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Antimalarial Sulfide, Sulfone, and Sulfonamide Trioxanes

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Abstract—A series of trioxanes featuring sulfide, sulfone, and sulfonamide substituents in diverse positions has been prepared. Structure–activity relationship (SAR) generalizations highlight two major factors controlling the antimalarial potency of these new chemical entities: (1) the *proximity* of the sulfur-containing substituent to the crucial peroxide bond and (2) the *oxidation state* of the sulfur-containing substituent. Generally, sulfones are more antimalarially potent than the corresponding sulfides.

A series of bicyclic sulfide and sulfone endoperoxides has been prepared in Israel via a very short procedure featuring thiol-oxygen co-oxidation of natural terpenes such as *R*-(+)-limonene;[1] illustrative of such sulfone endoperoxides is dioxabicyclononane **1** having an in vitro antimalarial IC_{50} of 17 nM (the corresponding sulfide is inactive) compared to an IC_{50} also of 17 nM for the natural dioxabicyclononane antimalarial yingzhaosu A (**2**).[2,3] We found that a sulfone group causes high in vitro antimalarial activity also in some new cyclic peroxy ketals;[4] sulfone **3** having an IC_{50} of 31 nM is structurally simple and easily prepared via a five step procedure. Additionally, a series of sulfide and sulfone 1,2,4-trioxanes has been prepared via a five step procedure starting with inexpensive cyclohexanone;[5] illustrative of such structurally simplified trioxanes are C_{12}-sulfones **4c** and **4d**, having in vitro IC_{50} values of 23–25 nM, compared to an IC_{50} of 9–10 nM for the considerably more complex natural trioxane artemisinin (qinghaosu, **5**) that is a clinically used antimalarial. In all three synthetic compounds **1**, **3** and **4**, the sulfones shown were more antimalarially potent than the corresponding sulfides. Based on the high antimalarial potencies of synthetic sulfone peroxides **1**, **3** and **4**, we have now prepared sulfide, sulfone, and sulfonamide trioxanes **6–10** in order to explore structure–activity relationship (SAR) issues; such additional antimalarially potent peroxides may be useful for chemotherapy in the worldwide fight against malaria, an increasingly widespread and multidrug resistant infectious disease that kills 1–2 million people, mostly children, each year.

Results and Discussion

Arbusov coupling and then α-lithiophosphonate condensation via Scheme 1 produced vinylic sulfide **11**. Methyllithium addition to the nitrile group of vinylic sulfide **11** formed methyl ketone **12** that underwent singlet oxygen photo-oxygenation[6] to form trioxane sulfides **4a** and **4b** in low yield as a mixture of C_{12} diastereomers that were easily separated and distinguished by ^{1}H NMR spectroscopy[7] (see Experimental). Although *sulfide* **4b** with $C_{12\beta}$-stereochemistry has an in vitro antimalarial IC_{50} of 110 nM, the $C_{12\alpha}$ stereoisomer **4a** is inactive. We have previously provided experimental support for the proposal that the lack of antimalarial activity specifically of the $C_{12\alpha}$ sulfide is probably due to the rapid interception and reduction by the α-oriented sulfide group of a highly oxidizing, cytotoxic, high-valent iron-oxo species formed specifically on the α-face of the molecule when iron(II) triggers reductive cleavage of the parent trioxane.[5] *m*-Chloroperbenzoic acid (*m*-CPBA) oxidation of sulfides **4a** and **4b** into sulfones **4c** and **4d** proceeded, as expected, without disruption of the trioxane peroxide linkage. In sharp contrast to $C_{12\alpha}$ *sulfide* **4a**, $C_{12\alpha}$ *sulfone* **4c** has high antimalarial potency (Table 1), as does $C_{12\beta}$ *sulfone* **4d**.

Based on Avery's observation that a C_3-*n*-propyl group raises antimalarial potency[8,9] and on trioxane SAR

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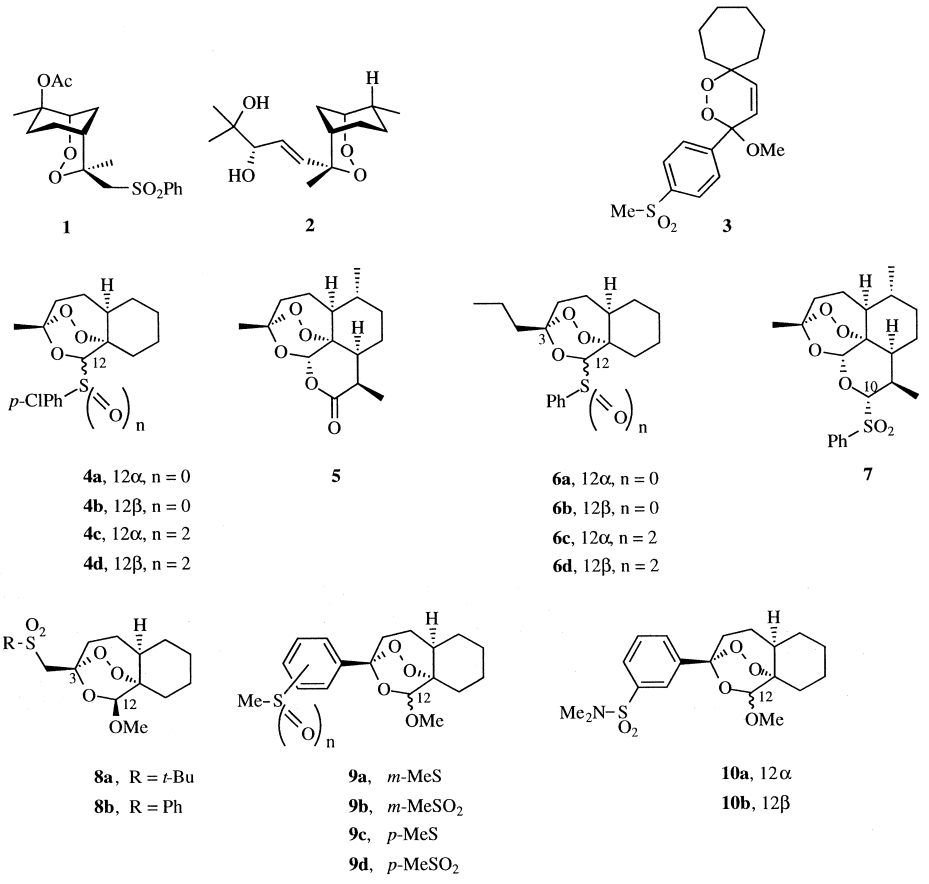
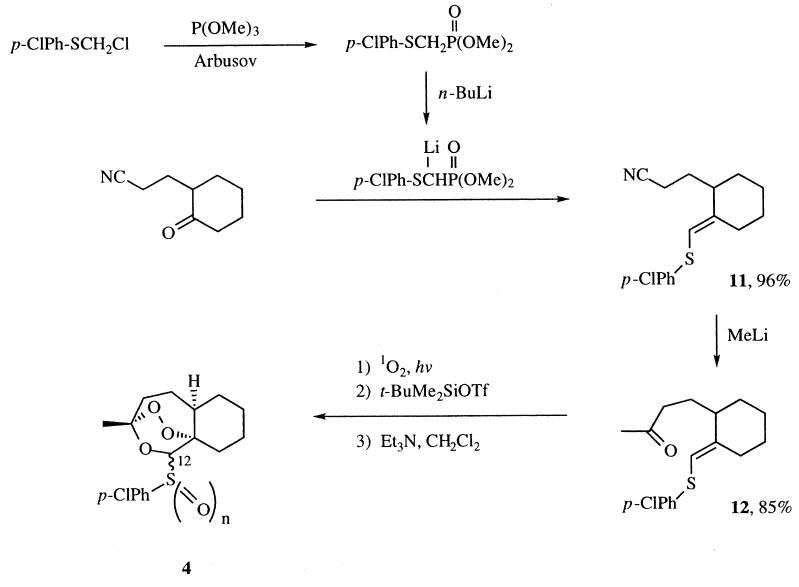
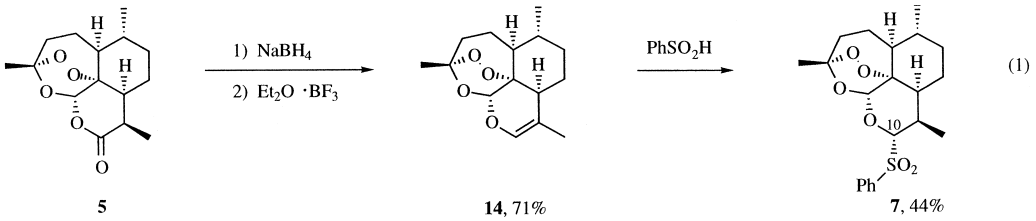


