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Article

Mechanistic Evaluation of the Stability of Arylvinyl-1,2,4-trioxanes under Acidic Conditions for Their Oral Administration as an Antimalarial Drug

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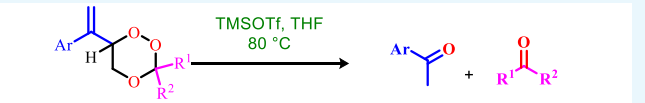
ABSTRACT: A mechanistic approach to understand the course of metabolism for synthetic 1,2,4-trioxanes, potent antimalarial compounds, to evaluate their bioavailability for antimalarial action has been studied in the present work. It is an important parameter to study the course of metabolism of a drug candidate molecule when administered via oral route during its journey from oral intake to its target site. From the pharmacokinetics point of view, it determines the bioavailability of an active drug or a prodrug at the target point. In this work, synthetic arylvinyl-1,2,4-trioxanes **1a−u** have been evaluated under various acidic conditions to mimic the milieu of the stomach (pH between 1.5 and 3.5) through which they have to pass when administered orally. The effect of acid on trioxanes led to their degradation into corresponding ketones and glyoxal. Under such acidic conditions glyoxal polymerized to form a nonisolable condensate product. The study indicates that the actual bioavailability of the drug is far less than the administered dose.



21 examples on the stability of various 1,2,4-trioxanes under acidic condition

INTRODUCTION

Malaria still remains an unbeatable disease due to the development of resistance against commonly available antimalarials and accounts for 241 million clinical cases around the world mostly in low-income areas.[1] Artemisinin,[2−7] a sesquiterpene lactone endoperoxide isolated from Chinese traditional medicinal herb *Artemisia annua*, and its semi-synthetic derivatives (e.g., arteether and artemether) are presently the drugs of choice for the treatment of multidrug resistant malaria (Figure 1).

These compounds are fast acting and are currently the drugs of choice for the treatment of cerebral malaria caused by multidrug-resistant *Plasmodium falciparum*. While these drugs show excellent activity by the parenteral route, the extra acetal−lactone or acetal−acetal linkages are linked with their poor hydrolytic stability under the acidic environment of the stomach and therefore poor absorption by the oral route.[8]

The discovery of peroxide present in the form of 1,2,4-trioxanes in artemisinin as an active pharmacophore for its antimalarial activity has encouraged scientists to develop simple, economical, and effective substitutes having a 1,2,4-trioxane unit. Since then, numerous simple molecules containing 1,2,4-trioxanes (Scheme 1) have been synthesized and evaluated for antimalarial activity by different groups including us.[9−29]

For a drug to be effective via oral or intramuscular administration, it should reach the target site in the form of an active species that can interact with pathogens in infected cells. For trioxanes, the active species is 1,2,4-trioxane, which interacts with the hemoglobin present in infected red blood cells and creates peroxy free radicals resulting in an oxidative atmosphere, which kills the malarial parasite present in cells.[30−37] During the course of its journey to the affected cells, the drug has to survive both acidic and basic environments in the body. If administered orally, it has to survive the strongly acidic environment of the stomach (pH 1.5−3.5), then the basic environment of bile juices (pH 7.5−8.5), and then in cells the basic environment of amino acids. Singh and Malik reported earlier the effect of basic conditions on 1,2,4-trioxanes (Scheme 2), which resulted in the generation of the corresponding ketones.[38,39] In continuation of that study, herein, we report the effect of acidic conditions on the stability of synthetic aryl vinyl-1,2,4-trioxanes thus mimicking the conditions that can prevail in the body. In the present study, the temperature has also been examined along with acidic conditions as certain activation energy is required to initiate the reaction, which is accomplished by various enzymes in the body in actual conditions thus bringing down the activation energy required to initiate the reaction.[40]

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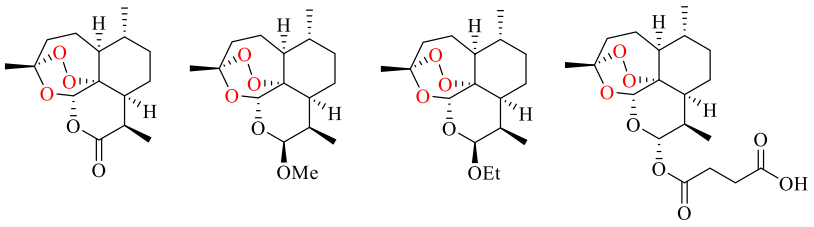
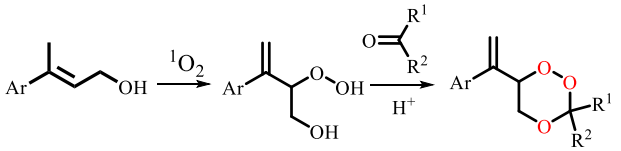


Figure 1. Artemisinin and its semisynthetic derivatives.

Scheme 1. Preparation of 6-Arylvinyl-1,2,4-trioxanes



CHEMISTRY

Naphthyloxy phenyl vinyl trioxane **1a** was used as a model to explore the scope of the reaction. Initially, we investigated the effect of different acids on the stability of trioxane; among them TMSOTf emerged as the most effective for the generation of the corresponding ketones from the trioxane (Table 1, entry 8). *p*-TSA and $BF_3{\cdot}Et_2O$ required a little longer time, 2.5 h, for the transformation of trioxane **1a** into ketone **2a** (Table 1, entries 1 and 3).[41−43] Amberlyst-15 took 3 h for the transformation to ketone **2a** (Table 1, entry 4). Concentrated HCl showed slow conversion of trioxane **1a** into **2a**, even after 16 h, only a trace of ketone **2a** was observed (Table 1, entry 2). Other acids, $HClO_4$, $TiCl_4$, and $AlCl_3$, showed decent conversion into ketones with longer duration of reaction (Table 1, entries 5, 6, and 7). We have screened different solvents for feasibility of the reaction with the TMSOTf and found that THF is the most appropriate solvent for catalysis, giving 52% of ketone **2a** and 88% of ketone **3a** (Table 1, entry 8). Use of other common solvents such as MeCN, DCM, EtOAc, toluene, and DMF allowed transformation to the corresponding ketones with longer reaction duration (Table 1, entries 9−13). Then, we optimized different equivalents of TMSOTf for catalytic activity and found that 0.1 equiv of TMSOTf required 1 h for completion of reaction while 0.01 equiv of TMSOTf required a longer reaction time with comparatively low yield. The 0.2 equiv amount was found to be the optimal conditions with excellent yield. We have monitored the stability of trioxane at room temperature for 48 h under TMSOTf condition and found no remarkable changes to the trioxane (Scheme 3). Moreover, the transformation of trioxane **1a** to ketones **2a** and **3a** did not take place in the absence of acid, which showed that the presence of some acid is essential to move the reaction in a forward direction (Table 1, entry 17).[44]

We have also explored the scope of reaction on different trioxanes to gain insight on the effect of acid on transformation to corresponding ketones. To our delight, we found that most of the trioxanes in the presence of TMSOTf gave the corresponding aromatic and aliphatic ketones in good to excellent yield with shorter reaction time (Table 2, entries 1−21). We have explored the effect of TMSOTf on different ether derivatives of mono-1,2,4-trioxanes **1a−l**, which resulted in the corresponding ether ketones **2a−d** and aliphatic ketones **3a−c** in good to excellent yield in shorter reaction time (Scheme 1, Table 2, entries 1−12). We have also screened the outcome of bis-trioxanes **1m−u** in the presence of TMSOTf, which resulted in the corresponding bis-ketones **2e−g** and aliphatic ketones **3a−c** in good yield with a little longer duration (Table 2, entries 13−21).

RESULTS AND DISCUSSION

A general plausible mechanism for this acid-catalyzed rearrangement of substituted arylvinyl-1,2,4-trioxanes is shown in Scheme 4 taking arylvinyl-trioxane **1a** as a representative compound, which involves protonation of peroxy oxygen followed by ring opening to furnish aliphatic ketone **3a,** coupled with migration of the phenylvinyl group to electropositive oxygen with subsequent cyclization to furnish an unstable epoxy product, which gets hydrolyzed to furnish the corresponding ketone **2a**.

