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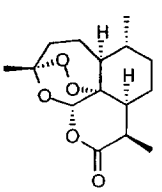
Synthesis and Antimalarial Activity of Heteroatom-Containing Bicyclic Endoperoxides

Gary H. Posner,*[a] Lluïsa González,[a] Jared N. Cumming,[a‡]
Donna Klinedinst,[b] and Theresa A. Shapiro[b]

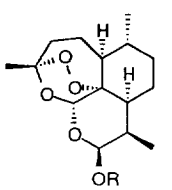
[a]Department of Chemistry, The Johns Hopkins University, Baltimore, MD 21218, USA
[b]Department of Medicine, The Johns Hopkins University, Baltimore, MD 21205, USA

Abstract: *Mechanism-based design and short syntheses involving novel Tebbe methylenations of α-heteroatom-substituted ketones led to preparation of heteroatom-containing bicyclic endoperoxides* ***4–6****. The crucial final photo-oxygenative cyclization step succeeded only when the intermediate 1,6-dienes carried anisyl but not phenyl substitutents. Distinguishing between endoperoxide and cyclobutane cyclization products was achieved reliably by* ^{13}C *NMR spectroscopy. Antimalarial testing of endoperoxides* ***4–6*** *in vitro showed them to have only weak activities (*IC_{50} *= 500–1100 nM). Ferrous bromide-induced reductions of sulfonamide endoperoxides* ***4****, although forming the expected hydroxylated ether and ring-contracted products* ***7*** *and* ***8****, caused virtually no rearrangement of hexamethyl Dewar benzene; therefore, the intermediacy of any oxidatively damaging high-valent iron–oxo intermediate appears unlikely.* Copyright © 1996 Elsevier Science Ltd

Despite their relatively weak and easily reduced oxygen–oxygen bond, some endoperoxides are found in nature as isolable compounds[1,2] or as important but short-lived intermediates (*e.g.* prostaglandin endoperoxide).[3-6] Because of the recent highly effective medical use of the Chinese 1,2,4-trioxane qinghaosu (artemisinin, **1**) and its semi-synthetic derivatives arteether (**2**) and sodium artesunate (**3**) as potent and fast-acting antimalarial drugs,[7-12] many of the fundamental aspects of the biological[13] and the chemical[14] mechanisms of action of these endoperoxides have been elucidated. Also, various structurally simpler endoperoxides have been designed and synthesized to probe the relationship between chemical structure and antimalarial efficacy.[15-22] A recent report on some antimalarially active, stable, heteroatom-containing ozonides[23] prompts us now to provide details of our syntheses and *in vitro* antimalarial testing of a series of aza-, oxa-, and thia-bicyclo[3.2.2]nonane endoperoxides.



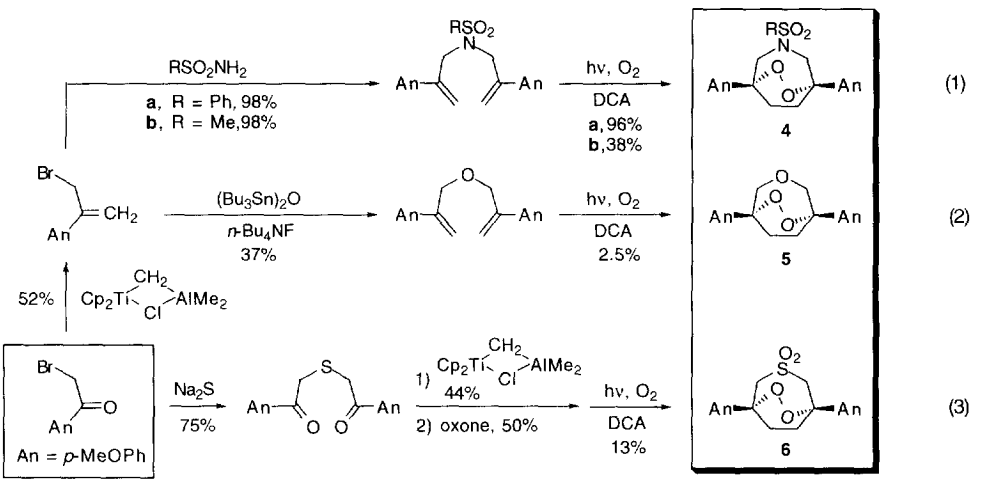
artemisinin
(qinghaosu, **1**)



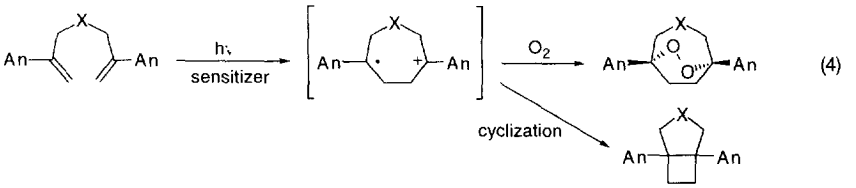
R = Et, arteether (**2**)
R = $C(O)CH_2CH_2COONa$,
sodium artesunate (**3**)

Results and Discussion

Syntheses of the endoperoxides containing a sulfonamide nitrogen atom (**4**), an ether oxygen atom (**5**), and a sulfone sulfur atom (**6**) are outlined in equations 1–3. A novel aspect of these transformations is the successful Tebbe methylenation[24-26] of α-bromoacetophenone to form the corresponding allylic bromide required for double coupling with a nitrogen nucleophile (eq. 1) and with an oxygen nucleophile (eq. 2). A similar successful Tebbe methylenation occurs also with the α-thioketone in eq. 3.

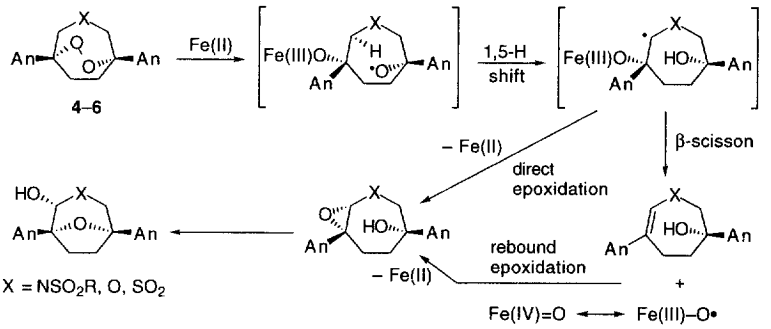


An important aspect of the final photo-oxygenative cyclizations of the 1,6-diene intermediates is their sensitivity to the nature of the aromatic groups on the 1,6-diene.[27] Besides the desired endoperoxide products, undesired cyclobutane products are often formed (eq. 4).[27] Distinguishing between these two types of cyclization products is difficult when only one is produced, as is the case (cyclobutane only) when the *p*-methoxyphenyl (anisyl) group is replaced by a phenyl group in equations 1–3. For example, endoperoxides often undergo the loss of O_2 upon mass spectroscopic study,[28,29] and therefore they often show *m/e* peaks at M-32, indistinguishable from those of the corresponding cyclobutane products. Likewise, high field ^1H NMR spectroscopy cannot easily distinguish between the endoperoxide and the cyclobutane cyclization products. Indeed, due to these confusing features, our preliminary assignment of endoperoxide structures to the cyclization products of the phenyl-substituted 1,6-dienes was incorrect.[30] Only when we used the corresponding electron-rich anisyl 1,6-dienes did we obtain a mixture of endoperoxide and cyclobutane cyclization products. With both types of separable cyclization products in hand, we then found that a reliably characteristic difference in the ^{13}C NMR spectra of these anisyl compounds allowed the endoperoxide product to be distinguished from the cyclobutane product. Thus, the ^{13}C NMR spectra of the anisyl endoperoxides have a tell-tale signal at 81–84 ppm due to the bridgehead carbon atom, and this signal is absent in the corresponding cyclobutanes.