studies,[10] we prepared C_3-*n*-propyl C_{12} sulfides **6a** and **6b** in low yields and subsequently the corresponding sulfones **6c** and **6d** in good yields following the general protocol outlined in Scheme 1. Although, as expected, $C_{12}\alpha$ sulfide **6a** is antimalarially inactive, $C_{12\beta}$ sulfide **6b** has $IC_{50} = 75$ nM. Significantly and desirably, both of the corresponding diastereomeric 3-*n*-propyl C_{12}-*sulfones* **6c** and **6d** are highly potent (Table 1).

Because C_{12} trioxane sulfones **4** and **6** were so antimalarially potent, we converted artemisinin (**5**) into the known anhydrodihydroartemisinin (**14**)[12] and then directly, using benzenesulfinic acid, into C_{10} sulfone **7**, formed as a single diastereomer (eq. (1)). Semi-synthetic, enantiomerically pure, artemisinin-derived C_{10} sulfone **7**, disappointingly, is about only 1/5 as antimalarially potent as natural artemisinin (**5**). Likewise, 3-



Scheme 1.



(1)

sulfonylmethyl trioxanes **8**, prepared via Scheme 2 in four steps and in moderate yields, have disappointingly poor antimalarial activities.

We have recently described the preparation and the antimalarial activity of a series of simplified 3-aryl trioxanes, with the most promising and orally active members of this series approaching the antimalarial potency of artemisinin (**5**).[13] We have now prepared such trioxanes, albeit in low yields due to difficulty in the trioxane-forming step, in which the 3-phenyl substituent bears a sulfide, sulfone, or sulfonamide group (Schemes 3 and 4). In each case, chromatographic separation of C_{12} diastereomers was achieved, and in vitro antimalarial testing of HPLC-purified material produced the data in Table 1. Strikingly, there is little difference in antimalarial potency between the *sulfides* **9a** and **9c** versus the corresponding *sulfones* **9b** and **9d**. This result is in sharp contrast to the dramatic difference between the lack of antimalarial activity of $C_{12\alpha}$ *sulfide* **6a** compared to the considerable antimalarial potency ($IC_{50}=26$ nM) of $C_{12\alpha}$ *sulfone* **6c** (Table 1). Thus, it appears that a sulfide group structurally remote from the antimalarially critical trioxane unit does not interfere with the biological mechanism of action[14,15] of such peroxidic compounds. Thus, all four 3-aryl-substituted sulfides and sulfones **9** are potent antimalarials, with IC_{50} values ranging from 33 to 92 nM. Likewise, both 3-aryl-substituted sulfonamides **10** have respectable antimalarial potencies (IC_{50} 53–70 nM).

Table 1. Chemical structure–antimalarial activity relationships in chloroquine-sensitive *Plasmodium Falciparum* (NF54) parasites in vitro[a]

Trioxane	C-12 Stereochemistry	IC_{50} (nM)
4a	α	>2500
4b	β	110
4c	α	25
4d	β	23
6a	α	>2500
6b	β	75
6c	α	26
6d	β	18
9a, *m*-MeS	α	62
	β	42
9b, *m*-$MeSO_2$	α	92
	β	41
9c, *p*-MeS	β	60
9d, *p*-$MeSO_2$	β	33
10a	α	70
10b	β	53
Artemisinin		9.4±1.3

[a]Antimalarial activity against chloroquine-sensitive strain NF-54 of *P. falciparum* was determined as reported previously.[11] The standard deviation for each set of quadruplicates was an average of 10% (≤39%) of the mean. R^2 values for the fitted curves were ≥0.981. Artemisinin is mean ±standard deviation of concurrent control ($n=16$).

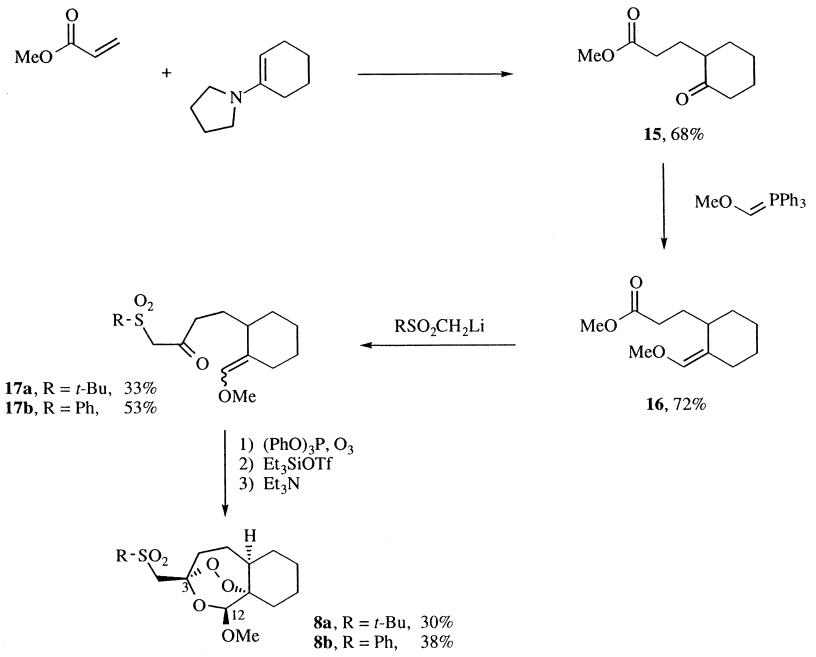
Conclusion

The effect of a sulfur atom on the antimalarial activity of a peroxide depends on the sulfur atom's spatial *proximity* to the peroxide bond and on the *oxidation state* of the sulfur atom. When the sulfur atom is adjacent to the peroxide bond, as in compounds **1**, **4**, and **6**, then *sulfones* are much more potent antimalarials than the corresponding *sulfides*. In rigid polycyclic trioxanes **4** and **6**, the *stereochemical orientation* of the sulfide group governs the trioxane's antimalarial potency: when the sulfide substituent is α-oriented close to the α-oriented peroxide oxygen atoms, then the trioxane is inactive; however, when the sulfide substituent is β-oriented and thus held fixed in space away from the α-oriented peroxide oxygen atoms, then good but not excellent antimalarial potency (IC_{50} values of 75–110 nM) is observed. When the sulfur atom is structurally remote from the peroxide bond, as in endoperoxide **3** and in trioxanes **8** and **9**, then sulfides and sulfones have similarly high (within a factor of 3 of each other) antimalarial potencies. Remotely situated methyl sulfone groups and remotely situated dimethylsulfonamide groups are comparable in their effect on the antimalarial potency of a trioxane (e.g. **9b**, **9d**, **10a** and **10b**). These SAR generalizations are expected to help in the future design of additional antimalarial peroxides for effective and safe[16] chemotherapy[17–21] against malaria.