This study suggests that during oral administration of an active drug or prodrug, it has to first of all survive the strongly acidic conditions of the stomach (pH 1.5−3.5), during its journey to the target site. The mechanism shown suggests how 1,2,4-trioxanes behave under such acidic conditions.

By virtue of this study, we have tried to show the effect of acidic conditions on the stability of synthetic arylvinyl-1,2,4-trioxanes by mimicking the conditions that can prevail in the

Scheme 2. Stability of 1,2,4-Trioxanes under Basic Conditions

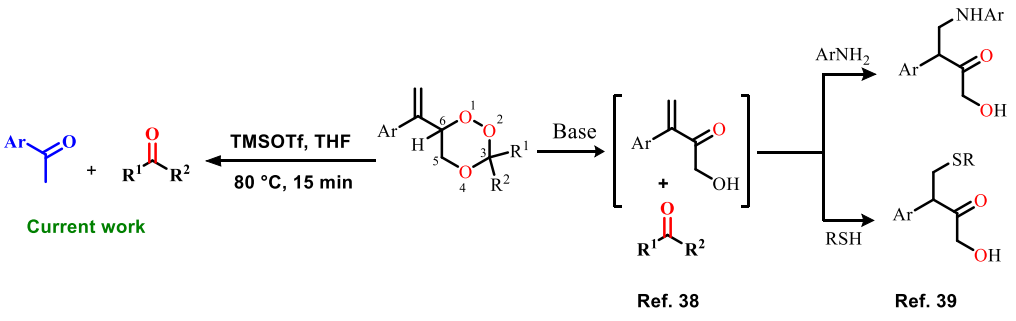


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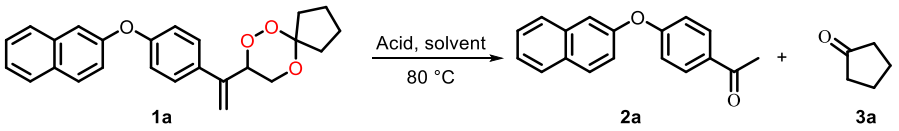
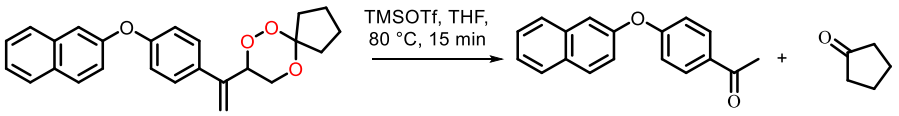
Table 1. Screening of Different Reaction Conditions for the Exploration of Acid Effects on Arylvinyl-1,2,4-trioxanes[a]



				product yield[b] (%)	
entry	acid	solvent	time	2a	3a
1	*p*-TSA	THF	2 h	32	69
2	concn HCl	THF	16 h	4	7
3	$BF_3{\cdot}Et_2O$	THF	2.5 h	38	72
4	Amberlyst-15	THF	3 h	32	78
5	$HClO_4$	THF	6 h	36	70
6	$TiCl_4$	THF	4 h	40	77
7	$AlCl_3$	THF	7 h	42	79
8[f]	**TMSOTf**	**THF**	**15 min**	**52**	**88**
9	TMSOTf	MeCN	12 h	10	69
10	TMSOTf	DCM	8 h	15	60
11	TMSOTf	EtOAc	5 h	5	72
12	TMSOTf	toluene	7 h	10	59
13	TMSOTf	DMF	6 h	10	69
14[c]	TMSOTf	THF	1 h	49	77
15[d]	TMSOTf	THF	3 h	45	75
16[e]	TMSOTf	THF	48 h	*g*	*g*
17		THF	48 h	*g*	*g*

[a]Reaction conditions: trioxane (1 equiv), solvent (1.0 mL), and TMSOTf (0.2 equiv) at 80 °C. [b]Isolated yield. [c]0.1 equiv of TMSOTf. [d]0.01 equiv of TMSOTf. [e]0.2 equiv of TMSOTf at room temperature. [f]Bold indicates the optimal reaction condition. [g]No reaction.

Scheme 3. Stability of 1,2,4-Trioxanes under Acidic Conditions



alimentary canal. In this study, elevated temperature has also been provided along with acidic conditions as a minimum amount of activation energy is required to initiate the reaction, which in actual *in vivo* conditions is affected by various enzymes in the body, which catalyze the reaction, thus bringing down the activation energy required to initiate the degradation process.

Thus, the study indicates that the actual bioavailability of active drug at the target site is far less than orally administered dose.[45]

CONCLUSION

In the present study, we have reported the effect of acidic conditions on the stability of arylvinyl-1,2,4-trioxanes, potent antimalarial agents, by reacting them with various acids. The main idea of this study was actually to mimic the acidic conditions prevailing in the stomach (pH 1.5−3.5) by artificially creating such conditions to evaluate the effect of such conditions on orally administered arylvinyl-1,2,4-trioxanes.We also analyzed the mechanistic behavior of these trioxanes under such conditions, which resulted in the generation of corresponding parent ketones from which the trioxanes were synthesized. The study revealed that actual bioavailability of the active drug, arylvinyl-1,2,4-trioxane, at the target site is far less than the orally administered dose. This study can pave the way to evaluate other synthetic peroxides under acidic conditions. We believe the outcome from the exploration of trioxanes under acidic conditions assists scientists in finding a better oral bioavailability profile of trioxane for malaria chemotherapy.

EXPERIMENTAL SECTION

All glass apparatus were oven-dried prior to use. Melting points were taken in open capillaries on Complab melting point apparatus and have been presented uncorrected. Infrared spectra were recorded on a PerkinElmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Supercon Magnet DPX-200, DRX-300, or AVANCE-III-HD 400 spectrometers (operating at 200, 300, and 400 MHz, respectively, for ^{1}H; 50, 75, and 100 MHz, respectively, for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) and $CDCl_3$ (δ 77.0 ppm) served as an internal standard in ^{1}H NMR and ^{13}C NMR, respectively. Chemical shifts have been reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quintet (quin), multiplet (m), and broad (br). Electrospray mass spectra (ES-MS) were recorded on a Micro mass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectra (ESI-HRMS) were obtained on Bruker Compass and TOF MS. Elemental analyses were performed on Vario EL-III C H N S analyzer (Germany), and values were within range (0.4% of the calculated values). Column chromatography was performed over Merck silica gel (particle size 60−120 mesh) procured

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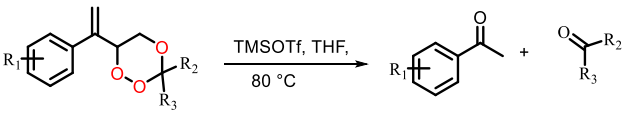
Table 2. Exploration of Different Arylvinyl-1,2,4-trioxanes with TMSOTf



