6$]DMSO, 300 MHz): δ = 3.81 (*s*, 3H, MeO-(C-5)), 3.93 (*s*, 3H, MeO-(C-5')), 5.18, 5.39 (2*s*, each 2H, CH_2), 7.10 (*s*, 2H, NH_2), 7.27 (*d*, *J* = 9 Hz, 1H, aromatic H), 7.32 (*s*, 1H, H-6'), 7.53 (*d*, *J* = 9 Hz, 1H, aromatic H).– MS (70 eV); *m/z* (%) = 441 (30) [M^+], 242 (100), 229 (42), 214 (74).– $C_{16}H_{15}N_3O_8S_2$ Calcd. 441.0297; found: 441.0297.

*5-Amino-1,3-benzoxathiole 3,3-Dioxide (**14**)*

Nitrosophenol ((60%) 34 g, 118 mmol) and chloromethanesulfinic acid (38 g, 330 mmol) in water (330 g) are warmed at 50 °C for 30 min (water bath). Then, a 10 M soln. of NaOH (45 ml) is added, the mixture is warmed with stirring for 1 h at 80 °C (oil bath), cooled to 0 °C, and the precipitate is separated: 16.8 g (77%). Light brown platelets, mp = 160 °C (MeOH 35%). IR: ν = 3424, 3357 cm^{-1} (NH_2), 1488 (CH_2), 1295, 1140, 1128 (SO_2).– ^{1}H-NMR ([D$_6$]acetone, 80 MHz): δ = 4.93 (br.*s*, 2H, NH_2), 5.04 (*s*, 2H, CH_2), 6.85–7.15 (*m*, 3H, aromatic H).– Anal. ($C_7H_7NO_3S$).

*3,3-Dioxo-1,3-benzoxathiole-5-diazonium Tetrafluoroborate (**15**)*

From **14** (2.0 g, 10.8 mmol), BF_3 etherate (2.4 ml, 15 mmol) in THF (70 ml), and *tert*-butyl nitrite (1.8 ml, 20 mmol) as described for **8**: 2.3 g (75%). Colorless needles, mp = 179 °C (dec., MeCN). IR: ν = 2281 cm^{-1} (N_2^+), 1455 (CH_2), 1351, 1158 (SO_2).– ^{1}H-NMR ([D$_6$]DMSO, 90 MHz): δ = 5.76 (*s*, 2H, CH_2), 7.88 (*d*, *J* = 9.4 Hz, 1H, H-7), 8.88 (*dd*, *J* = 9.4, 2.2 Hz, 1H, H-6), 9.38 (*d*, *J* = 2.2 Hz, 1H, H-4).– Anal. ($C_7H_5BF_4N_2O_3S$).

*5-Fluoro-1,3-benzoxathiol 3,3-Dioxide (**16**)*

From **15** (1.0 g, 3.5 mmol) as described for **9**. The soln. in CH_2Cl_2 is washed a) with a satd. soln. of $NaHCO_3$ (20 ml), and b) with water (50 ml), then it is dried (Na_2SO_4) and evaporated: 180 mg (27%). Colorless crystals, mp = 141 °C ($CHCl_3$/petroleum ether 1:4). IR: ν = 1482 cm^{-1} (CH_2), 1323, 1145 (SO_2). ^{1}H-NMR (300 MHz): ν = 5.01 (*s*, 2H, CH_2), 7.0–7.3 (*m*, 3H, aromatic H).– ^{19}F-NMR: δ = –117 (m_c, 1F, aromatic F).– MS (70 eV); *m/z* (%) = 188 (34) [M^+], 158 (100), 110 (50), 96 (84), 94 (80), 68 (32).– Anal. ($C_7H_5FO_3S$).

*5-(2-Pyridyl)-1,3-benzoxathiole 3,3-Dioxide (**17**)*

At 0 °C, **14** (925 mg, 5 mmol) is dissolved in pyridine/HF (40:60, 20 g), after 15 min $NaNO_2$ (415 mg) is added, the mixture is warmed to r.t. (30 min), then it is slowly heated to 85 °C, stirred for 1 h, cooled to r.t., hydrolyzed with water, and 3 times extracted with chlorobenzene (25 ml each). The combined org. layers are dried (Na_2SO_4) and concentrated: 320 mg (26%). Orange red crystals, mp = 171 °C (acetone). IR: ν = 1487 cm^{-1} (CH_2), 1319, 1150 (SO_2).– ^{1}H-NMR ([D$_6$]DMSO, 80 MHz): δ = 5.46 (*s*, 2H, CH_2), 7.3–7.5 (*m*, 2H, aromatic H), 7.8– 8.15 (*m*, 2H, aromatic H), 8.4–8.75 (*m*, 3H, aromatic H).– MS (70 eV); *m/z* (%) = 247 (75) [M^+], 217 (45), 169 (20), 153 (13), 103 (27), 85 (93), 79 (100).– $C_{12}H_9NO_3S$ Calcd. 247.0301; found: 247.0309.

*2-Fluoro-1,4-benzoquinone (**18a**). See*[19].

*2,5-Difluoro-1,4-benzoquinone (**18b**)*

1,2,4,5-Tetrafluorobenzene (2.0 g, 13.4 mmol) is added dropwise to an ice cold mixture of fuming H_2SO_4 (0.5 ml, 30% SO_3) and conc. HNO_3 (1.3 ml, *d* = 1.50). After stirring (15 min), the mixture is poured into ice water, the precipitate is immediately separated and washed with water: 150 mg (7.7%). Yellow crystals, mp = 169 °C. (ref.[16] 171.5-172 °C). IR: ν = 1685 cm^{-1} (CO), 1609 (C=C).– ^{1}H-NMR (80 MHz): δ = 5.9–7.5 (*m*, 2H, aromatic H).