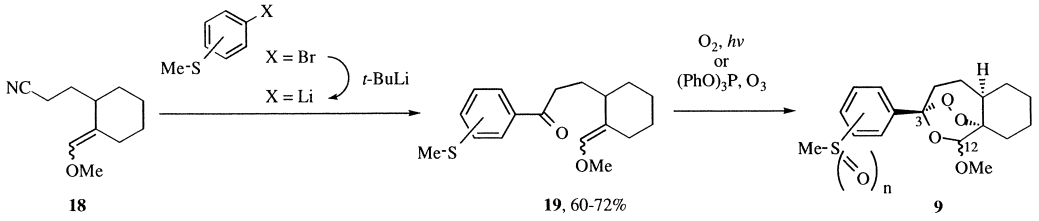
Experimental

General

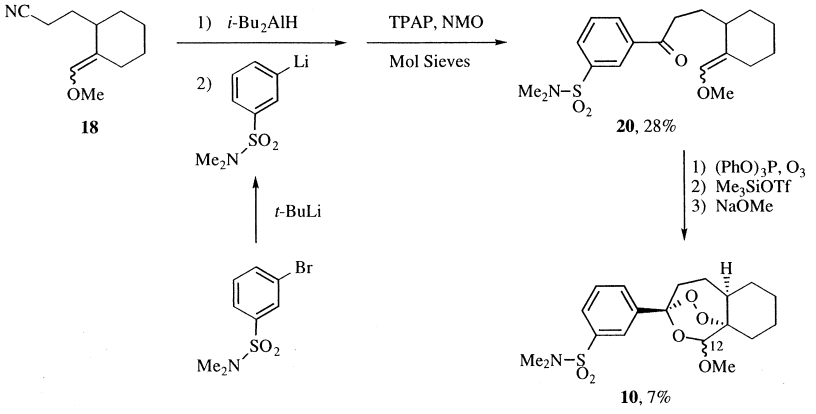
Unless otherwise noted, all compounds were purchased from Aldrich Chemical Company and used without further purification, and reactions were run in oven-dried glassware under an atmosphere of argon. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use. Column chromatography was performed using flash silica gel (partical size 400–230 mesh). Yields are not optimized. Purity of final products was judged to be >95% based on their chromatographic homogeneity. High performance liquid chromatography (HPLC) was carried out with a Rainin



Scheme 2.



Scheme 3.



Scheme 4.

HPLX system equipped with two 25 mL/min preparative pump heads using a Rainin Dynamax 10×250 mm (semi-preparative) column packed with 60 Å silica gel (8 μm pore size) as bare silica. Melting points were measured using a Mel-Temp metal-block apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian XL-400 spectrometer, operating at 400 M Hz for ^{1}H and 100 M Hz for ^{13}C. Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Infrared (IR) spectra were obtained using a Perkin–Elmer 1600 FT-IR spectrometer. Resonances are reported in wavenumbers (cm^{-1}). Low and high resolution mass spectra (LRMS and HRMS) were obtained with electronic or chemical ionization (EI or CI) either (1) at Johns Hopkins University on a VG Instruments 70-S Spectrometer

run at 70 eV for EI and run with ammonia (NH_3), butane (C_4H_{10}) or methane (CH_4) as carrier gas for CI or (2) at the University of Illinois at Champaign—Urbana on a Finnigan-MAT CH5, a Finnigan-MAT 731, or a VG Instruments 70-VERSUSE spectrometer run at 70 eV for EI and run with methane (CH_4) for CI. Combustion analyses were conducted by Atlantic Microlab (Norcross, GA).

General procedure 1: trioxane synthesis via singlet oxygen

In a three neck sulfonation flask equipped with a gas inlet and outlet, a stream of UHP oxygen was bubbled through a solution of ketone (1.0 equiv) and methylene blue (ca. 5 mg) in CH_2Cl_2 at −78 °C. The solution was irradiated with UV light from a low pressure Hg lamp until TLC analysis showed consumption of the ketone. A solution of TBSOTf or TMSOTf (1.2 equiv) in CH_2Cl_2 was then cannulated into the flask and the reaction was monitored by TLC until complete. When complete, sodium methoxide (3.2 equiv, 25 wt% in methanol) was syringed into the reaction flask and the solution was warmed to 0 °C, quenched with water, extracted with diethyl ether, washed with brine, dried over $MgSO_4$ or Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography and semi-prep HPLC. The $C_{12\alpha}$ and $C_{12\beta}$ diastereomers were identified by ^1H NMR using the acetal proton splitting pattern. The $C_{12\beta}$ diastereomer exhibits W-coupling with the angular $C_{5\alpha}$ proton, and appears as a doublet, whereas the acetal proton on the $C_{12\alpha}$ diastereomer appears as a singlet.[7]

General procedure 2: trioxane synthesis via phosphite ozonide

In a three neck sulfonation flask equipped with a gas inlet and outlet, a stream of UHP oxygen was passed through an ozone generator and bubbled through a solution of triphenyl phosphite (2.0 equiv) in CH_2Cl_2 (0.03 M) at −78 °C until blue, and then continued for an additional 15 min. The phosphite ozonide solution was then purged with a stream of prepurified argon for 45 min. A solution of ketone (1.0 equiv) in CH_2Cl_2 (0.07 M) at −78 °C was cannulated into the reaction mixture over 10 min. The reaction was monitored by TLC analysis until the starting ketone was consumed or remained unchanged. A solution of TMSOTf and TESOTf (1.1 equiv) in CH_2Cl_2 (0.15 M) at −78 °C was then cannulated into the reaction mixture. The nearly instantaneous reaction was monitored by TLC. Upon completion of reaction, a solution of sodium methoxide (25 wt%, 3.0 equiv) was syringed dropwise into the reaction mixture followed by addition of water (1–3 mL). The reaction mixture was removed from the dry ice/acetone bath and allowed to warm to RT. The contents were then transferred to a separatory funnel and the aqueous layer was extracted with CH_2Cl_2 (3×). The organic layers were combined, washed with brine, dried over $MgSO_4$ or Na_2SO_4, and concentrated under reduced pressure. The crude product mixture was purified by flash silica gel chromatography (EtOAc in pet ether) and silica gel semi-prep HPLC.

Preparation of trioxanes 4a, 4b, 4c and 4d

(4′-Chlorophenyl)sulfide 11. Chloromethyl 4-chlorophenyl sulfide (0.79 mL, 5.5 mmol) in trimethylphosphite (4.0 mL) was refluxed gently for 3 days. Trimethylphosphite was removed by Kugelrohr distillation, and then the product was purified by column chromatography on Florisil using 50% EtOAc/hexane as eluent to give 1.2 g of (4-chlorophenylmethyl)dimethylphosphonate (4.5 mmol, 81%) as a white solid, mp 45–49 °C; ^1H NMR ($CDCl_3$): δ 3.0 (d, 2H, $J=14$ Hz), 3.6 (d, 6H, $J=10.8$ Hz), 7.1 (d, 2H, $J=8.4$ Hz), 7.2 (d, 2H, $J=8.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 26.8, 28.3, 52.9 (d, $J=27.2$ Hz), 128.1, 130.8, 132.6, 133.4 (d, $J=21.2$ Hz); HRMS m/z (M^+) calcd for $C_9H_{12}SO_3PCl$ 265.9933, found 265.9929. The pure phosphonate (470 mg, 1.76 mmol) in THF (5.0 mL) at −78 °C was then treated with *n*-BuLi (1.6 M in hexane, 1.21 mL, 1.1 equiv). The solution turned yellow, and the reaction was stirred at −78 °C for 30 min, then at room temperature for 15 min. At −78 °C 2-(2′-cyanoethyl) cyclohexanone (242 mg, 1.60 mmol in 1.5 mL THF)[5] was added via cannula. The reaction was stirred at −78 °C for 2 h, then slowly warmed to room temperature and stirred for 1 h. The solution was viscous. The reaction was quenched (water), extracted (Et_2O), washed (brine), dried (Na_2SO_4) and concentrated to give 0.50 g of an oil. The product was purified by column chromatography on Florisil using 5% EtOAc/hexane as eluent to give 0.45 g of desired sulfide **11** (1.54 mmol, 96%). ^1H NMR ($CDCl_3$): δ 1.4–1.9 (m, 7H), 2.0–2.1 (m, 1H), 2.2–2.5 (m, 5H), 5.9 (s, 1H), 7.2–7.3 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 15.3, 22.4, 27.3, 32.7, 43.1, 114.1, 119.4, 128.9, 129.3, 135.2, 146.4; HRMS calcd for $C_{16}H_{18}ClNS$ m/z (M^+): 291.0848, found 291.0849.

