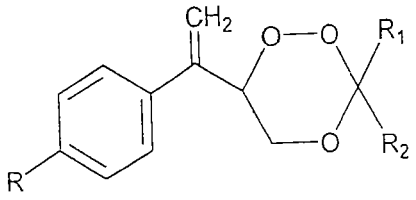
NOVEL SUBSTITUTED 1,2,4-TRIOXANES, USEFUL AS ANTIMALARIAL AGENTS AND A PROCESS FOR THE PREPARATION THEREOF

Technical Field

The present invention relates to a novel series of antimalarial 1,2,4-trioxanes analogues of general formula 7,



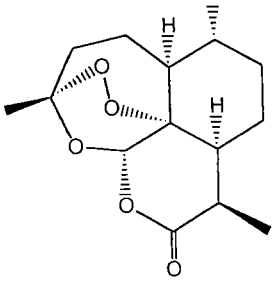
7

wherein R represents cycloalkyl groups selected from the groups consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl or aryl groups selected from phenyl, 4-bromophenyl and 4-chlorophenyl, R_1 and R_2 represent hydrogen, alkyl group selected from methyl, ethyl, propyl and decyl, aryl selected from phenyl or parts of a cyclic systems such as cyclopentane, cyclohexane, substituted cyclohexane, cycloheptane bicyclo(2.2.1)heptane, adamantane and its preparation thereof; several of these novel compounds show promising antimalarial activity against multidrug resistant malaria in mice.

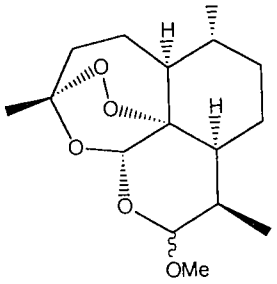
Background Art

Malaria, endemic in many parts of the tropical countries, with approximately 300-500 million episodes of clinical infection and nearly 2 million deaths per year worldwide, is a serious health problem. The rapid emergence of resistance by *Plasmodium falciparum* to the existing therapies, e.g. chloroquine, mefloquine etc, has added new dimensions to this problem. Against this background discovery of artemisinin **1**, a sesquiterpene lactone endoperoxide, isolated from the Chinese traditional herbal remedy against malaria, *Artemisia annua*, has been a welcome development in the chemotherapy of malaria. Some of the semisynthetic derivatives of artemisinin e.g. artemether **2**, arteether **3**, and artesunic acid **4** are more active than artemisinin and are currently being used clinically. These drugs are effective against both chloroquine sensitive and chloroquine resistant strains of *Plasmodium falciparum* [For reviews on artemisinin and its derivatives, see: (a) Klayman, D. L. *Science*, **1985**, 228, 1049; (b) Luo, X. D.; Shen, C. C. *Med. Res. Rev.*, **1987**, 7, 29; (c) Zaman, S. S.; Sharma, R. P. *Heterocycles*, **1991**,32,1593; (d) Butler, A. R.; Wu, Y. Lin. *Chem. Soc. Rev.*, **1993**, 21,85; (e) Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S.

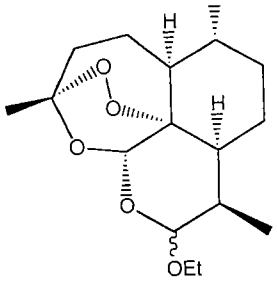
Microbiol. Rev.,**1996**, 60,301; (f) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles*,**1999**, 51, 1681; (g) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.*, **1997**, 73].



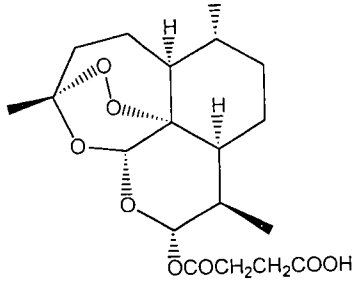
1



2

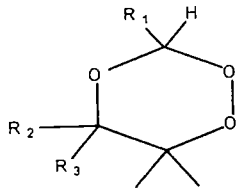


3

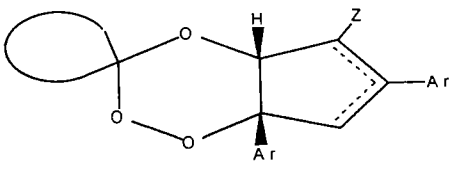


4

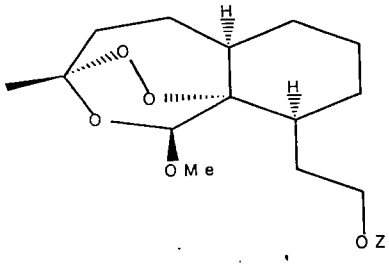
The limited availability of artemisinin from natural sources and the realization that 1,2,4-trioxane is the pharmacophore for the antimalarial activity of artemisinin and its analogues, has inspired major efforts towards the preparation and bioevaluation of structurally simple synthetic 1,2,4-trioxanes. As a result of these efforts, a number of methodologies have been developed by various workers for the preparation of 1,2,4-trioxanes (prototypes of these trioxanes are given in Figure 1). Several of these synthetic trioxanes have shown promising antimalarial activities both *in vitro* and *in vivo* [Cumming, J.M.; Ploypradith, P.; Posner, G. H. *Adv Pharmacol*, **1999**, 37,253].



where R_1=Me, Et, Pr, iPr....
R_2=Me
R_3=Me,CH_2I, CH_2Br.



where Ar= p-MePh, Ph. .
Z= OH,$OCH_2(OCH_2)_2OMe$,H,OEt....



Where Z= $PO(OPh)_2$
Z= CH_2Ph

FIGURE 1

Singh *et al.* have prepared 1,2,4-trioxanes by the regiospecific photooxygenation of allylic alcohols to furnish β-hydroxyhydroperoxide, which on condensation with aldehyde or ketone in the presence of an acid catalyst furnish 1,2,4-trioxane [(a) Singh, C. *Tetrahedron Lett.* **1990**,31,6901;(b) Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* ,**1992**, 2, 497; Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* , **1995,17**, 1913]. As an extension of this work we have prepared a new series of novel 1,2,4-trioxanes which have been found to be highly active against multi-drug resistant *P.yoelii* in mice and which are the subject matter of this patent.

This invention relates to novel substituted 1,2,4-trioxanes useful as antimalarial agents.

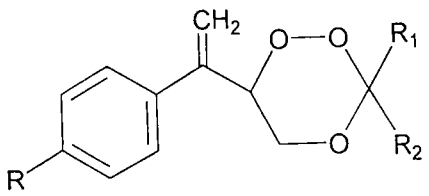
This invention also relates to a process for the preparation of novel substituted 1,2,4-trioxanes.

This invention particularly relates to a process for the preparation of 6-[(cycloalkylphenyl/Substituted biphenyl) vinyl]-1,2,4-trioxanes, a new series of antimalarial agents. More particularly the present invention provides a process for the preparation of 1,2,4-trioxanes of general formula 7 wherein R represents cycloalkyl groups selected from the groups consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl or aryl groups selected from phenyl, 4-bromophenyl and 4-chlorophenyl, R_1 and R_2 represent hydrogen, alkyl group selected from methyl, ethyl, propyl and decyl, aryl selected from phenyl, or part of a cyclic system such as cyclopentane, cyclohexane, substituted cyclohexane, cycloheptane, cyclo(2.2.1)heptane, adamantane. These trioxanes are new compounds and are useful as antimalarial agents. Some of these compounds have been tested against multi-drug resistant malaria in mice and have shown promising antimalarial activity. The invention, thus relates to pharmaceutical industry.

The trioxanes of the general formula 7 are new chemical entities and they have not been prepared earlier.

The main objective of the present invention is to provide novel substituted 1,2,4-trioxanes.

The objective of the present invention is also to provide a process for the preparation of novel substituted 1,2,4-trioxanes of general formula 7, a new series of antimalarial agents. Accordingly, the present invention provides a process for the preparation of novel substituted 1,2,4-trioxanes of general formula 7 as given below.