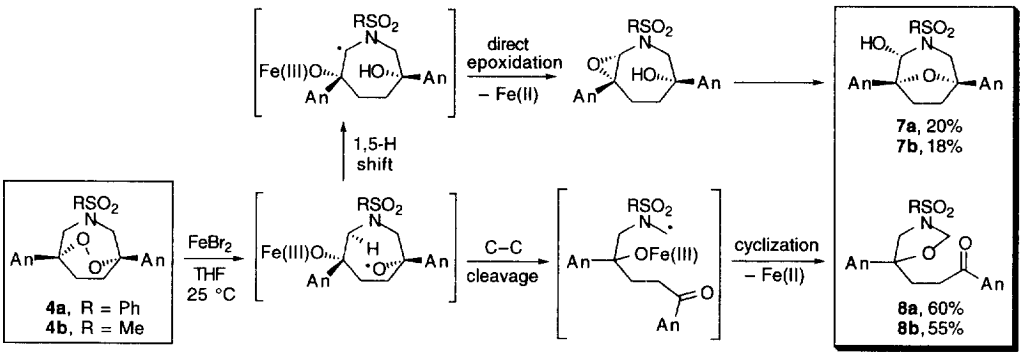


Design specifically of bicyclononane endoperoxides **4–6** was based on our recent mechanistic understanding of the importance of carbon-centered radicals,[30,31] of alkylating epoxides, and of reactive high-valent iron–oxo species for high antimalarial activity (Scheme I).[14] Indeed, when benzenesulfonamide and methanesulfonamide endoperoxides **4a** and **4b** were treated with ferrous bromide in tetrahydrofuran (THF) at 25 °C, reduction of the peroxidic bond occurred to produce the two major types of products **7** and **8** (Scheme II).[31] Both of these kinds of products are consistent with their mechanism-based design, involving an initial carbon-centered radical and then very likely an alkylating epoxide (Scheme II).[31] The absence of hexamethyl Dewar benzene (HMDB) rearrangement during $FeBr_2$ reduction of endoperoxides **4** is consistent with virtually no trappable high-valent iron–oxo intermediate being formed; a control experiment with artemisinin (**1**), $FeBr_2$, and HMDB showed considerable HMDB rearrangement into hexamethylbenzene.[31] In the upper pathway of Scheme II, therefore, it is likely that **direct** epoxidation leads from the carbon-centered radical intermediate to the putative epoxide intermediate and finally to the observed carbinolamide **7**.[31] Such direct **intramolecular** epoxidation in Scheme II, in sharp contrast to release of a high-valent iron–oxo species and then **intermolecular** rebound epoxidation in the case of the corresponding **carbocyclic** radical intermediate (Scheme I, X = CH_2),[30] may be due to the greater "nucleophilicity" of a carbon-centered radical adjacent to an amido nitrogen atom.[32] Unfortunately, endoperoxides **5** and **6** were not available in sufficient quantities to allow study in detail of their interactions with ferrous bromide. The importance of epoxides for antimalarial activity has recently been questioned,[22] and some alternative mechanisms have recently been proposed.[33,34]

Scheme I



Scheme II



Antimalarial testing *in vitro* of anisyl endoperoxides **4–6** showed them to be only weakly active, with IC_{50} values ranging from 500–1100 nM in chloroquine-sensitive *Plasmodium falciparum* (NF54) parasites (Table I). This low antimalarial biological activity is consistent with the virtual absence of any oxidatively damaging high-valent iron–oxo intermediate during $FeBr_2$-induced chemical reduction of endoperoxides **4**. Also, this marginal antimalarial activity of heteroatom-containing endoperoxides **4–6** is in sharp contrast to that of the corresponding hydrocarbon bicyclononane endoperoxides (Scheme I, X = CH_2) that have IC_{50} values of 62–89 nM and that do form high-valent iron–oxo intermediates when reduced by $FeBr_2$.[30] At this time, however, we cannot exclude the possibility that the low antimalarial acitvities of endoperoxides **4-6** may be due to their poorer bioavailability than those of the corresponding hydrocarbon bicyclononane endoperoxides.

Table I. Chemical Structure-Antimalarial Activity Relationships in Chloroquine-Sensitive *P. falciparum* (NF54)[35] Parasites *in vitro*[a]

Compound	Antimalarial Activity, IC_{50} (nM)
4a	500
4b	1100
5	670
6	540
Artemisinin (**1**)	8.8
Chloroquine	5.0

[a]The standard deviation for each set of quadruplicate drug concentrations was ≤25% of the mean. R^2 values for the fitted dose-response curves were ≥0.997. For complete details, see the Experimental section.

In conclusion we have shown here (1) the first examples of successful Tebbe methylenations of an α-bromoketone and an α-thioketone, (2) that ^{13}C NMR spectroscopy can be used reliably to distinguish unambiguously between a series of bicyclic endoperoxides and the corresponding cyclobutanes, (3) unexpectedly low antimalarial activities of the new series of heteroatom-containing bicyclic endoperoxides **4–6** even though they are reduced by ferrous iron to formed intermediate carbon-centered radicals and reactive epoxides, and (4) the likely importance of formation of a high-valent iron–oxo intermediate for high antimalarial activity of bicyclononane endoperoxides.

Experimental

General. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. All other compounds and anhydrous solvents were purchased from Aldrich Chemical Company and were used without further purification. Column chromatography was performed using short path silica gel (particle size <230 mesh). Nuclear magnetic resonance (NMR) spectra were obtained using a Varian XL-400 spectrometer, operating at 400 MHz for ^1H and at 100 MHz for ^{13}C. Chemical shifts are reported in parts per million (ppm, δ) relative to chloroform (7.26 δ). Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (b). Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrometer. Resonances are reported in wavenumbers (cm^{-1}). Low resolution (LRMS) and high resolution (HRMS) mass spectra were obtained on a VG Instruments 70-S spectrometer run at 70 eV for electronic ionization (EI) and run with ammonia (NH_3) as a carrier for chemical ionization (CI). High performance liquid chromatography (HPLC) was performed using a Rainin HPLX gradient system equipped with two 25 mL/min preparative pump heads.

Preparation of Endoperoxide Benzenesulfonamide 4a.

i) A solution of 2-bromo-4'-methoxyacetophenone (6.00 g, 26.2 mmol) in THF (96 mL) was treated with freshly prepared Tebbe reagent[36] (1 M, 39.3 mL, 39.3 mmol) at room temperature (r.t.) for 2 h. A solution of NaOH (0.1 M) was added dropwise to quench the reaction until evolution of gas was no longer observed, and the mixture was then extracted with ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. Chromatography of the crude product on silica gel (hexane/ethyl acetate, 9:1) afforded allylic bromide as an oil (3.09 g, 13.6 mmol, 52%). This product slowly isomerized to the corresponding vinylic bromide even upon storage neat at 0 °C. ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 9.0 Hz, 2H, Ar), 6.92 (d, J = 9.0 Hz, 2H, Ar), 5.50 (s, 1H, $H_{olefinic}$), 5.41 (s, 1H, $H_{olefinic}$), 4.38 (s, 2H, $H_{\alpha\text{-}Br}$), 3.84 (s, 3H, MeO). ^{13}C NMR ($CDCl_3$) δ 159.5 (C_{Ar}), 143.4 ($C_{olefinic}$), 129.7 (C_{Ar}), 127.2 (C_{Ar}), 115.4 ($C_{olefinic}$), 113.7 (C_{Ar}), 55.2 (MeO), 34.5 ($C_{\alpha\text{-}Br}$). FT-IR (neat) 2954, 2825, 1607, 1507, 1454, 1443, 1290, 1249, 1213, 1184, 1031, 902, 831 cm^{-1}. LRMS (EI, rel intensity) 228 (96), 226 (100), 147 (40), 135 (52), 133 (21), 132 (36), 115 (30), 104 (26), 103 (29), 91 (34), 77 (37), 63 (22). HRMS calcd. for $C_{10}H_{11}BrO$ 225.9993 (^{79}Br), found 225.9995.