Methyl ketone 12. Nitrile **11** (0.45 g, 1.6 mmol) in Et_2O (4.0 mL) at −78 °C was treated slowly with MeLi (1.4 M in Et_2O, 3.3 mL, 3 equiv The reaction was stirred at −78 °C for 2 h, then slowly warmed to room temperature (1 h). The reaction was quenched at 0 °C (water), extracted (Et_2O), washed (brine), dried (Na_2SO_4) and concentrated. The product was purified by column chromatography on Florisil using 5% EtOAc/hexane as eluent to give 424 mg of desired methyl ketone **12** (1.37 mmol, 85%); ^1H NMR ($CDCl_3$): δ 1.4–2.0 (m, 8H), 2.1 (s, 3H), 2.2–2.5 (m, 5H), 5.8 (s, 1H), 7.1–7.3 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 22.8, 25.6, 27.5, 28.2, 29.9, 33.4, 41.6, 43.9, 112.2, 128.7, 128.9, 129.0, 135.8, 149.6, 208.4; HRMS calcd for $C_{17}H_{21}ClOS$ m/z (M^+): 308.1002, found 308.1003.

(4′-Chlorophenyl)thio trioxanes 4a and 4b. Ketone **12** (196 mg, 0.64 mmol) in CH_2Cl_2 (70 mL) was treated according to General procedure 1. TBSOTf (160 μL, 1.1 equiv in 0.6 mL CH_2Cl_2) was used to effect dioxetane rearrangement, and the reaction was quenched with Et_3N (0.36 mL, 4 equiv). After slowly warming to −15 °C (2 h), the reaction mixture was concentrated, then column chromatographed on Florisil using 5% EtOAc/hexane. The less polar fractions containing UV active materials were recombined and chromatographed on Florisil using 3% EtOAc/hexane, resulting in better

resolution of the desired products. HPLC purification (silica semipreparative column, 5% EtOAc/hexane at 3 mL/min, observed at 254 nm) was neccessary to obtain pure samples of α-trioxane **4a** (10 mg, 30 μmol, 5%, retention time: 10 min) and β-trioxane **4b** (10 mg, 30 μmol, 5%, retention time: 8 min). **4a**, 12-α: ^{1}H NMR ($CDCl_3$): δ 1.0–1.4 (m, 4H), 1.45 (s, 3H), 1.4–1.5 (m, 1H), 1.6–1.7 (m, 3H), 1.7–1.85 (m, 2H), 1.9–2.0 (m, 1H), 2.4–2.6 (m, 2H), 5.6 (s, 1H), 7.3 (d, 2H, J=8.8 Hz), 7.5 (d, 2H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$): δ 23.1, 25.2, 26.6, 27.3, 32.4, 36.1, 36.6, 47.3, 85.4, 85.7, 105.1, 129.2, 133.7, 134.2, 134.3; HRMS calcd for $C_{17}ClH_{22}O_3S$ m/z ($M+H^+$): 340.0900, found 340.0883. **4b**, 12-β: ^{1}H NMR ($CDCl_3$): δ 1.2–1.4 (m, 2H), 1.41 (s, 3H), 1.6–2.0 (m, 8H), 2.05-2.3 (m, 2H), 2.3–2.4 (m, 1H), 5.5 (d, 1H, J=1.2 Hz), 7.3 (d, 2H, J=8.4 Hz, 7.4 (d, 2H, J=8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 24.2, 24.8, 26.1, 27.4, 30.8, 35.3, 37.6, 48.7, 85.8, 87.1, 105.7, 129.2, 131.1, 133.1, 134.1; HRMS calcd for $C_{17}H_{22}ClO_3S$ m/z ($M+H^+$): 340.0900, found 340.0885.

***α*-(4′-Chlorophenyl)sulfone trioxanes 4c and 4d.** Trioxane **4a**, 12-α (8 mg, ca. 23 μmol) in CH_2Cl_2 (2.0 mL) at 0 °C was treated with *m*-CPBA (repurified from tech. grade, 17 mg, 0.098 mmol, 4 equiv). After 30 min at 0 °C the reaction was warmed to room temperature and stirred 4 h. The reaction was diluted (Et_2O), washed (aq $NaHCO_3$, aq $NaHSO_3$, aq $NaHCO_3$, brine), dried (Na_2SO_4) and concentrated to give 10 mg of **4c**, 12-α (100%) as a white solid; mp 109–111 °C; ^{1}H NMR ($CDCl_3$): δ 1.1–1.5 (m, 4H), 1.26 (s, 3H), 1.6–2.0 (m, 7H), 2.3–2.5 (m, 1H), 2.9–3.0 (m, 1H), 5.2 (s, 1H), 7.5 (d, 2H, J=8.8 Hz), 7.9 (d, 2H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$): δ 23.7, 25.0, 25.8, 26.9, 32.3, 33.8, 36.2, 49.1, 83.5, 90.8, 105.3, 129.0, 131.1, 137.0, 140.5; HRMS m/z ($M+H^+$) calcd for $C_{17}H_{22}ClO_5S$ 373.0876, found 373.0863. Trioxane **4b**, 12-β (10 mg, 29 μmol) in CH_2Cl_2 (3.0 mL) at 0 °C was treated with *m*-CPBA (repurified from tech. grade, 21 mg, 0.12 mmol, 4 equiv). After 30 min at 0 °C the reaction was warmed to room temperature and stirred 4 h. The reaction was diluted (Et_2O), washed (aq $NaHCO_3$, aq $NaHSO_3$, aq $NaHCO_3$, brine), dried (Na_2SO_4) and concentrated to give 10 mg of **4d**, 12-β (90%) as a white solid; mp 126–129 °C (dec); ^{1}H NMR ($CDCl_3$): δ 1.16 (s, 3H), 1.2–1.5 (m, 2H), 1.5–1.6 (m, 1H), 1.6–1.9 (m, 4H), 2.0–2.4 (m, 6H), 5.0 (d, 1H, J=1.2 Hz), 7.5 (d, 2H, J=8.8 Hz), 7.9 (d, 2H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$): δ 23.0, 24.0, 25.8, 26.2, 29.1, 34.5, 37.8, 49.5, 87.9, 92.8, 106.4, 128.9, 131.0, 136.7, 140.6; HRMS calcd for $C_{17}H_{22}ClO_5S$ m/z ($M+H^+$): 373.0876, found 373.0867.

C10β-phenyl sulfone 7. Dihydroartemisinin (0.79 g, 2.8 mmol), prepared according to the literature,[22] in THF (50 mL) was treated with boron trifluoride diethyl etherate (0.40 mL, 3.2 mmol) then refluxed gently for 2.5 h. The reaction was cooled to room temperature then diluted with ether, washed (satd aq $NaHCO_3$, brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 7% EtOAc/petroleum ether as eluent to give 0.65 g of the desired product **14** as a solid (2.44 mmol, 71% from artemisinin); characteristic data were in accordance with the literature. To a solution of benzenesulfinic acid in CH_2Cl_2 (1.0 mL) was added via cannula anhydrodihydroartemisinin (**14**), (102 mg, 0.38 mmol in 2.0 mL CH_2Cl_2). The reaction was stirred 6 h at room temperature, then diluted (Et_2O), washed (5% aq $NaHCO_3$, brine), dried (Na_2SO_4) and concentrated. The crude product was column chromatographed on silica gel using 25% EtOAc/hexane as eluent to give 68 mg of **7** as a solid (0.17 mmol, 44%); mp 87–95 °C (dec.); ^{1}H NMR ($CDCl_3$): δ 0.85–1.05 (m, 1H), 0.92 (d, J=6.0 Hz, 3H), 1.05 (s, 3H), 1.16–1.47 (m, 5H), 1.43 (d, J=6.8 Hz, 3H), 1.56–1.63 (m, 1H), 1.69–1.76 (m, 1H), 1.84–1.95 (m, 2H), 2.08–2.27 (m, 2H), 5.14 (d, J=10.4 Hz, 1H), 5.40 (s, 1H), 7.51–7.57 (m, 2H), 7.60–7.66 (m, 1H), 7.97–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 19.7, 20.8, 24.7, 25.1, 31.0, 33.8, 34.9, 35.9, 37.2, 48.5, 50.7, 81.9, 89.6, 90.6, 102.3, 128.5, 129.1, 133.4, 137.4; HRMS calcd for $C_{21}H_{32}NO_6S$ ($M+NH_4^+$): 426.1950, found: 426.1950.