7

Wherein R represents cycloalkyl groups selected from the groups consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl or aryl groups selected from phenyl, 4-bromophenyl and 4-chlorophenyl, R_1 and R_2 represent hydrogen, alkyl group selected from methyl, ethyl, propyl and decyl, aryl selected from phenyl or parts of a cyclic systems such as cyclopentane, cyclohexane, substituted cyclohexane, cycloheptane, bicyclo (2.2.1) heptane, adamantane which comprises reacting aryl methyl ketone of formula **1**, wherein R represents cycloalkyl groups selected from the groups consisting of cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl or aryl groups selected from phenyl, 4-bromophenyl and 4-chlorophenyl with haloacetate such as ethyl bromoacetate or ethylchloroacetate and Zn in presence of catalytic amount of I_2 in an aprotic organic solvent at a temperature range of room temperature to refluxing temperature to give β-hydroxyester of formula **2**, wherein R has the same meaning as above, dehydrating the above said β-hydroxy esters of formula **2** using a catalyst selected from the group consisting of I_2, P_2O_5, PTSA and cation exchanger such as Amberlyst-15, in an aprotic organic solvent at room temperature to refluxing temperature to obtain α,β-unsaturated ester **3**, wherein R has the same meaning as above, reducing the above said esters of formula **3** with a metal hydride such as $LiAlH_4$ in an ether solvent at a temperature ranging from O°C to refluxing temperature to give allylic alcohols of the formula **4**, wherein R has the same meaning as above, photooxygenating the above said allylic alcohols of formula **4** in presence of a sensetizer in an organic solvent at temperature ranging from -10°C to room temperature to obtain β-hydroxyhydroperoxides of formula **5**, wherein R has the same meaning as above , reacting *in situ* or after isolating the β-hydroxyhydroperoxide of the formula **5** with an aldehyde or ketone of the general formula **6**, wherein, R_1 and R_2 represent hydrogen, alkyl group such as methyl, ethyl, propyl and decyl, aryl such as phenyl and parts of a cyclic system selected from groups consisting of cyclopentane, cyclohexane, cycloheptane, substituted cyclohexanes, bicyclo(2.2.1)heptane, adamantane, in presence of an acid catalyst in an aprotic organic solvent at a temperature range of 0°C to room temperature, followed by isolation and purification by known methods to furnish the trioxanes of general formula **7**, wherein R, R_1 and R_2 have the same meaning as above.

In the process aryl methyl ketone of formula **1** are reacted with haloacetate such as ethyl bromoacetate or ethylchloroacetate and Zn in presence of catalytic amount of I_2 in an aprotic organic solvent such as benzene, toluene, diethyl ether, THF to furnish β-hydroxy ester of formula **2**.

These β-hydroxy esters of formula **2** can be isolated and purified by standard laboratory methods such as column chromatography or crystallization or can be used without purification in the next step. β-Hydroxy esters of formula **2** except compound **2e** (formula **2**, R=Ph) are new compounds and they have not been prepared earlier. β-Hydroxy ester **2e** (formula **2**, R=Ph) is a known compound [*Farmaco. Ed. Sci* **1978**,33(12), 992-8 (Ital)].

In the process dehydration of β-hydroxy esters of formula **2** may be effected in aprotic organic solvent such as benzene, toluene, $CHCl_3$ in the presence of a dehydrating catalysts selected from I_2, P_2O_5, p-toluene sulfonic acid, H_2SO_4 or Amberlyst-15 (cation exchanger) to furnish α,β-unsaturated esters of formula **3**. These unsaturated esters can be isolated and purified by standard laboratory methods such as column chromatography or crystallization. The α,β-unsaturated esters of formula **3** except compound **3e** (formula **3**, R=Ph) are new compounds and they have not been prepared earlier. α,β-unsaturated ester of formula **3e** (formula **3**, R=Ph) is a known compound [*Chemical Abstract*, **1976**, 86, P106177d].

In the process reduction of α,β-unsaturated esters of formula **3** is effected with a complex metal hydride such as $LiAlH_4$ in an ether solvent such as diethyl ether, tetrahydrofuran, to furnish allylic alcohol of the formula **4**. These allylic alcohols of formula **4** can be isolated and purified by standard laboratory methods such as crystallization or column chromatography. The allylic alcohols of formula **4** are new compounds and they have not been prepared earlier.

In the process photooxygenation of allylic alcohols of formula **4** may be effected by passing oxygen gas or air in the solution of the alcohol in an organic solvent and in the presence of a dye and a light source which provides visible light for a period in the range of 2 to 5 h, to furnish ß-hydroxyhydroperoxides of formula **5**. These β-hydroxyhydroperoxide of formula **5** which are new chemical entities can be isolated and purified by standard laboratory methods such as crystallization or column chromatography or can be used *in situ*, without purification, in the next step. The dye which acts as a sensitizer i.e. converts $^3O_2$ to highly reactive $^1O_2$, may be selected from methylene blue, Rose Bengal, tetraphenylporphine and the like. Organic solvent used may be selected from CH_2Cl_2, benzene, CH_3CN, acetone, ethanol and the like.

In the process reaction of β-hydroxyhydroperoxide of formula **5** with aldehyde/ketones of formula **6** is done in an aprotic solvent in the presence of an acid catalyst to furnish trioxanes of formula **7**. The aldehyde and ketones used may be such as benzaldehyde, acetone, ethyl methyl ketone, methyl propyl ketone, decyl methyl ketone, cyclopentanone, cyclohexanone, and bicyclic ketone such as norcamphor and tricyclic ketones such as 2-adamantanone. The acid catalyst used may be such as HCl, *p*-toluenesulfonic acid, H_2SO_4, acidic resin like Amberlyst-15. The aprotic solvents used may be such as CH_2Cl_2, $CHCl_3$, benzene, CH_3CN. These trioxanes of formula **7** can be isolated and purified by standard laboratory methods such as column chromatography and crystallization. These trioxanes are new chemical entities and they have not been prepared earlier. Some of the trioxanes of formula **7** have been tested against malarial parasites in mice and show promising antimalarial activity.

The invention is further illustrated by the following examples which should not, however, be construed to limit the scope of the present invention.

EXAMPLE 1

ETHYL 3-HYDROXY-3-(4'-CYCLOPENTYLPHENYL)-BUTANOATE (COMPOUND 2a, FORMULA 2, R = CYCLOPENTYL)

To a refluxing mixture of 4'-cyclopentylacetophenone (17 g), I_2 (5 mg) and Zn dust (12 g) in benzene (150 ml) was added ethylbromoacetate (11 ml) dropwise over 30 minutes. The mixture was refluxed for next 45 min and then cooled to room temperature. It was acidified with 10% aqueous HCl solution (150 ml) and organic layer was separated out. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to furnish 22 g (88.1% yield) of ethyl 3-hydroxy-3-(4'-cyclopentylphenyl)-butanoate (**2a**) as oil.

ETHYL 3-(4'-CYCLOPENTYLPHENYL)-BUT-2-ENOATE (COMPOUND 3a, FORMULA 3, R = CYCLOPENTYL)

To a solution of ethyl 3-hydroxy-(4'-cyclopentylphenyl)-butanoate (**2a**, 12 g) in benzene (150 ml) was added *p*-toluenesulfonic acid and refluxed for 1 h. The mixture was diluted with sat. $NaHCO_3$ (100 ml) and organic layer was separated. The organic phase was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to give 8.9 g (79.4% yield) of ethyl 3-(4'-cyclopentylphenyl)-but-2-enoate (**3a**, formula **3**, R = cyclopentyl) as oil.

3-(4'-CYCLOPENTYLPHENYL)-2-BUTENOL (COMPOUND 4a, FORMULA 4, R = CYCLOPENTYL)

To an ice cooled slurry of $LiAlH_4$ (2.7 g) in dry ether (150 ml) was added a solution of ethyl 3-(4'-cyclopentylphenyl)-but-2-enoate (**3a**, 8.2 g) in dry ether (50 ml) dropwise. The mixture was stirred at 0°C for 3 h. The reaction mixture was quenched with water (10 ml). A solution of 10% NaOH (5 ml) was added and then ether layer was decanted. The precipitate was washed with ether and combined organic layer was concentrated. The crude product was purified by column chromatography on silica gel to give 5.6 g (82.3% yield) of 3-(4'-cyclopentylphenyl)-2-butenol (**4a**, formula **4**, R = cyclopentyl) as oil.

3-(4'-CYCLOPENTYLPHENYL)-1-HYDROXY-BUT-3-EN-2-HYDROPEROXIDE (COMPOUND 5a, FORMULA 5, R = CYCLOPENTYL)

A solution of 3-(4'-cyclopentylphenyl)-2-butenol (**4a**, 500 mg) and methylene blue (5 mg) in CH_2Cl_2 (30 ml) was irradiated with a 250-watt tungsten-halogen lamp at –10°C while oxygen was passed through the reaction mixture for 5 h. The reaction mixture was concentrated under reduced pressure at r.t. and purified by column chromatography on silica gel to furnish 0.29 g (51.7% yield) of hydroperoxide **5a** as a solid m.p. 95-97°C.

8-[(4'-CYCLOPENTYLPHENYL)VINYL]-6,7,10-TRIOXASPIRO-[4,5]-DECANE (TRIOXANE 7aa, FORMULA 7, R = CYCLOPENTYL; R_1 R_2 = $-CH_2CH_2CH_2CH_2$)

A solution of 3-(4'-cyclopentylphenyl)-2-butenol (**4a**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –10°C for 3 h. Cyclopentanone (1.5 ml) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was left at r.t. for 20 h. Reaction mixture was concentrated to remove CH_3CN under reduced pressure, diluted with $NaHCO_3$ (5 ml) and water (50 ml), extracted with ether (3 x 50 ml), dried over Na_2SO_4 and concentrated. The crude product was purified by chromatotron on silica gel to furnish 0.38 g (52.7% yield based on allylic alcohol, **4a** used) of trioxane **7aa** as oil.