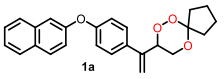
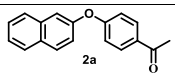
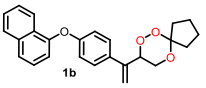
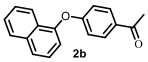
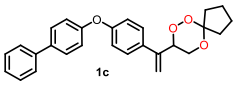
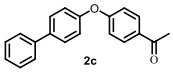
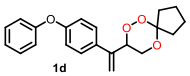
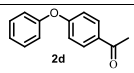
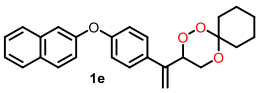
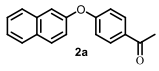
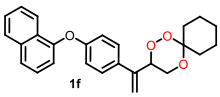
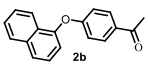
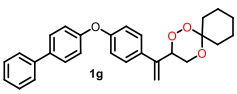
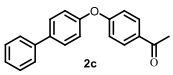
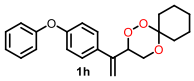
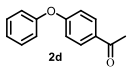
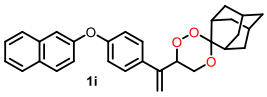
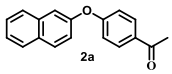
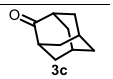
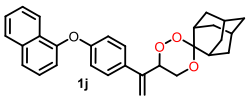
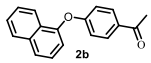
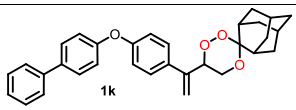
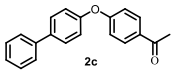
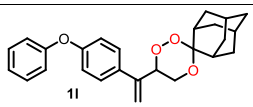
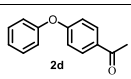
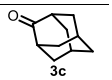
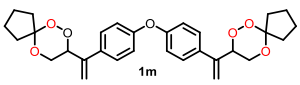
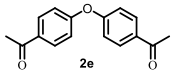
Entry	Trioxane	Time	Products	
			Aromatic ketone	Aliphatic ketone
1	 1a	15 min	 2a 52%	 3a 88%
2	 1b	20 min	 2b 45%	 3a 75%
3	 1c	20 min	 2c 48%	 3a 70%
4	 1d	20 min	 2d 49%	 3a 69%
5	 1e	15 min	 2a 50%	 3b 70%
6	 1f	20 min	 2b 49%	 3b 50%
7	 1g	20 min	 2c 45%	 3b 52%
8	 1h	20 min	 2d 44%	 3b 54%
9	 1i	20 min	 2a 42%	 3c 81%
10	 1j	25 min	 2b 38%	 3c 70%
11	 1k	30 min	 2c 36%	 3c 62%
12	 1l	35 min	 2d 30%	 3c 81%
13	 1m	1 h	 2e 42%	 3a 70%
14	1n	1.5 h	2f 38%	3a 66%

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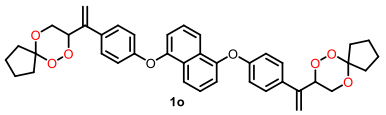
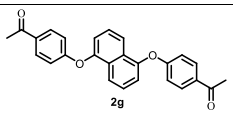
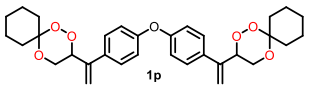
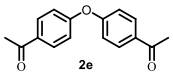
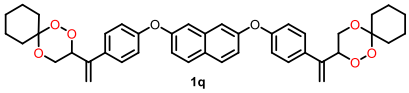
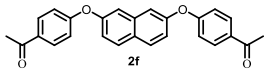
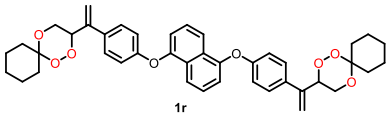
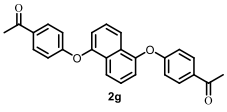
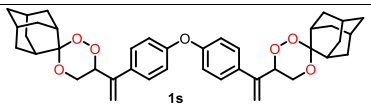
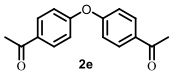
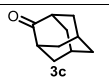
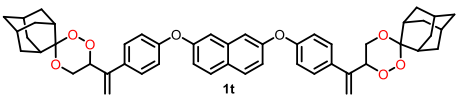
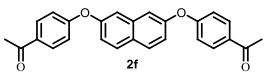
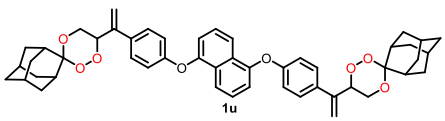
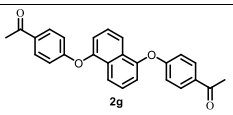
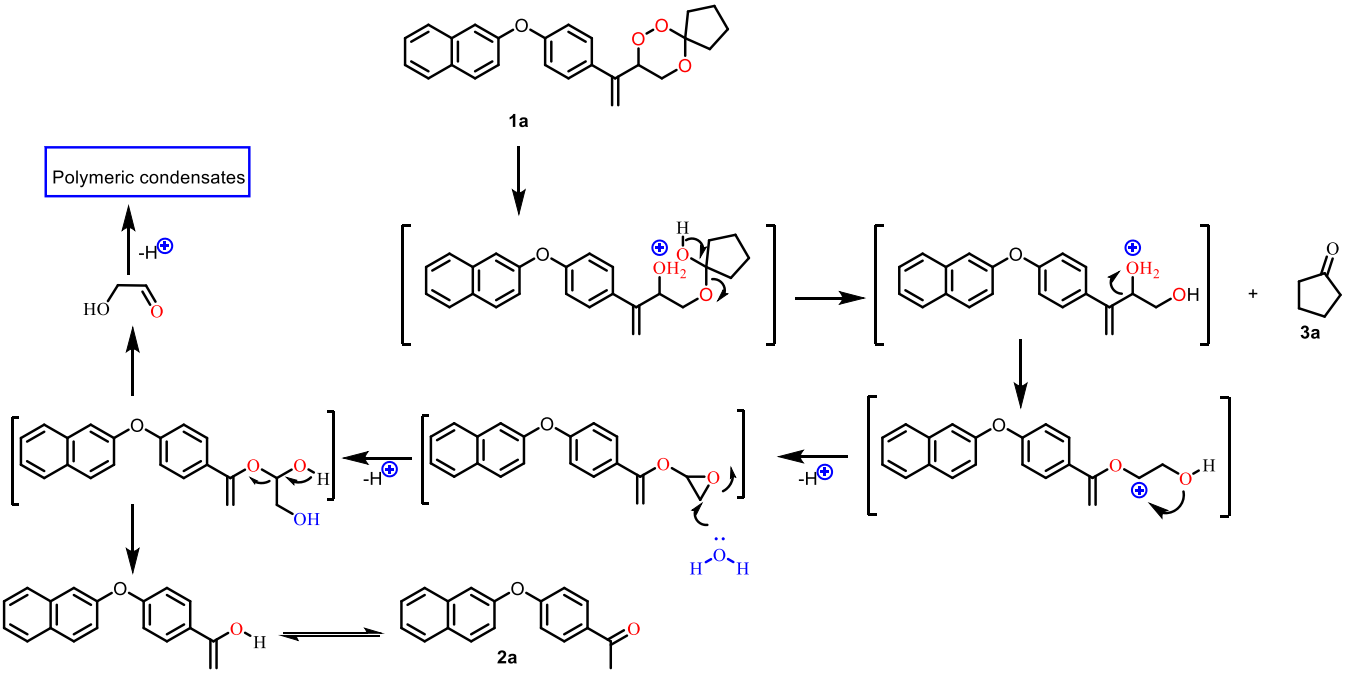
Table 2. continued

Entry	Trioxane	Time	Products	
			Aromatic ketone	Aliphatic ketone
15	 1o	1.5 h	 2g 40%	 3a 67%
16	 1p	1 h	 2e 45%	 3b 63%
17	 1q	1.5 h	 2f 48%	 3b 60%
18	 1r	1.5 h	 2g 44%	 3b 62%
19	 1s	1.5 h	 2e 38%	 3c 80%
20	 1t	1.5 h	 2f 34%	 3c 75%
21	 1u	1.5 h	 2g 31%	 3c 69%

Scheme 4. Plausible Mechanism for Acid-Catalyzed Rearrangement of Substituted Arylvinyl-1,2,4-trioxanes



from Qualigens (India) or flash silica gel (particle size 230−400 mesh). All chemicals and reagents were obtained from Aldrich (Milwaukee, WI), Lancaster (England), or Spectrochem (India) and were used without further purification. Nomenclature and log *p* values of the compounds were assigned using ChemDraw Professional 15.1.

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General Procedure for Exploration of TMSOTf Effect on Arylvinyl-1,2,4-trioxanes. TMSOTf (9 μL, 0.2 equiv) was added to a stirred solution of trioxane **1a** (100 mg, 0.257 mmol) in THF (2 mL). The reaction mixture was stirred at 80 °C, and progress of the reaction was monitored by TLC. After completion of the reaction, it was cooled to room temperature; reaction mixture was quenched with water (2 mL), extracted with EtOAc, dried over anhydrous Na_2SO_4, and concentrated. Column chromatography was done to obtain pure corresponding ketone products.

