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Synthesis of new 6-alkylvinyl/arylalkylvinyl substituted 1,2,4-trioxanes active against multidrug-resistant malaria in mice☆

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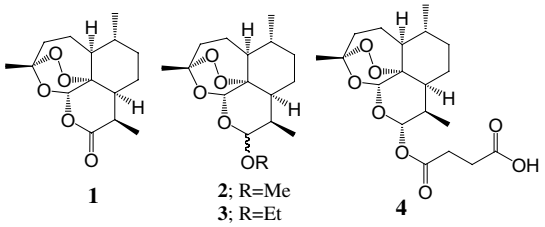
Abstract—3-Alkyl/arylalkyl substituted 2-butenols **9**, **10**, **23a–d** undergo regiospecific photooxygenation to furnish β-hydroxyhydroperoxides **11**, **12**, **24a–d**, respectively, in reasonable yields. Acid catalyzed condensation of **11**, **12**, **24a–d** with various ketones furnish new 1,2,4-trioxanes **13–18**, **25a–d**, **26a–d**, **27a–d** in good yields. Several of these trioxanes show promising antimalarial activity against multidrug-resistant *Plasmodium yoelii* in mice by oral and intramuscular routes.

1. Introduction

Artemisinin **1** the active principle of the Chinese traditional drug against malaria, *Artemisia annua* is active against both chloroquine sensitive and chloroquine resistant malaria.[1] Preparation of a large number of semisynthetic derivatives of artemisinin have been reported some of which, for example, artemether **2**, arteether **3**, and artesunic acid **4**, are several times more potent than the parent compound.[1] These compounds are rapidly acting and are currently the drugs of choice for the treatment of malaria caused by multidrug-resistant *Plasmodium falciparum*.[1c] The peroxide group present in the form of 1,2,4-trioxane is essential for the antimalarial activity. Preparation of a large number of structurally simple 1,2,4-trioxanes have been reported, several of which have shown activity both in vitro and in vivo.[2,3]



1 **2**; R=Me **3**; R=Et **4**

Using β-hydroxyhydroperoxides derived from photooxygenation of 3-aryl-2-butenols, we have earlier reported the preparation of several 6-arylvinyl substituted 1,2,4-trioxanes. Some of these trioxanes were active against chloroquine sensitive *P. berghei* by i.p. route but show poor activity against chloroquine resistant *P. yoelii* in mice by i.m. route.[4] In the present study we have prepared a new series of 3-alkyl and 3-arylalkyl substituted 2-butenols **9**, **10**, **23a–d**, which undergo regiospecific photooxygenation to furnish β-hydroxyhydroperoxides **11**, **12**, **24a–d** in acceptable yields. Acid catalyzed condensation of **11**, **12**, **24a–d** with various ketones furnish trioxanes **13–18**, **25a–d**, **26a–d**, **27a–d** in good yields. Several of these trioxanes have shown very promising antimalarial activity against multidrug-resistant *P. yoelii* in mice by both i.m. and oral routes. Also most of these trioxanes are hydroxyl-functionalized and are amenable for preparation of new derivatives such as water soluble hemisuccinates. Herein we report the details of this study.[5]

2. Chemistry

4-Hydroxybutyl and *n*-undecyl substituted allylic alcohols **9** and **10** were prepared in good yields from

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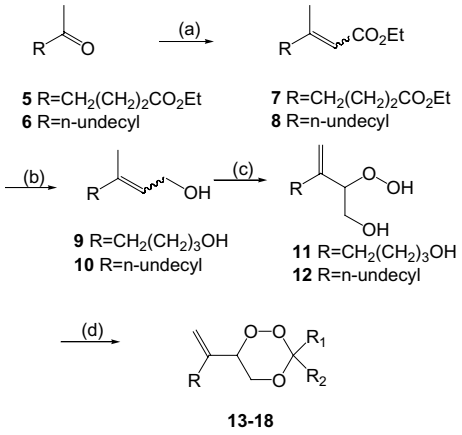
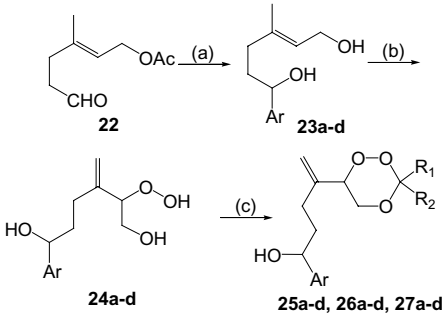


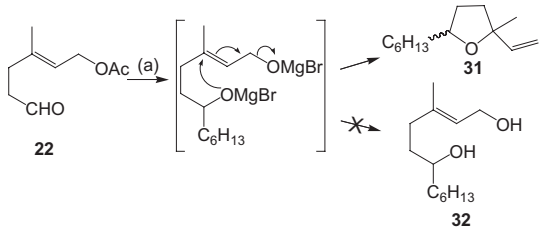
Scheme 1. Reagents and reaction conditions: (a) $(OEt)_2P(O)CH_2CO_2Et$, NaH, DME, rt, 24 h; (b) $LiAlH_4$, Et_2O, 0 °C, 6 h; (c) *hv*, O_2, methylene blue, MeCN, <0 °C, 7 h; (d) ketone, TsOH, CH_2Cl_2, rt, 1 h.

commercially available ethyl-4-acetylbutyrate **5** and 2-tridecanone **6**, respectively, by means of Wadsworth–Emmons olefination followed by reduction with $LiAlH_4$ (Scheme 1). Methylene blue sensitized photooxygenation of allylic alcohols **9** and **10** in MeCN furnished β-hydroxyhydroperoxides **11** and **12** in 37% and 43% yields, respectively. Acid catalyzed condensation of β-hydroxyhydroperoxide **11** with cyclopentanone, cyclohexanone, and 2-adamantanone, furnished trioxanes **13**, **14**, and **15** in 46%, 59%, and 50% yields, respectively. Similar condensation of β-hydroxyhydroperoxide **12** with cyclopentanone, cyclohexanone, 2-adamantanone, gave trioxanes **16**, **17**, and **18** in 65%, 76%, and 72% yields, respectively (Scheme 1, Fig. 1). Trioxanes **13**–**15** on treatment with succinic anhydride, triethyl amine, and DMAP (cat.) in CH_2Cl_2 furnished hemisuccinate derivatives **19**–**21** in 75–96% yields (Fig. 1).