EXAMPLE 2

TRIOXANE 8a, FORMULA 8, R = CYCLOPENTYL

A solution of 3-(4'-cyclopentylphenyl)-2-butenol (**4a**, 320 mg) and methylene blue (5 mg) in CH_3CN (25 ml) was photooxygenated at –10°C for 4 h. Norcamphor (800 mg) and *p*-toluenesulfonic acid (60 mg) were added and reaction mixture was stirred for 20 h at r.t. The reaction mixture was worked up as above and concentrated. Crude product was purified by chromatotron on silica gel to furnish 0.14 g (28% yield based on allylic alcohol **4a**, used) of trioxane **8a**, m.p. 91-93°C.

EXAMPLE 3

TRIOXANE 9a, FORMULA 9, R = CYCLOPENTYL

A solution of 3-(4'-cyclopentylphenyl)-2-butenol (**4a**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –10°C for 3 h. 2-Adamantanone (500 mg) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was stirred for 3.5 h at r.t. The reaction mixture was worked up as above and concentrated. Crude product was purified by chromatotron on silica gel to furnish 430 mg (49.4% yield, based on allylic alcohol, **4a** used) of trioxane **9a**, m.p. 74-76°C.

EXAMPLE 4

TRIOXANE 7ab, FORMULA 7, R = CYCLOPENTYL; R_1 R_2 = -$CH_2CH_2CH(Ph)CH_2CH_2$-

A solution of 3-(4'-cyclopentylphenyl)-2-butenol (**4a**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –10°C for 3 h. 4-Phenylcyclohexanone (1 g) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was stirred for 20 h at r.t. Reaction mixture was worked up as above and concentrated. Crude product was purified by chromatotron on silica gel to furnish 500 mg (60.2% yield, based on allylic alcohol, **4a** used) of trioxane **7ab**, m.p. 98-100°C.

EXAMPLE 5

ETHYL 3-HYDROXY-3-(4'-CYCLOHEXYLPHENYL)-BUTANOATE (COMPOUND 2b, FORMULA 2, R = CYCLOHEXYL)

To a refluxing mixture of 4'-cyclohexylacetophenone (25 g), I_2 (5 mg) and Zn (17 g) in benzene (150 ml) was added ethylbromoacetate (20.7 ml) dropwise during 30 minutes. The mixture was refluxed for 2 h and then cooled to room temperature. It was acidified with 10% HCl (200 ml) an organic layer separated out. The organic phase was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography using SiO_2 as adsorbent and hexane-ethylacetate mixture as eluant to give 28 g (80% yield) of ethyl 3-hydroxy-3-(4'-cyclohexylphenyl)-butanoate (**2b**, formula **2**, R = cyclohexyl) m.p. 45°C.

The above compound was also prepared using different reaction condition. **Table 1** gives the condition used and yield of compound **2b**.

TABLE 1

Solvent	Temperature	Reaction time	Yield
Diethyl ether	r.t.	No reaction	-
Diethyl ether	Refluxed	No reaction	-
Toluene	Refluxed	30 minutes	90%

ETHYL 3-(4'-CYCLOHEXYLPHENYL)-BUT-2-ENOATE (COMPOUND 3b, R = CYCLOHEXYL)

To a solution of ethyl 3-hydroxy-3-(4'-cyclohexylphenyl)-butanoate (**2b**, 29.5 g) in benzene (80 ml) was added *p*-toluenesulfonic acid (1.8 g) and was refluxed for 2 h. The reaction mixture was diluted with sat. $NaHCO_3$, benzene layer separated out. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to give 12.7 g (46.01% yield) of ethyl 3-hydroxy-3-(4'-cyclohexylphenyl)-but-2-enoate (**3b**, formula **3**, R = cyclohexyl) as oil.

The compound **3b** was also prepared using different reaction condition. **Table 2** gives the conditions used and the yield of compound **3b**.

TABLE 2

Acid catalyst	Solvent	Temperature	Reaction time	Yield (%)
P_2O_5	Toluene	Refluxed	1 h	65.2
Amberlyst-15	Toluene	Refluxed	1 h	35.1
I_2	Benzene	Refluxed	1.5 h	95.6
H_2SO_4	$CHCl_3$	r.t.	36 h	29.0

3-(4'-CYCLOHEXYLPHENYL)-2-BUTENOL (COMPOUND 4b, FORMULA 4, R = CYCLOHEXYL)

To an ice-cooled slurry of $LiAlH_4$ (3.8 g) in dry ether (200 ml) was added a solution of ethyl 3-(4'-cyclohexylphenyl)-but-2-enoate (**3b**, 12.7 g) in dry ether (50 ml) dropwise. The reaction mixture was stirred for 3 h at O°C. The reaction mixture was quenched with water (20 ml). A solution of 10% NaOH (10 ml) was added and the ether layer was decanted. The precipitate was washed with ether and combined extracts were concentrated. The crude product was purified by column chromatography on silica gel as adsorbent and hexane/ethylacetate as eluant to furnish 9.5 g (88.7% yield) of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**) m.p. 54-55°C.

The $LiAlH_4$ reduction of ethyl 3-(4'-cyclohexylphenyl)-but-2-enoate (**3b**) using THF as solvent under refluxing conditions did not provide the desired compound.

3-(4'-CYCLOHEXYLPHENYL)-1-HYDROXY-BUT-3-EN-2-HYDROPEROXIDE (COMPOUND 5b, FORMULA 5, R =CYCLOHEXYL)

A solution of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**, 600 mg) and methylene blue (20 mg) in acetonitrile (35 ml) was irradiation with a 250-watt tungsten-halogen lamp at –6°C while oxygen was passed through the reaction mixture for 5 h. The crude product obtained by usual aqueous workup was crystallized from CH_2Cl_2 to give 80 mg of hydroperoxide **5b**. The filtrate was chromatographed on silica gel to give 400 mg of hydroperoxide **5b**. The combined yield of hydroperoxide (compound **5b**, formula 5, R = cyclohexyl) was 480 mg (70% yield), m.p. 95-97°C.

Photooxygenation of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**) in benzene at –6°C using tetraphenylphorphine as sensitizer furnished the above hydroperoxide **5b** in 85.2% yield.

3,3-DIMETHYL-6-[4'-CYCLOHEXYLPHENYL]VINYL-1,2,4-TRIOXANE (TRIOXANE 7ba, FORMULA 7, R = CYCLOHEXYL)

A solution of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**, 500 mg) and methylene blue (50 mg) in acetone (30 ml) was photooxygenated at –6°C for 3 h to give compound **5b** (as shown by TLC). To the mixture was added *p*-toluenesulfonic acid (60 mg) and stirred for 3 h at r.t. The reaction mixture was worked up as above and concentrated. The crude product was purified by column chromatography on silica gel to furnish 500 mg (76.9% yield based on allylic alcohol, **4b** used) of trioxane **7ba**, m.p. 54-55°C.

EXAMPLE 6

3-DECYL,3-METHYL-6-[(4'-CYCLOHEXYLPHENYL)VINYL]-1,2,4-TRIOXANE (TRIOXANE 7bb, FORMULA 7, R = CYCLOHEXYL)

A solution of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –6°C for 3 h. 2-Dodecanone (1 ml) and *p*-toluenesulfonic acid were added and reaction mixture was stirred at r.t for 18 h. The reaction mixture was worked up as above and concentrated. The crude product was purified by chromatotron on silica gel to furnish 290 mg (31.1% yield, based on allylic alcohol, **4b** used) of trioxane **7bb** as oil.

EXAMPLE 7

6-[(4'-CYCLOHEXYLPHENYL)VINYL]-3-PHENYL-1,2,4-TRIOXANE (TRIOXANE 7bc, FORMULA 7, R = CYCLOHEXYL]

A solution of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**, 500 mg) and methylene blue (5 mg)

in CH_3CN (25 ml) was photooxygenated at –6°C for 2.5 h. Benzaldehyde (1 ml) and *p*-toluenesulfonic acid (50 mg) were added and the mixture was left at r.t. for 18 h. Reaction mixture was worked up and crude product was purified by flash column chromatography on silica gel to furnish 340 mg (44.7% yield based on allylic alcohol, **4b** used) of trioxane **7bc**, m.p. 86-88°C.

EXAMPLE 8

3-[(4'-CYCLOHEXYLPHENYL)VINYL]-1,2,5-TRIOXASPIRO(5,5)UNDECANE (TRIOXANE 7bd, FORMULA 7, R= CYCLOHEXYL, R_1R_2 = -$CH_2CH_2CH_2CH_2CH_2$-)

A solution of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –6°C for 3 h. Cyclohexanone (1.5 ml) and *p*-toluenesulfonic acid (50 mg) were added and the mixture was stirred for 4 h. The reaction mixture was worked up and crude product was purified by flash column chromatography on silica gel to furnish 550 mg (74.3% yield based on allylic alcohol, **4b** used) of trioxane **7bd**, m.p. 60-62°C.

EXAMPLE 9

TRIOXANE 8b, FORMULA 8, R = CYCLOHEXYL

A solution of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –8°C for 4 h. Norcamphor (1 g) and *p*-toluenesulfonic acid (50 mg) were added and the mixture was left at 5°C for 16 h. The reaction mixture was worked up and the crude product was purified by flash column chromatography on silica gel to furnish 300 mg (40.8% yield based on allylic alcohol, **4b** used) of trioxane **8b**, m.p. 70-71°C.