All the 1,2,4-trioxanes, **1a−u**, were prepared by the reported procedure. The obtained analytical data for compounds **1a−i**, **1k−u**, and **2a−g** are in agreement with the reported literature.[10,16]

*8-{1-[4-(Naphthalen-2-yloxy)-phenyl]-vinyl}-6,7,10-trioxa-spiro[4.5]decane (**1a**).* White solid was obtained in 27% yield; mp 87−90 °C; IR (KBr, cm^{-1}) 1591; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.68−1.96 (m, 7H), 2.51−2.57 (m, 1H), 3.86 (d, 2H, *J* = 5.8 Hz), 5.30−5.33 (m, 2H), 5.51 (s, 1H), 7.05 (d, 2H, Ar, *J* = 8.8 Hz), 7.27−7.29 (m, 1H, Ar), 7.37−7.51 (m, 5H, Ar), 7.75 (d, 1H, Ar, *J* = 8 Hz), 7.86 (t, 2H, Ar, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.58 (CH_2), 24.99 (CH_2), 33.00 (CH_2), 37.24 (CH_2), 66.25 (CH_2), 80.48 (CH), 114.81 (C), 116.12 (CH_2), 118.99 (CH), 120.25 (CH), 125.08 (CH), 126.80 (CH), 127.37 (CH), 127.97 (CH), 128.11 (CH), 130.19 (CH), 130.51 (C), 133.79 (C), 134.49 (C), 142.66 (C), 154.75 (C), 157.58 (C); FAB-MS (*m*/*z*) 389 $[M + H]^+$; HRMS calcd for $C_{25}H_{24}O_4$ 388.1675, found 388.1674. Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23%. Found: C, 77.35; H, 6.28.

*8-{1-[4-(Naphthalen-1-yloxy)-phenyl]-vinyl}-6,7,10-trioxa-spiro[4.5]decane (**1b**).* Compound **1b** was obtained in 49% yield as oil; IR (neat, cm^{-1}) 1599; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67−1.93 (m, 7H), 2.48−2.55 (m, 1H), 3.86 (d, 2H, *J* = 5.8 Hz), 5.27−5.30 (m, 2H), 5.46 (s, 1H), 6.98−7.02 (m, 3H, Ar), 7.36−7.45 (m, 3H, Ar), 7.47−7.55 (m, 2H, Ar), 7.65 (d, 1H, Ar, *J* = 8.2 Hz), 7.88 (d, 1H, Ar, *J* = 7.4 Hz), 8.15 (d, 1H, Ar, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.57 (CH_2), 24.99 (CH_2), 32.99 (CH_2), 37.24 (CH_2), 65.26 (CH_2), 80.47 (CH), 114.31 (CH), 114.79 (C), 115.97 (CH_2), 118.37 (CH), 122.22 (CH), 124.00 (CH), 126.00 (CH), 126.27 (CH), 126.86 (CH), 127.09 (C), 128.02 (CH), 128.08 (CH), 133.48 (C), 135.15 (C), 142.67 (C), 152.69 (C), 158.32 (C); FAB-MS (*m*/*z*) 389 $[M + H]^+$; HRMS calcd for $C_{25}H_{24}O_4$ 388.1674, found 388.1672. Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23. Found: C, 77.36; H, 6.28.

*8-{1-[4-(Biphenyl-4-yloxy)-phenyl]-vinyl}-6,7,10-trioxa-spiro[4.5]decane (**1c**).* Compound **1c** was obtained in 29% yield as oil; IR (KBr, cm^{-1}) 1598; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67−1.95 (m, 7H), 2.51−2.58 (m, 1H), 3.88 (d, 2H, *J* = 6.1 Hz), 5.30−5.33 (m, 2H), 5.49 (s, 1H), 7.04 (d, 2H, Ar, *J* = 8.6 Hz), 7.11 (d, 2H, Ar, *J* = 8.6 Hz), 7.33−7.47 (m, 5H, Ar), 7.57−7.61 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.56 (CH_2), 24.97 (CH_2), 32.97 (CH_2), 37.21 (CH_2), 65.21 (CH_2), 80.43 (CH), 114.77 (C), 116.05 (CH_2), 118.87 (CH), 119.51 (CH), 127.09 (CH), 127.28 (CH), 128.06 (CH), 128.67 (CH), 128.98 (CH), 133.70 (C), 136.80 (C), 140.60 (C), 142.62 (C), 156.50 (C), 157.50 (C); ESI (*m*/*z*) 415 $[M + H]^+$; HRMS calcd for $C_{27}H_{26}O_4$ 414.1831, found 414.1834. Anal. Calcd for $C_{27}H_{26}O_4$: C, 78.24; H, 6.32. Found: C, 78.29; H, 6.37.

*8-[1-(4-Phenoxy-phenyl)-vinyl]-6,7,10-trioxa-spiro[4.5]-decane (**1d**).* White solid was obtained in 27% yield; mp 51−52 °C; IR (KBr, cm^{-1}) 1590; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66−1.93 (m, 7H), 2.48−2.55 (m, 1H), 3.85 (d, 2H, *J* = 6.0 Hz), 5.27−5.30 (m, 2H), 5.46 (s, 1H), 6.96 (d, 2H, Ar, *J* = 8.6 Hz), 7.02 (d, 2H, Ar, *J* = 7.6 Hz), 7.12 (t, 1H, Ar, *J* = 7.4 Hz), 7.33−7.38 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.57 (CH_2), 24.98 (CH_2), 32.99 (CH_2), 37.23 (CH_2), 65.25 (CH_2), 80.48 (CH), 114.80 (C), 116.00 (CH_2), 118.75 (CH), 119.38 (CH), 123.80 (CH), 128.03 (CH), 130.02 (CH), 133.57 (C), 142.67 (C), 156.95 (C), 157.64 (C); FAB-MS (*m*/*z*) 339 $[M + H]^+$; HRMS calcd for $C_{21}H_{22}O_4$ 338.1518; found 338.1529. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.61; H, 6.58.

*3-{1-[4-(Naphthalen-2-yloxy)-phenyl]-vinyl}-1,2,5-trioxa-spiro[5.5]undecane (**1e**).* White solid was obtained in 43% yield; mp 108−110 °C; IR (KBr, cm^{-1}) 1596; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40−1.66 (m, 8H), 1.96−2.02 (m, 1H), 2.21−2.26 (m, 1H), 3.77 (dd, 1H, *J* = 11.9 and 2.9 Hz), 3.98 (dd, 1H, *J* = 11.8 and 10.6 Hz), 5.22 (dd, 1H, *J* = 10.3 and 2.7 Hz), 5.28 (s, 1H), 5.47 (s, 1H), 7.01 (d, 2H, Ar, *J* = 8.7 Hz), 7.22−7.25 (m, 1H, Ar), 7.32−7.46 (m, 5H, Ar), 7.70 (d, 1H, Ar, *J* = 8 Hz), 7.81 (t, 2H, Ar, *J* = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.49 (CH_2), 22.54 (CH_2), 25.73 (CH_2), 29.20 (CH_2), 34.85 (CH_2), 62.86 (CH_2), 80.46 (CH), 102.85 (C), 114.73 (CH), 116.03 (CH_2), 119.03 (CH), 120.23 (CH),125.07 (CH), 126.80 (CH), 127.37 (CH), 127.97 (CH),128.10 (CH), 130.18 (CH), 130.50 (C), 133.92 (C), 134.49 (C), 142.88 (C), 154.79 (C), 157.54 (C); FAB-MS (*m*/*z*) 403 $[M + H]^+$; HRMS calcd for $C_{26}H_{26}O_4$ 402.1831; found 402.1828. Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 77.65; H, 6.56.