ii) A solution of this allylic bromide (325 mg, 1.43 mmol) in benzene (0.25 mL) was added dropwise with stirring to a mixture of benzenesulfonamide (102 mg, 0.651 mmol), powdered sodium hydroxide (78.0 mg, 1.95 mmol), potassium carbonate (90 mg, 0.65 mmol), and tetrabutylammonium hydrogen sulfate (22 mg, 0.065 mmol) in benzene (2.5 mL) at 40 °C.[37] The reaction mixture was heated at reflux for 1 h. The resulting mixture was cooled to r.t. and filtered. The precipitate of inorganic compounds was washed with benzene. The filtrate was combined with washings, washed with water until neutralized, dried over $MgSO_4$, and evaporated under reduced pressure. Chromatography of the crude product on silica gel (hexane/ethyl acetate, 9:1) afforded diene benzenesulfonamide as an oil (285 mg, 0.635 mmol, 98%). ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 2H, Ar), 7.53 (t, J = 8.0 Hz, 1H, Ar), 7.43 (t, J = 8.0 Hz, 2H, Ar), 7.22 (d, J = 8.0 Hz, 4H, Ar), 6.78 (d, J = 8.0 Hz, 4H, Ar), 5.26 (s, 2H, $H_{olefinic}$), 5.02 (s, 2H, $H_{olefinic}$), 4.21 (s, 4H, $H_{\alpha\text{-}NSO_2Ph}$), 3.76 (s, 6H, MeO). ^{13}C NMR ($CDCl_3$) δ 159.1 (C_{Ar}), 141.3 ($C_{olefinic}$), 139.5 (C_{Ar}), 132.2 (C_{Ar}), 130.9 (C_{Ar}), 128.7 (C_{Ar}), 127.2 (C_{Ar}), 127.0 (C_{Ar}), 114.5 ($C_{olefinic}$), 113.4 (C_{Ar}), 54.9 (MeO), 51.0 ($C_{\alpha\text{-}NSO_2Ph}$). FT-IR (neat) 2989, 2931, 2825, 1607, 1513, 1443, 1337, 1249, 1184, 1161, 1090, 1031, 902, 837, 691 cm^{-1}. LRMS (EI, rel intensity) 449 (59), 309 (23), 308 (100), 174 (25), 148 (94), 147 (47), 135 (25), 133 (74), 121 (75), 91 (35), 78 (23), 77 (73). HRMS calcd. for $C_{26}H_{27}NO_4S$ 449.1661, found 449.1656.

iii) A flame-dried 25 mL 3-necked Pyrex flask with magnetic stirring bar, gas inlet tube, and gas outlet tube was charged with this diene benzenesulfonamide (61.0 mg, 0.136 mmol), DCA (1.4 mg, 0.061 mmol) and anhydrous acetonitrile (12 mL). Magnesium perchlorate (273 mg, 1.22 mmol) was added to the mixture. Oxygen was bubbled through the mixture for 1 h to saturate the solution. This solution was then photooxygenated for 1 h at r.t. by exposure to a medium pressure mercury lamp with continuous oxygen bubbling.[38] Acetonitrile was evaporated under reduced pressure, and the residue was treated with water, and extracted with chloroform (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. Chromatography of the crude product on silica gel (starting hexane, then hexane/ethyl acetate, 9:1) afforded endoperoxide benzenesulfonamide **4a** (62.7 mg, 0.130 mmol, 96%) without formation of the corresponding cyclobutane. Recrystallization from ethyl acetate/hexane afforded white needles (m.p. = 166 °C). Final purification was by HPLC (Rainin Dynamax-60 Å silica gel, 8 μm pore size, 10 mm x 250 mm, hexane/ethyl acetate 25%, 4.0 mL/min, 240 nm, $R_{f\ endoperoxide}$ = 11.4 min). ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H, Ar), 7.57 (t, J = 8.0 Hz, 1H, Ar), 7.49 (t, J =

8.0 Hz, 2H, Ar), 7.32 (d, J = 9.2 Hz, 4H, Ar), 6.90 (d, J = 9.2 Hz, 4H, Ar), 4.20 (d, J = 13.2 Hz, 2H, $H_{\alpha\text{-}NSO_2Ph}$), 3.84 (s, 6H, MeO), 3.29 (d, J = 13.2 Hz, 2H, $H_{\alpha\text{-}NSO_2Ph}$), 2.77 (dd, J = 13.0 Hz, J = 4.7 Hz, 2H, CH_2), 2.31 (dd, J = 13.0 Hz, J = 4.7 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 159.2 (C_{Ar}), 137.6 (C_{Ar}), 134.12 (C_{Ar}), 132.8 (C_{Ar}), 129.2 (C_{Ar}), 126.9 (C_{Ar}), 125.7 (C_{Ar}), 113.9 (C_{Ar}), 83.6 (C_q), 58.2 ($C_{\alpha\text{-}NSO_2Ph}$), 55.3 (MeO), 28.6 ($CH_2$). FT-IR (neat) 2954, 2942, 1601, 1507, 1448, 1343, 1249, 1155, 1090, 1025, 978 cm^{-1}. LRMS (CI, NH_3, rel intensity) 499 (M+18, 13), 483 (32), 482 (M+1, 100), 342 (49), 324 (44), 160 (33). HRMS (CI, NH_3) calcd. for $C_{26}H_{28}NO_6S$ (M+1) 482.1637, found 482.1649.

Preparation of Endoperoxide Methanesulfonamide 4b.

i) A solution of the allylic bromide from the above procedure (254 mg, 1.12 mmol) in benzene (0.25 mL) was added dropwise with stirring to a mixture of methanesulfonamide (48.4 mg, 0.508 mmol), powdered sodium hydroxide (61.0 mg, 1.53 mmol), potassium carbonate (70.0 mg, 0.509 mmol), and tetrabutylammonium hydrogen sulfate (17.3 mg, 0.0509 mmol) in benzene (2 mL) at 40 °C.[37] The reaction mixture was heated at reflux for 2.5 h. The resulting mixture was cooled to r.t. and filtered. The precipitate of inorganic compounds was washed with benzene. The filtrate was combined with washings, washed with water until neutralized, dried over $MgSO_4$, and evaporated under reduced pressure. Chromatography of the crude product on silica gel (hexane/ethyl acetate, 9:1) afforded diene methanesulfonamide as an oil (193 mg, 0.499 mmol, 98%). ^1H NMR ($CDCl_3$) δ 7.35 (d, J = 9.0 Hz, 4H, Ar), 6.87 (d, J = 9.0 Hz, 4H, Ar), 5.39 (s, 2H, $H_{olefinic}$), 5.20 (s, 2H, $H_{olefinic}$), 4.22 (s, 4H, $H_{\alpha\text{-}NSO_2Me}$), 3.82 (s, 6H, MeO), 2.50 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) δ 159.5 (C_{Ar}), 142.0 ($C_{olefinic}$), 131.4 (C_{Ar}), 127.8 (C_{Ar}), 115.4 ($C_{olefinic}$), 113.8 (C_{Ar}), 55.3 (MeO), 50.0 ($C_{\alpha\text{-}NSO_2Me}$), 39.8 (Me). FT-IR (neat) 2919, 2825, 1607, 1507, 1460, 1325, 1249, 1178, 1149, 1031, 908, 837, 802 cm^{-1}. LRMS (CI, NH_3, rel intensity) 407 (24), 406 (27), 405 (M+18, 100), 389 (21), 388 (M+1, 85), 309 (47), 229 (20), 227 (21), 163 (40), 149 (79). HRMS calcd. for $C_{21}H_{25}NO_4S$ 387.1504, found 387.1509.

ii) A flame-dried 25 mL 3-necked Pyrex flask with magnetic stirring bar, gas inlet tube, and gas outlet tube was charged with this diene methanesulfonamide (60 mg, 0.16 mmol), DCA (1.6 mg, 0.0070 mmol) and anhydrous acetonitrile (14.5 mL). Magnesium perchlorate (311 mg, 1.40 mmol) was added to the mixture. Oxygen was bubbled through the mixture for 1 h to saturate the solution. This solution was then photooxygenated for 45 min at r.t. by exposure to a medium pressure mercury lamp with continuous oxygen bubbling.[38] Acetonitrile was evaporated under reduced pressure, the residue was treated with water and extracted with chloroform (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Chromatography of the crude product on silica gel (starting hexane, then hexane/ethyl acetate, 9:1) afforded endoperoxide methanesulfonamide **4b** as a solid (24.7 mg, 0.0589 mmol, 38%) and cyclobutane methanesulfonamide as an oil (18.6 mg, 0.0481 mmol, 31%). Recrystallization of endoperoxide methanesulfonamide **4b** from ethyl acetate/pentane afforded a white solid (m.p. = 163–165 °C). Final purification was by HPLC (Rainin Dynamax-60 Å silica gel, 8 μm pore size, 10 mm x 250 mm, hexane/ethyl acetate 30%, 4.0 mL/min, 240 nm, $R_{t\ endoperoxide}$ = 15.3 min).