EXAMPLE 10

TRIOXANE 9b, FORMULA 9, R = CYCLOHEXYL

A solution of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**, 500 mg) and methylene blue (5 mg) in CH_3CN (50 ml) was photooxygenated at –6°C for 3 h. 2-Adamantanone (1 g) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was stirred at r.t. for 2 h. and then left unstirred at 5°C for 15 h. Reaction mixture was worked up and crude product was purified by column chromatography on silica gel to furnish 500 mg (58.8% yield based on allylic alcohol, **4b** used) of trioxane **9b**, m.p. 75-76°C. Trioxane **9b** was also prepared by the following method using purified hydroperoxide **5b**.

To a solution of hydroperoxide **5b** (290 mg) and 2-adamantanone (300 mg) in $CHCl_3$ (20 ml) was added one drop conc. H_2SO_4 and the reaction was kept at r.t.for 14 h. The reaction

mixture was diluted with sat. $NaHCO_3$ (5 ml) and water (10 ml), extracted with ether (2 x 20 ml), dried over Na_2SO_4 and concentrated. The crude product was purified by chromatotron on silica gel to furnish 250 mg (49.0% yield) of trioxane **9b**, m.p. 75-76°C. The above trioxane was also prepared using different reaction conditions. **Table 3** gives the conditions used and the yields of the trioxane **9b**.

TABLE 3

Dye	Temperature	Solvent	Acid catalyst	Reaction time	Yield
Tetraphenyl-Porphine	-10°C	CH_2Cl_2	HCl	18 h	52.9%
Rose Bengal	r.t.	EtOH *	Amberlyst-15	18 h	56.8%

*EtOH was removed under reduced pressure after photooxygenation and replaced by CH_2Cl_2 in the second step before the addition of 2-Adamantanone.

EXAMPLE 11

TRIOXANE 7be, FORMULA 7, R = CYCLOHEXYL, R_1R_2=-CH_2-CH_2-CH(Ph)CH_2CH_2-

A solution of 3-(4'-cyclohexylphenyl)-2-butenol (**4b**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –10°C for 2.5 h. 4-Phenylcyclohexanone (1 g) and *p*-toluenesulfonic acid (50 mg) were added and the reaction mixture was left at r.t. for 20 h. The reaction mixture was worked up as above and concentrated. The crude product was purified by column chromatography on silica gel to furnish 570 mg (63.3% yield based on allylic alcohol **4b**, used) of trioxane **7be** as a mixture of two stereoisomers m.p. 107-109°C.

EXAMPLE 12

ETHYL 3-HYDROXY-3-(4'-CYCLOHEPTYLPHENYL)-BUTANOATE (COMPOUND 2c, FORMULA 2, R = CYCLOHEPTYL)

To a refluxing mixture of 4'-cycloheptylacetophenone (25 g), I_2 (5 mg) and Zn (15 g) in benzene (200 ml) was added ethylbromoacetate (15 ml) dropwise during 1 h. The mixture was refluxed for 4.5 h and then cooled to room temperature. It was acidified with 10% HCl (200 ml) and benzene layer separated out. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to give 30.9 g (87.8% yield) of ethyl 3-hydroxy-3-(4'-cycloheptylphenyl)-butanoate (**2c** formula **2**, R = cycloheptyl) as viscous oil.

ETHYL 3-(4'-CYCLOHEPTYLPHENYL)-BUT-2-ENOATE (COMPOUND 3c, FORMULA 3, R = CYCLOHEPTYL)

To a solution of ethyl 3-hydroxy-3-(4'-cycloheptylphenyl)-butanoate (**2c**, 28.75 g) in benzene (175 ml) was added *p*-toluenesulfonic acid and was refluxed for 1 h. The reaction mixture was diluted with $NaHCO_3$ and benzene layer was separated out. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to give 11.6 g (42.9% yield) of ethyl 3-(4'-cycloheptylphenyl)-but-2-enoate (**3c**, formula **3**, R = cycloheptyl) as viscous oil.

3-(4'-CYCLOHEPTYLPHENYL)-2-BUTENOL (COMPOUND 4c, FORMULA 4, R = CYCLOHEPTYL)

To an ice cooled slurry of $LiAlH_4$ (2.7 g) in dry ether (175 ml) was added a solution of ethyl 3-(4'-cycloheptylphenyl)-but-2-enoate (**3c**, 9.5 g) in dry ether (50 ml) dropwise. The mixture was stirred for 4 h. at 0°C. The reaction mixture was quenched with water (7 ml). A solution of 10% NaOH (3 ml) was added. The precipitate was washed with ether and combined ether extract was dried (Na_2SO_4) and concentrated. Crude product was purified by column chromatography on silica gel to give 6.1 g (75.3% yield) of allylic alcohol (**4c**, formula 4, R = cycloheptyl) as oil.

3-(4'-CYCLOHEPTYLPHENYL)-1-HYDROXY-BUT-3-EN-2-HYDROPEROXIDE (COMPOUND 5c, FORMULA 5, R = CYCLOHEPTYL)

A solution of 3-(4'-cycloheptylphenyl)-2-butenol (**4c**, 150 mg) and methylene blue (2 mg) in acetonitrile (10 ml) was irradiated with a 250-watt tungsten-halogen lamp at –6°C while oxygen was passed through the reaction mixture for 2.5 h. The reaction mixture was concentrated and crude product was purified by column chromatography on silica gel to furnish 120 mg (75% yield) of hydroperoxide **5c**, m.p. 106-108°C

3-[(4'-CYCLOHEPTYLPHENYL)VINYL]-1,2,5-TRIOXASPIRO-[5,5]-UNDECANE (TRIOXANE 7ca, FORMULA 7, R = CYCLOHEPTYL; R_1 R_2 = -$CH_2CH_2CH_2CH_2CH_2$-)

A solution of 3-(4'-cycloheptylphenyl)-2-butenol (**4c**, 1 g) and methylene blue (5 mg) in CH_3CN (50 ml) was photooxygenated at –10°C for 3 h. Cyclohexanone (3 ml) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was stirred for 18 h at r.t. The reaction mixture was worked up as above and concentrated. Crude product was purified by chromatography on silica gel to give 700mg (50% yield, based on allylic alcohol, **4c** used) of trioxane **7ca** m.p. 55-57°C.

EXAMPLE 13

TRIOXANE 8c, FORMULA 8, R = CYCLOHEPTYL

A solution of 3-(4'-cycloheptylphenyl)-2-butenol (**4c**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –6°C for 3.5 h. Norcamphor (500 mg) and *p*-toluenesulfonic acid (30 mg) were added and reaction mixture was stirred for 18 h. at r.t. The reaction mixture was worked up as above and concentrated. Crude product was purified by chromatotron on silica gel to furnish 290 mg (38.6% yield, based on allylic alcohol, **4c** used) of trioxane **8c** m.p. 65-68°C.

EXAMPLE 14

TRIOXANE 9c, FORMULA 9, R = CYCLOHEPTYL

A solution of 3-(4'-cycloheptylphenyl)-2-butenol (**4c**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –6°C for 2 h. 2-Adamantanone (600 mg) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was stirred for 22 h. at r.t. The reaction mixture was worked up as above and concentrated. Crude product was purified by chromatotron on silica gel to furnish 420 mg (50.6% yield, based on allylic alcohol, **4c** used) of trioxane **9c** as oil.

EXAMPLE 15

TRIOXANE 7cb, FORMULA 7, R = CYCLOHEPTYL; R_1R_2 =-CH_2-CH_2-CH[$C(CH_3)_2CH_2CH_3$]-CH_2CH_2-

A solution of 3-(4'-cycloheptylphenyl)-2-butenol (**4c**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –6°C for 3 h. 4-*t*-Amylcyclohexanone (1.5 ml) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was stirred for 18 h. at r.t. The reaction mixture was worked up as above and concentrated. Crude product was purified by chromatotron on silica gel to furnish 400 mg (45.9% yield, based on allylic alcohol, **4c**, used) of trioxane **7cb** m.p. 58-60°C.

EXAMPLE 16

ETHYL 3-HYDROXY-3-(4'-CYCLOOCTYLPHENYL)-BUTANOATE (COMPOUND 2d, FORMULA 2, R = CYCLOOCTYL)

To a refluxing mixture of 4'-cyclooctylacetophenone (30 g), I_2 (5 mg) and Zn (17.2 g) in benzene (300 ml) was added ethylbromoacetate (18 ml) dropwise during 30 minutes. The mixture was refluxed for 2 h and then cooled to room temperature. It was acidified with 10% HCl (200 ml), benzene layer was separated out. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column

chromatography on silica gel to give 39.4 g (95% yield) of ethyl 3-hydroxy-3-(4'-cyclooctylphenyl)-butanoate (**2d**, formula 2, R = cyclooctyl) as viscous oil.