Preparation of trioxanes 8a and 8b

Ketone ester 15. To a solution of cyclohexanone (28 mL, 0.27 mol) in benzene (50 mL) was added pyrrolidine (29 mL, 0.35 mol, 1.3 equiv) over the course of 10 min via a dropping funnel. The reaction was refluxed with azeotroping off water using a Dean-Stark trap. After 3 h the reaction was concentrated by distilling off benzene/excess pyrrolidine, then cooled to room temperature. The crude enamine was diluted with dioxane (100 mL), then treated with methyl acrylate (25 mL, 0.28 mol). The reaction was refluxed for 4 h, then cooled to room temperature. The reaction was diluted with water (50 mL) and HCl (10% aq, 50 mL) and stirred for 30 min. The solution was extracted with Et_2O (2×), the organics were washed (brine), dried (Na_2SO_4) and concentrated. The crude product was vacuum distilled through a short vigreux column (bp 110–130 °/1 mm) to give 35 g of the desired product **15** as faint yellow oil. The product was still contaminated with pyrrolidine, as detected by odor. The oil was diluted with Et_2O (100 mL), washed (10% aq HCl, brine), dried (Na_2SO_4) and concentrated to give 33.8 g of pure ketone ester (184 mmol, 68%), which solidifies upon storage at −15 °C; ^{1}H NMR ($CDCl_3$): δ 1.25–1.37 (m, 1H), 1.43–1.54 (m, 1H), 1.55–1.68 (m, 2H), 1.77–1.85 (m, 1H), 1.94–2.09 (m, 3H), 2.20–2.40 (m, 5H), 3.60 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 24.7, 24.9, 27.9, 31.5, 34.0, 42.0, 49.5, 51.4, 173.8, 212.4.

Methyl enol ether 16. A slurry of methoxymethylphosphonium chloride (17 g, 50 mmol) in THF (50 mL) at −78 °C was slowly treated with lithium bis(trimethylsilyl)amide (1.0 M in THF, 55 mL, 55 mmol), added via syringe. The reaction was stirred at −78 °C for 15 min, then at room temperature for 2 h. At −78 °C ketone ester **15** (7.4 g, 40 mmol in 12 mL THF), was slowly added via cannula. The reaction was stirred at −78 °C for 30 min, then at room temperature for 14 h. The reaction was quenched at room temperature with satd aq NH_4Cl, extracted (Et_2O), the organics were washed (brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 5% EtOAc/hexane as eluent to give 6.13 g of the desired product as an oil (29 mmol, 72%), ^{1}H

NMR indicated a 1:1 mixture of ***Z/E*-16**; ^{1}H NMR ($CDCl_3$): δ 1.25–1.37 (m, 1H), 1.43–1.54 (m, 1H), 1.55–1.68 (m, 2H), 1.77–1.85 (m, 1H), 1.94–2.09 (m, 3H), 2.20–2.40 (m, 5H), 3.60 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 1.1–2.0 (m, 25H), 2.20–2.34 (m, 4H), 2.78–2.86 (m, 1H), 3.49 (s, 3H), 3.54 (s, 3H), 3.66 (s, 3H), 3.67 (s, 3H), 5.73 (s, 1H), 5.81 (s, 1H). Column chromatography on a flash silica gel column with 5% EtOAc/hexane as eluent to gave fractions with pure (less polar) ***Z*-isomer** and then the ***E*-isomer** contaminated with some ***Z***.

***t*-Butyl sulfone ketone 17a.** A solution of methyl *t*-butyl sulfone (0.59 g, 4.3 mmol) in THF (8.0 mL) at −78 °C was slowly treated with *n*-BuLi (1.6 M in hexane, 3.4 mL, 1.2 equiv), added via syringe. The reaction was stirred at −78 °C for 30 min, and then at −78 °C ester-enol ether ***Z*-16** (1.0 g, 4.7 mmol in 3 mL THF) was added via cannula. The reaction was stirred at −78 °C for 30 min, then warmed to room temperature and stirred a further 60 min, then quenched (H_2O), extracted (Et_2O), the organics were washed (brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 20% EtOAc/hexane as eluent to give 450 mg of the desired product **17a** as an oil (1.42 mmol, 33%); ^{1}H NMR ($CDCl_3$): δ 1.12–1.25 (m, 1H), 1.43 (s, 9H), 1.45–1.98 (m, 9H), 2.64–2.82 (m, 3H), 3.50 (s, 3H), 4.01 (d, J = 1.2 Hz, 2H), 5.81 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.2, 23.0, 24.7, 26.0, 27.8, 31.2, 31.8, 42.4, 58.4, 58.82, 58.85, 61.2, 118.4, 140.2, 199.2.

***t*-Butyl sulfone trioxane 8a.** Trioxane **8a** was prepared according to General procedure 2 utilizing triphenyl phosphite (0.52 mL, 2.0 mmol, 2 equiv) in CH_2Cl_2 (40 mL) and keto-sulfone **17a** (0.32 g, 1.0 mmol) in CH_2Cl_2 (4.0 mL). TESOTf (0.28 mL, 1.2 mmol) in CH_2Cl_2 (2.0 mL) was used as the acid catalyst and the reaction was quenched with Et_3N (0.6 mL, 6 mmol). After work up, silica gel chromatography using 20:30% EtOAc/hexane as eluent yielded 104 mg (30%) of β-trioxane, followed by 29 mg (8%) of α-trioxane; **8a**, 12-α: ^{1}H NMR ($CDCl_3$): δ 1.09–1.28 (m, 4H), 1.41 (s, 9H), 1.57–1.77 (m, 7H), 1.82–1.89 (m, 1H), 2.33–2.48 (m, 2H), 2.66–2.74 (m, 1H), 3.27 (dd, J = 13.6, 32.4 Hz, 2H), 3.57 (s, 3H), 5.04 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.1, 23.2, 25.1, 26.5, 32.3, 33.3, 33.9, 45.2, 52.6, 56.0, 60.8, 84.6, 95.6, 102.8; **8a**, 12-β: ^{1}H NMR ($CDCl_3$): δ 1.12–1.29 (m, 2H), 1.42 (s, 9H), 1.57–1.74 (m, 7H), 1.83–1.95 (m, 2H), 2.41–2.59 (m, 2H), 3.33 (dd, J = 14.0, 27.6 Hz, 2H), 3.53 (s, 3H), 5.03 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.2, 23.7, 24.9, 26.1, 30.6, 35.3, 35.9, 47.1, 53.4, 57.1, 60.6, 84.4, 103.8, 104.5; HRMS calcd for $C_{16}H_{32}NO_6S$ ($M+NH_4^+$): 366.1950, found 366.1955.