Spectroscopic data of endoperoxide methanesulfonamide **4b**:

^1H NMR ($CDCl_3$) δ 7.35 (d, J = 9.0 Hz, 4H, Ar), 6.90 (d, J = 9.0 Hz, 4H, Ar), 4.17 (d, J = 13.6 Hz, 2H, $H_{\alpha\text{-}NSO_2Me}$), 3.81 (s, 6H, MeO), 3.60 (d, J = 13.6 Hz, 2H, $H_{\alpha\text{-}NSO_2Me}$), 2.84 (s, 3H, Me), 2.71 (dd, J = 13.4 Hz, J = 4.8 Hz, 2H, CH_2), 2.30 (dd, J = 13.4 Hz, J = 4.8 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 159.2 (C_{Ar}), 134.0 (C_{Ar}),

125.7 (C_{Ar}), 113.9 (C_{Ar}), 83.8 (C_q), 57.8 ($C_{\alpha\text{-}NSO_2Me}$), 55.3 (MeO), 37.1 (Me), 28.5 (CH_2). FT-IR (neat) 2931, 2837, 1607, 1513, 1331, 1249, 1149, 1025, 973, 826, 732 cm^{-1}. LRMS (CI, NH_3, rel intensity) 438 (24), 437 (M+18, 100), 420 (M+1, 39), 324 (30), 299 (32), 296 (55), 292 (39), 151 (23), 135 (21). HRMS (CI, NH_3) calcd. for $C_{21}H_{26}NO_6S$ (M+1) 420.1481, found 420.1488.

Spectroscopic data of the corresponding cyclobutane methanesulfonamide:

^1H NMR ($CDCl_3$) δ 6.80 (d, J = 8.8 Hz, 4H, Ar), 6.68 (d, J = 8.8 Hz, 4H, Ar), 3.84 (d, J = 9.8 Hz, 2H, $H_{\alpha\text{-}NSO_2Me}$), 3.73 (s, 6H, MeO), 3.41 (d, J = 9.8 Hz, 2H, $H_{\alpha\text{-}NSO_2Me}$), 2.96 (s, 3H, Me), 2.48 (m, 4H, $H_{cyclobutane}$). ^{13}C NMR ($CDCl_3$) δ 157.7 (C_{Ar}), 134.1 (C_{Ar}), 128.0 (C_{Ar}), 113.3 (C_{Ar}), 61.5 ($C_{\alpha\text{-}NSO_2Me}$), 55.7 ($C_q$ / MeO), 55.1 (C_q / MeO), 34.4 (Me), 29.9 ($C_{cyclobutane}$). FT-IR (neat) 2943, 2837, 1613, 1507, 1460, 1331, 1249, 1161, 1031, 1008, 831 cm^{-1}. LRMS (CI, NH_3, rel intensity) 406 (24), 405 (M+18, 100), 388 (M+1, 60). HRMS calcd. for $C_{21}H_{25}NO_4S$ 387.1504, found 387.1505.

Preparation of Endoperoxide Ether 5.

i) An oven-dried 50 mL three-necked round-bottomed flask was charged with the allylic bromide from the above procedure (733 mg, 3.23 mmol), bis(tributyltin)oxide (971 μL, 1.91 mmol), tetrabutylammonium iodide (298 mg, 0.807 mmol), and acetonitrile (15 mL). After the mixture was stirred for 5 min, tetrabutylammonium fluoride trihydrate (1.22 mg, 3.87 mmol) was added in one portion.[39] The reaction was stirred at r.t. for 16 h. The mixture became cloudy due to the formation of tributyltin fluoride. Evaporation of the solvent and addition of ethyl acetate resulted in the formation of a precipitate which was removed by filtration through Celite. Filtrate was passed through a short column of silica gel with ethyl acetate and the solvent was then removed under reduced pressure. Chromatography of the crude product on silica gel (hexane/ethyl acetate, 9:1) afforded diene ether as an oil (370 mg, 1.19 mmol, 37%). ^1H NMR ($CDCl_3$) δ 7.43 (d, J = 8.4 Hz, 4H, Ar), 6.88 (d, J = 8.4 Hz, 4H, Ar), 5.51 (s, 2H, $H_{olefinic}$), 5.30 (s, 2H, $H_{olefinic}$), 4.43 (s, 4H, $H_{\alpha\text{-}O}$), 3.83 (s, 6H, MeO). ^{13}C NMR ($CDCl_3$) δ 159.1 (C_{Ar}), 143.3 ($C_{olefinic}$), 131.0 (C_{Ar}), 127.2 (C_{Ar}), 113.5 (C_{Ar}), 112.9 ($C_{olefinic}$), 71.8 ($C_{\alpha\text{-}O}$), 55.1 (MeO). FT-IR (neat) 2954, 2931, 2837, 1607, 1513, 1460, 1443, 1284, 1249, 1178, 1031, 831 cm^{-1}. LRMS (EI, rel intensity) 310 (65), 163 (100), 148 (33), 147 (28), 135 (79), 133 (26), 103 (23), 91 (33), 77 (21). HRMS calcd. for $C_{20}H_{22}O_3$ 310.1569, found 310.1577.

ii) A flame-dried 50 mL 3-necked Pyrex flask with magnetic stirring bar, gas inlet tube, and gas outlet tube was charged with this diene ether (80 mg, 0.26 mmol), DCA (2.6 mg, 0.012 mmol) and anhydrous acetonitrile (22.5 mL). Magnesium perchlorate (518 mg, 2.32 mmol) was added to the mixture. Oxygen was bubbled through the mixture for 1 h to saturate the solution. This solution was then photooxygenated for 1 h at r.t. by exposure to a medium pressure mercury lamp with continuous oxygen bubbling.[38] Acetonitrile was then evaporated under reduced pressure, the residue was treated with water, and extracted with chloroform (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. Chromatography of the crude product on silica gel (starting hexane, then hexane/ethyl acetate, 9:1) afforded the cyclobutane ether as an oil (11 mg, 0.035 mmol, 13%) and impure endoperoxide ether **5**. Further purification by HPLC (Rainin Dynamax-60 Å silica gel, 8 μm pore size, 10 mm x 250 mm, hexane/ethyl acetate 10%, 3.0 mL/min, 240 nm, $R_{t\ endoperoxide}$ = 33.2 min), afforded endoperoxide ether **5** as a white solid (2.2 mg, 0.0064 mmol, 2.5%).

Spectroscopic data of endoperoxide ether **5**:

^{1}H NMR ($CDCl_3$) δ 7.30 (d, *J* = 9.0 Hz, 4H, Ar), 6.88 (d, *J* = 9.0 Hz, 4H, Ar), 4.17 (d, *J* = 12.8 Hz, 2H, $H_{\alpha\text{-}O}$), 4.01 (d, *J* = 12.8 Hz, 2H, $H_{\alpha\text{-}O}$), 3.79 (s, 6H, MeO), 2.69 (dd, *J* = 12.8 Hz, *J* = 5.2 Hz, 2H, CH_2), 2.31 (dd, *J* = 12.8 Hz, *J* = 5.2 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 159.1 (C_{Ar}), 133.1 (C_{Ar}), 126.1 (C_{Ar}), 113.8 (C_{Ar}), 85.1 ($C_{\alpha\text{-}O}$), 78.7 ($C_{\alpha\text{-}O}$), 55.3 (MeO), 28.0 (CH_2). FT-IR (neat) 2954, 2837, 1607, 1513, 1290, 1249, 1178, 1102, 1031, 943, 814 cm^{-1}. LRMS (CI, NH_3, rel intensity) 360 (M+18, 4), 343 (M+1, 92), 325 (36), 219 (100), 135 (29), 121 (28). HRMS (CI, NH_3) calcd. for $C_{20}H_{23}O_5$ (M+1) 343.1545, found 343.1543.