*6-Fluoro-5-hydroxy-1,3-benzoxathiole 3,3-Dioxide (**19**)*

a) Chloromethanesulfinic acid (3.0 g, 26 mmol) and conc. HCl (0.3 ml) in water (20 ml) are warmed to 50 °C, **18a** (2.7 g, 20.8 mmol) is added in small portions, while the temp. is raised to 70 °C. After 30 min, the pH is continuously adjusted to 8 by dropwise addition of a 10 M NaOH soln. Then the pH is adjusted to 1 by conc. HCl, the mixture is cooled to 10 °C, and the precipitate is separated. The filtrate is 4 times extracted with CH_2Cl_2 (40–50 ml each), the org. layers are twice washed with water, dried (Na_2SO_4), and evaporated. b) From chloromethanesulfinic acid (0.5 g, 3 mmol), conc. HCl (0.1 ml), and **18b** (300 mg, 2 mmol) in water (4 ml) as described for a): a) 2.2 g (51%), b) 20 mg (5%). Yellow crystals, mp = 191 °C (MeOH 50%). IR: ν = 3523 cm^{-1} (OH), 1484 (CH_2), 1310, 1146, 1114 (SO_2).– ^{1}H-NMR ([D$_6$]acetone, 80 MHz): δ = 5.19 (*s*, 2H, CH_2), 7.04 (*d*, J_{HF} = 11Hz, 1H, aromatic H), 7.28 (*d*, J_{HF} = 9 Hz, 1H, aromatic H).– ^{19}F-NMR: δ = –123 (*dd*, J_{HF} = 10.5, 8.4 Hz, 1F, aromatic F).– MS (70eV); *m/z* (%) = 204 (84) [M^+], 174 (100), 157 (41), 126 (96), 110 (69). Calcd. 203.9893; found: 203.9891.– Anal. ($C_7H_5FO_4S$).

*6-Fluoro-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**20**)*

Under N_2, **19** (2.4 g, 12 mmol) is dissolved in a soln. of KOH (10 ml, 10%). At 5 °C, dimethyl sulfate (1.8 ml) is added, the mixture is warmed to 100 °C (30 min), cooled to r.t., diluted with a few ml of water, the precipitate is separated, suspended in dil. NaOH soln. (30 ml), and 4 times extracted with CH_2Cl_2 (30 ml each), the combined org. layers are twice washed with water, dried (Na_2SO_4), and evaporated: 1.9 g (73%). Colorless crystals, mp = 165 °C (MeOH). IR: ν = 1306, 1155, 1122 cm^{-1} (SO_2).– ^{1}H-NMR ([D$_6$]acetone, 300 MHz): δ = 3.99 (*s*, 3H, OMe), 5.23 (*s*, 2H, CH_2), 7.12 (*d*, J_{HF} = 11.0 Hz, 1H, aromatic H), 7.46 (*d*, J_{HF} = 8.2 Hz, 1H, aromatic H).– ^{13}C-NMR ([D$_6$]acetone): δ = 57.34 (*q*, *J* = 145.6 Hz, OMe), 84.25 (*t*, *J* = 164.6 Hz, C-2), 104.43 (*dd*, *J* = 169.2 Hz, J_{CF} = 24.2 Hz, C-7), 105.25 (*dd*, *J* = 168.7 Hz, J_{CF} = 4.0 Hz, C-4), 119.66 (*m*, *J* = 9.3 Hz, J_{CF} = 3.85 Hz, C-3a), 145.8 (*m*, *J* = 4.1 Hz, J_{CF} = 12.9 Hz, C-5), 151.88 (*m*, *J* = 21.6 Hz, J_{CF} = 4.9 Hz, C-7a), 157.36 (*dq*, *J* = 9.6 Hz, J_{CF} = 255.5 Hz, C-6).– ^{19}F-NMR: δ = –119 (*dd*, J_{HF} = 8.2, 10.5 Hz, 1F, aromatic F).– Anal. ($C_8H_7FO_4S$).

*2,6-Dibromo-3-fluoro-1,4-benzoquinone (**21**)*

At 0 °C, 2,4,6-tribromo-3-fluorophenol (5.0 g, 14.3mmol) is added with vigorous stirring to conc. HNO_3 (50 ml, *d* = 1.50), after 15 min, the mixture is added to ice water (100 ml), the precipitate is separated, and washed once with water (100 ml): 2.7 g (66%). Yellow crystals, mp = 145 °C (ref.[21] = 150 °C). IR: ν = 1691, 1675 cm^{-1} (CO), 1595 (C=C).– ^{1}H-NMR ([D$_6$]acetone): δ = 7.58 (*d*, J_{HF} = 7.6 Hz, 1H, aromatic H).– Anal. ($C_6HBr_2FO_2$).

*7-Bromo-6-fluoro-5-hydroxy-1,3-benzoxathiole 3,3-Dioxide (**22**)*

From chloromethanesulfinic acid (0.4 g, 3 mmol) in water (4 ml), 2 drops of conc. HCl, and **21** (0.8 g, 2.8 mmol) as described for **19**. The precipitate and the residue of evaporation are combined, dissolved in acetone, and purified by CC (cyclohexane/ ethyl acetate 1:1), R_F = 0.45: 140 mg (18%). Colorless crystals, mp = 218 °C (MeOH 50%). IR: ν = 3377 cm^{-1} (OH), 1451 (CH_2), 1307, 1142 (SO_2).– ^{1}H-NMR ([D$_6$]acetone, 300 MHz): δ = 5.35

(*s*, 2H, CH_2), 7.33 (*d*, J_{HF} = 7.9 Hz, 1H, aromatic H).– ^{13}C-NMR ([D$_6$]acetone): δ = 84.60 (*t*, *J* = 165.4 Hz, C-2), 97.36 (*dd*, *J* = 1.6 Hz, J_{CF} = 24.2 Hz, C-7), 108.03 (*dd*, *J* = 169.8 Hz, J_{CF} = 4.4 Hz, C-4), 120.77 (*d*, J_{CF} = 2.5 Hz, C-3a), 143.42 (*dd*, *J* = 3.8 Hz, J_{CF} = 15.4 Hz, C-5), 148.57 (m_c, C-7a), 154.42 (*dd*, *J* = 9.3 Hz, J_{CF} = 251.1 Hz, C-6).– MS (70 eV); *m/z* (%) = 284 (36) [M$^+$], 282 (35) [M$^+$], 109 (100).– Anal. ($C_7H_4BrFO_4S$).

*6-Fluoro-5-methoxy-2,2-bis(trimethylsilyl)-1,3-benzoxathiole 3,3-Dioxide (**23**)*

From **20** (1.1 g, 5 mmol) in THF (20 ml), LDA (10 mmol) in THF (10 ml), and CTMS (1.6 ml, 15 mmol), 4 h at –78 °C, as described for **25**. Hydrolysis with a mixture of satd. NaCl soln. (35 ml) and dil. HCl (15 ml): 520 mg (22%). Colorless crystals, mp = 130 °C (subl.). IR: ν = 1286, 1145, 1128 cm^{-1} (SO_2), 1255, 855 (SiMe).– ^{1}H-NMR (80 MHz): δ = 0.21 (*s*, 18H, 2 $SiMe_3$), 3.88 (*s*, 3H, OMe), 6.83 (*d*, J_{HF} = 12 Hz, 1H, aromatic H), 7.10 (*d*, J_{HF} = 9 Hz, 1H, aromatic H).– Anal. ($C_{14}H_{23}FO_4SSi_2$).