*3-{1-[4-(Naphthalen-1-yloxy)-phenyl]-vinyl}-1,2,5-trioxa-spiro[5.5]undecane (**1f**).* This was obtained in 50% yield as oil; IR (Neat, cm^{-1}) 1598; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44−1.65 (m, 8H), 2.01−2.05 (m, 1H), 2.21−2.26 (m, 1H), 3.79 (dd, 1H, *J* = 11.8 and 2.9 Hz), 4.01 (dd, 1H, *J* = 11.8 and 10.6 Hz), 5.25 (dd, 1H, *J* = 10.3 and 2.8 Hz), 5.30 and 5.49 (2 × s, 2H), 7.01 (d, 3H, Ar, *J* = 8.6 Hz), 7.37−7.43 (m, 3H, Ar), 7.48−7.56 (m, 2H, Ar), 7.66 (d, 1H, Ar, *J* = 8.2 Hz), 7.90 (d, 1H, Ar, *J* = 7.4 Hz), 8.18 (d, 1H, Ar, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.46 (CH_2), 22.50 (CH_2), 25.71 (CH_2), 29.16 (CH_2), 34.82 (CH_2), 62.84 (CH_2), 80.41 (CH), 102.79 (C), 114.22 (CH), 115.82 (CH_2), 118.38 (CH), 122.19 (CH), 123.95 (CH), 125.97 (CH), 126.24 (CH), 126.83 (CH), 127.05 (C), 128.01 (CH), 128.03 (CH), 133.57 (C), 135.13 (C), 142.84 (C), 152.69 (C), 158.26 (C); FAB-MS (*m*/*z*) 403 $[M + H]^+$; HRMS calcd for $C_{26}H_{26}O_4$ 402.1831; found 402.1830. Anal. Calcd for $C_{26}H_{26}O_4$: C, 77.95; H, 6.51. Found: C, 77.99; H, 6.55.

*3-{1-[4-(Biphenyl-4-yloxy)-phenyl]-vinyl}-1,2,5-trioxa-spiro[5.5]undecane (**1g**).* White solid was obtained in 50% yield; mp 54−56 °C; IR (KBr, cm^{-1}) 1594; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43−1.64 (m, 8H), 1.99−2.05 (m, 1H), 2.20−2.25 (m, 1H), 3.79 (dd, 1H, *J* = 11.8 and 2.8 Hz), 4.02 (t, 1H, *J* = 11.7 Hz), 5.24 (dd, 1H, *J* = 10.3 and 2.6 Hz), 5.30 (s, 1H), 5.49 (s, 1H), 7.02 (d, 2H, Ar, *J* = 8.6 Hz), 7.09 (d, 2H, Ar, *J* = 8.6 Hz), 7.32−7.46 (m, 5H, Ar), 7.56−7.58 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.48 (CH_2), 22.52 (CH_2), 25.73 (CH_2), 29.19 (CH_2), 34.84 (CH_2), 62.84 (CH_2), 80.45 (CH), 102.83 (C), 115.98 (CH_2), 118.92 (CH), 119.50 (CH), 127.12 (CH), 127.30 (CH), 128.07 (CH), 128.69 (CH), 128.99 (CH), 133.86 (C), 136.82 (C), 140.65 (C), 142.87 (C), 156.56 (C), 157.49 (C); ESI (*m*/*z*) 428 $[M + H]^+$; HRMS calcd for $C_{28}H_{28}O_4$ 428.1988; found 428.1990.

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Anal. Calcd for $C_{28}H_{28}O_4$: C, 78.48; H, 6.59; Found: C, 78.58; H, 6.77.

*3-[1-(4-Phenoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]-undecane (**1h**).* White solid was obtained in 46% yield; mp 54−55 °C; IR (KBr, cm^{-1}) 1590; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40−1.67 (m, 8H), 1.97−2.05 (m, 1H), 2.19−2.24 (m, 1H), 3.76 (dd, 1H, J = 11.9 and 2.9 Hz), 3.98 (dd, 1H, J = 11.8 and 10.4 Hz), 5.22 (dd, 1H, J = 10.4 and 2.8 Hz), 5.28 and 5.47 (2 × s, 2H), 6.96 (d, 2H, Ar, J = 8.8 Hz), 7.02 (dd, 2H, Ar, J = 8.6 and 1.1 Hz), 7.10−7.15 (m, 1H, Ar), 7.32−7.38 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.48 (CH_2), 22.52 (CH_2), 25.72 (CH_2), 29.16 (CH_2), 34.85 (CH_2), 62.86 (CH_2), 80.45 (CH), 102.83 (C), 115.92 (CH_2), 118.78 (CH), 119.35 (CH), 123.78 (CH), 128.00 (CH), 130.03 (CH), 133.67 (CH), 142.84 (C), 156.95 (C), 157.60 (C); FAB-MS (m/z) 353 $[M + H]^+$; HRMS calcd for $C_{22}H_{24}O_4$ 352.1675; found 352.1677. Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.99; H, 6.87.

*(1R,3R,5R,7R)-6′-(1-(4-(Naphthalen-2-yloxy)phenyl)vinyl)-spiro[adamantane-2,3′-[1,2,4]trioxane] (**1i**).* White solid was obtained in 57% yield; mp 103−105 °C; IR (KBr, cm^{-1}) 1593; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.62−2.08 (m, 13H), 2.97 (s, 1H), 3.77 (dd, 1H, J = 11.8 and 2.9 Hz), 3.98 (dd, 1H, J = 11.8 and 10.6 Hz), 5.26 (dd, 1H, J = 10.4 and 2.8 Hz), 5.29 (s, 1H), 5.49 (s, 1H), 7.02 (d, 2H, Ar, J = 8.7 Hz), 7.24−7.27 (m, 1H, Ar), 7.34 (d, 1H, Ar, J = 2.8 Hz) 7.37−7.49 (m, 4H, Ar), 7.72 (d, 1H, Ar, J = 7.9 Hz), 7.83 (t, 2H, Ar, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.33 (2 × CH), 29.56 (CH), 33.19 (CH_2), 33.43 (CH_2), 33.66 (CH_2), 33.77 (CH_2), 36.42 (CH), 37.38 (CH_2), 62.34 (CH_2), 80.29 (CH), 104.91 (C), 114.71 (CH), 115.97 (CH_2), 119.04 (CH), 120.23 (CH), 125.06 (CH), 126.80 (CH), 127.37 (CH), 127.97 (CH), 128.07 (CH), 130.18 (CH), 130.49 (C), 134.00 (C), 134.49 (C), 142.89 (C), 154.80 (C), 157.52 (C); FAB-MS (m/z) 455 $[M + H]^+$; HRMS calcd for $C_{30}H_{30}O_4$ 454.2144; found 454.2156. Anal. Calcd for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 79.35; H, 6.68.

*(1R,3R,5R,7R)-6′-(1-(4-(Naphthalen-1-yloxy)phenyl)vinyl)-spiro[adamantane-2,3′-[1,2,4]trioxane] (**1j**).* See ref 16.

*(1R,3R,5R,7R)-6′-(1-(4-([1,1′-Biphenyl]-4-yloxy)phenyl)-vinyl)spiro[adamantane-2,3′-[1,2,4]trioxane] (**1k**).* White solid was obtained in 50% yield; mp 122−125 °C; IR (KBr, cm^{-1}) 1592; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60−2.10 (m, 13H), 2.96 (s, 1H), 3.79 (dd, 1H, J = 11.8 and 2.8 Hz), 3.98 (t, 1H, J = 11.6 Hz), 5.25 (dd, 1H, J = 10.4 and 2.6 Hz), 5.29 (s, 1H), 5.48 (s, 1H), 7.02 (d, 2H, Ar, J = 8.6 Hz), 7.09 (d, 2H, Ar, J = 8.6 Hz), 7.32−7.46 (m, 5H, Ar), 7.55−7.58 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.33 (2 × CH), 29.58 (CH), 33.19 (CH_2), 33.43 (CH_2), 33.67 (CH_2), 33.77 (CH_2), 36.43 (CH), 37.38 (CH_2), 62.34 (CH_2), 80.30 (CH), 104.89 (C), 115.93 (CH_2), 118.93 (CH), 119.49 (CH), 127.13 (CH), 127.30 (CH), 128.05 (CH), 128.70 (CH), 129.01 (CH), 133.96 (C), 136.81 (C), 140.67 (C), 142.91 (C), 156.59 (C), 157.48 (C); FAB-MS (m/z) 481 $[M + H]^+$; HRMS calcd for $C_{32}H_{32}O_4$ 480.2301; found 480.2250. Anal. Calcd for $C_{32}H_{32}O_4$: C, 79.97; H, 6.71. Found: C, 79.99; H, 6.78.