Spectroscopic data of the corresponding cyclobutane ether:

^{1}H NMR ($CDCl_3$) δ 6.81 (d, *J* = 8.8 Hz, 4H, Ar), 6.69 (d, *J* = 8.8 Hz, 4H, Ar), 4.20 (d, *J* = 9.0 Hz, 2H, $H_{\alpha\text{-}O}$), 3.96 (d, *J* = 9.0 Hz, 2H, $H_{\alpha\text{-}O}$), 3.73 (s, 6H, MeO), 2.47-2.32 (m, second order system, 4H, $H_{cyclobutane}$). ^{13}C NMR ($CDCl_3$) δ 157.5 (C_{Ar}), 134.2 (C_{Ar}), 128.2 (C_{Ar}), 113.2 (C_{Ar}), 81.3 ($C_{\alpha\text{-}O}$), 56.7 (C_q), 55.1 (MeO), 29.5 ($C_{cyclobutane}$). FT-IR (neat) 2919, 2848, 1607, 1513, 1466, 1296, 1249, 1178, 1055, 1031, 826 cm^{-1}. LRMS (EI, rel intensity) 310 (77), 148 (100), 147 (34), 133 (40), 121 (29). HRMS calcd. for $C_{20}H_{22}O_3$ 310.1569, found 310.1564.

Preparation of Endoperoxide Sulfone 6.

i) To a stirred solution of 2-bromo-4'-methoxyacetophenone (5.00 g, 21.8 mmol) in acetone (50 mL) cooled in a ice bath was added a solution of sodium sulfide (0.850 g, 10.9 mmol) in water (12 mL) over a period of 15 min. After stirring for 3 h at r.t., crystals of diketone sulfide formed and were collected and washed with water and methanol. Recrystallization from benzene/methanol (1:1) yielded colorless needles (5.39 g, 16.3 mmol, 75%) (m.p. = 87–88 °C, lit[38] m.p. = 88–89 °C). ^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 4H, Ar), 6.94 (d, *J* = 8.8 Hz, 4H, Ar), 3.94 (s, 4H, $H_{\alpha\text{-}S}$), 3.87 (s, 6H, MeO). ^{13}C NMR ($CDCl_3$) 192.9 (CO), 163.8 (C_{Ar}), 131.0 (C_{Ar}), 128.3 (C_{Ar}), 113.8 (C_{Ar}), 55.5 (MeO), 37.5 ($C_{\alpha\text{-}S}$).

ii) A solution of this diketone sulfide (1.97 g, 5.97 mmol) in THF (33 mL) was treated with freshly prepared Tebbe reagent[36] (1 M, 14.9 mL, 14.9 mmol) at r.t. for 6 h. A solution of NaOH (0.1 M) was added dropwise to quench the reaction until evolution of gas was no longer observed. The mixture was then extracted with ether (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. Chromatography of the crude product on silica gel (hexane/ethyl acetate, 9:1) afforded diene sulfide as an oil (856 mg, 2.63 mmol, 44%). ^{1}H NMR ($CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 4H, Ar), 6.88 (d, *J* = 8.8 Hz, 4H, Ar), 5.43 (s, 2H, $H_{olefinic}$), 5.17 (s, 2H, $H_{olefinic}$), 3.82 (s, 6H, MeO), 3.55 (s, 4H, $H_{\alpha\text{-}S}$). ^{13}C NMR ($CDCl_3$) δ 159.2 (C_{Ar}), 142.5 ($C_{olefinic}$), 131.6 (C_{Ar}), 127.3 (C_{Ar}), 113.6 (C_{Ar} / $C_{olefinic}$), 113.5 (C_{Ar} / $C_{olefinic}$), 55.2 (MeO), 35.7 ($C_{\alpha\text{-}S}$). FT-IR (neat) 2954, 2837, 1607, 1507, 1454, 1255, 1184, 1031, 890, 837 cm^{-1}. LRMS (EI, rel intensity) 326 (59), 148 (100), 133 (31), 121 (17). HRMS calcd. for $C_{20}H_{22}O_2S$ 326.1341, found 326.1349.

iii) A slurry of this diene sulfide (290 mg, 0.891 mmol) in MeOH (5 mL) was cooled to 0 °C. To this mixture was added $KHSO_5$ (49.5% oxone, 822 mg, 2.67 mmol) as a solution in water (5 mL).[41] The resulting cloudy slurry was stirred for 2 days at r.t., diluted with water, and extracted with chloroform (3 x 4 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the crude product on silica gel (hexane/ethyl acetate, 9:1) afforded diene sulfone as a white solid (159 mg, 0.444 mmol, 50%) (m.p. = 80–81 °C). ^{1}H NMR ($CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 4H, Ar), 6.87 (d, *J* = 8.8 Hz, 4H, Ar), 5.65 (s, 2H, $H_{olefinic}$), 5.38 (s, 2H, $H_{olefinic}$), 4.05 (s, 4H, $H_{\alpha\text{-}SO2}$), 3.81 (s, 6H, MeO). ^{13}C NMR ($CDCl_3$) δ 159.6 (C_{Ar}), 135.1

($C_{olefinic}$), 131.3 (C_{Ar}), 127.5 (C_{Ar}), 120.3 ($C_{olefinic}$), 113.9 (C_{Ar}), 58.4 ($C_{\alpha\text{-}SO2}$), 55.2 (MeO). FT-IR (neat) 2966, 2942, 2837, 1601, 1507, 1460, 1407, 1307, 1284, 1249, 1184, 1119, 1020, 926, 831, 714 cm^{-1}. LRMS (CI, NH_3, rel intensity) 376 (M+18, 4), 296 (22), 295 (100), 149 (96). HRMS (CI, NH_3) calcd. for $C_{20}H_{26}NO_4S$ ($M+NH_4$) 376.1583, found 376.1581.

iv) A flame-dried 25 mL 3-necked Pyrex flask with magnetic stirring bar, gas inlet tube, and gas outlet tube was charged with this diene sulfone (30 mg, 0.084 mmol), 9,10-dicyanoanthracene (DCA, 0.8 mg, 0.004 mmol) and anhydrous acetonitrile (7.3 mL). Oxygen was bubbled through the mixture for 1 h to saturate the solution. This solution was then photooxygenated for 30 min at r.t. by exposure to a medium pressure mercury lamp with continuous oxygen bubbling.[38] Acetonitrile was then evaporated under reduced pressure. Chromatography of the crude product on silica gel (starting hexane, then hexane/ethyl acetate, 9:1) afforded a mixture of cyclobutane sulfone and endoperoxide sulfone **6** (8.2 mg total mass of the mixture). Separation of cyclobutane and endoperoxide **6** was done by HPLC (Rainin Dynamax-60 Å silica gel, 8 μm pore size, 10 mm x 250 mm, hexane/ethyl acetate 25%, 3.0 mL/min, 240 nm, $R_{f\ cyclobutane}$ = 21.3 min, $R_{f\ endoperoxide}$ = 25.8 min), affording cyclobutane sulfone as an oil (1.5 mg, 0.0042 mmol, 5%) and white solid endoperoxide sulfone **6** (4.3 mg, 0.011 mmol, 13%).