*2-(tert-Butyldimethylsilyl)-6-fluoro-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**24**)*

From LDA (50 mmol) in THF (20 ml), *tert*-butylchlorodimethylsilane (4.6 g, 30 mmol) in THF (30 ml), and **20** (4.4 g, 20 mmol) in THF (90 ml), 40 min, as described for **25**: 4.8 g (72%). Colorless crystals, mp = 110 °C (MeOH). IR: ν = 1311, 1149 cm^{-1} (SO_2), 1257, 828 (SiMe).– ^{1}H-NMR (90 MHz): δ = 0.28, 0.39 (2*s*, 6H, $SiMe_2$), 1.06 (*s*, 9H, *t*-BuSi), 3.92 (*s*, 3H, OMe), 4.87 (*s*, 2H, CH_2), 6.84 (*d*, J_{HF} = 10.6 Hz, 1H, aromatic H), 7.17 (*d*, J_{HF} = 8.1 Hz, 1H, aromatic H).– ^{19}F-NMR: δ = –121 (*dd*, J_{HF} = 8.2, 10.5 Hz, 1F, aromatic F).– Anal. ($C_{14}H_{21}FO_4SSi$).

*2-(tert-Butyldimethylsilyl)-5-fluoro-1,3-benzoxathiol 3,3-Dioxide (**25**)*

At –78 °C, a soln. of *tert*-butylchlorodimethylsilane (1.15 g, 7.5 mmol) in THF (30 ml) is added to a soln. of LDA (12.5 mmol) in THF (20 ml), then **16** (940 mg) in THF (40 ml) is added, the mixture is stirred for 1 h at –78 °C, hydrolyzed with a satd. soln. of NH_4Cl, the org. layer is separated, the aq. layer is extracted with THF, the combined org. layers are dried (Na_2SO_4) and evaporated: 600 mg (40%). Colorless crystals, mp = 163 °C (MeOH). IR: ν = 1315, 1307, 1142 $\chi\mu^{-1}$ (SO_2), 1252, 832 (SiMe).– ^{1}H-NMR (80 MHz): δ = 0.29, 0.39 (2*s*, 6H, $SiMe_2$), 1.04 (*s*, 9H, *t*-BuSi), 4.86 (*s*, 2H, CH_2), 6.95–7.35 (*m*, 3H, aromatic H).– Anal. ($C_{13}H_{19}FO_3SSi$).

*2-(tert-Butyldimethylsilyl)-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**26**)*

From **1** (2.0 g, 10 mmol), LDA (20 mmol), and *tert*-butylchlorodimethylsilane (2.3 g, 15 mmol) in THF as described for **25**: 2.5 g (80%). Colorless crystals, mp = 122 °C (MeOH). IR: ν = 1309, 1141 cm^{-1} (SO_2), 1245, 839 (SiMe).– ^{1}H-NMR (90 MHz): δ = 0.27, 0.38 (2*s*, 6H, $SiMe_2$), 1.06 (*s*, 9H, *t*-BuSi), 3.83 (*s*, 3H, OMe), 4.86 (*s*, 2H, CH_2), 7.06 (*m*, 3H, aromatic H).– Anal. ($C_{14}H_{22}O_4SSi$).

*(E/Z)-2-Ethylidene-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**27a**)*

From **26** (1.6 g, 5 mmol) in DME (40 ml), and acetaldehyde (1.2 ml, 20 mmol) in DME (10 ml) as described for **27b**, R_F = 0.66: 0.6 g (53%). Colorless crystals, mp = 132 °C (MeOH), (*E*:*Z* = 1:2). See[9].

*(E/Z)-2-Ethylidene-6-fluoro-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**27b**)*

At –78 °C, under N_2, **24** (1.0 g, 3 mmol) in dimethoxyethane (DME, 20 ml) is added to a soln. of LDA (6 mmol) in DME (10 ml). Then, a mixture (cooled to –10 °C) of freshly distilled acetaldehyde (150 mg, 3 mmol) and freshly distilled DME (1.5 g) is added, stirring is continued for 1 h at –78 °C, the mixture is hydrolyzed with a satd. NH_4Cl soln., the org. layer is separated, the aq. layer is once extracted with THF, the combined org. layers are dried (Na_2SO_4), and evaporated. The residue is purified by CC (cyclohexane/ethyl acetate 3:1), R_F = 0.27: 390 mg (53%). Colorless crystals, mp = 105 °C (MeOH), (*E*:*Z* = 1:1.7, from ^{1}H NMR signal integration). IR: ν = 1684 cm^{-1} (C=C), 1492 (Me), 1310, 1135 (SO_2).– ^{1}H-NMR (80 MHz): δ = 1.95 and 2.13 (2*d*, *J* = 7 Hz, *J* = 8 Hz, 3H, Me), 3.90 (*s*, 3H, OMe), 5.91 (2*q*, 1H, =CH), 6.83 (2*d*, *J* = 10 Hz, 1H, H-7), 7.21 (2*d*, *J* = 8 Hz, 1H, H-4).– Anal. ($C_{10}H_9FO_4S$).

*2-(2,2,2-Trifluoroethylidene)-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**27c**)*

Under N_2, at –78 °C, *tert*-butylchlorodimethylsilane (2.3 g, 15 mmol) in THF (30 ml) is added to a soln. of LDA (25 mmol) in THF (20 ml). Then **1** (2.0 g, 10 mmol) in THF (50 ml) is dropwise added during 20 min. After 40 min, a soln. of trifluoroacetaldehyde[24] (10 ml) is added, stirring is continued for 1 h, the mixture is hydrolyzed with satd. NH_4Cl soln., the org. layer is separated, the aq. layer is twice extracted with THF, the combined org. layers are dried (Na_2SO_4), and evaporated. The residue is purified by CC (cyclohexane/ethyl acetate 3:1), R_F = 0.58 (**26**), R_F = 0.41 (*E*-**27c**), R_F = 0.28 (*Z*-**27c**).

E-**27c**: 160 mg (6%). Colorless crystals, mp = 158 °C (MeOH). IR: ν = 1692 cm^{-1} (C=C), 1485 (Me), 1318, 1168 (SO_2).– ^{1}H-NMR (300 MHz): ν = 3.84 (*s*, 3H, OMe), 5.79 (*q*, *J* = 7.3 Hz, 1H, =CH), 7.15–7.25 (*m*, 3H, aromatic H).– ^{19}F-NMR: δ = –58 (*d*, *J* = 7.6 Hz, 3F, CF_3).– MS (70 eV); *m/z* (%) = 280 (100) [M$^+$]. Calcd. 280.0017; found: 280.0013. Anal. ($C_{10}H_7F_3O_4S$).