ETHYL 3-(4'-CYCLOOCTYLPHENYL)-BUT-2-ENOATE (COMPOUND 3d, FORMULA 3, R = CYCLOOCTYL)

To a solution of ethyl 3-hydroxy-3-(4'-cyclooctylphenyl)-butanoate (**2d**, 36 g) in benzene (350 ml) was added *p*-toluenesulfonic acid and refluxed for 2.5 h. The mixture was diluted with saturated $NaHCO_3$ solution (20 ml) and water (50 ml) and benzene layer was separated out. Aqueous layer was extracted with benzene (2 x 200 ml) combined organic layer was washed with water (2 x 20 ml), dried over Na_2SO_4 and concentrated. Crude product was purified by column chromatography to furnish 27.5 g (81.1% yield) of ethyl 3-(4'-cyclooctylphenyl)-but-2-enoate (**3d**, formula 3, R = cyclooctyl) as oil.

3-(4'-CYCLOOCTYLPHENYL)-2-BUTENOL (COMPOUND 4d, FORMULA 4, R = CYCLOOCTYL)

To an ice cooled slurry of $LiAlH_4$ (2.9 g) in dry ether (200 ml) was added a solution of ethyl 3-(4'-cyclooctylphenyl)-but-2-enoate (**3d**, 10 g) in dry ether (50 ml) dropwise. The reaction mixture was stirred at O°C for 2 h. The reaction mixture was quenched with water (11 ml). A solution of 10% NaOH (10 ml) was added and ether layer was decanted. The precipitate was washed with ether and combined extracts were concentrated. The crude product was purified by column chromatography on silica gel to give 6.82 g (79.3% yield) of 3-(4'-cyclooctylphenyl)-2-butenol (**4d**, formula **4**, R = cyclooctyl) m.p. 40-44°C.

3-(4'-CYCLOOCTYLPHENYL)-1-HYDROXY-BUT-3-EN-2-HYDROPEROXIDE (COMPOUND 5d, FORMULA 5, R = CYCLOOCTYL)

A solution of 3-(4'-cyclooctylphenyl)-2-butenol (**4d**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was irradiation with a 250-watt tungsten-halogen lamp at –6°C while oxygen was passed through the reaction mixture. After 2.5 h the reaction mixture was concentrated and crude product was purified by column chromatography on silica gel to furnished 400 mg (71.4% yield), m.p.83-85°C.

3-ETHYL-3-METHYL-6-[(4'-CYCLOOCTYLPHENYL)VINYL]-1,2,4-TRIOXANE (COMPOUND 7da, FORMULA 7, R = CYCLOOCTYL)

A solution of 3-(4'-cyclooctylphenyl)-2-butenol (**4d**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at -6°C for 3 h. Ethyl methyl ketone (1 ml) and HCl (1 drop) were added and the reaction mixture was left at r.t. for 18 h. The reaction mixture was concentrated to remove CH_3CN, diluted with $NaHCO_3$ and water and extracted with ether (3 x 30 ml). The organic layer was dried over Na_2SO_4 and

concentrated. The crude product was purified by chromatotron over silica gel to give 190 mg (28.7% yield based on allylic alcohol, **4d**, used) of trioxane **7da** as oil.

EXAMPLE 17

3-[(4'-CYCLOOCTYLPHENYL)VINYL]-1,2,5-TRIOXASPIRO-(5,5)-UNDECANE (TRIOXANE 7db, FORMULA 7, R = CYCLOOCTYL; R_1 R_2 = -$CH_2CH_2CH_2CH_2CH_2$-)

A solution of 3-(4'-cyclooctylphenyl)-2-butenol (**4d**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –6°C for 2.5 h. Cyclohexanone (1.5 ml) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was left at r.t. for 18 h. The reaction mixture was worked up as above and concentrated. The crude product was purified by chromatron on silica gel to give 340 mg (47.8% yield, based on allylic alcohol, **4d** used) of trioxane **7db** as solid m.p. 58-60°C.

EXAMPLE 18

3-[(4'-CYCLOOCTYLPHENYL)VINYL]-1,2,5-TRIOXASPIRO-(6,5)-DODECANE (TRIOXANE 7dc, R = CYCLOOCTYL; R_1 R_2 = -$CH_2CH_2CH_2CH_2CH_2CH_2$-)

A solution of 3-(4'-cyclooctylphenyl)-2-butenol (**4d**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –6°C for 2.5 h. Cycloheptanone (1.5 ml) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was left at r.t. for 18 h. The reaction mixture was worked up as above and concentrated. The crude product was purified by chromatotron on silica gel to furnish 210 mg (28.3% yield, based on allylic alcohol, **4d** used) of trioxane **7dc** as oil.

EXAMPLE 19

TRIOXANE 7dd, FORMULA 7, R = CYCLOOCTYL; R_1 R_2 = -$CH_2CH_2CH(Ph)CH_2CH_2$-)

A solution of 3-(4'-cyclooctylphenyl)-2-butenol (**4d**, 500 mg) and methylene blue (5 mg) in CH_3CN (30 ml) was photooxygenated at –8°C for 2.5 h. 4-Phenylcyclohexanone (1 g) and *p*-toluenesulfonic acid (50 mg) were added and reaction mixture was left at r.t. for 18 h. The reaction mixture was worked up as above and concentrated. The crude product was purified by chromatotron on silica gel to furnish 340 mg (39.5% yield, based on allylic alcohol, **4d** used) of trioxane **7dd** as solid m.p. 95-97°C.

EXAMPLE 20

TRIOXANE 8d, FORMULA 8, R = CYCLOOCTYL

A solution of 3-(4'-cyclooctylphenyl)-2-butenol (**4d**, 500 mg) and methylene blue (5 mg) in CH_3CN (30ml) was photooxygenated at –6°C for 2.5 h. Norcamphor (500 mg) and *p*-

toluenesulfonic acid (50 mg) were added and reaction mixture was kept at 10°C for 48 h. Reaction mixture was worked up as above and concentrated. Crude product was purified by chromatotron on silica gel to furnish 350mg (47.5 % yield, based on allylic alcohol **4d,** used) of trioxane **8d** as oil.

EXAMPLE 21

TRIOXANE 9d, FORMULA 9, R = CYCLOOCTYL

A solution of 3-(4'-cyclooctylphenyl)-2-butenol (**4d**, 500 mg) and methylene blue (5 mg) in CH_3CN (30ml) was photooxygenated at –10°C for 3h. 2-Adamantanone (500 mg) and *p*-toluenesulfonic acid (80 mg) were added and reaction mixture was stirred at r.t. for 4 h and then left at r.t. for 14h. Reaction mixture was worked up as above and concentrated. Crude product was purified by chromatotron on silica gel to furnish 360mg (44.4% yield, based on allylic alcohol **4d,** used) of trioxane **9d** as oil.

EXAMPLE 22

ETHYL 3-HYDROXY-3-([1,1'-BIPHENYL]-4YL)-BUTANOATE (COMPOUND 2e, FORMULA 2, R =Ph)

To a refluxing mixture of 4-acetylbiphenyl (20 g), I_2 (5 mg) and Zn (6.8 g) in benzene (200 ml) was added ethylbromoacetate (12 ml) dropwise during 30 minutes. The mixture was refluxed for 1 h and then cooled to room temperature. It was acidified with 10% HCl (100 ml) and benzene layer was separated out. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to give 20.6g (72.1% yield) of ethyl 3-hydroxy-3-([1,1'-biphenyl]-4yl) butanoate (**2e,** formula **2,** R=Ph) m.p. 58-60°C.

The above compound was also prepared using different reaction condition. **Table 4** gives the condition used and yield of compound **2e**.

TABLE 4

Solvent	Temperature	Reaction time	Yield
Diethyl ether	r.t.	No reaction	-
Diethyl ether	Refluxed	No reaction	-
Toluene	Refluxed	1 h	92.8%

The compound **2e** was also prepared using ethylchloroacetate under same reaction conditions to furnish 17.8% yield of ethyl 3-hydroxy-3-([1,1'-biphenyl]-4yl) butanoate (**2e**).

ETHYL 3-([1,1'-BIPHENYL]-4YL)-BUT-2-ENOATE (COMPOUND 3e, FORMULA 3, R = Ph)

To a solution of ethyl 3-hydroxy-3-([1,1'-biphenyl]-4yl)-butanoate (**2e**, 11g) in benzene (250 ml) was added phosphorus pentoxide (4g) and refluxed for 3 h. The benzene layer was decanted and then concentrated. The crude product was purified by column chromatography on silica gel to furnish 11g (57.3% yield) of ethyl 3-([1,1'-biphenyl]-4yl)-but-2-enoate (**3e**, formula **3**, R =Ph) m.p. 76-78°C.

The compound **3e** was also prepared using different reaction condition. **Table 5** gives the conditions used and the yield of compound **3e**.

TABLE 5

Acid catalyst	Solvent	Temperature	Reaction time	Yield (%)
PTSA	Benzene	Refluxed	1 h	55.5
Amberlyst-15	Toluene	Refluxed	1 h	77.7
I_2	Benzene	Refluxed	1 h	88.8
H_2SO_4	$CHCl_3$	r.t.	18 h	33.3

3-([1,1'-BIPHENYL]-4YL)-2-BUTENOL (COMPOUND 4e, FORMULA 4, R =Ph)

To an ice cooled slurry of $LiAlH_4$ (4.0g) in dry ether (400 ml) was added ethyl 3-([1,1'-biphenyl]-but-2-enoate (**3e**, 11g) in dry ether (200ml) dropwise. The mixture was stirred at 0°C for 2h. The reaction mixture was quenched with water (10 ml). A solution of 10% NaOH (5 ml) was added, stirred and then ether layer was decanted. The precipitate was washed with ether and combined ether extracts were concentrated. The crude product was purified by chromatography on silica gel to give 7.2 g (77.4% yield) of 3-([1,1'-biphenyl]-4yl)-2-butenol (**4e** formula **4**, R=Ph), m.p. 112-114°C.