Geranyl acetate was converted to aldehyde acetate **22** using a literature procedure.[6] Reaction of **22** with 6-equiv of Grignard reagents, prepared from bromobenzene, 4-bromochlorobenzene, 1-bromonaphthalene, and 4-bromobiphenyl furnished allylic alcohols **23a**–**d** in 60–75% yields (Scheme 2). Surprisingly, reaction of aldehyde **22** with 6-equiv of *n*-hexylmagnesiumbromide furnished tetrahydrofuran derivative **31** instead of the desired allylic alcohol **32** (Scheme 3).[7] Methylene blue sensitized photooxygenation of allylic alcohols **23a**–**d** in MeCN furnished β-hydroxyhydroperoxides **24a**–**d** in 30–45% yield, as inseparable mixture of diastereomers (analyzed by ^1H NMR). Acid catalyzed condensation of β-hydroxyhydroperoxides **24a**–**d** with cyclopentanone, cyclohexanone, and 2-adamantanone furnished hydroxy-functionalized 1,2,4-trioxanes **25a**–**d**, **26a**–**d**, **27a**–**d** in 50–74% yields (Scheme 2, Fig. 2), also as inseparable mixture of diastereomers (analyzed by ^1H and ^{13}C NMR). Oxidation of trioxanes **26a** and **27a** with chromiumtrioxide–pyridine complex[8] in CH_2Cl_2 furnished keto-functionalized trioxanes **28** and **29** in 92% and 89% yields, respectively (Fig. 2). 6-Phenylvinyl



Scheme 2. Reagents and reaction conditions: (a) (i) ArMgBr, dry Et_2O, 0 °C to rt, 3 h, (ii) H_2O, 0 °C; (b) *hv*, O_2, methylene blue, MeCN, <0 °C, 4–6 h; (c) ketone, TsOH, CH_2Cl_2, rt, 1 h.



Scheme 3. Reagents and reaction conditions: (a) (i) *n*-hexylMgBr, dry Et_2O, 0 °C to rt, 4 h, (ii) H_2O, 0 °C.

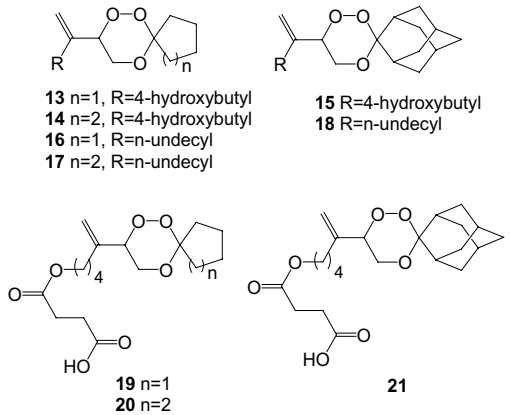


Figure 1.

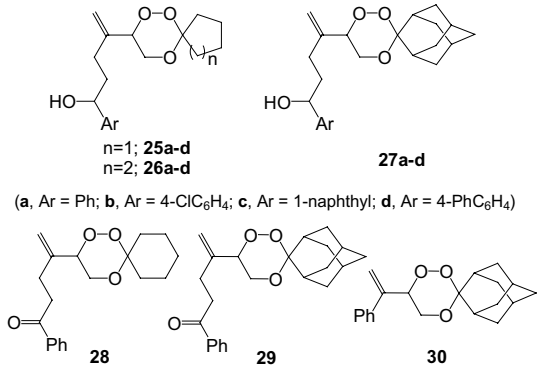


Figure 2.

trioxane **30** (Fig. 2) was prepared by published procedure.[4a]

3. Antimalarial activity

Trioxanes **13**–**21**, **25a**–**d**, **26a**–**d**, **27a**–**d**, **28**, and **29** were initially screened for their antimalarial activity against multidrug-resistant *P. yoelii* in Swiss mice at 96 mg/kg by intramuscular (i.m.) and oral routes. The trioxanes showing activity at 96 mg/kg by either routes (100% suppression of parasitaemia on day 4) were further evaluated at 48 and 24 mg/kg (if active at 48 mg/kg). The detailed activity results are shown in Table 1.

4. Results and discussion

As can be seen from Table 1, 6-arylalkylvinyl substituted trioxanes (**25a**–**d**, **26a**–**d**, **27a**–**d**, and **29**) are the more active than the 6-alkylvinyl substituted trioxanes (**13**–**21**). These trioxanes are also more active than the 6-phenylvinyl substituted trioxane **30**. Among the active trioxanes, **27b** is the best compound of the series. At 96 mg/kg it shows 100% clearance of parasitaemia on day 4 by both i.m. and oral routes, and all the treated mice survive beyond day 28. Even at 48 mg/kg it shows more than 90% suppression of parasitaemia by oral route. Trioxane **27a** is more active than **27b** by i.m. route as it shows 100% clearance of parasitaemia at 96 as well as 48 mg/kg and provides 100% and 40% protection, respectively, in the 28-day observation period. It also shows 100% clearance of parasitaemia on day 4 at 96 mg/kg by oral route but only 40% of the mice are protected. Both the trioxanes are adamantane based. Trioxanes **27c** and **27d**, the other adamantane based trioxanes show 100% clearance of parasitaemia at 96 mg/kg by oral route but provide only partial protection. Trioxane **29** the keto analog of trioxane **27a** is less active than the parent compound. All the 3-spiropentano trioxanes (**25a**–**d**) show 100% or near 100% clearance of parasitaemia both at 96 and 48 mg/kg by i.m. route, but with the exception of **26d**, which shows 100% clearance of parasitaemia at 96 mg/kg, all these trioxanes show poor activity by oral route. Among the 3-spirohexano trioxanes (**26a**–**d**) two trioxanes **26b** and **26c** show 100% clearance of parasitaemia at 96 mg/kg by i.m. route and provide 100% and 80% protection, respectively. Even at 48 mg/kg by i.m. route they show more than 90% suppression of parasitaemia on day 4, though none of the treated mice survive beyond day 28. Trioxane **26d**, on the other hand show 96% and 100% clearance of parasitaemia at 96 mg/kg by i.m. and oral routes, respectively, but only 80% of the mice treated by i.m. route survive beyond day 28.

Both in 3-spiropentane and 3-spirohexane series introduction of biphenyl, a highly hydrophobic moiety, leads to improvement in activity by oral route. On the other hand in 3-spiroadamantane series the compounds having phenyl or chlorophenyl show good activity and introduction of the more hydrophobic groups like naphthyl and biphenyl leads to decrease in activity.

5. Conclusion

In conclusion, we have shown that like 3-aryl substituted 2-butenols, 3-alkyl substituted butenols also undergo regiospecific photooxygenation to give β-hydroxyhydroperoxides in acceptable yields. These hydroperoxides undergo facile acid-catalyzed condensation with various ketones to give 1,2,4-trioxanes in good yields and that some of these trioxanes show very promising activity both by oral and i.m. route. Most of these trioxanes carry hydroxy-functionalized side chains and that this hydroxyl group can be further manipulated to give new series of 1,2,4-trioxanes.

6. Experimental

All glass apparatus were oven dried prior to use. Melting points were determined on complab melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-200 spectrometer (operating at 200 MHz) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR. Fast Atom Bombardment Mass Spectra (FAB-MS) were obtained on JEOL SX 102 spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Elemental analyses were done on Vario EL-III analyzer (Germany). Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel, obtained from Merck). Detecting agents used (for TLC) were: iodine vapors and/or spraying with an aq solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatography was performed over silica gel (60–120 mesh) procured from Qualigens™ (India). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (England), or Spectrochem (India) and were used without further purification. Anhydrous diethyl ether (ether) used in Grignard reactions was obtained from Spectrochem and was kept over sodium overnight prior to use.