Z-**27c**: 1.4 g (50%). Colorless crytals, mp = 161 °C ($CHCl_3$). IR: ν = 1685 cm^{-1} (C=C), 1330, 1186, 1146 (SO_2).– ^{1}H-NMR (300 MHz): δ = 3.85 (*s*, 3H, OMe), 5.91 (*q*, *J* = 8.6 Hz, 1H, =CH), 7.12 (*d*, *J* = 9.3 Hz, 1H, H-7), 7.16 (*d*, *J* = 2.2 Hz, 1H, H-4), 7.21 (*dd*, *J* = 9.2, 2.6 Hz, 1H, H-6).– ^{19}F-NMR: δ = –57 (*d*, *J* = 8.8 Hz, 3F, CF_3).– Anal. ($C_{10}H_7F_3O_4S$).

*6-Fluoro-2-(2,2,2-trifluoroethylidene)-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (**27d**)*

From LDA (25 mmol) in THF (20 ml), *tert*-butylchlorodimethylsilane (2.3 g, 15 mmol) in THF (30 ml), **20** (2.2 g, 10 mmol) in THF (50 ml), and trifluoroacetaldehyde soln. (10 ml) as described for **27c**: R_F = 0.69 (**24**), R_F = 0.48 (*E*-**27d**), R_F = 0.39 (*Z*-**27d**).

E-**27d**: 160 mg (4%). Colorless crystals, mp = 154 °C (MeOH). IR: ν = 1696 cm^{-1} (C=C), 1491 (Me), 1314, 1136 (SO_2).– ^{1}H-NMR (300 MHz): δ 3.92 (*s*, 3H, OMe), 5.82 (*q*, *J* = 7.2 Hz, 1H, =CH), 7.09 (*d*, J_{HF} = 9.8 Hz, 1H, H-7), 7.25 (*d*, J_{HF} = 7.6 Hz, 1H, H-4).– ^{19}F-NMR: δ = –58 (*d*, *J* = 7.0 Hz, 3F, CF_3), -116.5 (*dd*, J_{HF} = 10.2, 7.8 Hz, 1F, aromatic F).– MS (70 eV); *m/z* (%) = 298 (100) [M$^+$]. $C_{10}H_6F_4O_4S$ Calcd. 297.9923; found: 297.9913.

Z-**27d**: 1.1 g (37%). Colorless crystals, mp = 159 °C ($CHCl_3$). IR: ν = 1681 cm^{-1} (C=C), 1500 (Me), 1329, 1160, 1134 (SO_2).– ^{1}H-NMR (300 MHz): δ = 3.96 (*s*, 3H, OMe), 5.91 (*q*, *J* = 8.5 Hz, 1H, =CH), 6.99 (*d*, J_{HF} = 9.8 Hz, 1H, H-7), 7.28 (*d*, J_{HF} = 7.8 Hz, 1H, H-4).– ^{19}F-NMR: δ = –57 (*d*, *J* = 8.2 Hz, 3F, CF_3), –117 (*dd*, J_{HF} = 9.7, 7.8 Hz, 1F, aromatic F).– Anal. ($C_{10}H_7F_4O_4S$).

*Crystal Structure Analysis of Z-***27d**

A platelet shaped crystal of $C_{10}H_6F_4O_4S$ having approximate dimensions of 0.30 × 0.30 × 0.10 mm was mounted on a glass fiber. All measurements were made on a Philips PW1100 diffractometer with graphite monochromated MoK_α radiation. The crystal belongs to the monoclinic space group $P2_1/c$ with *a* = 15.037(2) Å, *b* = 6.528(1) Å, *c* = 24.780(2) Å, β = 106.62(1)°, *V* = 2323 Å^3, *Z* = 8, D_{calc}=1.705 g/cm^3. The intensities were corrected for Lorentz and polarization effects. A total of 3737 independent intensities were measured of which 1306 were classified as observed with I2σ (I). The structure was solved by direct methods using the computer program SHELXS86 and refined by full matrix least-squares calculations with anisotropic displacement parameters for non-hydrogen atoms. The positions of the hydrogen atoms were calculated assuming normal geometry. Their parameters were not refined. The final *R* -factor for 343 variables was 0.076. The highest peak in the final difference Fourier map was 0.66 e/ Å^3. The conformations of the two crystallographically independent molecules are very similar to each other. Selective distances (Å): S-(C-2) 1.76(1), O-(C-2) 1.41(1), (C-2)-(C-α) 1.37(1), (C-α)-(C-β) 1.52(1). Selected bond angles (°): S-(C-2)-(C-α) 138.4(8), O-(C-2)-(C-α) 110(1), (C-2)-(C-α)-(C-β) 117.2(9), (C-2)-(C-α)-H 117(5). Complete positional and thermal parameters, bond length and bond angles and FoFc lists have been deposited as supplementary material.

(E)- and (Z)-4,7-Dibromo-2-ethylidene-5-methoxybenzoxathiole 1,1-Dioxide (**27e**) *and (Z)-2-Ethylidene-5-methoxy-4-trimethylsilylbenzoxathiole 1,1-Dioxide* (**27f**). *See*[9].

2-Ethylidene-4-(1-hydroxyethyl)-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (Mixture of Diastereomers) (**28**)

As a by-product obtained during CC of **27a**, R_F = 0.40: 290 mg (21%). Colorless crystals, mp = 145 °C (MeOH). IR: ν = 3552 cm^{-1} (OH), 1309, 1133 (SO_2).– ^{1}H-NMR (300 MHz): δ = 1.55 and 1.58 (2*d*, *J* = 1.9 Hz, *J* = 1.7 Hz, 3H, Me), 1.91 and 2.10 (2*d*, *J* = 7.3 Hz, *J* = 7.8 Hz, 3H, =CH*Me*), 2.85 and 2.88 (2*d*, *J* = 6.8 Hz, 1H, OH), 3.84 and 3.85 (2*s*, 3H, OMe), 5.36 (m_c, 1H, CH), 5.74 and 5.79 (2*q*, *J* = 7.3 Hz, *J* = 7.8 Hz, 1H, =CH), 6.92, 7.02, 7.06, 7.08 (4*d*, each *J* = 9.0 Hz, 2H, aromatic H).– MS (70 eV); *m/z* (%) = 270 (26) [M^+], 153 (100).– Anal. ($C_{12}H_{14}O_5S$).