Spectroscopic data of endoperoxide sulfone **6**:

^1H NMR ($CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 4H, Ar), 6.90 (d, *J* = 8.8 Hz, 4H, Ar), 4.10 (d, *J* = 14.0 Hz, 2H, $H_{\alpha\text{-}SO2}$), 3.83 (s, 6H, MeO), 3.72 (d, *J* = 14.0 Hz, 2H, $H_{\alpha\text{-}SO2}$), 3.04 (dd, *J* = 13.6 Hz, *J* = 5.6 Hz, 2H, CH_2), 2.45 (d, *J* = 13.6 Hz, *J* = 5.6 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 159.6 (C_{Ar}), 134.7 (C_{Ar}), 125.4 (C_{Ar}), 114.2 (C_{Ar}), 80.6 (C_q), 68.9 ($C_{\alpha\text{-}SO2}$), 55.4 (MeO), 27.9 (CH_2). FT-IR (neat) 2931, 2837, 1601, 1513, 1302, 1255, 1178, 1114, 1031, 826 cm^{-1}. LRMS (CI, NH_3, rel intensity) 408 (M+18, 6), 168 (11), 163 (12), 151 (100) 149 (19). HRMS calcd. for $C_{20}H_{22}O_6S$ 390.1137, found 390.1145.

Spectroscopic data of the corresponding cyclobutane sulfone:

^1H NMR ($CDCl_3$) δ 6.84 (d, *J* = 8.8 Hz, 4H, Ar), 6.65 (d, *J* = 8.8 Hz, 4H, Ar), 3.76 (d, *J* = 14.2 Hz, 2H, $H_{\alpha\text{-}SO2}$), 3.71 (s, 6H, MeO), 3.54 (d, *J* = 14.2 Hz, 2H, $H_{\alpha\text{-}SO2}$), 2.72 (s, 4H, $H_{cyclobutane}$). ^{13}C NMR ($CDCl_3$) δ 158.0 (C_{Ar}), 133.6 (C_{Ar}), 127.8 (C_{Ar}), 113.4 (C_{Ar}), 64.6 ($C_{\alpha\text{-}SO2}$), 55.2 (MeO), 53.8 (C_q), 29.1 ($C_{cyclobutane}$). FT-IR (neat) 2954, 2825, 1607, 1507, 1302, 1255, 1184, 1114, 1031, 826 cm^{-1}. LRMS (CI, NH_3, rel intensity) 377 (23), 376 (M+18, 100), 295 (23). HRMS (CI, NH_3) calcd. for $C_{20}H_{26}NO_4S$ 376.1583 ($M+NH_4$), found 376.1577.

Ferrous Bromide Reduction of Endoperoxide Sulfonamide 4a.

A. In the Absence of Hexamethyl Dewar Benzene (HMDB).

An oven-dried 10 mL one-necked round-bottomed flask with magnetic bar was charged with $FeBr_2$ (19 mg, 0.087 mmol) and anhydrous THF (1 mL). Another 10 mL flask was charged with endoperoxide sulfonamide **4a** (60.0 mg, 0.125 mmol) and THF (1 mL). The peroxide solution was added *via* syringe to the $FeBr_2$ solution at r.t. The reaction mixture was stirred at r.t. for 7 h then quenched with water and extracted with chloroform (3 x 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the crude product on silica gel (starting hexane, then hexane/ethyl acetate, 9:1) afforded ring-contracted benzenesulfonamide **8a** as an oil (36 mg, 0.075 mmol, 60%) and hydroxylated benzenesulfonamide **7a** as an oil (12 mg, 0.025 mmol, 20%).

Spectroscopic data of hydroxylated benzenesulfonamide **7a**:

^{1}H NMR ($CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 2H, Ar), 7.62 (d, *J* = 9.2 Hz, 2H, Ar), 7.62 (t, *J* = 7.6 Hz, 1H, Ar), 7.47 (t, *J* = 7.6 Hz, 2 H, Ar), 6.93 (d, *J* = 9.2 Hz, 2H, Ar), 6.82 (d, *J* = 9.2 Hz, 2H, Ar), 6.73 (d, *J* = 9.2 Hz, 2H, Ar), 5.48 (d, *J* = 1.6 Hz, 1H, $H_{\alpha\text{-}O}$), 3.84 (s, 3H, MeO), 3.78 (s, 3H, MeO), 3.70 (d, *J* = 10.2 Hz, 1H, $H_{\alpha\text{-}N}$), 3.26 (d, *J* = 10.2 Hz, 1H, $H_{\alpha\text{-}N}$), 2.60 (m, 1H, CH), 2.18 (m, 2H, CH_2), 1.95 (m, 1H, CH). ^{13}C NMR ($CDCl_3$) δ 159.2 (C_{Ar}), 159.1 (C_{Ar}), 136.6 (C_{Ar}), 133.1 (C_{Ar}), 132.5 (C_{Ar}), 132.3 (C_{Ar}), 129.1 (C_{Ar}), 128.2 (C_{Ar}), 127.7 (C_{Ar}), 125.5 (C_{Ar}), 113.7 (C_{Ar}), 113.4 (C_{Ar}), 94.7 ($C_{\alpha\text{-}O}$), 83.7 ($C_{\alpha\text{-}O}$), 72.4 ($C_{\alpha\text{-}O}$), 56.2 ($C_{\alpha\text{-}N}$), 55.3 (MeO), 55.2 (MeO), 31.1 (CH_2), 29.1 (CH_2). FT-IR (neat) 3518, 2954, 2931, 1613, 1513, 1448, 1349, 1249, 1172, 1090, 1031, 1002, 826, 755, 720, 602 cm^{-1}. LRMS (CI, NH_3, rel intensity) 500 (27), 499 (M+18, 85), 483 (24), 482 (M+1, 35), 465 (25), 464 (90), 379 (32), 342 (38), 341 (23), 340 (100), 324 (27), 323 (43), 175 (57), 163 (34), 160 (90), 151 (73), 135 (39). HRMS (CI, NH_3) calcd. for $C_{26}H_{28}NO_6S$ (M+1) 482.1637, found 482.1644.

Spectroscopic data of ring-contracted benzenesulfonamide **8a**:

^{1}H NMR ($CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H, Ar), 7.74 (d, *J* = 9.2 Hz, 2H, Ar), 7.53 (t, *J* = 7.2 Hz, 1H, Ar), 7.42 (t, *J* = 7.2 Hz, 2H, Ar), 7.03 (d, *J* = 9.2 Hz, 2H, Ar), 6.85 (d, *J* = 9.2 Hz, 2H, Ar), 6.77 (d, *J* = 9.2 Hz, 2H, Ar), 5.08 (d, *J* = 5.2 Hz, 1H, $H_{\alpha\text{-}N,\ \alpha\text{-}O}$), 4.90 (d, *J* = 5.2 Hz, 1H, $H_{\alpha\text{-}N,\ \alpha\text{-}O}$), 3.84 (s, 3H, MeO), 3.78 (s, 3H, MeO), 3.71 (d, *J* = 10.2 Hz, 1H, $H_{\alpha\text{-}N}$), 3.56 (d, *J* = 10.2 Hz, 1H, $H_{\alpha\text{-}N}$), 2.81 (m, 1H, CH), 2.43 (m, 1H, CH), 2.05 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 197.5 (CO), 163.3 (C_{Ar}), 158.7 (C_{Ar}), 136.8 (C_{Ar}), 133.1 (C_{Ar}), 133.1 (C_{Ar}), 130.1 (C_{Ar}), 129.6 (C_{Ar}), 129.1 (C_{Ar}), 127.6 (C_{Ar}), 125.9 (C_{Ar}), 113.9 (C_{Ar}), 113.5 (C_{Ar}), 86.2 ($C_{\alpha\text{-}N,\ \alpha\text{-}O}$), 79.4 ($C_{\alpha\text{-}O}$), 57.5 ($C_{\alpha\text{-}N}$), 55.4 (MeO), 55.2 (MeO), 34.0 (CH_2), 32.7 (CH_2). FT-IR (neat) 2954, 2942, 2837, 1672, 1601, 1513, 1349, 1307, 1255, 1166, 1031, 831, 720 cm^{-1}. LRMS (CI, NH_3, rel intensity) 499 (M+18, 0.82), 483 (17), 482 (M+1, 54), 351 (45), 334 (56), 323 (100), 306 (46), 175 (28), 166 (35), 151 (28), 135 (45). HRMS (CI, NH_3) calcd. for $C_{26}H_{28}NO_6S$ (M+1) 482.1637, found 482.1639.