6.1. 3-Methyl-hept-2-enedioic acid diethyl ester (7)[10]

This was prepared in 90% yield by the literature procedure, with a stereoisomeric composition of *E*:*Z* = 3:1,[10] as a colorless oil: IR (neat, cm^{-1}) 1649.2, 1725.1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.2 Hz), 1.81 (m, 2H), 2.15 (s, 3H), 2.11–2.66 (m, 4H), 4.12 (q, 2H, J = 7.2 Hz), 4.16 (q, 2H, J = 7.2 Hz), 5.66 (s, 1H); FAB-MS (*m*/*z*) 229 $[M+H]^+$.

Ester **8** was also prepared by the same procedure.

6.2. 3-Methyl-tetradec-2-enoic acid ethyl ester (8)[11]

This was obtained in 85% yield as a 3:1 mixture of *E* and *Z* isomers, respectively, as a colorless oil: IR (neat, cm^{-1}) 1648.3, 1713.3; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 5.8 Hz), 1.26 (m, 21H), 1.87 and 2.14

Table 1. In vivo antimalarial activity of trioxanes against *P. yoelii* in Swiss mice

Compound	Dose (mg/kg/day)	Route	% Suppression on day-4[a]	Mice alive on day-28	MST[b] ± SE
13	96	i.m.	42.5	0/5	07.20 ± 0.37
	96	Oral	63.1	0/5	09.20 ± 0.37
14	96	i.m.	64.5	0/5	08.60 ± 0.60
	96	Oral	31.5	0/5	07.20 ± 0.37
15	96	i.m.	84.0	0/5	10.80 ± 0.92
	96	Oral	26.3	0/5	07.40 ± 0.24
16	96	i.m.	21.2	0/5	07.80 ± 0.37
	96	Oral	94.4	0/5	11.25 ± 0.55
17	96	i.m.	36.9	0/5	07.60 ± 0.24
	96	Oral	80.1	0/5	09.2 ± 0.80
18	96	i.m.	10.3	0/5	07.00 ± 0.55
	96	Oral	51.3	0/5	08.20 ± 0.53
19	96	i.m.	25.7	0/5	06.60 ± 0.24
	96	Oral	95.1	0/5	11.80 ± 0.97
20	96	i.m.	37.3	0/5	07.40 ± 0.24
	96	Oral	36.3	0/5	07.40 ± 0.57
21	96	i.m.	46.0	0/5	10.80 ± 0.92
	96	Oral	12.5	0/5	07.40 ± 0.24
25a	96	i.m.	100.0	0/5	14.80 ± 1.06
	48	i.m.	97.0	0/5	12.60 ± 1.12
	96	Oral	30.0	0/5	08.20 ± 0.53
25b	96	i.m.	100.0	2/5	14.57 ± 0.83
	48	i.m.	98.4	0/5	14.75 ± 0.75
	96	Oral	29.6	0/5	07.40 ± 0.51
25c	96	i.m.	100.0	1/5	14.75 ± 1.48
	48	i.m.	93.4	0/5	15.75 ± 2.37
	96	Oral	81.3	0/5	10.40 ± 0.93
25d	96	i.m.	100.0	2/5	17.33 ± 1.75
	48	i.m.	100.0	0/5	16.75 ± 1.23
	24	i.m.	85.2	0/5	11.80 ± 1.53
	96	Oral	100.0	0/5	16.00 ± 1.22
	48	Oral	94.3	0/5	12.00 ± 1.14
26a	96	i.m.	94.5	0/5	14.40 ± 1.21
	96	Oral	65.0	0/5	11.60 ± 1.12
26b	96	i.m.	100.0	5/5	>28
	48	i.m.	97.1	0/5	16.00 ± 1.93
	96	Oral	88.8	0/5	10.20 ± 0.53
26c	96	i.m.	100.0	4/5	16.00 ± 0.00
	48	i.m.	93.4	0/5	14.20 ± 1.33
	96	Oral	68.4	0/5	13.00 ± 1.67
26d	96	i.m.	96.4	4/5	14.00 ± 0.00
	96	Oral	100.0	0/5	13.80 ± 0.53
	48	Oral	77.5	0/5	11.20 ± 1.36
27a	96	i.m.	100.0	5/5	>28
	48	i.m.	100.0	2/5	15.57 ± 0.33
	96	Oral	100.0	2/5	16.57 ± 1.21
	48	Oral	62.4	0/5	09.00 ± 0.71
27b	96	i.m.	100.0	5/5	>28
	48	i.m.	78.9	0/5	15.00 ± 0.95
	96	Oral	100.0	5/5	>28
	48	Oral	90.8	0/5	10.20 ± 0.85
27c	96	i.m.	72.1	2/5	15.33 ± 2.31
	96	Oral	100.0	3/5	17.00 ± 3.00
	48	Oral	100.0	2/5	15.57 ± 1.75
	24	Oral	87.1	0/5	10.40 ± 1.24
27d	96	i.m.	79.0	3/5	14.50 ± 0.50
	96	Oral	100.0	2/5	17.33 ± 1.45
	48	Oral	100.0	2/5	17.57 ± 2.02
	24	Oral	90.4	0/5	08.80 ± 0.53
28	96	i.m.	93.7	0/5	15.57 ± 1.45
	96	Oral	51.7	0/5	07.60 ± 0.40
29	96	i.m.	89.5	4/5	14.00 ± 0.00
	96	Oral	99.6	0/5	13.80 ± 1.45
30	96	i.m.	97.1	0/5	15.40 ± 1.20
	96	Oral	83.9	0/5	10.50 ± 1.14

Table 1 (*continued*)

Compound	Dose (mg/kg/day)	Route	% Suppression on day-4[a]	Mice alive on day-28	MST[b] ± SE
Artemisinin	48	i.m.	100.0	5/5	>28
	24	i.m.	100.0	4/5	16.00 ± 0.00
Chloroquine	96	Oral	100.0	4/5	20.00 ± 0.00
	48	Oral	100.0	2/5	17.60 ± 1.33
Vehicle control	—	—	—	0/15	07.00 ± 0.14

[a] Percent suppression = $[(C-T)/C] \times 100$; where C = parasitaemia in control group, and T = parasitaemia in treated group.
[b] Mean survival time (MST) calculated (in days) only for the mice, which died during 28-day observation period.

(2 × s, 3H), 2.12 and 2.61 (2 × t, 2H, $J = 8.0$ Hz each), 4.14 (q, 2H, $J = 7.2$ Hz), 5.65 (s, 1H); FAB-MS (*m/z*) 269 $[M+H]^+$.