$LiAlH_4$ reduction of ethyl 3-([1,1'-biphenyl]-but-2-enoate (**3e**) using THF as solvent under similar conditions furnished 40.6% yield of 3-([1,1'-biphenyl]-4yl)-2-butenol (**4e**).

3-([1,1'-BIPHENYL]-4YL)-1-HYDROXY-BUT-3-EN-2-HYDROPEROXIDE (COMPOUND 5e, FORMULA 5, R =Ph)

A solution of 3-([1,1'-biphenyl]-4yl)-2-butenol (**4e**, 200 mg) and methylene blue (2 mg) in acetonitrile (15 ml) was irradiated with 250-watt tungsten – halogen lamp at –6°C while oxygen was passed through the reaction mixture. After 4h the reaction mixture was concentrated. The reaction mixture was filtered through a cintered crucible to furnish 80 mg of hydroperoxide. Mother liquor was purified by column chromatography to furnish 40

mg of hydroperoxide. The combined yield of hydroperoxide (compound **5e**, formula **5**, R=Ph) was 120 mg (54.5% yield) m.p. 124°C.

Phototoxygenation of 3-([1,1'-biphenyl]-4yl)-2-butenol (**4e**), in $CHCl_3$ at 0°C, using tetraphenylporphine as sensetizer furnished **5e** in 81.8% yield.

6-[([1,1'-BIPHENYL]-4YL)VINYL]-3-PHENYL-1,2,4-TRIOXANE (TRIOXANE 7ea, FORMULA 7, R=Ph, R_1, R2 = H, Ph).

To a solution of 3-([1,1'-biphenyl]-4yl)-1-hydroxy-but-3-en-2-hydroperoxide (**5e**, 400 mg) and benzaldehyde (350 mg) in acetonitrile (10 ml) was added p-toluenesulfonic acid (20 mg) and was stirred at r.t. for 2 h. The reaction mixture was worked up as above and concentrated. Crude product was purified by column chromatography to furnish 280 mg (70% yield) of trioxane **7ea** m.p. 110-112°C.

EXAMPLE 23

8-[([1,1'-BIPHENYL]-4YL)VINYL]-6,7,10-TRIOXASPIRO (4,5) DECANE (TRIOXANE 7eb, FORMULA 7, R=Ph, R_1R_2 =-$CH_2CH_2CH_2CH_2$-)

To a solution of 3-([1,1'-biphenyl]-4yl)-1-hydroxy-but-3-en-hydroperoxide (**5e**, 430 mg) and cyclopentanone (700 mg) in acetonitrile (10 ml) was added p-toluenesulfonic acid (30 mg) and the reaction mixture was stirred at r.t. for 3 h. The reaction mixture was worked up as above and concentrated. The crude product was purified by column chromatography followed by crystallization from hexane to furnish 250 mg (45.1% yield) of trioxane **7eb**, m.p. 102-104°C.

EXAMPLE 24

3-[([1,1'-BIPHENYL]-4YL)VINYL]-1,2,5-TRIOXASPIRO (5,5) UNDECANE (TRIOXANE 7ec, FORMULA 7, R=Ph, R_1R_2 =-$CH_2CH_2CH_2CH_2CH_2$-)

To a solution of 3-([1,1'-biphenyl]-4yl)-1-hydroxy-but-3-en-2-hydroperoxide (**5e**, 600 mg) and cyclohexanone (1 ml) in acetonitrile (20 ml) was added p-toluenesulfonic acid (20 mg) and the reaction mixture was stirred at r.t. for 1 h. The reaction mixture was worked up as above and concentrated. The crude product was purified by column chromatography followed by crystallization from hexane to furnish 360 mg (46.1% yield) of trioxane **7ec**, m.p. 96-98°C.

EXAMPLE 25

3-DECYL-3-METHYL-6-[([1,1'-BIPHENYL]-4-YL)-VINYL]-1,2,4-TRIOXANE (TRIOXANE 7ed, FORMULA 7, R =Ph; R_1, R_2=CH_3, -$CH_2(CH_2)_8CH_3$)

A solution of 3-([1,1'-biphenyl]-4yl)-2-butenol (**4e**, 200 mg) and methylene blue (2 mg) in acetonitrile (10 ml) and chloroform (10 ml) was photooxygenated at 0°C for 3 h. 2-

dodecanone (0.5 ml) and hydrochloric acid (2 drops) were added and reaction mixture of left at r.t. for 18 h. The reaction mixture was worked up and concentrated. Crude product was purified by column chromatography on silica gel to furnish 100mg mg (27% yield, based on allylic alcohol, **4e,** used) of trioxane **7ed** m.p. 86-90°C.

EXAMPLE 26

TRIOXANE 8e, FORMULA 8, R =Ph

A solution of 3-([1,1'-biphenyl]-4yl)-2-butenol (**4e**, 200 mg) and methylene blue (2 mg) in acetonitrile (15 ml) was photooxygenated at –10°C for 3 h. Norcamphor (250 mg) and p-toluene sulfonic acid (30 mg) were added and reaction mixture was left at r.t. for 18 h. The reaction mixture was worked up and concentrated. Crude product was purified by column chromatography on silica gel to furnish 140 mg (45.1% yield, based on allylic alcohol, **4e,** used) of trioxane **8e** m.p. 86-90°C.

EXAMPLE 27

TRIOXANE 9e, FORMULA 9, R =Ph

To a solution of 3-([1,1'-biphenyl]-4yl)-1-hydroxy-but-3-en-2- hydroperoxide (**5e**, 300 mg) and 2-Adamantanone (250 mg) in acetonitrile (20 ml) was added p-toluenesulfonic acid (30 mg) and was stirred for 1 h at r.t. The reaction mixture was worked up and concentrated. Crude product was purified by column chromatography on silica gel to furnish 320 mg (71.04% yield) of trioxane **9e**, m.p. 94-96°C.

The above trioxane was also prepared from **4e** using different reaction conditions. **Table 6** gives the conditions used and the yields of the trioxane **9e.**

TABLE 6

Dye	Temperature	Solvent	Acid catalyst	Reaction time	Yield[a]
Tetraphenyl-Porphine	r.t.	$CHCl_3$	H_2SO_4	30 min	55.5%
Rose Bengal	-6°C	EtOH *	Amberlyst-15	2 h	24.4%

*EtOH was removed under reduced pressure after photooxygenation and replaced by $CHCl_3$ in the second step before the addition of 2-Adamantanone.

[a] Yields based on allylic alcohols **4e** used.

EXAMPLE 28

ETHYL 3-HYDROXY-3-(4'-BROMO[1,1'-BIPHENYL]-4-YL)-BUTANOATE (COMPOUND 2f, FORMULA 2, R = *p*-Br-C_6H_4)

To a refluxing mixture of 4-(4-bromophenyl)acetophenone (10 g), I_2 (5mg) and Zn (4.9g) in benzene (100 ml) was added ethylbromoacetate (6.1 ml) dropwise during 45 minutes. The mixture was refluxed for 45 minutes and then cooled to room temperature. It was

acidified with 10% HCl (75 ml) and benzene layer was separated. Organic layer was washed with water, dried (Na_2SO_4) and concentrated. Crude product was crystallized from hexane to furnish 8g of ß-hydroxyester (**2f**). Mother liquor was purified by column chromatography on silica gel to furnish 3.7 g of ß-hydroxyester (**2f**). The combined yield of ß-hydroxyester (compound **2f**, formula **2**, R = *p*-Br-C_6H_4) was 11.7 g (88.9%), m.p. 70°C.

ETHYL 3-(4'-BROMO-[1,1'-BIPHENYL]-4-YL)-BUT-2-ENOATE (COMPOUND 3f, FORMULA 3, R = *p*-Br-C_6H_4)

To a solution of ethyl 3-hydroxy-3-(4'-bromo[1,1'-biphenyl]-4-yl)-butanoate (**2f**, 8.0g) in benzene (75 ml) was added p-toluenesulfonic acid (420 mg) and was refluxed for 1h 15 minutes. The reaction mixture was cooled, neutralized with $NaHCO_3$ solution, diluted with water and organic layer was extracted. Organic layer was washed with water, dried (Na_2SO_4) and concentrated. Crude product was purified by column chromatography on silica gel to furnish 5g (65.7% yield) of ethyl 3-hydroxy-3-(4'-bromo[1,1'-biphenyl]-4-yl)-but-2-enoate (**3f**, formula **3**, R = *p*-Br-C_6H_4) m.p. 96-98°C.