B. In the Presence of HMDB.

An oven-dried 10 mL one-necked round-bottomed flask with magnetic bar was charged with $FeBr_2$ (1.6 mg, 0.0073 mmol) and anhydrous THF (0.25 mL), and HMDB (11 μl, 0.052 mmol). Another 10 mL flask was charged with endoperoxide sulfonamide **4a** (5 mg, 0.01 mmol) and THF (0.25 mL). The peroxide solution was added *via* syringe to the $FeBr_2$ solution at r.t. The reaction mixture was stirred at r.t. for 6 h and then quenched with water. Dimethyl terephthalate (20 mg, 0.10 mmol) was added as a internal standard. The reaction mixture was extracted with chloroform (3 x 2 mL), the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. HMDB rearrangement was not observed (the characteristic methyl resonance of hexamethylbenzene at 2.21 δ was not present in the ^{1}H NMR spectrum).

Ferrous Bromide Reduction of Endoperoxide Sulfonamide 4b.

A. In the Absence of Hexamethyl Dewar Benzene (HMDB).

An oven-dried 10 mL one-necked round-bottomed flask with magnetic bar was charged with $FeBr_2$ (5.2 mg, 0.024 mmol) and anhydrous THF (0.50 mL). Another 10 mL flask was charged with endoperoxide sulfonamide **4b** (14 mg, 0.034 mmol) and THF (0.50 mL). The peroxide solution was added *via* syringe to the $FeBr_2$ solution at r.t. The reaction mixture was stirred at r.t. for 1.5 h then quenched with water and extracted with chloroform (3 x 1 mL).

The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the crude product on silica gel (starting hexane, then hexane/ethyl acetate, 9:1) afforded ring contracted methanesulfonamide **8b** as an oil (7.9 mg, 0.019 mmol, 55%) and hydroxylated methanesulfonamide **7b** as an oil (2.5 mg, 0.0060 mmol, 18%).

Spectroscopic data of hydroxylated methanesulfonamide **7b**:

^{1}H NMR ($CDCl_3$) δ 7.59 (d, J = 9.2 Hz, 2H, Ar), 7.34 (d, J = 9.2 H, 2H, Ar), 6.94 (d, J = 9.2 Hz, 2H, Ar), 6.93 (d, J = 9.2 Hz, 2H, Ar), 5.37 (d, J = 1.2 Hz, 1H, $H_{\alpha\text{-}O}$), 3.83 (s, 3H, MeO), 3.81 (s, 3H, MeO), 3.77 (d, J = 10.0 Hz, 1H, $H_{\alpha\text{-}N}$), 3.54 (dd, J = 10.0 Hz, J = 1.6 Hz, 1H, $H_{\alpha\text{-}N}$), 2.65 (m, 1H, CH), 2.50 (s, 3H, Me), 2.22 (m, 2H, CH_2), 1.92 (m, 1H, CH). ^{13}C NMR ($CDCl_3$) δ 159.2 (C_{Ar}), 159.1 (C_{Ar}), 132.5 (C_{Ar}), 132.3 (C_{Ar}), 128.2 (C_{Ar}), 127.7 (C_{Ar}), 113.7 (C_{Ar}), 113.4 (C_{Ar}), 94.7 ($C_{\alpha\text{-}O}$), 83.7 ($C_{\alpha\text{-}O}$), 72.3 ($C_{\alpha\text{-}O}$), 58.0 ($C_{\alpha\text{-}N}$), 55.3 (MeO), 55.2 (MeO), 38.5 (Me), 31.2 (CH_2), 29.1 (CH_2). FT-IR (neat) 3448, 2954, 2837, 1601, 1513, 1296, 1178, 1031, 826, 779 cm^{-1}. LRMS (CI, NH_3, rel intensity) 438 (23), 437 (M+18, 91), 421 (20), 420 (M+1, 56), 402 (100), 323 (64), 150 (22). HRMS (CI, NH_3) calcd. for $C_{21}H_{26}NO_6S$ (M+1) 420.1481, found 420.1488.

Spectroscopic data of ring-contracted methanesulfonamide **8b**:

^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 8.8 Hz, 2H, Ar), 7.27 (d, J = 8.8 Hz, 2H, Ar), 6.90 (d, J = 8.8 Hz, 2H, Ar), 6.88 (d, J = 8.8 Hz, 2H, Ar), 5.02 (d, J = 6.0 Hz, 1H, $H_{\alpha\text{-}N,\ \alpha\text{-}O}$), 4.94 (d, J = 6.0 Hz, 1H, $H_{\alpha\text{-}N,\ \alpha\text{-}O}$), 3.86 (d, J = 11.0 Hz, 1H, $H_{\alpha\text{-}N}$), 3.85 (s, 3H, MeO), 3.81 (s, 3H, MeO), 3.70 (d, J = 11.0 Hz, 1H, $H_{\alpha\text{-}N}$), 3.03 (ddd, J = 15.4 Hz, J = 10.4 Hz, J = 5.2 Hz, 1H, CH), 2.63 (s, 3H, Me), 2.55 (ddd, J = 15.4 Hz, J = 10.0 Hz, J = 5.2 Hz, 1H, CH), 2.40 (ddd, J = 14.2 Hz, J = 10.0 Hz, J = 5.2 Hz, 1H, CH), 2.27 (ddd, J = 14.2 Hz, J = 10.4 Hz, J = 5.2 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$) δ 197.5 (CO), 163.3 (C_{Ar}), 159.2 (C_{Ar}), 135.2 (C_{Ar}), 134.0 (C_{Ar}), 125.2 (C_{Ar}), 123.6 (C_{Ar}), 114.2 (C_{Ar}), 114.1 (C_{Ar}), 86.2 ($C_{\alpha\text{-}N,\ \alpha\text{-}O}$), 79.4 ($C_{\alpha\text{-}O}$), 61.5 ($C_{\alpha\text{-}N}$), 55.7 (MeO), 55.1 (MeO), 39.8 (Me), 34.0 (CH_2), 32.7 (CH_2). FT-IR (neat) 2931, 2848, 1678, 1595, 1448, 1266, 1196, 737, 690 cm^{-1}. LRMS (CI, NH_3, rel intensity) 437 (M+18, 4), 421 (25), 420 (M+1, 100). HRMS (CI, NH_3) calcd. for $C_{21}H_{26}NO_6S$ (M+1) 420.1481, found 420.1484.

B. In the Presence of HMDB.

An oven-dried 10 mL one-necked round-bottomed flask with magnetic bar was charged with $FeBr_2$ (1.8 mg, 0.0084 mmol) and anhydrous THF (0.25 mL), and HMDB (12 µl, 0.060 mmol). Another 10 mL flask was charged with endoperoxide sulfonamide **4b** (5 mg, 0.01 mmol) and THF (0.25 mL). The peroxide solution was added *via* syringe to the $FeBr_2$ solution at r.t. The reaction mixture was stirred at r.t. for 2 h, then quenched with water. Dimethyl terephthalate (20 mg, 0.10 mmol) was added as a internal standard. The reaction mixture was extracted with chloroform (3 x 2 mL), the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. HMDB rearrangement was not observed (the characteristic methyl resonance of hexamethylbenzene at 2.21 δ was not present in the ^{1}H NMR spectrum).

Determination of Antimalarial Activity. Activity was determined by measuring the incorporation of [^{3}H]hypoxanthine, by the methods of Desjardins[42] and Milhous,[43] with the following modifications. Chloroquine-sensitive *Plasmodium falciparum* (NF54)[35] were maintained in a 2.4% suspension of type O^+ human erythrocytes (obtained weekly from a rotating pool of screened healthy volunteers) in RPMI 1640 (Gibco BRL #13200-076),

supplemented with 25 mM *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (HEPES; Calbiochem #391338), 27 mM $NaHCO_3$ (Gibco BRL #11810-025), and 10% heat-inactivated human type O^+ serum (Interstate Blood Bank, Inc.), under 3% O_2, 4% CO_2, and 93% N_2. Parasitemia was maintained at 0.05–3% and doubling time at ~15 h by twice weekly change of medium and replenishment with fresh erythrocytes.