6.3. 3-Methyl-hept-2-ene-1,7-diol (9)[12]

To a precooled (0 °C) magnetically stirred slurry of $LiAlH_4$ (9.7 g, 0.255 mol) in anhydrous ether (75 mL) was added a solution of di-ester **7** (9.2 g, 0.064 mol) in anhydrous ether (75 mL), under nitrogen and stirred at 0 °C for 8 h. Excess $LiAlH_4$ was quenched by careful addition of cold water followed by 10% aq NaOH, during which the gray color changed to snow-white. The ether was decanted off and the white precipitate rinsed with ether (4 × 50 mL). Combined ether layers were concentrated to give crude diol as a colorless oil that was chromatographed over a silica gel column, using AcOEt–hexane (2:3) as eluent, to furnish 4.6 g (79%) of pure **9** as a colorless oil: IR (neat, cm^{-1}) 1664.5, 3340.3; ^1H NMR (200 MHz, $CDCl_3$) δ 1.50 (m, 4H), 1.66 and 1.73 (2 × s, 3H), 2.05 (m, 2H), 3.63 (t, 2H, $J = 6.0$ Hz), 4.10 and 4.13 (2 × d, 2H, $J = 6.8$ Hz each), 5.40 (t, 1H, $J = 6.8$ Hz); FAB-MS (*m/z*) 145 $[M+H]^+$.

Allylic alcohol **10** was also prepared by the same procedure.

6.4. 3-Methyl-tetradec-2-en-1-ol (10)

This was obtained in 77% yield as a colorless oil: IR (neat, cm^{-1}) 1668.4, 3330.5; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.26 (m, 18H), 1.66 and 1.73 (2 × s, 3H), 2.00 (t, 2H, $J = 7.5$ Hz), 4.13 (d, 2H, $J = 6.8$ Hz), 5.40 (t, 1H, $J = 6.8$ Hz); FAB-MS (*m/z*) 227 $[M+H]^+$; Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.71; H, 13.12.

6.5. 3-Methyl-6-phenyl-hex-2-ene-1,6-diol (23a)

Into an oven dried 1 L three-necked round-bottomed flask, equipped with a magnetic stirring unit, a double surfaced reflux condenser, and a pressure equalizing dropping funnel, was placed Mg-turnings (2.55 g, 0.105 g atom), under a static nitrogen atmosphere. The Mg was covered with anhydrous ether (100 mL) and a small aliquot of a solution of bromobenzene (16.63 g, 0.105 mol) in anhydrous ether (75 mL) together with a small crystal of iodine were added with stirring and moderated heating (warm water bath ~45–50 °C). As the reaction started the water bath was removed and the solution of bromobenzene in ether was added at such a rate to maintain a gentle reflux. After the addition was complete the warm water bath was again placed under the flask and stirring and refluxing continued for 30 min followed by cooling to 0 °C (ice bath). To the cold solution of phenyl magnesium bromide in ether was added dropwise a solution of aldehyde acetate **22** (3.0 g, 17.6 mmol) in anhydrous ether (50 mL), over 20 min. After the addition was complete Grignard reaction mixture was stirred for 3 h at rt followed by again cooling to 0 °C. Cold water was added to decompose the Grignard complex. Ether was decanted off and the residual inorganic matter rinsed with ether (3 × 70 mL). Standard work-up gave crude diol **23a** that was subjected to silica gel column chromatography, using AcOEt–hexane (1:3) as eluent, to furnish pure **23a** (2.60 g, 72%) as a colorless oil: IR (neat, cm^{-1}) 1596.4, 3262.7; ^1H NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 3H), 1.81–2.12 (m, 4H), 4.11 (d, 2H, $J = 7.0$ Hz), 4.63 (dd, 1H, $J = 7.2, 5.6$ Hz), 5.39 (t, 1H, $J = 7.0$ Hz), 7.25–7.42 (m, 5H); FAB-MS (*m/z*) 207 $[M+H]^+$; Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.51; H, 8.66.

6.6. 6-(4-Chloro-phenyl)-3-methyl-hex-2-ene-1,6-diol (23b)

This was prepared in 75% yield by the same procedure as for compound **23a** as a colorless oil: IR (neat, cm^{-1}) 1596.3, 3384.8; ^1H NMR (200 MHz, $CDCl_3$) δ 1.66 (s, 3H), 1.71–2.11 (m, 4H), 4.14 (d, 2H, $J = 6.8$ Hz), 4.65 (dd, 1H, $J = 6.6, 5.8$ Hz), 5.42 (t, 1H, $J = 6.8$ Hz), 7.30 (m, 4H); FAB-MS (*m/z*) 241 and 243 $[M+H]^+$; Anal. Calcd for $C_{13}H_{17}ClO_2$: C, 64.86; H, 7.12. Found: C, 65.08; H, 7.31.

6.7. 3-Methyl-6-naphthalen-1-yl-hex-2-ene-1,6-diol (23c)

The procedure for this compound was otherwise same as for **23a** except that the Grignard reagent was prepared as per the literature procedure.[13] This was obtained in 74% yield as a white solid: mp 81–83 °C; IR (KBr, cm^{-1}) 1597.3, 3264.9; ^1H NMR (200 MHz, $CDCl_3$): δ 1.63 (s, 3H), 1.92–2.05 (m, 2H), 2.15–2.24 (m, 2H), 4.08 (d, 2H, $J = 6.8$ Hz), 5.37–5.43 (m, 2H), 7.42–8.06 (m, 7H); FAB-MS (*m/z*) 257 $[M+H]^+$; Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.49; H, 7.92.

6.8. 6-Biphenyl-4-yl-3-methyl-hex-2-ene-1,6-diol (23d)

The experimental procedure for this compound was otherwise same as for **23a** except that the Grignard reagent

was prepared by 'entrainment method' as follows. Into an oven dried 1 L three-necked round-bottomed flask, equipped with a magnetic stirring unit, a double surfaced reflux condenser, and a pressure equalizing dropping funnel, was placed Mg-turnings (5.14 g, 0.211 g atom), under a static nitrogen atmosphere. The Mg was covered with anhydrous ether (100 mL) and a small aliquot of a solution of 4-bromobiphenyl (24.67 g, 0.105 mol) and 1,2-dibromoethane (9.9 g, 52.6 mmol) in anhydrous ether (250 mL) was added with stirring and moderated heating (warm water bath ~45–50 °C). As the reaction initiated the water bath was removed and the solution of 4-bromobiphenyl and 1,2-dibromoethane in ether was added at such a rate to maintain a gentle reflux. After the addition was complete the warm water bath was again placed under the flask and stirring and refluxing continued for 1 h, to drive the reaction to completion. The Grignard reagent that settled as heavy oil was dissolved by the addition of 80 mL of dry benzene, prior to cooling. Diol **23d** was obtained in 60% yield as a white solid: mp 120–122 °C; IR (KBr, cm^{-1}) 1594.5, 3360.6; ^1H NMR (200 MHz, $CDCl_3$) δ 1.68 (s, 3H), 1.78–2.20 (m, 4H), 4.14 (d, 2H, $J = 6.8$ Hz), 4.70 (dd, 1H, $J = 7.0$, 5.4 Hz), 5.44 (t, 1H, $J = 6.8$ Hz), 7.29–7.59 (m, 9H); FAB-MS (*m/z*) 283 $[M+H]^+$; Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.62; H, 8.03.