*(1R,3R,5R,7R)-6′-(1-(4-Phenoxyphenyl)vinyl)spiro-[adamantane-2,3′-[1,2,4]trioxane] (**1l**).* White solid was obtained in 49% yield; mp 53−56 °C; IR (KBr, cm^{-1}) 1591; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58−2.07 (m, 13H), 2.95 (s, 1H), 3.77 (dd, 1H, J = 11.8 and 2.9 Hz), 3.96 (dd, 1H, J = 11.8 and 10.4 Hz), 5.24 (dd, 1H, J = 10.4 and 2.8 Hz), 5.27 (s, 1H), 5.47 (s, 1H), 6.96 (d, 2H, Ar), 7.02 (dd, 2H, Ar, J = 8.7 and 1.1 Hz), 7.10−7.15 (m, 1H, Ar), 7.33−7.38 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.31 (2 × CH), 29.53 (CH), 33.16 (CH_2), 33.42 (CH_2), 33.64 (CH_2), 33.75 (CH_2), 36.42 (CH), 37.36 (CH_2), 62.34 (CH_2), 80.28 (CH), 104.88 (C), 115.85 (CH_2), 118.79 (CH), 119.33 (CH), 123.77 (CH), 127.97 (CH), 130.02 (CH), 133.75 (C), 142.86 (C), 156.98 (C), 157.58 (C); FAB-MS (m/z) 405 $[M + H]^+$; HRMS calcd for $C_{26}H_{28}O_4$ 404.1988, found 404.1967. Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.24; H, 6.99.

*8,8′-((Oxybis(4,1-phenylene))bis(ethene-1,1-diyl))bis-(6,7,10-trioxaspiro[4.5]decane) (**1m**).* Compound **1m** was obtained in 43% yield as white solid; mp 78−80 °C; IR (KBr, cm^{-1}) 1596; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64−1.91 (m, 14H, 7 × CH_2), 2.46−2.52 (m, 2H), 3.84 (d, 4H, 2 × CH_2, J = 6.2 Hz), 5.24−5.27 (m, 3H), 5.45 (s, 2H), 6.96 (d, 4H, Ar, J = 8.7 Hz), 7.35 (d, 4H, Ar, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.57 (2 × CH_2), 24.99 (2 × CH_2), 32.99 (2 × CH_2), 37.23 (2 × CH_2), 65.22 (2 × CH_2), 80.45 (2 × CH), 114.81 (2 × C), 116.22 (2 × CH_2), 119.06 (4 × CH), 128.10 (4 × CH), 133.95 (2 × C), 142.60 (2 × C), 157.14 (2 × C); FAB-MS (m/z) 507 $[M + H]^+$; HRMS calcd for $C_{30}H_{34}O_7$ 506.2305; found 506.2317. Anal. Calcd for $C_{30}H_{34}O_7$: C, 71.13; H, 6.77. Found: C, 71.25; H, 6.82.

*2,7-Bis(4-(1-(6,7,10-trioxaspiro[4.5]decan-8-yl)vinyl)-phenoxy)naphthalene (**1n**).* Compound **1n** was obtained in 35% yield as oil; IR (neat, cm^{-1}) 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67−1.93 (m, 14H, 7 × CH_2), 2.50−2.56 (m, 2H), 3.89 (d, 4H, 2 × CH_2, J = 5.9 Hz), 5.28−5.32 (m, 4H), 5.51 (s, 2H), 7.02 (d, 4H, Ar, J = 8.7 Hz), 7.16−7.19 (m, 4H), 7.39 (d, 4H, Ar, J = 8.7 Hz), 7.81 (d, 2H, Ar, J = 9.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.57 (2 × CH_2), 24.98 (2 × CH_2), 32.99 (2 × CH_2), 37.22 (2 × CH_2), 65.22 (2 × CH_2), 80.42 (2 × CH), 113.72 (2 × CH), 114.80 (2 × C), 116.20 (2 × CH_2), 118.96 (2 × CH), 119.26 (4 × CH), 127.16 (C), 128.11 (4 × CH), 130.02 (2 × CH), 133.99 (2 × C), 135.58 (C), 142.58 (2 × C), 155.72 (2 × C), 157.22 (2 × C); FAB-MS (m/z) 649 $[M + H]^+$. Anal. Calcd for $C_{40}H_{40}O_8$: C, 74.06; H, 6.22. Found: C, 74.20; H, 6.35.

*1,5-Bis(4-(1-(6,7,10-trioxaspiro[4.5]decan-8-yl)vinyl)-phenoxy)naphthalene (**1o**).* Compound **1o** was obtained in 30% yield as white solid; mp 148−150 °C; IR (KBr, cm^{-1}) 1596; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67−1.93 (m, 14H, 7 × CH_2), 2.48−2.54 (m, 2H), 3.86 (d, 4H, J = 6 Hz), 5.27−5.32 (m, 4H), 5.47 (s, 2H), 7.01−7.04 (m, 6H), 7.37−7.42 (m, 6H), 7.95 (d, 2H, Ar, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.58 (2 × CH_2), 24.99 (2 × CH_2), 33.01 (2 × CH_2), 37.24 (2 × CH_2), 65.25 (2 × CH), 80.50 (2 × C), 114.82 (2 × CH_2), 114.88 (2 × CH), 116.09 (4 × CH), 118.01 (2 × CH), 118.58 (4 × CH), 126.21 (2 × C), 128.16 (2 × C), 128.68 (2 × C), 133.75 (2 × C), 142.69 (2 × C), 152.91 (2 × C) 158.09 (2 × C); FAB-MS (m/z) 649 $[M + H]^+$. Anal. Calcd for $C_{40}H_{40}O_8$: C, 74.06; H, 6.22. Found: C, 74.17; H, 6.38.

*3,3′-((Oxybis(4,1-phenylene))bis(ethene-1,1-diyl))bis-(1,2,5-trioxaspiro[5.5]undecane) (**1p**).* Compound **1p** was obtained in 51% yield as white solid; mp 98−100 °C; IR (KBr, cm^{-1}) 1596; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40−1.60 (m, 16H, 8 × CH_2), 1.95−2.01 (m, 2H), 2.16−2.21 (m, 2H), 3.37 (dd, 2H, J = 11.8 and 2.8 Hz), 3.96 (dd, 2H, J = 11.8 and 10.5 Hz), 5.20 (dd, 2H, J = 10.4 and 2.3 Hz), 5.27 (s, 2H), 5.46 (s, 2H), 6.96 (d, 4H, Ar, J = 8.7 Hz), 7.35 (d, 4H, Ar, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.49 (2 × CH_2), 22.53 (2 × CH_2), 25.73 (2 × CH_2), 29.18 (2 × CH_2), 34.84 (2 × CH_2),

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62.83 (2 × CH_2), 80.45 (2 × CH), 102.85 (2 × C), 116.12 (2 × CH_2), 119.07 (4 × CH), 128.09 (4 × CH), 134.06 (2 × C), 142.82 (2 × C), 157.14 (2 × C); FAB-MS(m/z) 535 $[M + H]^+$. Anal. Calcd for $C_{32}H_{38}O_7$: C, 71.89; H,7.16. Found: C, 71.98; H, 7.22. HRMS calcd for $C_{32}H_{38}O_7$ 534.2618; found 534.2614.