Phenyl sulfone ketone 17b. A solution of methyl phenyl sulfone (0.26 g, 1.5 mmol) in THF (3.0 mL) at −78 °C was slowly treated with *n*-BuLi (1.6 M in hexane, 1.0 mL, 1.6 mmol), added via syringe. The reaction was stirred at −78 °C for 30 min, then at −78 °C ketone ***Z*-16** (0.29 g, 1.4 mmol in 1 mL THF) was added via cannula. The reaction was stirred at −78 °C for 1 h, warmed to room temperature (ca. 10 min), then quenched (H_2O), extracted (Et_2O), the organics were washed (brine), dried (Na_2SO_4) and concentrated. The crude product was chromatographed on a flash silica gel column with 30% EtOAc/hexane as eluent to give 244 mg of the desired product **17b** as an oil (0.73 mmol, 53%); ^{1}H NMR ($CDCl_3$): δ 1.11–1.24 (m, 1H), 1.43–1.93 (m, 9H), 2.52–2.68 (m, 2H), 2.70–2.77 (m, 1H), 3.49 (s, 3H), 4.17 (d, J = 3.2 Hz, 2H), 5.77 (d, J = 2.0 Hz, 1H), 7.55–7.60 (m, 2H), 7.65–7.71 (m, 1H), 7.88–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 24.9, 26.3, 28.1, 31.5, 32.1, 42.4, 59.2, 66.9, 118.7, 128.3, 129.2, 134.1, 138.8, 140.5, 198.8.

Phenyl sulfone trioxane 8b. Trioxane **8b** was prepared according to General procedure 2 utilizing triphenyl phosphite (0.26 mL, 1.0 mmol, 2 equiv) in CH_2Cl_2 (20 mL) and ketone **17b** (0.17 g, 0.50 mmol) in CH_2Cl_2 (2.0 mL). TESOTf (0.14 mL, 0.6 mmol) in CH_2Cl_2 (1.0 mL) was used as the acid catalyst and the reaction was quenched with Et_3N (0.3 mL, 3 mmol). After work up, silica gel chromatography using 15% EtOAc/hexane as eluent yielded 70 mg of **8b**, 12-β (0.19 mmol, 38%); ^{1}H NMR ($CDCl_3$): δ 1.06–1.24 (m, 2H), 1.52–1.66 (m, 7H), 1.72–1.84 (m, 2H), 2.30–2.39 (m, 1H), 2.44–2.51 (m, 1H), 3.20 (s, 3H), 3.57 (d, J = 3.6 Hz, 2H), 4.64 (s, 1H), 7.52–7.59 (m, 2H), 7.61–7.66 (m, 1H), 7.94–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 23.6, 24.8, 26.1, 30.5, 35.4, 36.2, 47.1, 57.0, 62.9, 84.3, 103.1, 104.4, 128.4, 128.9, 133.5, 140.8; HRMS calcd for $C_{18}H_{28}NO_6S$ ($M+NH_4^+$): 386.1637, found 386.1634.

Preparation of trioxanes 9a and 9b

***m*-Methylthiophenyl ketone 19.** 3-Bromothioanisole (619 mg, 3.05 mmol, 1.3 equiv) obtained from known methods[23] in diethyl ether (30 mL) at −78 °C was treated with *t*-butyllithium (1.7 M in pentane, 3.50 mL, 5.95 mmol, 2.5 equiv). After 20 min a solution of nitrile **18** (422 mg, 2.36 mmol, 1.0 equiv) in diethyl ether (20 mL) at −78 °C was added to the reaction via cannula. The reaction was continued for 4 h and then quenched with water (5 mL), transferred to a separatory funnel, extracted with diethyl ether (3×15 mL), washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (10% EtOAc in pet ether) to yield 512 mg of *m*-methylthiophenyl ketone **19** (1.69 mmol, 72%). ^{1}H NMR ($CDCl_3$): δ 7.82 (t, J = 1.6 Hz, 1H), 7.69 (dt, J = 7.6, 1.2 Hz, 1H), 7.34–7.44 (m, 2H), 5.79 (d, J = 2 Hz, 1H), 3.42 (s, 3H), 2.83–2.95 (m, 3H), 2.53 (s, 3H), 1.95–2.05 (m, 2H), 1.52–1.85 (m, 7H), 1.14–1.28 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 200.62, 140.65, 139.48, 137.99, 130.53, 128.91, 125.63, 124.79, 119.08, 59.25, 37.06, 32.75, 31.81, 28.40, 26.59, 25.94, 21.80, 15.76. HRMS calcd for $C_{18}H_{25}O_2S$ m/z ($M+H^+$): 304.1497, found 304.1494.

Sulfide trioxanes 9a. *m*-Methylthiophenyl ketone **19** (266 mg, 0.875 mmol, 1.0 equiv) was treated according to General procedure 2. TMSOTf (1.2 equiv) was used to effect rearrangement. The crude product was purified by silica gel chromatography (10% EtOAc in hexanes) to yield 8.7 mg **9a**, 12-α (0.026 mmol, 2.6%) and 37 mg **9a**, 12-β (0.11 mmol, 11.2%). **9a**, 12-α: ^{1}H NMR ($CDCl_3$): δ 7.46 (t, J = 1.6 Hz, 1H), 7.24–7.33 (m, 2H), 7.20 (dt,

$J=7.6$, 1.6 Hz, 1H), 5.18 (s, 1H), 3.61 (s, 3H), 2.78–2.86 (m, 1H), 2.48 (s, 3H), 2.40–2.44 (m, 1H), 2.25 (ddd, $J=14.4$, 4.4, 2.4, 1H), 1.84–1.94 (m, 1H), 1.60–1.82 (m, 6H), 1.18–1.30 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 141.45, 138.66, 128.80, 127.10, 123.59, 122.30, 104.02, 96.30, 83.90, 56.23, 45.59, 37.82, 33.58, 32.72, 27.35, 25.45, 23.35, 16.03. HRMS calcd for $C_{18}H_{25}O_4S$ m/z (M^+): 336.1395, found 336.1392. **9a**, 12-β: ^{1}H NMR ($CDCl_3$): δ 7.46 (t, $J=1.2$ Hz, 1H), 7.26–7.33 (m, 2H), 7.22 (dt, $J=6.4$, 2 Hz, 1H), 5.13 (d, $J=1.2$ Hz, 1H), 3.65 (s, 3H), 2.75 (ddd, $J=13.2$, 10.2, 3.6 Hz, 1H), 2.49 (s, 3H), 2.22–2.31 (m, 1H), 1.84–2.00 (m, 2H), 1.60–1.81 (m, 8H), 1.22–1.36 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 141.73, 138.68, 128.68, 126.99, 123.47, 122.16, 105.25, 105.08, 84.09, 57.39, 47.62, 39.41, 35.82, 30.99, 26.99, 25.22, 24.01, 16.03. HRMS calcd for $C_{18}H_{25}O_4S$ m/z (M^+): 336.1395, found 336.1395.