(Z)-5-Fluoro-2-(2,2,2-trifluoroethylidene)-1,3-benzoxathiole 3,3-Dioxide (**29**)

From LDA (25 mmol) in THF (20 ml), *tert*-butylchlorodimethylsilane (2.3 g, 15 mmol) in THF (30 ml), **16** (1.9 g, 10 mmol) in THF (50 ml), and trifluoroacetaldehyde (10 ml) as described for **27c**: R_F = 0.87 (**25**), R_F = 0.49 (**29**): 580 mg (23%). Colorless crystals, mp = 149 °C (MeOH). IR: ν = 1686 cm^{-1} (C=C), 1481 (Me), 1330, 1170, 1160 (SO_2).– ^{1}H-NMR (300 MHz): δ = 5.95 (*q*, *J* = 8.5 Hz, 1H, =CH), 7.20 (*dd*, *J* = 9.1 Hz, J_{HF} = 3.6 Hz, 1H, H-7), 7.37 (*ddd*, J_{HF} = 8.6 Hz, *J* = 2.8, 1.1 Hz, 1H, H-4), 7.43 (*ddd*, J_{HF} = 6.2 Hz, *J* = 9.0, 2.8 Hz, 1H, H-6).– MS (70 eV): *m/z* (%) = 268 (42) [M^+], 94 (100). $C_9H_4F_4O_3S$ Calcd. 267.9817; found: 267.9813.

*cis-2',5-Dimethoxy-6'-methylspiro[1,3-benzoxathiol-2,1'-cyclohex-2'-en]-4'-one 3,3-Dioxide (cis-***31a**)

Under Ar and in darkness, *Z*-**27a** (500 mg, 2.2 mmol) and **30** (890 mg, 4.4 mmol) are heated with a trace of hydroquinone to 113 °C for 36 h. The excess of diene is separated by distillation, the residue is extracted at 60 °C with a mixture from THF (15 ml), H_2O (6 ml), and a HCl soln. (0.1 N, 1 ml) for 1 h, then added to a mixture of diethyl ether (75 ml) and H_2O (50 ml), the org. layer is separated, the aq. layer is again extracted with diethyl ether (50 ml), the combined org. layers are washed with a satd. $NaHCO_3$ soln. (50 ml), then with a satd. NaCl soln. (50 ml), dried (Na_2SO_4) and evaporated. The residue is purified by CC (cyclohexane/ethyl acetate 1:1): 108 mg (15%) of *cis*-**31a**. Colorless crystals, mp = 208 °C (*i*-propanol). IR: ν = 1650 cm^{-1} (CO), 1600 (C=C), 1310, 1140 (SO_2).– ^{1}H-NMR (250 MHz): δ = 1.33 (*d*, *J* = 7 Hz, 3H, Me), 2.62 (*m*, 1H, H-5'), 3.07 (*m*, 2H, H-5', H-6'), 3.74 (*s*, 3H, (C-2')-OMe), 3.87 (*s*, 3H, (C-5)-OMe), 5.66 (*s*, 1H, H-3'), 7.13 (*m*, 3H, aromatic H).– Anal. ($C_{15}H_{16}O_6S$).

*Crystal Structure Analysis of cis-***31a**

A crystal of $C_{15}H_{16}O_6S$ having approximate dimensions of 0.3 × 0.3 × 0.25 mm was mounted on a glass fiber. Measurements were made with ω/Θ scan at 20 °C. The crystal belongs to the monoclinic space group $P2_1/c$ with *a* = 8.442(4) Å, *b* = 14.110(3) Å, *c* = 12.558(3) Å, β = 97.38(1)°, *V* = 1483.5 $Å^3$, *Z* = 4, D_{calc}=1.452 g/cm^3. The intensities were corrected for Lorentz and polarization effects. A total of 2608 independent intensities were measured of which 1542 were classified as observed with $I > 4\sigma(I)$. The structure was solved by direct methods using the computer program SHELXS86 and refined by full matrix least-squares calculations with anisotropic displacement parameters for non-hydrogen atoms. The positions of the hydrogen atoms were calculated assuming normal geometry. Their parameters were not refined. The final *R* factor for 263 variables was 0.0387. The highest peak in the final difference Fourier map was 0.2 e/$Å^3$. Selective distances (Å): O-(C-2) 1.430, (C-2)-S 1.883(1), (C-2)-(C-2') 1.510(1), (C-2)-(C-6') 1.528(1). Selected bond angles (°): O-(C-2)-S 104.2, O-(C-2)-(C-2') 110.8, (C-2')-(C-2)-(C-6') 109.7, (C-6')-(C-2)-S 114.5, (C-2)-(C-6')-(C-5') 108.8, (C-2)-(C-6')-CH_3 116.8. Complete positional and thermal parameters, bond length and bond angles have been deposited as supplementary material.

*trans-2',5-Dimethoxy-6'-methylspiro[1,3-benzoxathiol-2,1'-cyclohex-2'-en]-4'-one 3,3-Dioxide (trans-***31a**)

From *E*-**27a** (750 mg, 3.3 mmol) and **30** (1.5 g, 7.5 mmol), 48 h as described for *cis*-**31a**: 29 mg (3%) of *trans*-**31a**. Colorless crystals, mp = 188 °C (MeOH). IR: ν = 1655 cm^{-1} (CO), 1610 (C=C), 1318, 1145 (SO_2).– ^{1}H-NMR (250 MHz): δ = 1.34 (*d*, *J* = 7 Hz, 3H, Me), 2.50 (*m*, 1H, H-5'), 3.10 (*m*, 2H, H-5', H-6'), 3.68 (*s*, 3H, (C-2')-OMe), 3.87 (*s*, 3H, (C-5)-OMe), 5.62 (*s*, 1H, H-3'), 7.11 (*m*, 3H, aromatic H).– MS (70 eV); *m/z* (%) = 324 (4) [M^+], 170 (100). $C_{15}H_{16}O_6S$ Calcd. 324.06676; found: 324.06819.