3-(4'-BROMO-[1,1'-BIPHENYL]-4-YL)-2-BUTENOL (COMPOUND 4f, FORMULA 4, R = *p*-Br-C_6H_4)

To an ice cooled slurry of $LiAlH_4$ (2.0g) in dry ether (200 ml) was added a solution of ethyl 3-hydroxy-3-(4'-bromo-[1,1'-biphenyl]-4-yl)-but-2-enoate (**3f**, 4.4g) in dry ether (100 ml) dropwise. The reaction mixture was stirred for 5 h at O°C. The reaction mixture was quenched with water (5 ml). A solution of 10% NaOH (5 ml) was added and the ether layer was decanted. The precipitate was washed with ether and the combined ether extract was concentrated. The crude product was chromatographed on silica gel to give 2g (52.6% yield) of 3-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-butenol (**4f**, formula **4**, R = *p*-Br-C_6H_4) m.p. 145-148°C.

3-(4'-BROMO-[1,1'-BIPHENYL]-4YL)-1-HYDROXY-BUT-3-EN-2-HYDROPEROXIDE (COMPOUND 5f, FORMULA 5, R = *p*-Br-C_6H_4)

A solution of 3-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-butenol (**4f**, 100 mg) and methylene blue (5 mg) in acetonitrile (7 ml) and CH_2Cl_2 (7 ml) was irradiated with a 250 watt tungsten-halogen lamp at –6°C while oxygen was passed through the reaction mixture for 5 h. The crude product obtained by usual aqueous workup was crystallized from CH_2Cl_2 to give 20 mg of hydroperoxide **5f**. The filtrate was chromatographed on silica gel to give 40 mg of hydroperoxide **5f**. The combined yield of hydroperoxide (compound **5f**, formula 5, R = *p*-Br-C_6H_4) was 60 mg (55% yield).

3,3-DIMETHYL-6-[(4'-BROMO-[1,1'-BIPHENYL]-4-YL)-VINYL]-1,2,4-TRIOXANE (TRIOXANE 7fa, FORMULA 7, R = *p*-Br-C_6H_4; R_1, R_2=CH_3, CH_3)

A solution of 3-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-butenol (**4f**, 350 mg) and methylene blue (2 mg) in acetone (40 ml) was photooxygenated at –10°C for 5 h. To the mixture was added p-toluenesulfonic acid (50 mg) and left at r.t. for 18 h and then concentrated. The crude product was purified by column chromatography to give 300 mg (69.7% yield) of trioxane **7fa** m.p. 92-95°C.

EXAMPLE 29

3-ETHYL-3-METHLY-6-[(4'-BROMO-[1,1'-BIPHENYL]-4-YL)-VINYL]-1,2,4-TRIOXANE (TRIOXANE 7fb, FORMULA 7, R = *p*-Br-C_6H_4; R_1, R_2=CH_3, CH_2CH_3)

A solution of 3-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-butenol (**4f**, 500 mg) and methylene blue (5 mg) in CH_3CN (40 ml) and CH_2Cl_2 was photooxygenated at –6°C for 3 h. To the mixture was added ethyl methyl ketone (3 ml) and p-toluenesulfonic acid (40 mg) and left at r.t. for 18 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (5 ml) and worked up as above and concentrated. The crude product was purified by column chromatography to give 240 mg (37.5% yield) of trioxane **7fb** as a mixture of two stereoisomers, which were further, purified to furnish the more polar isomer, m.p. 72-74 °C and less polar isomer, m.p. 82-85°C.

EXAMPLE 30

3-[(4'-BROMO-[1,1'-BIPHENYL]-4-YL)-VINYL]-1,2,5-TRIOXASPIRO (5,5) UNDECANE (TRIOXANE 7fc, FORMULA 7, R = *p*-Br-C_6H_4; R_1 R_2=$CH_2CH_2CH_2CH_2CH_2$-)

A solution of 3-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-butenol (**4f**, 500mg) and methylene blue (5 mg) in CH_3CN (35 ml) and CH_2Cl_2 (35 ml) was photooxygenated at –6°C for 3.5 h. Cyclohexanone (1 ml) and p-toluenesulfonic acid (60 mg) were added and reaction mixture was left at r.t. for 18 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (5 ml) and worked up as above and concentrated. Crude product was purified by column chromatography to furnish 320 mg (47% yield, based on allylic alcohol **4f**, used) of trioxane **7fc**, m.p. 118-120°C.

EXAMPLE 31

TRIOXANE 7fd,FORMULA 7, R = *p*-Br-C_6H_4, R_1 R_2 = =-CH_2.CH_2-$CH[C(CH_3)_2CH_2CH_3]$-CH_2.CH_2-

A solution of 3-(4'-bromo-[1,1'-biphenyl]-4yl)-2-butenol (**4f**, 500gm) and methylene blue (2 mg) in CH_3CN (40 ml) and CH_2Cl_2 (40 ml) was photooxygenated at –6°C for 3 h. 4-t-

amyl cyclohexanone (1.5 ml) and p-toluenesulfonic acid (50 mg) were added and reaction mixture was left at r.t. for 17h . The reaction mixture was worked up and concentrated. Crude product was purified by column chromatography to furnish 480 mg (60% yield, based on allylic alcohol, **4f** used) of trioxane **7fd** m.p. 122-124°C

EXAMPLE 32

TRIOXANE 8f, FORMULA 8, R = *p*-Br-C_6H_4

A solution of 3-(4'-bromo-[1,1'-biphenyl]-4yl)-2-butenol (**4f**, 350 mg) and methylene blue (2 mg) in CH_3CN (25 ml) and CH_2Cl_2 (25 ml) was photooxygenated at –6°C for 3h. Norcamphor (750 mg) and p-toluenesulfonic acid (50 mg) were added and the reaction mixture was stirred at r.t. for 18 h. The reaction mixture was worked up as above and concentrated. Crude product was purified by column chromatography on silica gel to furnish 300 mg (42.8% yield, based on allylic alcohol, **4f** used) of trioxane **8f**, m.p. 122-124°C.

EXAMPLE 33

TRIOXANE 9f, FORMULA 9, R = *p*-Br-C_6H_4

A solution of 3-(4'-bromo-[1,1'-biphenyl]-4yl)-2-butenol (**4f**, 500 mg) and methylene blue (2 mg) in CH_3CN (40 ml) and CH_2Cl_2 (40 ml) was photoooxygenated at 5°C for 5 h. 2-Adamantanone (1g) and p-toluenesulfonic acid (60 mg) were added and reaction mixture was stirred for 30 minutes and then left at r.t. for 16 h. Reaction mixture was worked as above and concentrated. Crude product was purified by column chromatography to furnish 490 mg (63.6% yield, based on allylic alcohol **4f**, used) of trioxane **9f** mp 118°C.

EXAMPLE 34

ETHYL 3-(4'-CHLORO-[1,1'-BIPHENYL]-4-YL)-BUT-2-ENOATE (COMPOUND 3g, FORMULA 3, R = *p*-Cl-C_6H_4)

To a refluxing mixture of 4-(4-chlorophenyl)acetophenone (8.46 g), I_2 (5mg) and Zn (2.55g) in benzene (200 ml) was added ethylbromoacetate (4.35 ml) dropwise during 30 minutes. The mixture was refluxed for 2 h and then cooled to room temperature. It was acidified with 10% HCl (75 ml) and benzene layer was separated. Organic layer was washed with water, dried (Na_2SO_4) and concentrated. Crude ß-hydroxyester (compound **2g**, formula **2**, R = *p*- Cl -C_6H_4) was used as such without purification for the preparation of ethyl 3-(4'-chloro-[1,1'-biphenyl]-4-yl)-but-2-enoate as follows:

To a solution of crude ethyl 3-hydroxy-3-(4'-chloro-[1,1'-biphenyl]-4-yl)-butanoate (**2g**) in benzene (200 ml) was added p-toluenesulfonic acid (3 gm) and was refluxed for 3h 30 minutes. The reaction mixture was cooled, neutralized with $NaHCO_3$ solution, diluted

with water and organic layer was extracted. Organic layer was washed with water, dried ($NaHCO_3$) and concentrated. Crude product was purified by column chromatography on silica gel to furnish 5.27g (47. =91% yield) of ethyl 3-(4'-chloro-[1,1'-biphenyl]-4-yl)-but-2-enoate (**3g**, formula **3**, R = *p*-Cl-C_6H_4) m.p. 91-94°C.

3-(4'-CHLORO-[1,1'-BIPHENYL]-4-YL)-2-BUTENOL (COMPOUND 4g, FORMULA 4, R = *p*-Cl-C_6H_4)

To an ice cooled slurry of $LiAlH_4$ (1.4g) in dry ether (200 ml) was added a solution of ethyl 3-(4'-chloro-[1,1'-biphenyl]-4-yl)-but-2-enoate (**3g**, 2.8g) in dry ether (50 ml) dropwise. The reaction mixture was stirred for 2 h at O°C. The reaction mixture was quenched with water. A solution of 10% NaOH was added and the ether layer was decanted. The precipitate was washed with ether and the combined ether extract was concentrated. The crude product was chromatographed on silica gel to give 1.8g (75% yield) of 3-(4'-chloro-[1,1'-biphenyl]-4-yl)-butenol (**4g**, formula **4**, R = *p*-Cl-C_6H_4) m.p. 130-132°C.