Stock solutions (~2.5 mg/mL) of HPLC-purified or recrystallized test compound were prepared in dimethylsulfoxide (DMSO; Sigma-Aldrich #27,043-1). DMSO solutions were diluted 500-fold in medium, serially diluted in 0.2% DMSO in medium (to maintain constant solvent concentration), then 100 μL aliquots were pipetted into microtiter plate wells (Costar 3595). Provisional EC_{50} values were obtained in a survey of seven 5-fold dilutions yielding final concentrations (in triplicate) of 0.16–2500 ng/mL. Assays were later expanded to include ten concentrations (in quadruplicate) of ~1.8-fold dilutions which flank the provisional EC_{50}. Plates included at least 8 wells of no drug controls (4 with and 4 without DMSO) and 4 wells of uninfected erythrocytes. Parasite culture (0.25% parasitemia in 2.4% hematocrit; 100 μL per well) was added and the plate was incubated for 48 h prior to the addition of 25 μL [^{3}H]hypoxanthine (14.1 Ci/mmol, 1 mCi/mL in 70% ethanol, New England Nuclear NET-177, diluted to 25 μCi/mL with medium) and subsequent 20 h incubation. Cells were harvested (Brandel MB-48R) onto GF-C glass filters (Brandel). The filters were washed four times with 3 mL water per sample spot, dried under a heat lamp, and counted (Beckman Model LS-6500) in scintillation cocktail (ICN Cytoscint).

Decays per minute (dpm) values were downloaded and analyzed (Power Macintosh 7200/90; Microsoft Excel 5.0), to yield the mean and standard deviation at each drug concentration. Dose-response curves were fit to the experimental data (Delta Point DeltaGraph 3.5.3) by means of the Marquardt algorithm,[44] were solved for the drug concentration that kills 50% of parasites, and were analyzed for goodness of fit (R^2 value).

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References

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1. Casteel, D. A. *Natural Prod. Reports* **1992**, 289.
2. Capon, R. J. in *Studies in Natural Products Chemistry*, Atta-ur-Rahman, Ed., Elsevier Science, Amsterdam, **1991**, Vol. 9, pp 15–33.
3. Samuelsson, B. *J. Am. Chem. Soc.* **1965**, *87*, 3011.
4. Hahmberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA* **1973**, *70*, 899.
5. Nugteren, D. H.; Hazelhof, E. *Biochim. Biophys. Acta* **1973**, *326*, 448.
6. Pace-Asciak, C.; Nashat, M. *Biochim. Biophys. Acta* **1975**, *388*, 243.
7. Klayman, D. L. *Science* **1985**, *228*, 1049.
8. White, N. J. *Trans. R. Soc. Trop. Med. Hyg.* **1994**, *88* (Suppl. 1), 3.
9. Zhou, W. S.; Xu, X. X. *Acc. Chem. Res.* **1994**, *27*, 211.

10. Jung, M. *Curr. Med. Chem.* **1994**, *1*, 46.

11. McCullough, K. J. *Contemp. Org. Syn.* **1995**, *2*, 225.

12. See also, Avery, M. A.; Gao, F.; Chong, W. K. M.; Hendrickson, T. F.; Inman, W. D.; Crews, P. *Tetrahedron* **1994**, *50*, 9547.

13. Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301.

14. Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1996**, *37*, 253.

15. Boukouvalas, J.; Pouliot, R.; Fréchette, Y. *Tetrahedron Lett.* **1995**, *35*, 4167.

16. Jiang, H.-L.; Chen, K.-X.; Tang, Y.; Chen, J.-Z.; Ji, R.-Y. *Chinese J. Chem.* **1995**, *13*, 131.

17. Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1913.

18. Venugopalan, B.; Bapat, C. P.; Karnik, P. J.; Catterjee, D. K.; Iyer, N.; Lepcha, D. *J. Med. Chem.* **1995**, *38*, 1922.

19. Jefford, C. W.; Kohmoto, S.; Jaggi, D.; Timári, G.; Rossier, J.-C.; Rudaz, M.; Barbuzzi, O.; Gérard, D.; Burger, U.; Kamalaprija, P.; Mareda, J.; Bernardinelli, G.; Manzanares, I.; Canfield, C. J.; Fleck, S. L.; Robinson, B. L.; Peters, W. *Helv. Chim. Acta* **1995**, *78*, 647.

20. Posner, G. H.; McGarvey, D. J.; Oh, C. H.; Kumar, N.; Meshnick, S. R.; Asawamahasakda, W. *J. Med. Chem.* **1995**, *38*, 607.

21. Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *Heteroatom Chem.* **1995**, *6*, 105.

22. Avery, M. A.; Fan, P.; Karle, J. M.; Bank, J. D.; Miller, R.; Goins, D. K. *J. Med. Chem.* **1996**, *39*, 1885.

23. de Almeida Barbosa, L.-C.; Cutler, D.; Mann, J.; Crabbe, M. J.; Kirby, G. C.; Warhurst, D. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1101.

24. Pine, S. H. *Org. Reactions* **1993**, *43*, 1.

25. For methylenation of a β-bromoketone, see Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *101*, 4831.

26. For methylenation of a α-selenoketone, see Burnier, G.; Schwager, L.; Vogel, P. *Helv. Chim. Acta* **1986**, *69*, 1310.

27. For a recent report with reading references, see Griesbeck, A. G.; Sadlek, O.; Polborn, K. *Liebigs Ann.* **1996**, 545.

28. Balci, M.; Saracoglu, N.; Menzek, A. *Tetrahedron Lett.* **1996**, *37*, 921.

29. Adam, W.; Duran, N. *J. Chem. Soc. Chem. Comm.* **1972**, 798.

30. Posner, G. H.; Wang, D. W.; González, L.; Tao, X.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron Lett.* **1996**, *37*, 815.

31. Posner, G. H.; Cumming, J. N.; Ploypradith, P.; Oh, C. H. *J. Am. Chem. Soc.* **1995**, *117*, 5885.

32. Jeon, Y.T.; Lee, C.-P.; Mariano, P.S. *J. Am. Chem. Soc.* **1991**, *113*, 8847.

33. Haynes, R.K.; Vonwiller, S.C. *Tetrahedron Lett.*, **1996**, *37*, 253 and 257.

34. Jefford, C.W.; Vicente, M.G.H.; Jacquier, Y.; Favarger, F.; Maredo, J.; Millasson-Schmidt, P.; Brunner, G.; Burger, U. *Helv. Chim. Acta*, **1996**, *79*, 1475.

35. Ponnudurai, T.; Leeuwenberg, A. D. E. M.; Meuwissen, J. H. E. T. *Trop. Geogr. Med.* **1981**, *33*, 50.

36. Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

37. Gajda, T.; Zwierzak, A. *Synthesis* **1981,** 1005.

38. Takahashi, Y.; Okitsu, O.; Ando, M.; Miyashi, T. *Tetrahedron Lett.* **1994**, *35*, 3953.

39. Harpp, D.N.; Gingras, M. *J. Am. Chem. Soc.* **1988**, *110*, 7737.

40. Miyahara, Y. *J. Heterocyclic Chem.* **1979**, *16*, 1147.

41. Trost, B.M.; Curran, D.P. *Tetrahedron Lett.* **1981**, *22*, 1287.

42. Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. *Antimicrob. Agents Chemother.* **1979**, *16*, 710.

43. Milhous, W. K.; Weatherly, N. F.; Bowdre, J. H.; Desjardins, R. *Antimicrob. Agents Chemother.* **1985**, *27*, 525.

44. Bard, Y. *Nonlinear Parameter Estimation*; Academic Press: New York, 1974; p 94.

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