*2,7-Bis(4-(1-(1,2,5-trioxaspiro[5.5]undecan-3-yl)vinyl)-phenoxy)naphthalene (**1q**).* Compound **1q** was obtained in 34% yield as oil; IR (neat, cm^{-1}) 1603; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40−1.65 (m, 16H, 8 × CH_2), 1.97−2.04 (m, 2H), 2.18−2.23 (m, 2H), 3.78 (dd, 2H, J = 11.8 and 2.8 Hz), 3.99 (dd, 2H, J = 11.9 and 10.5 Hz), 5.23 (dd, 2H, J = 10.5 and 2.2 Hz), 5.29 and 5.49 (2 × s, 4H), 7.02 (d, 4H, Ar, J = 8.8 Hz), 7.17−7.18 (m, 4H, Ar), 7.39 (d, 4H, Ar, J = 8.8 Hz), 7.81 (d, 2H, Ar, J = 9.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.48 (2 × CH_2), 22.52 (2 × CH_2), 25.72 (2 × CH_2), 29.17 (2 × CH_2), 34.83 (2 × CH_2), 62.83 (2 × CH_2), 80.41 (2 × CH_2), 102.84 (2 × C), 113.67 (2 × CH), 116.11 (2 × CH), 118.94 (2 × CH), 119.29 (4 × CH), 127.14 (C), 128.10 (4 × CH), 130.01 (2 × C), 134.11 (2 × C), 135.58 (C), 142.79 (2 × C), 155.75 (2 × C), 157.19 (2 × C); FAB-MS (m/z) 677 $[M + H]^+$. Anal. Calcd for $C_{42}H_{44}O_8$: C, 74.54; H, 6.55. Found: C, 74.66; H, 6.68.

*1,5-Bis(4-(1-(1,2,5-trioxaspiro[5.5]undecan-3-yl)vinyl)-phenoxy)naphthalene (**1r**).* Compound **1r** was obtained in 32% yield as white solid; mp 158−160 °C; IR (KBr, cm^{-1}) 1596; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30−1.63 (m, 16H, 8 × CH_2), 1.96−2.02 (m, 2H), 2.17−2.21 (m, 2H), 3.76 (dd, 2H, J = 11.9 and 2.9 Hz), 3.97 (dd, 2H, J = 11.9 and 10.4 Hz), 5.21 (dd, 2H, J = 10.3 and 2.7 Hz), 5.27 and 5.46 (2 × s, 4H), 6.99−7.01 (m, 6H, Ar), 7.34−7.40 (m, 6H, Ar), 7.93 (d, 2H, Ar, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.49 (2 × CH_2), 22.53 (2 × CH_2), 25.73 (2 × CH_2), 29.20 (2 × CH_2), 34.84 (2 × CH_2), 62.86 (2 × CH_2), 80.46 (2 × CH), 102.85 (2 × C), 114.84 (2 × CH), 115.99 (2 × CH_2), 118.00 (2 × CH), 118.59 (4 × CH), 126.20 (2 × CH), 128.13 (4 × CH), 128.66 (2 × C), 133.84 (2 × C), 142.87 (2 × C), 152.91 (2 × C), 158.07 (2 × C); FAB-MS (m/z) 677 $[M + H]^+$. Anal. Calcd for $C_{42}H_{44}O_8$: C, 74.54; H, 6.55. Found: C, 74.82; H, 6.78.

*(1R,1″R,3R,3″R,5R,5″R,7R,7″R)-6′,6‴-((Oxybis(4,1-phenylene))bis(ethene-1,1-diyl))dispiro[adamantane-2,3′-[1,2,4]trioxane (**1s**).* Compound **1s** was obtained in 19% yield as white solid; mp 60−63 °C; IR (KBr, cm^{-1}) 1596; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60−2.11 (m, 26H), 2.96 (s, 2H), 3.79 (dd, 2H, J = 11.8 and 2.9 Hz), 3.99 (dd, 2H, J = 11.7 and 10.5 Hz), 5.25 (dd, 2H, J = 10.3 and 2.7 Hz), 5.31 and 5.49 (2 × s, 4H), 6.99 (d, 4H, Ar, J = 8.6 Hz), 7.4 (d, 4H, Ar, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.38 (4 × CH), 29.64 (2 × CH), 33.22 (2 × CH_2), 33.46 (2 × CH_2), 33.69 (2 × CH_2), 33.79 (2 × CH_2), 36.44 (2 × CH), 37.42 (2 × CH_2), 62.33 (2 × CH_2), 80.33 (2 × CH), 104.89 (2 × C), 116.02 (2 × CH_2), 119.07 (4 × CH), 128.09 (4 × CH), 134.20 (2 × C), 142.97 (2 × C), 157.18 (2 × C); FAB-MS (m/z) 639 $[M + H]^+$. Anal. Calcd for $C_{40}H_{46}O_7$: C, 75.21; H, 7.26. Found: C, 75.10; H, 7.30.

*2,7-Bis(4-(1-(spiro[adamantane-2,3′-[1,2,4]trioxan]-6′-yl)-vinyl)phenoxy)naphthalene (**1t**).* Compound **1t** was obtained in 33% yield as oil; IR (neat, cm^{-1}) 1598; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55−2.05 (m, 26 H), 2.92 (s, 2H), 3.76 (dd, 2H, J = 11.8 and 2.8 Hz), 3.95 (t, 2H, J = 11.7 Hz), 5.22 (dd, 2H, J = 10.5 and 2.3 Hz), 5.26 (s, 2H), 5.47 (s, 2H), 7.01 (d, 4H, Ar, J = 8.6 Hz), 7.15−7.17 (m, 4H, Ar), 7.37 (d, 4H, Ar, J = 8.6 Hz), 7.79 (d, 2H, Ar, J = 9.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.34 (4 × CH), 29.58 (2 × CH), 33.19 (2 × CH_2), 33.43 (2 × CH_2), 33.66 (2 × CH_2), 33.77 (2 × CH_2), 36.42 (2 × CH), 37.38 (2 × CH_2), 62.32 (2 × CH_2), 80.27 (2 × CH), 104.89 (2 × C), 113.68 (2 × CH), 116.04 (2 × CH_2), 118.94 (2 × CH), 119.31 (4 × CH), 127.16 (C), 128.09 (4 × CH), 130.01 (2 × CH), 134.22 (2 × CH), 135.61 (C), 142.87 (2 × C), 155.79 (2 × C), 157.19 (2 × C); FAB-MS (m/z) 781 $[M + H]^+$. Anal. Calcd for $C_{50}H_{52}O_8$: C, 76.90; H, 6.71. Found: C, 76.97; H, 6.98.

*1,5-Bis(4-(1-(spiro[adamantane-2,3′-[1,2,4]trioxan]-6′-yl)-vinyl)phenoxy)naphthalene (**1u**).* Compound **1u** was obtained in 29% yield as white solid; mp 155−157 °C; IR (KBr, cm^{-1}) 1598; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56−2.03 (m, 26H), 2.92 (s, 2H), 3.76 (dd, 2H, 2 × CH, J = 11.8 and 2.9 Hz), 3.96 (dd, 2H, J = 11.8 and 10.9 Hz), 5.22 (dd, 2H, J = 10.9 and 2.9 Hz), 5.26 (s, 2H), 5.46 (s, 2H), 6.99−7.01 (m, 6H, Ar), 7.36−7.40 (6H, Ar), 7.93 (d, 2H, Ar, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.40 (4 × CH), 29.67 (2 × CH), 33.24 (2 × CH_2), 33.48 (2 × CH_2), 33.71 (2 × CH_2), 38.81 (2 × CH_2), 36.46 (2 × CH), 37.44 (2 × CH_2), 62.37 (2 × CH_2), 80.34 (2 × CH), 104.90 (2 × C), 114.84 (2 × CH), 115.89 (2 × CH_2), 118.03 (2 × CH), 118.62 (4 × CH), 126.20 (2 × CH), 128.14 (4 × CH), 128.72 (2 × C), 134 (2 × C), 143.01 (2 × C), 152.99 (2 × C), 158.10 (2 × C); FAB-MS (m/z) 781 $[M + H]^+$. Anal. Calcd for $C_{50}H_{52}O_8$: C, 76.90; H, 6.71. Found: C, 76.87; H, 6.95.