6-Fluoro-2',5-dimethoxy-6'-methylspiro[1,3-benzoxathiole-2,1'-cyclohex-2'-en]-4'-one 3,3-Dioxide (**31b**)

From *E/Z*-**27b** (1.1 g, 4.5 mmol) and **30** (3.3 g, 16 mmol), 72 h, as described for **31a**. Separation of isomers by CC (cyclohexane/ethyl acetate 1:1).

cis-**31b**: 190 mg (12%). Colorless crystals, mp = 214 °C (MeOH). IR: ν = 1655 cm^{-1} (CO), 1612 (C=C), 1493 (Me), 1318, 1139 (SO_2).– ^{1}H-NMR ([D_6]benzene, 300 MHz): δ = 1.14 (*d*, *J* = 6.9 Hz, 3H, Me), 2.42 (*dd*, *J* = 17.6, 4.4 Hz, 1H, H_e-5'), 2.61 (m_c, 1H, H_a-6'), 2.84 (*s*, 3H, (C-2')-OMe), 2.89 (*s*, 3H, (C-5)-OMe), 3.14 (*dd*, *J* = 17.6, 13.3 Hz, 1H, H_a-5'), 5.51 (*s*, 1H, H-3'), 6.36 (*d*, J_{HF} = 10.3 Hz, 1H, H-7), 6.56 (*d*, J_{HF} = 8.1 Hz, 1H, H-4).– ^{19}F-NMR: δ = –119 (*dd*, J_{HF} = 10.2, 8.2 Hz, 1F, F-6).– MS (70 eV); *m/z* (%) = 342 (13) [M^+], 188 (100). $C_{15}H_{15}FO_6S$ Calcd.: 342.0575; found: 342.0585.

trans-**31b**: 120 mg (8%). Colorless crystals, mp = 227 °C dec. IR: ν = 1667 cm^{-1} (CO), 1613 (C=C), 1490 (Me), 1319, 1136 (SO_2).– ^{1}H-NMR ([D_6]benzene, 300 MHz): δ = 1.03 (*d*, *J* = 6.8 Hz, 3H, Me), 2.32 (*ddd*, *J* = 17.2, 2.4, 1.0 Hz, 1H, H_e-5'), 2.75 (*s*, 3H, (C-2')-OMe), 2.81 (*s*, 3H, (C-5)-OMe), 2.96 (m_c, 1H, H_e-6'), 3.18 (*dd*, *J* = 17.4, 4.9 Hz, 1H, H_a-5'), 5.43 (*s*, 1H, H-3'), 6.28 (*d*, J_{HF} = 10.3 Hz, 1H, H-7), 6.57 (*d*, J_{HF} = 8.1 Hz, 1H, H-4).– ^{19}F-NMR: δ = –119 (*dd*, J_{HF} = 11.2, 7.8 Hz, 1F, F-6).– MS (70 eV); *m/z* (%) = 342 (12) [M^+], 188 (100). $C_{15}H_{15}FO_6S$ Calcd.: 342.0574; found: 342.0568.

*cis-2',5-Dimethoxy-6'-(trifluoromethyl)spiro[1,3-benzoxathiole-2,1'-cyclohex-2'-en]-4'-one 3,3-Dioxide (cis-***31c**)

From *Z*-**27c** (0.56 g, 2 mmol) and **30** (1.3 g, 6 mmol), 15 h, 125 °C, as described for **31a**: 250 mg (33 %) of *cis*-**31c**. Yellow crystals, mp = 163 °C (MeOH). IR: ν = 1667 cm^{-1} (CO), 1613 (C=C), 1487 (Me), 1315, 1188, 1152 (SO_2).– ^{1}H-NMR (300 MHz): δ = 2.86 (*ddd*, *J* = 17.8, 4.5, 0.8 Hz, 1H, H_e-5'), 3.29 (*dd*, *J* = 17.7, 13.9 Hz, 1H, H_a-5'), 3.65–3.75 (m_c, 1H, H-6'), 3.72 (*s*, 3H, (C-2')-OMe), 3.82 (*s*, 3H, (C-5)-OMe), 5.66 (*s*, 1H, H-3'), 7.05 (*d*, *J* = 2.7 Hz, 1H, H-4), 7.06 (*d*, *J* = 8.9 Hz, 1H, H-7), 7.18 (*dd*, *J* = 8.9, 2.7 Hz, 1H, H-6).– ^{19}F-NMR: δ = –62 (*dd*, J_{HF} = 8.8, 1.8 Hz, 3F, CF_3).– MS (70 eV); *m/z* (%) = 378 (12) [M^+], 170 (100). $C_{15}H_{13}F_3O_4S$ Calcd.: 378.0385; found: 378.0398.

6-Fluoro-2',5-dimethoxy-6'-(trifluoromethyl)spiro[1,3-benzoxathiole-2,1'-cyclohex-2'-en]-4'-one 3,3-Dioxide (**31d**)

From **27d** (1.0 g, 3.3 mmol) and **30** (2.6 g, 13 mmol), 20 h, 120 °C as described for **31a**. Separation of isomers by CC (cyclohexane/ethyl acetate 1:1). R_F = 0.53 (*cis*-**31d**), R_F = 0.67(*trans*-**31d**).

cis-**31d**: 190 mg (15%). Colorless crystals, mp = 206 °C (MeOH). IR: ν = 1666 cm^{-1} (CO), 1618 (C=C), 1493 (Me), 1335, 1161, 1141 (SO_2).– ^{1}H-NMR ([D_6]benzene, 300 MHz): δ = 2.64 (*dd*, *J* = 17.5, 2.6 Hz, 1H, H_e-5'), 2.73 (*s*, 3H, (C-2')-OMe), 2.81 (*s*, 3H, (C-5)-OMe), 3.09 (m_c, 1H, H_a-6'), 3.34 (*dd*, *J* = 17.4, 13.9 Hz, 1H, H_a-5'), 5.34 (*s*, 1H, H-3'), 6.32 (*d*, J_{HF} = 10.2 Hz, 1H, H-7), 6.43 (*d*, J_{HF} = 8.1 Hz, 1H, H-4).– ^{19}F-NMR: δ = –62 (*d*, J_{HF} = 8.8 Hz, 3F, CF_3), –118 (*dd*, J_{HF} = 10.0, 8.2 Hz, 1F, F-6).– MS (70 eV); *m/z* (%) = 396 (29) [M^+], 188 (100). $C_{15}H_{12}F_4O_6S$ Calcd.: 396.0291; found: 396.0307.