6.9. General method for photooxygenation of allylic alcohols (photooxygenation of 23a representative)

A slow stream of oxygen was bubbled into a solution of **23a** (1.0 g, 4.8 mmol), and methylene blue (10 mg) in MeCN (50 mL) in a 100 mL jacketed round-bottomed flask, maintained below 0 °C by circulating coolant ethanol through an ultra cryostat. The mixture was irradiated with visible light by means of a tungsten–halogen lamp (500 W) kept at a distance of 6-in. from the flask. Reaction was complete in about 6 h as shown by silica gel TLC monitoring. MeCN was evaporated on the rotavapor (bath temp <40 °C) and the crude hydroperoxide **24a** subjected to column chromatography over silica gel (deactivated with 12% v/w of water), using AcOEt–hexane (2:3) as eluent to furnish reasonably pure **24a** (0.41 g, 35%).

6.10. 2-Hydroperoxy-3-methylene-heptane-1,7-diol (11)

This was obtained in 37% yield as a colorless oil: IR (neat, cm^{-1}) 1565.1, 3382.6; ^1H NMR (200 MHz, $CDCl_3$) δ 1.50 (m, 4H), 2.13 (m, 2H), 3.67–3.75 (m, 4H), 4.53 (t, 1H, $J = 6.0$ Hz), 5.08 and 5.14 (2 × s, 2H), 8.78 (s, 1H, OOH); FAB-MS (*m/z*) 177 $[M+H]^+$.

6.11. 2-Hydroperoxy-3-undecyl-but-3-en-1-ol (12)

This was obtained in 43% yield as a colorless oil: IR (neat, cm^{-1}) 1647.7, 3375.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.26 (m, 18H), 2.03 (m, 2H), 3.74 (d, 2H, $J = 6.0$ Hz), 4.52 (t, 1H, $J = 6.0$ Hz), 5.06 and 5.11 (2 × s, 2H), 8.53 (br s, 1H, OOH); FAB-MS (*m/z*) 259 $[M+H]^+$.

6.12. 5-Hydroperoxy-4-methylene-1-phenyl-hexane-1,6-diol (24a)

This was obtained in 35% yield as colorless oil: IR (neat, cm^{-1}) 1597.1, 1641.2, 3360.9; ^1H NMR (200 MHz, $CDCl_3$) δ 1.86–2.01 (m, 2H), 2.08–2.36 (m, 2H), 3.30 (br s, 2H, 2 × OH), 3.67 (m, 2H), 4.50 (m, 1H), 4.70 (m, 1H), 5.03 and 5.04 (2 × s, 1H), 5.11 and 5.13 (2 × s, 1H), 7.27 (m, 5H), 10.12 (br s, 1H, OOH); FAB-MS (*m/z*) 239 $[M+H]^+$.

6.13. 1-(4-Chloro-phenyl)-5-hydroperoxy-4-methylene-hexane-1,6-diol (24b)

This was obtained in 35% yield as a colorless oil: IR (neat, cm^{-1}) 1596.1, 1647.5, 3376.2; ^1H NMR (200 MHz, $CDCl_3$) δ 1.82–1.94 (m, 2H), 2.15–2.42 (m, 2H), 3.01 (br s, 2H, 2 × OH), 3.68 (m, 2H), 4.51 (m, 1H), 4.69 (m, 1H), 5.04 (s, 1H), 5.11 and 5.14 (2 × s, 1H), 7.26 (m, 4H), 9.99 (br s, 1H, OOH); FAB-MS (*m/z*) 273 and 275 $[M+H]^+$.

6.14. 5-Hydroperoxy-4-methylene-1-naphthalen-1-yl-hexane-1,6-diol (24c)

This was obtained in 40% yield as a colorless oil: IR (neat, cm^{-1}) 1595.4, 1648.3, 3370.1; ^1H NMR (200 MHz, $CDCl_3$) δ 1.94–2.22 (m, 4H), 3.72 (m, 2H), 4.52 (m, 1H), 5.10, 5.16, and 5.22 (3 × s, 2H), 5.54 (m, 1H), 7.46–8.07 (m, 7H); FAB-MS (*m/z*) 289 $[M+H]^+$.

6.15. 1-Biphenyl-4-yl-5-hydroperoxy-4-methylene-hexane-1,6-diol (24d)

This was obtained in 45% yield as colorless oil.

6.16. General procedure for condensation of hydroperoxides with ketones (preparation of trioxane 27a representative)

A solution of hydroperoxy diol **24a** (300 mg, 1.26 mmol), 2-adamantanone (750 mg, 5.0 mmol), and $TsOH{\cdot}H_2O$ (50 mg, 0.26 mmol) in CH_2Cl_2 (25 mL) was stirred at rt for 1 h. Reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (20 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 15 mL). Standard work-up gave crude trioxane that was chromatographed over a silica gel column, using AcOEt–hexane (1:9) as eluent, to furnish pure **27a** (0.34 g, 73%).

6.17. 5-(6,7,10-Trioxa-spiro[4.5]dec-8-yl)-hex-5-en-1-ol (13)

This was obtained in 46% yield as a colorless oil: IR (neat, cm^{-1}) 1646.2, 3393.2; ^1H NMR (200 MHz, $CDCl_3$) δ 1.52–1.90 (m, 11H), 2.08 (t, 2H, $J = 6.8$ Hz), 2.46 (m, 1H), 3.65 (t, 2H, $J = 5.8$ Hz), 3.82 (d, 2H, $J = 6.6$ Hz), 4.74 (t, 1H, $J = 6.6$ Hz), 5.02 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.68 (t), 24.39 (t), 25.06 (t), 32.56 (t), 33.06 (t), 33.99 (t), 37.37 (t), 62.89 (t), 65.01 (t), 81.44 (d), 114.38 (t), 114.78 (s), 143.94 (s); FAB-MS (*m/z*) 243 $[M+H]^+$.

6.18. 5-(1,2,5-Trioxa-spiro[5.5]undec-3-yl)-hex-5-en-1-ol (14)

This was prepared in 59% yield as a colorless oil: IR (neat, cm^{-1}) 1645.6, 3409.6; ^1H NMR (200 MHz, $CDCl_3$) δ 1.59 (m, 12H), 1.93–2.22 (m, 4H), 3.64 (t, 2H, $J = 6.0$ Hz),3.72 (dd, 1H, $J = 11.8$, 3.0 Hz), 3.96 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.70 (dd, 1H, $J = 10.4$, 3.0 Hz), 5.03 (s, 2H); FAB-MS (*m/z*) 257 $[M+H]^+$; Anal. Calcd for $C_{14}H_{24}O_4 \cdot H_2O$: C, 61.28; H, 9.55. Found: C, 61.24; H, 9.18.

6.19. Trioxane 15

This was prepared in 50% yield as a colorless oil: IR (neat, cm^{-1}) 1648.7, 3404.8; ^1H NMR (200 MHz, $CDCl_3$) δ 1.54–2.09 (m, 19H), 2.90 (br s, 1H), 3.65 (t, 2H, $J = 5.8$ Hz), 3.72 (dd, 1H, $J = 12.0$, 2.8 Hz), 3.94 (dd, 1H, $J = 12.0$, 10.6 Hz), 4.70 (dd, 1H, $J = 10.6$, 2.8 Hz), 5.03 (s, 2H); FAB-MS (*m/z*) 309 $[M+H]^+$; Anal. Calcd for $C_{18}H_{28}O_4 \cdot 0.3H_2O$: C, 68.89; H, 9.18. Found: C, 68.57; H, 8.98.