*1-[4-(Naphthalen-2-yloxy)-phenyl]-ethanone (**2a**).* White solid was obtained in 52% yield; mp 75−85 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, CH_3), 7.06 (d, 2H, Ar, J = 8.8 Hz), 7.25 (dd, 1H, Ar, J = 8.8 and 2.4 Hz), 7.44−7.52 (m, 3H, Ar), 7.76 (d, 1H, Ar, J = 8.5 Hz), 7.87 (t, 2H, Ar, J = 9.1 Hz), 7.96 (d, 2H, Ar, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.67 (CH_3), 116.40 (CH), 117.73 (CH), 120.53 (CH), 125.56 (CH), 126.97 (CH), 127.50 (CH), 128.03 (CH), 130.45 (CH), 130.83 (CH), 130.98 (C), 132.27 (C), 134.45 (C), 153.40 (C), 162.13 (C), 196.93 (C); FAB-MS (m/z) 263 $[M + H]^+$; HRMS calcd for $C_{18}H_{14}O_2$ 262.0994, found 262.0991. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.48; H, 5.41.

*1-[4-(Naphthalen-1-yloxy)-phenyl]-ethanone (**2b**).* White solid was obtained in 45% yield; mp 52−55 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, CH_3), 7.01 (d, 2H, Ar,), 7.01 (d, 2H, Ar, J = 8.9 Hz), 7.12 (dd, 1H, Ar, J = 7.5 and 0.9 Hz), 7.90−7.56 (m, 3H, Ar), 7.73 (d, 1H, Ar, J = 8.2 Hz), 7.90−7.96 (m, 3H, Ar), 8.02 (d, 1H, Ar, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.65 (CH_3), 116.10 (CH), 117.03 (CH), 122.04 (CH), 125.17 (CH), 126.03 (CH), 126.59 (CH), 126.98 (CH), 127.23 (CH), 128.21 (CH), 130.90 (CH), 132.02 (C), 135.30 (C), 151.32 (C), 162.87 (C), 196.96 (C); FAB-MS (m/z) 263 $[M + H]^+$; HRMS calcd for $C_{18}H_{14}O_2$ 262.3080, found 262.3081. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.48; H, 5.41.

*1-[4-(Biphenyl-4-yloxy)-phenyl]-ethanone (**2c**).* White solid was obtained in 48% yield; mp 113−118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, CH_3), 7.05 (d, 2H, Ar, J = 8.9 Hz), 7.13 (d, 2H, Ar, J = 8.7 Hz), 7.33−7.38 (m, 1H, Ar), 7.43−7.48 (m, 2H, Ar), 7.57−7.64 (m, 4H, Ar), 7.95−7.98 (m, 2H, Ar); ^{13}C NMR (100 MHz, CDCl3) δ 26.71 (CH_3), 117.60 (CH), 120.58 (CH), 127.19 (CH), 127.53 (CH), 128.94 (CH), 129.07 (CH), 130.85 (CH), 132.19 (CH), 137.91 (C), 140.46 (C), 155.18 (C), 162.11 (C), 197.02 (C); FAB-MS (m/z) 289 $[M + H]^+$; HRMS calcd for $C_{20}HO_4$

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288.1150, found 288.1155. Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.36; H, 5.62.

*1-(4-Phenoxy-phenyl)-ethanone (**2d**).* White crystalline solid was obtained in 49% yield; mp 47−49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, CH_3), 6.99 (d, 2H, Ar, J = 8.9 Hz), 7.07 (dd, 2H, Ar, J = 8.7 and 1.1 Hz), 7.18−7.22 (m, 1H, Ar), 7.37−7.41 (m, 2H, Ar), 7.93 (d, 2H, Ar, J = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.69 (CH_3), 117.48 (CH), 120.39 (CH), 124.84 (CH), 130.27 (CH), 130.81 (CH), 132.07 (CH), 155.67 (CH), 162.20 (CH), 197.01 (C); FAB-MS (m/z) 213 $[M + H]^+$; HRMS calcd for $C_{14}H_{12}O_2$ 212.0837, found 212.0857. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.28; H, 5.75.

*1-[4-(4-Acetyl-phenoxy)-phenyl]-ethanone (**2e**).* Compound **2e** was obtained in 42% yield as white solid; mp 98−100 °C; IR (KBr, cm^{-1}) 1678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 6H, 2 × CH_3), 7.06 (d, 4H, Ar, J = 8.8 Hz), 7.97 (d, 4H, Ar, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.76 (2 × CH_3), 118.96 (4 × CH), 130.94 (4 × CH), 133.24 (2 × C), 160.39 (2 × C), 196.92 (2 × C); FAB-MS (m/z) 255 $[M + H]^+$.

*1-{4-[7-(4-Acetyl-phenoxy)-naphthalen-2-yloxy]-phenyl}-ethanone (**2f**).* Compound **2f** was obtained in 38% yield as reddish brown solid; mp 135−137 °C; IR (KBr, cm^{-1}) 1673; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 6H, 2 × CH_3), 7.04 (d, 4H, Ar, J = 8.8 Hz), 7.19 (dd, 2H, J = 8.9 and 2.3 Hz), 7.29 (d, 2H, Ar, J = 2.3 Hz), 7.86 (d, 2H, Ar, J = 8.9 Hz), 7.94 (dd, 4H, Ar, J = 8.9 and 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.71 (2 × CH_3), 115.44 (2 × CH), 118.03 (4 × CH), 119.75 (2 × CH), 128.07 (C), 130.36 (2 × CH), 130.86 (4 × CH), 132.45 (C), 135.52 (2 × C), 154.48 (2 × C), 161.70 (2 × C), 197.02 (2 × C); FAB-MS (m/z) 397 $[M + H]^+$.

*1-{4-[5-(4-Acetyl-phenoxy)-naphthalen-1-yloxy]-phenyl}-ethanone (**2g**).* Compound **2g** was obtained in 40% yield as gray solid; mp 180−183 °C; IR (KBr, cm^{-1}) 1680; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 6H, 2 × CH_3), 7.05 (d, 4H, Ar, J = 8.6 Hz), 7.15 (d, 2H, Ar, J = 7.4 Hz), 7.44 (t, 2H, J = 7.6 Hz), 7.91 (d, 2H, Ar, J = 8.5 Hz), 7.96 (d, 4H, Ar, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.65 (2 × CH_3), 116.60 (2 × CH), 117.39 (2 × CH), 118.94 (2 × CH), 126.55 (4 × CH), 128.95 (2 × C), 130.94 (4 × CH), 132.29 (2 × C), 151.78 (2 × C), 162.47 (2 × C), 196.83 (2 × C); FAB-MS (m/z) 397 $[M + H]^+$.

*Cyclopentanone (**3a**).* Compound **3a** was obtained in 88% yield as oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87−1−91(m, 4H), 2.09 (t, 4H, J = 3.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.32 (2 × CH_2), 38.45(2 × CH_2), 220.90 (C).

*Cyclohexanone (**3b**).* Compound **3b** was obtained in 70% yield as oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61−1.66 (m, 2H), 1.74−1.81 (m, 4H), 2.25 (t, 4H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.03 (CH_2), 27.09 (2 × CH_2), 42.03(2 × CH_2), 212.45 (C).

*2-Adamantanone (**3c**).* Compound **3c** was obtained in 81% yield as a white powder; mp 256−258 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89−2.06 (m, 12H), 2.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.61 (2 × CH), 36.46 (CH_2), 39.43 (4 × CH_2), 47.14 (2 × CH), 218.81 (C).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01321.

^{1}H NMR and ^{13}C NMR spectral data of trioxanes **1a−u**, aromatic ketones **2a−g**, and aliphatic ketones **3a−c** (PDF)

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Notes

The authors declare no competing financial interest.

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(44) During the course of our work on antimalarial 1,2,4-trioxanes, we have prepared a large number of β-hydroxyhydroperoxides and 1,2,4-trioxanes on a multigram scale. In our hands, these compounds

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have behaved well, but the usual precautions for handling of peroxides are recommended.

(45) The SAR analysis of reported trioxanes revealed that compounds **1a**,**b** and **1m** showed 100% antimalarial efficacy at a dose of 48 mg/kg for 4 days, while compound **1m** also showed activity at 24 mg/kg dose with 80% protection against multidrug-resistant *Plasmodium yoelii* in Swiss mice by oral route.

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