Separation of enantiomers: Column ChiraSpher 250-4 (5 µm), methanol/water 6:5, 0.5 ml/min, detection by UV (Pharmacia LKB-VWM 2141), polarimeter Perkin-Elmer 241 with HPLC: (-)-*cis*-**31d** 28.3 min, (+)-*cis*-**31d** 31.8 min[28].

trans-**31d**: 50 mg (4%). Colorless crystals, mp = 172 °C (MeOH). IR: ν = 1685 cm^{-1} (CO), 1621 (C=C), 1489 (Me), 1324, 1137 (SO_2).– ^{1}H-NMR ([D_6]benzene, 300 MHz): δ = 2.71 (*s*, 3H, (C-2')-OMe), 2.81 (*s*, 3H, (C-5)-

OMe), 2.87 (*ddd*, J = 17.3, 2.0, 1.0 Hz, 1H, H_e-5'), 3.58 (m_c, 1H, H-6'), 3.07 (*dd*, J = 17.3, 6.5 Hz, 1H, H_a-5'), 5.49 (*s*, 1H, H-3'), 6.25 (*d*, J_{HF} = 10.4 Hz, 1H, H-7), 6.53 (*d*, J_{HF} = 7.9 Hz, 1H, H-4).– ^{19}F-NMR: δ = –64 (*d*, J_{HF} = 8.2 Hz, 3F, CF_3), -117 (*dd*, J_{HF} = 10.3, 7.8 Hz, 1F, F-6).– MS (70 eV); *m/z* (%) = 396 (16) [M^+], 188 (100). $C_{15}H_{12}F_4O_6S$ Calcd.: 396.0291; found: 396.0311.

*cis-4,7-Dibromo-2',5-dimethoxy-6'-methylspiro[1,3-benzoxathiole-2,1'-cyclohex-2'-en]-4'-one 3,3-Dioxide (cis-***31e***)*

From *Z*-**27e** (700 mg, 1.8 mmol) and **30** (1.8 g, 8.9 mmol) in xylene (5 ml), 48 h, CC (cyclohexane/ethyl acetate 2:1), as described for **31a**: 338 mg (39%) of *cis*-**31e**. Yellowish crystals, mp = 194 °C (MeOH). IR: ν = 1650 cm^{-1} (CO), 1605 (C=C), 1315, 1150 (SO_2).– ^{1}H-NMR (250 MHz): δ = 1.34 (*d*, J = 6.8 Hz, 3H, Me), 2.66 (*m*, 1H, H-5'), 3.10 (*m*, 2H, H-5', H-6'), 3.74 (*s*, 3H, (C-2')-OMe), 3.97 (*s*, 3H, (C-5)-OMe), 5.67 (*s*, 1H, H-3'), 7.31 (*s*, 1H, aromatic H).– Anal. ($C_{15}H_{14}Br_2O_6S$).

*trans-4,7-Dibromo-2',5-dimethoxy-6'-methylspiro[1,3-benzoxathiole-2,1'-cyclohex-2'-en]-4'-one 3,3-Dioxide (trans-***31e***).*

From *E*-**27e** (750 mg, 1.9 mmol) and **30** (2.0 g, 10 mmol) in xylene (5 ml), 48 h, CC (cyclohexane/ethyl acetate 2:1), as described for **31a**: 265 mg (31%) of *trans*-**31e**. Colorless crystals, mp = 294 °C (acetone). IR: ν = 1650 cm^{-1} (CO), 1610 (C=C), 1330, 1140 (SO_2).– ^{1}H-NMR ([D_6]DMSO): δ = 1.28 (*d*, J = 7 Hz, 3H, Me), 1.8-3.4 (*m*, 2H, H-5', H-6'), 3.65 (*s*, 3H, (C-2')-OMe), 3.93 (*s*, 3H, (C-5)-OMe), 5.78 (*s*, 1H, H-3'), 7.83 (*s*, 1H, aromatic H).– Anal. ($C_{15}H_{14}Br_2O_6S$).

*cis-2',5-Dimethoxy-6'-methyl-4-(trimethylsilyl)spiro[1,3-benzoxathiole-2,1'-cyclohex-2'-en]-4'-one 3,3-Dioxide (cis-***31f***)*

From *Z*-**27f** (0.9 g, 3 mmol) and **30** (1.8 g, 8.9 mmol), 38 h, as described for **31a**: 18 mg (2%) of *cis*-**31f**. Colorless crystals, mp = 208 °C (MeOH). IR: ν= 1655 cm^{-1} (CO), 1605 (C=C), 1312, 1151(SO_2).– ^{1}H-NMR (250 MHz): δ = 0.40 (*s*, 6H, $SiMe_3$), 1.27 (*d*, J = 9.75 Hz, 3H, Me), 2.54 (*m*, 1H, H-5'), 3.03 (*m*, 2H, H-5', H-6'), 3.73 (*s*, 3H, (C-2')-OMe), 3.85 (*s*, 3H, (C-5)-OMe), 5.61 (*s*, 1H, H-3'), 7.07 (*m*, 2H, aromatic H).– MS (70eV); *m/z* (%) = 396 (16) [M^+], 227 (100). $C_{18}H_{24}O_6SSi$ Calcd. 396.1056; found: 396.10730.

(2S,2'R*,6'S*)-2',5-Dimethoxy-6'-methylspiro[1,3-benzoxathiole-2,1'-cyclohexan]-4'-one 3,3-Dioxide (***33***)*

From Z-**27a** (750 mg, 3.3 mmol) and **32** (1.0 g, 6 mmol), 48 h, as described for **31**: 160 mg (5%) of **33**. Colorless crystals, mp = 134 °C (MeOH). IR: ν = 1722 cm^{-1} (CO), 1585 (Me), 1308, 1150 (SO_2).– ^{1}H-NMR (250 MHz): δ = 1.43 (*d*, J = 7 Hz, 3H, Me), 2.40 (*m*, 1H, H-5'), 2.6–3.2 (*m*, 4H, H-3', H-5', H-6'), 3.38 (*s*, 3H, (C-2')-OMe), 3.80 (*s*, 3H, (C-5)-OMe), 4.15 (*s*, 1H, H-2'), 7.08 (*m*, 3H, aromatic H).– Anal. ($C_{15}H_{18}O_6S$).

*2-Acetyl-5-methoxy-1,3-benzoxathiole 3,3-Dioxide (***34***). See*[9].

*2-[1,1-Bis(phenylthio)ethyl]-1,3-benzoxathiole 3,3-Dioxide (***35***)*

As a by-product from the synthesis of **36**. After separation of **36B**, the filtrate is cooled to –20 °C: a) 590 mg (25%), c) 4.8 g (18%) of **35**. Colorless crystals, mp = 103 °C (MeOH). IR: ν = 1485 (Me), 1315, 1148 (SO_2).– ^{1}H-NMR (80 MHz): δ = 1.63 (*s*, 3H, Me), 3.83 (*s*, 3H, OMe), 5.08 (*s*, 1H, CH), 6.9–8.0 (*m*, 13H, aromatic H).– Anal. ($C_{22}H_{20}O_4S_3$).