6.20. 8-(1-Undecyl-vinyl)-6,7,10-trioxa-spiro[4.5]decane (16)

This was prepared in 65% yield as a colorless oil: IR (neat, cm^{-1}) 1646.3; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.26 (m, 18H), 1.66–1.87 (m, 7H), 2.04 (m, 2H), 2.46 (m, 1H), 3.80 (d, 2H, $J = 6.6$ Hz), 4.74 (t, 1H, $J = 6.6$ Hz), 4.99 (s, 2H); FAB-MS (*m/z*) 325 $[M+H]^+$; Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.03; H, 11.18. Found: C, 74.27; H, 11.09.

6.21. 3-(1-Undecyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecane (17)

This was prepared in 76% yield as a colorless oil: IR (neat, cm^{-1}) 1645.1; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.26 (m, 18H), 1.43–1.60 (m, 9H), 1.94–2.22 (m, 3H), 3.71 (dd, 1H, $J = 11.8$, 3.2 Hz), 3.95 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.68 (dd, 1H, $J = 10.4$, 3.2 Hz), 5.00 (s, 2H); FAB-MS (*m/z*) 339 $[M+H]^+$ Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H, 11.31. Found: C, 74.36; H, 11.23.

6.22. Trioxane 18

This was prepared in 76% yield as a colorless oil: IR (neat, cm^{-1}) 1646.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.8$ Hz), 1.26 (m, 18H), 1.60–2.08 (m, 15H), 2.91 (br m, 1H), 3.71 (dd, 1H, $J = 11.8$, 3.2 Hz), 3.93 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.69 (dd, 1H, $J = 10.4$, 3.2 Hz), 5.00 (s, 2H); FAB-MS (*m/z*) 391 $[M+H]^+$; Anal. Calcd for $C_{25}H_{42}O_3$: C, 76.87; H, 10.84. Found: C, 77.00; H, 11.08.

6.23. Succinic acid mono-[5-(6,7,10-trioxa-spiro[4.5]dec-8-yl)-hex-5-enyl] ester (19)

To a solution of trioxane **13** (0.28 g, 1.16 mmol), Et_3N (0.35 g, 3.46 mmol), and DMAP (5 mg) in CH_2Cl_2 was added succinic anhydride (0.29 g, 2.9 mmol) at rt and stirred for 1 h. CH_2Cl_2 was removed under vacuum and the residue taken up in Et_2O (30 mL) washed successively with 10% aq HCl (20 mL) and water (20 mL). Standard work-up of the ether layer gave crude hemisuccinate that was purified by column chromatography over silica gel using MeOH–$CHCl_3$ (1:99) as eluent to furnish pure **19** (0.30 g, 75%) as a colorless oil: IR (neat, cm^{-1}) 1729.8, 3185.6; ^1H NMR (200 MHz, $CDCl_3$) δ 1.51–1.81 (m, 11H), 2.07 (t, 2H, $J = 6.2$ Hz), 2.40–2.52 (m, 1H), 2.65 (m, 4H), 3.83 (d, 2H, $J = 6.8$ Hz), 4.11 (t, 2H, $J = 6.0$ Hz), 4.75 (t, 1H, $J = 6.8$ Hz), 5.024 (s, 2H); FAB-MS (*m/z*): 343 $[M+H]^+$; Anal. Calcd for $C_{17}H_{26}O_7 \cdot 1.7H_2O$: C, 54.73; H, 7.94. Found: C, 54.48; H, 7.67.

Hemisuccinates **20** and **21** were also prepared by the same procedure.

6.24. Succinic acid mono-[5-(1,2,5-trioxa-spiro[5.5]undec-3-yl)-hex-5-enyl] ester (20)

This was obtained in 96% yield as a colorless oil: IR (neat, cm^{-1}) 1731.9, 3194.4; ^1H NMR (200 MHz, $CDCl_3$) δ 1.59 (m, 12H), 1.90–2.12 (m, 4H), 2.64 (m, 4H), 3.74 (dd, 1H, $J = 11.8$, 3.0 Hz), 3.95 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.11 (t, 2H, $J = 5.8$ Hz), 4.69 (dd, 1H, $J = 10.4$, 3.0 Hz), 5.03 (s, 2H); FAB-MS (*m/z*) 357 $[M+H]^+$; Anal. Calcd for $C_{18}H_{28}O_7 \cdot 0.4H_2O$: C, 59.45; H, 7.98. Found: C, 59.90; H, 8.00.

6.25. Trioxane 21

This was obtained in 87% yield as colorless oil: IR (neat, cm^{-1}) 1722.7, 3190.1; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42–2.08 (m, 19H), 2.64 (m, 4H), 2.90 (br s, 1H), 3.75 (dd, 1H, $J = 11.6$, 3.0 Hz), 3.93 (dd, 1H, $J = 11.6$, 10.2 Hz), 4.11 (t, 2H, $J = 5.6$ Hz), 4.72 (dd, 1H, $J = 10.2$, 3.0 Hz), 5.02 (s, 2H); FAB-MS (*m/z*) 409 $[M+H]^+$; Anal. Calcd for $C_{22}H_{32}O_7 \cdot 1.2H_2O$: C, 61.43; H, 8.06. Found: C, 61.42; H, 7.98.

6.26. 1-Phenyl-4-(6,7,10-trioxa-spiro[4.5]dec-8-yl)-pent-4-en-1-ol (25a)

This was prepared in 58% yield as a colorless oil: IR (neat, cm^{-1}) 1598.5, 1645.5, 3421.1; ^1H NMR (200 MHz, $CDCl_3$) δ 1.63–2.20 (m, 11H), 2.40–2.48 (m, 1H), 3.77–3.81 (m, 2H), 4.65–4.77 (m, 2H), 5.04 (s, 2H), 7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.70 (t), 25.08 (t), 30.35 (t), 33.08 (t), 37.36 (t), 37.54 (t), 64.93 (t), 74.11 (d), 81.56 (d), 81.60 (d), 114.59 (t), 114.80 (s), 126.24 (2 × d), 128.02 (d), 128.90 (2 × d), 143.67 (s), 144.89 (s); FAB-MS (*m/z*): 305 $[M+H]^+$; Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.18; H, 7.31.

6.27. 1-(4-Chloro-phenyl)-4-(6,7,10-trioxa-spiro[4.5]dec-8-yl)-pent-4-en-1-ol (25b)

This was prepared in 70% yield as a colorless oil: IR (neat, cm^{-1}) 1597.4, 1646.8, 3435.1; ^1H NMR (200 MHz, $CDCl_3$) δ 1.70–2.16 (m, 11H), 2.38–2.44 (m, 1H), 3.78–3.82 (m, 2H), 4.64–4.76 (m, 2H), 5.05 (s,

2H), 7.29 (m, 4H); FAB-MS (*m/z*) 339 and 341 $[M+H]^+$; Anal. Calcd for $C_{18}H_{23}ClO_4$: C, 63.81; H, 6.84. Found: C, 63.58; H, 7.02.