Sulfone trioxanes 9b. A solution of trioxane **9a**, 12-α (5.5 mg, 16 μmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at 0 °C was treated with *m*-CPBA (repurified from tech. grade, 12 mg, 68 μmol, 4.3 equiv). The reaction was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for an additional 30 min. The reaction was diluted with diethyl ether, washed with satd $NaHCO_3$ (aq), satd $NaHSO_3$ (aq), $NaHCO_3$ (aq), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (25% EtOAc in hexane) to yield 4 mg of **9b**, 12-α (11 μmol, 68%). ^{1}H NMR ($CDCl_3$): δ 8.17 (t, $J=1.6$ Hz, 1H), 7.92 (ddd, $J=8$, 2, 1.2 Hz, 1H), 7.83 (ddd, $J=8$, 2, 1.2 Hz, 1H), 7.58 (t, $J=7.6$ Hz, 1H), 5.20 (s, 1H), 3.62 (s, 3H), 3.04 (s, 3H), 2.82–2.90 (m, 1H), 2.40–2.44 (m, 1H), 2.23 (ddd, $J=14.8$, 4.4, 2 Hz, 1H), 1.88–1.94 (m, 2H), 1.70–1.84 (m, 4H), 1.20–1.31 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 142.60, 140.85, 130.87, 129.63, 127.82, 124.73, 103.52, 96.51, 84.29, 56.51, 45.50, 44.68, 37.74, 33.53, 32.68, 27.21, 25.39, 23.32. A solution of trioxane **9a**, 12-β (30 mg, 89 μmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C was treated with *m*-CPBA (repurified from tech. grade, 62 mg, 360 μmol, 4.0 equiv). The reaction was stirred at 0 °C for 1 h, warmed to RT, and stirred for an additional 30 min. The reaction was diluted with diethyl ether, washed with satd $NaHCO_3$ (aq), satd $NaHSO_3$ (aq), $NaHCO_3$ (aq), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (25% EtOAc in hexane) to yield 27.5 mg of **9b**, 12-β (75 μmol, 84%). ^{1}H NMR ($CDCl_3$): δ 8.14 (t, $J=1.6$ Hz, 1H), 7.92 (ddd, $J=8$, 1.6, 0.8 Hz, 1H), 7.82 (ddd, $J=8$, 1.6, 0.8 Hz, 1H), 7.57 (t, $J=7.6$ Hz, 1H), 5.14 (d, $J=1.6$ Hz, 1H), 3.66 (s, 3H), 3.05 (s, 3H), 2.79 (ddd, $J=14.4$, 13.2, 8 Hz, 1H), 2.25 (ddd, $J=10.8$, 4.4, 3.2 Hz, 1H), 1.88–2.02 (m, 2H), 1.58–1.82 (m, 6H), 1.14–1.36 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 142.82, 140.82, 130.83, 129.60, 127.79, 124.48, 105.32, 104.55, 84.36, 57.51, 47.52, 44.65, 39.34, 35.77, 30.93, 26.83, 25.11, 23.95. HRMS calcd for $C_{18}H_{28}NO_6S$ m/z ($M+NH_4^+$): 386.1637, found 386.1634.

Preparation of trioxanes 9c and 9d:

***p*-Methylthiophenyl ketone 19.** A solution of 4-bromothioanisole (1.02 g, 5.01 mmol, 1.3 equiv) in diethyl ether (20 mL) at −78 °C was then treated with *t*-butyllithium (1.7 M in pentane, 7.20 mL, 12.24 mmol, 2.4 equiv). After 45 min a solution of nitrile **18** (688 mg, 3.84 mmol, 1.0 equiv)[5] in diethyl ether (10 mL) at −78 °C was added to the reaction via cannula over 5 min. The reaction was continued overnight and then quenched with water (5 mL), transferred to a separatory funnel and extracted with diethyl ether (3×15 mL), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (10% EtOAc in hexanes) to yield 686 mg of *p*-methylthiophenyl ketone **19** (2.27 mmol, 59%) as a yellow oil which solidified upon refrigeration at −10 °C. ^{1}H NMR ($CDCl_3$): δ 7.85–7.88 (m, 2H), 7.24–7.26 (m, 2H), 5.79 (d, $J=2$ Hz, 1H), 3.42 (s, 3H), 2.80–2.95 (m, 3H), 2.51 (s, 3H), 1.95–2.05 (m, 2H), 1.50–1.76 (m, 7H), 1.14–1.28 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 199.87, 145.06, 140.36, 133.61, 128.39, 124.83, 119.03, 59.06, 36.61, 32.59, 31.62, 28.23, 26.40, 25.87, 21.51, 14.73. HRMS calcd for $C_{18}H_{24}O_2S$ m/z (M^+): 304.1497, found 304.1491.

***p*-Sulfide trioxanes 9 via singlet oxygen.** *p*-Methylthiophenyl ketone **19** (144 mg, 0.474 mmol, 1.0 equiv) was treated according to General procedure 1. TMSOTf (1.2 equiv) was used to effect rearrangement. The crude product was purified by silica gel chromatography (10% EtOAc in hexanes) and the diastereomers were further purified on silica gel semi-prep HPLC (2% EtOAc in hexanes, 3 mL/min) to yield 4 mg trioxane **9c**, 12-α (0.012 mmol, 2.5%) and 10 mg trioxane **9c**, 12-β(0.030 mmol, 6.3%). **9c**, 12-α^{1}H NMR ($CDCl_3$): δ 7.45–7.48 (m, 2H), 7.21–7.23 (m, 2H), 5.17 (s, 1H), 3.61 (s, 3H), 2.78–2.85 (m, 1H), 2.48 (s, 3H), 2.38–2.45 (m, 1H), 2.20–2.30 (m, 1H), 1.86–1.92 (m, 1H), 1.68–1.80 (m, 7H), 1.18–1.30 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 139.38, 137.22, 125.94, 125.88, 103.85, 96.15, 83.57, 56.09, 45.41, 37.47, 33.39, 32.53, 27.15, 25.26, 23.15, 15.52. **9c**, 12-β^{1}H NMR ($CDCl_3$): δ 7.45–7.49 (m, 2H), 7.21–7.25 (m, 2H), 5.13 (d, $J=1.6$ Hz, 1H), 3.64 (s, 3H), 2.73–2.82 (m, 1H), 2.48 (s, 3H), 2.35–2.43 (m, 1H), 1.86–2.02 (m, 3H), 1.60–1.80 (m, 5H), 1.17–1.35 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 139.56, 137.72, 126.17, 126.00, 105.33, 105.11, 83.97, 57.36, 47.65, 39.20, 35.81, 31.00, 27.00, 25.23, 24.03, 15.80. HRMS calcd for $C_{18}H_{25}O_4S$ m/z ($M+H^+$): 337.1474, found 337.1474.

***p*-Sulfide trioxane 9 via triphenylphosphite ozonide.** *p*-Methylthiophenyl ketone **19** (136 mg, 0.448 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) was treated according to General procedure 2 utilizing triphenyl phosphite (295 mg, 0.951 mmol, 2.1 equiv) in CH_2Cl_2 (30 mL). TMSOTf (1.2 equiv) in CH_2Cl_2 was used to effect rearrangement and the reaction was quenched with sodium methoxide (3.2 equiv, 25 wt% in methanol). After work up, the crude product was purified by silica gel chromatography (10% EtOAc in hexane) to yield 10 mg of **9c**, 12-α (0.030 mmol, 7%) and 1 mg **9c**, 12-β (0.003 mmol, 0.7%). Spectral data as reported above.

Trioxanes 9d, 12-β. A solution of trioxane **9c**, 12-β (5 mg, 15 μmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at 0 °C was treated with *m*-CPBA (repurified from tech. grade, 11 mg,

63 μmol, 4.2 equiv). The reaction was stirred at 0 °C for 15 min, warmed to room temperature, stirred for 2.5 h then diluted with diethyl ether. The solution was washed with satd $NaHCO_3$ (aq), satd $NaHSO_3$ (aq), $NaHCO_3$ (aq), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel semi-prep HPLC (50% EtOAc in hexane, 3 mL/min) to yield 4 mg **9d**, 12-β (11 μmol, 78%) as a white solid (mp 137–139 °C). ^1H NMR ($CDCl_3$): δ 7.93–7.96 (m, 2H), 7.73–7.77 (m, 2H), 5.14 (d, $J=1.6$ Hz, 1H), 3.66 (s, 3H), 3.04 (s, 3H), 2.73–2.82 (m, 1H), 2.18–2.25 (m, 1H), 1.88–2.02 (m, 2H), 1.62–1.74 (m, 6H), 1.20–1.35 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 146.80, 140.79, 127.63, 126.39, 105.28, 104.65, 84.48, 57.48, 47.55, 44.70, 39.47, 35.79, 30.94, 26.89, 25.14, 23.97. HRMS calcd for $C_{18}H_{25}O_6S$ m/z ($M+H^+$): 369.1372, found 369.1371.