*5-Methoxy-2-[1-(phenylthio)ethylidene]-1,3-benzoxathiole 3,3-Dioxide (***36***)*

a) Under N_2, **34** (1.28 g, 5.3 mmol), thiophenol (2.44 g, 22.3 mmol), and pTSA×H_2O (0.2 g) in benzene are refluxed for 40 h using a water separator. Then, all volatiles are separated by distillation (100 °C, 0.4 Torr), MeOH (50 ml) is added to the residue, from which isomer **A** crystallizes at 40 °C during 3 h. The filtrate is cooled to r.t., MeOH (30 ml) is added, isomer **B** is separated during 12 h.

Isomer **A**: 0.53 g (30%). Colorless crystals, mp = 160 °C (MeOH). IR: ν = 1485 cm^{-1} (Me), 1302, 1141 (SO_2).– ^{1}H-NMR (80 MHz): δ = 2.15 (*s*, 3H, Me), 3.84 (*s*, 3H, OMe), 7.0–7.6 (*m*, 8H, aromatic H).– Anal. ($C_{16}H_{14}O_4S_2$).

Isomer **B**: 177 mg (10%). Colorless crystals, mp = 167 °C (MeOH). IR: ν = 1485 cm^{-1} (Me), 1311, 1148 (SO_2).– ^{1}H-NMR (80 MHz): δ = 2.10 (*s*, 3H, Me), 3.85 (*s*, 3H, OMe), 7.0-7.6 (*m*, 8H, aromatic H).– Anal. ($C_{16}H_{14}O_4S_2$).

b) From **34** (15.2 g, 67.3 mmol), thiophenol (11.7 g, 100.9 mmol), pTSA×H_2O (1.6 g) in benzene (500 ml) for 18 h isomer **A** is obtained: 5.2 g (25%).

c) **35** (4.8 g, 10.8 mmol) and pTSA×H_2O (0.5 g) are refluxed in toluene (300 ml) for 1 h. At r.t. the solvent is evaporated, MeOH (30 ml) is added to the residue: 2.9 g (81%) of **36A**.

*5-Methoxy-2-[1-(phenylsulfinyl)ethylidene]-1,3-benzoxathiole 3,3-Dioxide (***37***, Isomer* **A***)*

36A (1.4 g, 4.2 mmol) is dissolved in CH_2Cl_2 (50 ml) and cooled to –20 °C. Then a soln. of mCPBA (0.93 g, 4.2 mmol) in CH_2Cl_2 (20 ml) is dropwise added during 1 h. Stirring is continued for 1 h, the precipitate is separated, the filtrate is 4 times washed with $KHCO_3$ soln. (5%, 50 ml each), dried (Na_2SO_4) and evaporated. MeOH (30 ml) is added to the residue: 1.2 g (82%) of **37A**. Colorless crystals, mp = 185 °C (MeOH). IR: ν = 1475 cm^{-1} (Me), 1302, 1137 (SO_2).– ^{1}H-NMR (60 MHz): δ = 2.13 (*s*, 3H, Me), 3.87 (*s*, 3H, OMe), 7.1–7.8 (*m*, 8H, aromatic H).– Anal. ($C_{16}H_{14}O_5S_2$).

*5-Methoxy-2-[1-(phenylsulfinyl)ethylidene]-1,3-benzoxathiole 3,3-Dioxide (***37***, Isomer* **B***)*

From **36B** as described for **37A**. Colorless crystals, mp = 204 °C (MeOH). IR: ν = 1483 cm^{-1} (Me), 1318, 1145 (SO_2).– ^{1}H-NMR (60 MHz): δ = 1.93 (*s*, 3H, Me), 3.93 (*s*, 3H, OMe), 7.0– 8.0 (*m*, 8H, aromatic H).– MS (70 eV) m/z (%) = 351 (100) [M^+].– Anal. ($C_{16}H_{14}O_5S_2$).

*2',5-Dimethoxy-6'-methylspiro[1,3-benzoxathiole-2,1'-cyclohexa-2',5'-dien]-4'-one 3,3-Dioxide (***38a***)*

Under argon, **37A** (1.0 g, 2.8 mmol) and **30** (2.3 g, 11.3 mmol) are stirred in toluene (10 ml) at 124 °C for 6 h, ethyl acetate (50 ml) is added, the mixture is twice washed with HCl soln. (0.1 N, 30 ml each) and twice with satd. NaCl soln. (30 ml each), the org. layer is dried (Na_2SO_4) and evaporated. The residue is purified by preparative tlc (cyclohexane/*i*-propanol/ethyl acetate 80:5:20, elut. chloroform): 57 mg (7%) of **38a**. Colorless crystals, mp = 198 °C (MeOH). IR: ν = 1655 cm^{-1} (CO), 1602 (C=C), 1308, 1145 (SO_2).– ^{1}H-NMR: δ = 2.08 (*d*, J = 1 Hz, 3H, Me), 3.65 (*s*, 3H, OMe), 3.85 (*s*, 3H, OMe), 5.70 (*d*, J = 1Hz, 1H, H-3'), 6.30 (*m*, 1H, H-5'), 7.15 (*m*, 3H, aromatic H).– Anal. ($C_{15}H_{14}O_6S$).

*5-Methoxy-6'-methylspiro[1,3-benzoxathiole-2,1'-cyclohexa-2',5'-dien]-4'-one 3,3-Dioxide (***38b***)*

From **37A** (1.0 g, 2.8 mmol) and **32** (2.4 g, 14 mmol) as described for **38a**: 18 mg (3%) of **38b**. Colorless crystals, mp = 226 °C (MeOH). IR: ν = 1663 cm^{-1} (CO), 1475 (Me), 1310, 1135 (SO_2).– ^{1}H-NMR: δ = 2.03 (*d*, J = 0.7 Hz, 3H, Me), 3.83 (*s*, 3H, OMe), 6.38 (*m*, 1H, H-5'), 6.43 (*dd*, J = 1.5, 10 Hz, 1H, H-3'), 6.78 (*d*, J = 10 Hz, 1H, H-2'), 7.13 (*m*, 3H, aromatic H).– MS (70 eV); *m/z* (%) = 292 (10) [M^+], 170 (100). $C_{14}H_{12}O_5S$ Calcd. 292.0402; found 292.0412.

Antifungal Activity

The measurements of the antifungal activity were done as described[36] in Sabouraud-2% Dextrose Bouillon (initial pH = 6.5); the MIC values were obtained after an incubation period of 7 days at 30 °C.

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☆ Dedicated to Professor Thorsten Beyrich, Greifswald, on the occasion of his 65th birthday.

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