6.28. 1-Naphthalen-1-yl-4-(6,7,10-trioxa-spiro[4.5]dec-8-yl)-pent-4-en-1-ol (25c)

This was prepared in 54% yield as a colorless oil: IR (neat, cm^{-1}) 1598.3, 1646.2, 3448.5; ^1H NMR (200 MHz, $CDCl_3$) δ 1.68–1.81 (m, 7H), 2.01–2.10 (m, 2H), 2.20–2.35 (m, 3H), 3.78–3.83 (m, 2H), 4.76 (dd, 1H, $J = 7.6$, 5.8 Hz), 5.05 and 5.08 (2 × s, 2H), 5.48 (dd, 1H, $J = 7.4$, 5.0 Hz), 7.43–8.11 (m, 7H); FAB-MS (*m/z*) 355 $[M+H]^+$; Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.54; H, 7.36.

6.29. 1-Biphenyl-4-yl-4-(6,7,10-trioxa-spiro[4.5]dec-8-yl)-pent-4-en-1-ol (25d)

This was prepared in 73% yield as a colorless oil: IR (neat, cm^{-1}) 1602.6, 1646.0, 3428.8; ^1H NMR (200 MHz, $CDCl_3$) δ 1.66–2.31 (m, 11H), 2.40–2.49 (m, 1H), 3.79–3.83 (m, 2H), 4.70–7.79 (m, 2H), 5.06 (s, 2H), 7.34–7.60 (m, 9H). FAB-MS (*m/z*) 381 $[M+H]^+$; Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 76.06; H, 7.81.

6.30. 1-Phenyl-4-(1,2,5-trioxa-spiro[5.5]undec-3-yl)-pent-4-en-1-ol (26a)

This was prepared in 62% yield as a colorless oil: IR (neat, cm^{-1}) 1598.2, 1646.3, 3424.4; ^1H NMR (200 MHz, $CDCl_3$) δ 1.47–1.87 (m, 10H), 1.88–1.96 (m, 2H), 2.09–2.16 (m, 2H), 3.69 (dd, 1H, $J = 11.8$, 3.0 Hz), 3.93 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.65–4.71 (m, 2H), 5.05 (s, 2H), 7.23–7.35 (m, 5H); FAB-MS (*m/z*) 319 $[M+H]^+$; Anal. Calcd for $C_{19}H_{26}O_4 \cdot 0.1H_2O$: C, 71.26; H, 8.24. Found: C, 70.79; H, 7.86.

6.31. 1-(4-Chloro-phenyl)-4-(1,2,5-trioxa-spiro[5.5]undec-3-yl)-pent-4-en-1-ol (26b)

This was prepared in 50% yield as a colorless oil: IR (neat, cm^{-1}) 1596.2, 1645.1, 3419.0; ^1H NMR (200 MHz, $CDCl_3$) δ 1.47–1.60 (m, 10H), 1.82–1.97 (m, 2H), 2.09–2.19 (m, 2H), 3.70 (dd, 1H, $J = 11.8$, 3.0 Hz), 3.93 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.64–4.70 (m, 2H), 5.06 (s, 2H), 7.29 (m, 4H); FAB-MS (*m/z*) 353 and 355 $[M+H]^+$; Anal. Calcd for $C_{19}H_{25}ClO_4$: C, 64.67; H, 7.14. Found: C, 64.79; H, 7.25.

6.32. 1-Naphthalen-1-yl-4-(1,2,5-trioxa-spiro[5.5]undec-3-yl)-pent-4-en-1-ol (26c)

This was prepared in 74% yield as a colorless oil: IR (neat, cm^{-1}) 1597.5, 1645.4, 3443.8; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42–1.58 (m, 9H), 1.84–2.15 (m, 3H), 2.20–2.31 (m, 2H), 3.68 (dd, 1H, $J = 11.8$, 3.0 Hz), 3.91 and 3.93 (2 × dd, 1H, $J = 11.8$, 10.2 Hz each), 4.69 (dd, 1H, $J = 10.2$, 3.0 Hz), 5.04 and 5.06 (2 × s, 2H), 5.44 (dd, 1H, $J = 7.2$, 5.0 Hz), 7.45–8.08 (m, 7H); FAB-MS (*m/z*) 369 $[M+H]^+$; Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.20; H, 7.49.

6.33. 1-Biphenyl-4-yl-4-(1,2,5-trioxa-spiro[5.5]undec-3-yl)-pent-4-en-1-ol (26d)

This was prepared in 71% yield as a colorless oil: IR (neat, cm^{-1}) 1602.0, 1648.1, 3423.9; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45–1.59 (m, 10H), 1.83–2.04 (m, 2H), 2.10–2.26 (m, 2H), 3.71 (dd, 1H, $J = 11.8$, 3.0 Hz), 3.96 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.67–4.76 (m, 2H), 5.07 (s, 2H), 7.33–7.61 (m, 9H); FAB-MS (*m/z*) 395 $[M+H]^+$; Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11; H, 7.66. Found: C, 76.48; H, 8.04.

6.34. Trioxane 27a

This was prepared in 73% yield as a colorless oil: IR (neat, cm^{-1}) 1596.1, 1646.1, 3422.5; ^1H NMR (200 MHz, $CDCl_3$) δ 1.62–2.17 (m, 17H), 2.87 (br s, 1H), 3.65 (dd, 1H, $J = 11.8$, 3.2 Hz), 3.91 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.62–4.73 (m, 2H), 5.05 (s, 2H), 7.30 (m, 5H); FAB-MS (*m/z*) 371 $[M+H]^+$; Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.25; H, 8.43.

6.35. Trioxane 27b

This was prepared in 59% yield as a colorless oil: IR (neat, cm^{-1}) 1599.4, 1646.5, 3427.6; ^1H NMR (200 MHz, $CDCl_3$) δ 1.60–2.17 (m, 17H), 2.85 (br m, 1H), 3.70 (dd, 1H, $J = 11.8$, 3.0 Hz), 3.91 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.64–4.73 (m, 2H), 5.06 (s, 2H), 7.30 (m, 4H); FAB-MS (*m/z*) 405 and 407 $[M+H]^+$; Anal. Calcd for $C_{23}H_{29}ClO_4$: C, 68.22; H, 7.22. Found: C, 68.45; H, 7.34.