Preparation of trioxane 10

3-Bromo-*N,N*-dimethylbenzenesulfonamide. A solution of 3-bromobenzenesulfonyl chloride (932 mg, 3.65 mmol, 1.0 equiv, purchased from Lancaster Synthesis, Ltd.) in THF (35 mL) at 0 °C was treated with dimethylamine (2.0 M in THF, 5.5 mL, 11.0 mmol, 3.0 equiv) and stirred overnight at room temperature. The reaction mixture was then transferred to a separatory funnel and washed with water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product mixture was recrystallized from diethyl ether/pet ether to yield 927 mg 3-bromo-*N,N*-dimethylbenzenesulfonamide (3.50 mmol, 96%) as a white crystalline solid (mp 86–87 °C). ^1H NMR ($CDCl_3$): δ 7.93 (t, $J=2$ Hz, 1H), 7.23 (m, 2H), 7.43 (t, $J=8$ Hz, 1H), 2.74 (s, 6H). Anal. Calcd for $C_8H_{10}BrNO_2S$: C, 36.28; H, 3.82; N, 5.30, found C, 36.49; H, 3.72; N, 5.21.

***m*-Benzenesulfonamide ketone 20.** A solution of nitrile **18** (734 mg, 4.10 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C was treated with DIBAL-H (1.5 M in toluene, 3.7 mL, 5.54 mmol, 1.35 equiv) and stirred for 4 h at 0 °C. The reaction mixture was then diluted with diethyl ether (80 mL), quenched with water (10–15 mL) and stirred for 15 min, during which time the reaction mixture went from clear to cloudy. The contents were transferred to a separatory funnel and the aqueous layer was extracted with diethyl ether (4×), the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product mixture was purified by flash silica gel chromatography (25% EtOAc in pet ether) to yield 347 mg of the resulting aldehyde (1.91 mmol, 47%) as a clear colorless oil. Spectral data is consistent with that reported in the literature.[24] A solution of 3-bromo-*N,N*-dimethylbenzenesulfonamide (752 mg, 2.84 mmol, 1.04 equiv) in THF (28 mL) at −78 °C was then treated with freshly titrated *t*-butyllithium (1.69 M in pentane, 3.35 mL, 5.70 mmol, 2.08 equiv). After 10 min a solution of the above aldehyde (499 mg, 2.74 mmol, 1.0 equiv) in THF (14 mL) at −78 °C was added to the reaction via cannula over 15 min. After 60 min at −78 °C the majority of the starting aldehyde was consumed as indicated by TLC analysis (40% EtOAc in petroleum ether; *p*-anisaldehyde stain). The reaction was continued at 0 °C for 3 h and then quenched by pouring the reaction mixture into water (15 mL) in a separatory funnel. The aqueous layer was extracted with diethyl ether (4×), a brine solution was added and another diethyl ether extraction was performed. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was passed through a plug of flash silica gel (40% EtOAc in pet ether) to yield 710 mg of the crude alcohol which was confirmed by ^1H NMR to be an equal mixture of the four possible diastereomers. This crude alcohol (568 mg, 1.55 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (15 mL) at room temperature. To this solution NMO (543 mg, 4.63 mmol, 3.0 equiv), MS 4A, and TPAP (8 mg, 0.02 mmol, 0.01 equiv) were added. The solution turned greenish brown upon addition of TPAP, and as the reaction was stirred at RT the color darkened to brown. TLC analysis after 4 h indicated consumption of starting material. The reaction mixture was passed through a plug of silica gel (25% EtOAc in pet ether) and then further purified by flash silica gel chromatography (25% EtOAc in pet ether) to yield 483 mg of ketone **20** (1.32 mmol, *E*:*Z*:1:1, 28% overall yield) as a clear colorless oil. ^1H NMR ($CDCl_3$): δ 8.30–8.32 (m, 2H), 8.16–8.19 (m, 2H), 7.93–7.98 (m, 2H), 7.65–7.70 (m, 2H), 5.79 (d, $J=2$ Hz, 1H), 5.74 (s, 1H), 3.50 (s, 3H), 3.39 (s, 3H), 2.88–3.04 (m, 4H), 2.75 (s, 6H), 2.74 (s, 6H), 2.29 (dt, $J=13.6$, 4.8 Hz, 2H), 1.94–2.10 (m, 6H), 1.48–1.86 (m, 12H), 1.32–1.42 (m, 1H), 1.16–1.27 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 199.25, 199.11, 140.77, 139.88, 138.28, 138.01, 136.65, 136.48, 132.02, 131.96, 131.54, 131.34, 129.66, 129.52, 127.09, 119.69, 118.78, 59.45, 59.19, 38.60, 37.98, 37.18, 37.10, 33.63, 32.58, 31.75, 28.26, 27.30, 26.52, 26.08, 25.67, 23.03, 22.67, 21.76. FTIR (cm^{-1}): 2927.0, 2853.8, 1692.9, 1460.0, 1345.7, 954.8. HRMS: calcd for $C_{19}H_{28}NO_4S$ m/z ($M+H^+$): 366.1735, found 366.1739.

Trioxanes 10a and 10b. Trioxanes **10a** and **10b** were prepared according to General procedure 2 utilizing triphenyl phosphite (450 mg, 1.45 mmol, 2.0 equiv) in CH_2Cl_2 (50 mL) and ketone **20** (269 mg, 0.736 mmol, 1.0 equiv) in CH_2Cl_2 (10.5 mL). TMSOTf (148 μL, 0.810 mmol, 1.1 equiv) in CH_2Cl_2 (5.5 mL) was used to effect rearrangement and the reaction was quenched with sodium methoxide (25 wt% in methanol, 125 μL, 2.21 mmol, 3.0 equiv). After work up, the crude product mixture was purified by flash silica gel chromatography (20–25% EtOAc in pet ether) to yield three major fractions which were columned again to obtain further separation of the product from impurities. The pure product was obtained after silica gel semi-prep HPLC separation to yield 10 mg of **10a**, 12-α (0.026 mmol, 3.5%) and 9 mg of **10b**, 12-β (0.023 mmol, 3%) as colorless oils. **10a**: ^1H NMR ($CDCl_3$): δ 7.99 (dt, $J=1.6$, 0.4 Hz, 1H), 7.73–7.80 (m, 2H), 7.54 (dt, $J=7.6$, 0.4 Hz, 1H), 5.20 (s, 1H), 3.61 (s, 3H), 2.82–2.90 (m, 1H), 2.68 (s, 6H), 2.39–2.42 (m, 1H), 2.17–2.24 (m, 1H), 1.88–1.92 (m, 1H), 1.59–1.84 (m, 4H), 1.67–1.29 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 142.20, 135.75, 129.74, 129.23, 128.16, 124.96, 103.61, 96.45, 84.28, 56.34, 45.55, 38.12, 37.90, 33.55, 32.69, 27.24, 25.39, 23.32. HRMS: calcd for $C_{19}H_{28}NO_6S$ m/z ($M+H^+$): 398.1637, found 398.1638.

HPLC retention time (Rainin Instrument Co, DYNAMAX-60A silica gel semi-prep column, 25% EtOAc in hexane, 3 mL/min): 24.8 min. **10b**: ^{1}H NMR ($CDCl_3$): δ 7.94 (t, J = 1.2 Hz, 1H), 7.74–7.81 (m, 2H), 7.55 (t, J = 8.0 Hz, 1H), 5.14 (d, J = 1.2 Hz, 1H), 3.65 (s, 3H), 2.79 (ddd, J = 14.4, 13.2, 3.6 Hz, 2H), 2.70 (s, 6H), 2.23–2.29 (m, 1H), 1.89–2.03 (m, 2H), 1.63–1.86 (m, 5H), 1.21–1.40 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 142.48, 135.87, 129.63, 129.20, 128.10, 124.82, 105.31, 104.65, 84.38, 57.42, 47.58, 39.38, 38.12, 35.81, 30.96, 26.89, 25.16, 23.99. HRMS calcd for $C_{19}H_{28}NO_6S$ m/z ($M+H^+$): 398.1637, found 398.1638. HPLC retention time (Rainin Instrument Co, DYNAMAX-60A silica gel semi-prep column, 25% EtOAc in hexanes, 3 mL/min): 15.7 min.

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