6.36. Trioxane 27c

This was prepared in 50% yield as a colorless oil: IR (neat, cm^{-1}) 1597.1, 1647.2, 3447.5; ^1H NMR (200 MHz, $CDCl_3$) δ 1.57–2.36 (m, 17H), 2.86 (br m, 1H), 3.71 (dd, 1H, $J = 11.8$, 3.0 Hz), 3.92 and 3.94 (2 × dd, 1H, $J = 11.8$, 10.4 Hz each), 4.73 (dd, 1H, $J = 10.4$, 3.0 Hz), 5.06 and 5.09 (2 × s, 2H), 5.48 (dd, 1H, $J = 7.0$, 5.2 Hz), 7.43–8.11 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) 27.59 (2 × d), 29.82 (d), 30.78 (t), 33.40 (t), 33.69 (t), 33.95 (2 × t), 36.57 (d), 36.84 (t), 37.64 (t), 62.06 (t), 70.67 (d), 70.83 (d), 81.59 (d), 81.62 (d), 104.92 (s), 114.64 (t), 114.94 (t), 123.22 (d), 123.34 (d), 123.54 (d), 125.84 (d), 125.97 (d), 126.50 (d), 128.40 (d), 129.32 (d), 130.75 (s), 134.26 (s), 140.69 (s), 143.98 (s); FAB-MS (*m/z*) 421 $[M+H]^+$; Anal. Calcd for $C_{27}H_{32}O_4$: C, 74.55; H, 7.39. Found: C, 73.71; H, 7.06.

6.37. Trioxane 27d

This was prepared in 70% yield as a colorless oil: IR (neat, cm^{-1}) 1600.8, 1646.5, 3407.3; ^1H NMR (200 MHz, $CDCl_3$) δ 1.56–2.18 (m, 17H), 2.88 (br s, 1H), 3.72 (dd, 1H, $J = 11.6$, 3.0 Hz), 3.93 (dd, 1H, $J = 11.6$, 10.4 Hz), 4.69–4.78 (m, 2H), 5.07 (s, 2H), 7.33–7.60 (m, 9H); FAB-MS (*m/z*) 447 $[M+H]^+$; Anal. Calcd for $C_{29}H_{34}O_4$: C, 78.00; H, 7.67. Found: C, 77.69; H, 8.01.

6.38. 1-Phenyl-4-(1,2,5-trioxa-spiro[5.5]undec-3-yl)-pent-4-en-1-one (28)

A 100 mL round-bottomed flask, equipped with a magnetic stirrer and a $CaCl_2$ guard tube was, charged with dry pyridine (1.04 g, 13.2 mmol) and CH_2Cl_2 (20 mL). The solution was cooled to 0–5 °C (ice bath) and CrO_3 (0.66 g, 6.6 mmol; stored in a vacuum desiccator overnight over P_2O_5 prior to use) was added in one portion. The deep burgundy solution was stirred in the cold for an additional 5 min and then allowed to warm to 20 °C over a period of 30 min. A solution of trioxane **26a** (0.35 g, 1.10 mmol) in CH_2Cl_2 (20 mL) was added rapidly with immediate separation of a tarry black deposit. The reaction mixture was stirred for an additional 30 min and then decanted from the tarry residue. The organic layer was washed successively with 5% aq NaOH (40 mL), 5% aq HCl (40 mL), and saturated aq $NaHCO_3$ solution (40 mL). The organic layer was dried over anhyd Na_2SO_4 and evaporated under vacuum to afford crude keto trioxane **28** that was purified by column chromatography over silica gel using AcOEt–hexane (1:19) as eluent to furnish pure **28** as a white solid (0.32 g; 92%): mp 59–61 °C; IR (KBr, cm^{-1}) 1595.0, 1689.7; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45–1.61 (m, 8H), 1.92–2.05 (m, 1H), 2.11–2.20 (m, 1H), 2.52 (t, 2H, $J = 7.4$ Hz), 3.16 (m, 2H), 3.76 (dd, 1H, $J = 11.8$, 3.2 Hz), 4.00 (dd, 1H, $J = 11.8$, 10.4 Hz), 4.76 (dd, 1H, $J = 10.4$, 3.0 Hz), 5.07 and 5.09 (2 × s, 2H), 7.46 (t, 2H, $J = 7.5$ Hz), 7.57 (t, 1H, $J = 7.5$ Hz), 7.97 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2 (t), 22.3 (t), 25.5 (t), 27.8 (t), 29.0 (t), 34.5 (t), 36.9 (t), 62.0 (t), 81.4 (d), 102.5 (s), 114.5 (t), 128.0 (2 × d), 128.6 (2 × d), 133.1 (d), 136.7 (s), 142.9 (s), 198.9 (s); FAB-MS (*m*/*z*) 317 $[M+H]^+$; Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.22; H, 7.39.

6.39. Trioxane 29

This compound was also prepared by the same procedure described for compound **28** in 89% yield as a white solid: mp 66–68 °C; IR (KBr, cm^{-1}): 1682.0; ^1H NMR (200 MHz, $CDCl_3$) δ 1.59–2.08 (m, 13H), 2.52 (t, 2H, $J = 7.4$ Hz), 2.90 (br s, 1H), 3.16 (m, 2H), 3.76 (dd, 1H, $J = 11.8$, 3.0 Hz), 3.98 (dd, 1H, $J = 11.8$, 10.2 Hz), 4.78 (dd, 1H, $J = 10.2$, 3.0 Hz), 5.07 and 5.09 (2 × s, 2H), 7.46 (t, 2H, $J = 7.0$ Hz), 7.57 (t, 1H, $J = 7.0$ Hz), 7.97 (d, 2H, $J = 7.0$ Hz); FAB-MS (*m*/*z*) 369 $[M+H]^+$; Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.84; H, 7.79.

6.40. 5-Hexyl-2-methyl-2-vinyl-tetrahydro-furan (31)

This was prepared by the same procedure as diol **23a** in 62% yield as a colorless oil: IR (neat, cm^{-1}) 1641.7; ^1H NMR (200 MHz, $CDCl_3$) δ 0.80 (t, 3H, $J = 6.2$ Hz), 1.23 (m, 13H), 1.49–1.84 (m, 4H), 3.93–4.01 (m, 1H), 4.96 (dd, 1H, $J = 10.6$, 1.4 Hz), 5.09 and 5.13 (2 × dd, 1H, $J = 17.4$, 1.4 Hz each), 5.79 and 5.84 (2 × dd, 1H, $J = 17.4$, 10.6 Hz each); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.38 (q), 21.11 (q), 22.96 (t), 26.36 (t), 26.57 (t), 26.96 (q), 27.77 (q), 29.81 (t), 30.29 (t), 31.58 (t), 31.80 (t), 31.92 (t), 32.19 (t), 36.67 (t), 36.85 (t), 37.39 (t), 38.51 (t), 79.40 (d), 79.92 (d), 82.69 (s), 111.36 (t), 111.56 (t), 144.63 (d), 145.48 (d); FAB-MS (*m*/*z*) 197 $[M+H]^+$.

6.41. Antimalarial activity

The in vivo efficacy of compounds was evaluated against *P. yoelii* (MDR) in Swiss mice model. The colony bred Swiss mice (25 ± 1g) were inoculated with 1×10^6 parasitized RBC on day zero and treatment was administered to a group of five mice at each dose, from day 0 to 3, in two divided doses daily. The drug dilutions were prepared in groundnut oil so as to contain the required amount of the drug (1.2 mg for a dose of 96 mg/kg, 0.6 mg for a dose of 48 mg/kg and 0.3 mg for a dose of 24 mg/kg) in 0.1 mL and administered either intramuscularly or orally for each dose. Parasitaemia level were recorded from thin blood smears between day 4 and 28.[9] Mice treated with artemisinin and chloroquine served as positive controls.

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