3-(4'-CHLORO-[1,1'-BIPHENYL]-4YL)-1-HYDROXY-BUT-3-EN-2-HYDROPEROXIDE (COMPOUND 5g, FORMULA 5, R = *p*-Cl-C_6H_4)

A solution of 3-(4'-chloro-[1,1'-biphenyl]-4-yl)-2-butenol (**4g**, 1g) and methylene blue (40 mg) in acetonitrile (30 ml) was irradiation with a 250-watt tungsten-halogen lamp at 10°C while oxygen was passed through the reaction mixture for 5 h 30 minutes. Solid hydroperoxide separated out during the reaction was collected by filtration to furnish 600mg of hydroperoxide **5g**. The filtrate was chromatographed on silica gel to give 260 mg of hydroperoxide **5g**. The combined yield of hydroperoxide (compound **5g**, formula 5, R = *p*-Cl-C_6H_4) was 860 mg (76.7 % yield).

8-[(4'-CHLORO-[1,1'-BIPHENYL]-4YL)VINYL]-6,7,10-TRIOXASPIRO (4,5) DECANE (TRIOXANE 7ga, FORMULA 7, R = *p*-Cl-C_6H_4, R_1R_2 =-$CH_2CH_2CH_2CH_2$)

A solution of 3-(4'-chloro-[1,1'-biphenyl]4yl)-2-butenol (**4g**, 500gm) and methylene blue (40 mg) in CH_3CN (30 ml) was photooxygenated at 5°C for 5 h. Cyclopentanone (0.5 ml) and hydrochloric acid (5 drops) were added and reaction mixture was stirred at r.t. for 1.5h and then left at r.t for 48 h. The reaction mixture was concentrated. Crude product was purified by column chromatography to furnish 230 mg (33.8% yield, based on allylic alcohol, **4g** used) of trioxane **7ga** m.p. 105-107°C.

EXAMPLE 35

3-[(4'-CHLORO-[1,1'-BIPHENYL]-4-YL)-VINYL]-1,2,5-TRIOXASPIRO (5,5) UNDECANE (TRIOXANE 7gb, FORMULA 7, R = *p*- Cl -C_6H_4; R_1 R_2=$CH_2CH_2CH_2CH_2CH_2$-)

A solution of 3-[(4'-chloro-[1,1'-biphenyl]-4-yl)-2-butenol (**4g**, 500mg) and methylene blue (40 mg) in CH_3CN (30 ml) was photooxygenated at 5°C for 5 h. Cyclohexanone (0.5 ml) and hydrochloric acid (5 drops) were added and reaction mixture was stirred at r.t. for 1.5h and then left at r.t for 24 h. The reaction mixture was concentrated. Crude product was purified by column chromatography to furnish 360 mg (50% yield, based on allylic alcohol **4g**, used) of trioxane **7gb**, m.p. 109-111°C.

EXAMPLE 36

TRIOXANE 8g, FORMULA 8, R = *p*-Cl-C_6H_4

To a solution of 3-(4'-chloro-[1,1'-biphenyl]-4yl)-1-hydroxy-but-3-en-2-hydroperoxide (**5g**, 500mg) and norcamphor (500mg) in chloroform (100 ml) was added hydrochloric acid (5 drops) and the reaction mixture was stirred at r.t. for 1 h and then left at r.t for 18 h. The reaction mixture was worked up as above and concentrated. Crude product was purified by column chromatography on silica gel followed by crystallization to furnish 420mg (64.6 % yield) of trioxane **8g**, m.p. 122-124°C.

EXAMPLE 37

TRIOXANE 9g, FORMULA 9, R = *p*-Cl-C_6H_4

A solution of 3-(4'-chloro-[1,1'-biphenyl]-4yl)-2-butenol (**4g**, 500 mg) and methylene blue (50 mg) in CH_3CN (60 ml) was photoooxygenated at 5°C for 5 h. 2-Adamantanone (1g) and hydrochloric acid (5 drops) were added and reaction mixture was stirred at r.t. for 2h and then left at r.t for 16 h. The reaction mixture was worked up and concentrated. Crude product was purified by column chromatography to furnish 560 mg (69.14% yield, based on allylic alcohol **4g**, used) of trioxane **9g**, m.p. 112-115°C.

FOLLOWING THE ABOVE PROCEDURE THE FOLLOWING TRIOXANES WERE PREPARED:

S.No.	Trioxane	m.p.	% Yield
1.	8-[(4'-Cyclopentylphenyl)vinyl]-6,7,10-trioxaspiro-[4,5]-decane (trioxane **7aa**, formula 7, R = cyclopentyl; R_1 R_2 = -$CH_2CH_2CH_2CH_2$)	oil	52.7

2.	Trioxane **7ab**, formula 7, R = cyclopentyl ; R_1 R_2 = -$CH_2CH_2CH(Ph)CH_2CH_2$-	98-100 °C	60.2
3.	3-[(4'-cyclopentylphenyl)vinyl]-1,2,5-trioxaspiro(5,5)undecane (**7ac**, formula 7, R = cyclopentyl, R_1 R_2= -$CH_2CH_2CH_2CH_2CH_2$-)	57-58°C	50.6
4.	3-[(4'-cyclopentylphenyl)vinyl-1,2,5-trioxaspira (5,6)dodecane (**7ad**, formula 7, R=cyclopentyl, R_1R_2=-$CH_2CH_2CH_2CH_2CH_2$ CH_2-)	Oil	29.1
5.	Trioxane **7ae**, formula 7, R = cyclopentyl, R_1 R_2 =CH_2-CH_2-CH($C(CH_3)_2CH_2CH_3$)-CH_2CH_2-	95-97°C	47.8
6.	Trioxane belonging to norcamphor group(**8a** R = cyclopentyl)	91-93°C	28
7.	Trioxane belonging to adamantane group (**9a** R = cyclopentyl)	74-76°C	49.4
8.	3,3-dimethyl-6-[4'-cyclohexylphenyl]vinyl-1,2,4-trioxane (trioxane **7ba**, formula 7, R = cyclohexyl)	54-55°C	76.9
9.	3-Decyl-3-methyl-6-[(4'-cyclohexylphenyl) vinyl]-1,2,4-trioxane (trioxane **7bb**, formula 7, R = cyclohexyl)	oil	31.1
10	6-[(4'-cyclohexylphenyl)vinyl]-3-phenyl-1,2,4-trioxane (trioxane **7bc**, formula 7, R = cyclohexyl]	86-88°C	44.7
11	3-[(4'-Cyclohexylphenyl)vinyl]-1,2,5-trioxaspiro(5,5)undecane (trioxane **7bd**, formula 7, R= cyclohexyl, R_1R_2 = -$CH_2CH_2CH_2CH_2CH_2$-)	60-62°C	74.3
12.	Trioxane **7be**, formula 7, R = cyclohexyl, R_1R_2=-CH_2-CH_2-CH(Ph)CH_2CH_2-	107-109°C	63.3
13.	3-ethyl-3-methyl-6-[4'-cyclohexyl phenyl)vinyl]-1,2,4-trioxane (**7bf**, formula 7, R = cyclohexyl, R_1, R_2= CH_3, -CH_2CH_3)	Oil	20
14.	3-Methyl-3-propyl-6-[4'-cyclohexyl phenyl)vinyl]-1,2,4-trioxane (**7bg**, formula 7, R = cyclohexyl, R_1, R_2= CH_3, -$CH_2CH_2CH_3$)	Oil	28.1
15.	8-[(4'-cyclohexylphenyl)vinyl]-6,7,10-trioxaspiro (4,5) decane (**7bh**, formula 7, R=cyclohexyl, R_1 R_2=-CH_2-CH_2-CH_2-CH_2-)	43-45°C	39.4
16.	Trioxane**7bi**, formula 7, R = cyclohexyl, R_1 R_2 = CH_2-CH_2-CH($C(CH_3)_2CH_2CH_3$)-CH_2CH_2-	90-92°C	50.5
17.	Trioxane belonging to norcamphor group(**8b** R = cyclohexyl)	70-71°C	40.8
18.	Trioxane belonging to adamantane group (**9b** R = cyclohexyl)	75-76°C	58.8
19.	3-[(4'-cycloheptylphenyl)vinyl]-1,2,5-trioxaspiro-[5,5]-undecane (trioxane **7ca**, formula 7, R = cycloheptyl; R_1 R_2 = -$CH_2CH_2CH_2CH_2CH_2$-).	55-57°C	50

20.	Trioxane **7cb**, formula 7, R = cycloheptyl ; R_1R_2 =-CH_2-CH_2-CH($C(CH_3)_2CH_2CH_3$)-CH_2CH_2-	58-60°C	45.9
21.	8-[(4'-cycloheptylphenyl)vinyl]-6,7,10-trioxaspiro(4,5)decane (**7cc**,formula 7, R = cycloheptyl, R_1 R_2 = CH_2-CH_2-CH_2-CH_2-	Oil	65
22.	Trioxane **7cd**, formula 7, R = cycloheptyl, R_1R_2 = CH_2-CH_2-CH(Ph)-CH_2-CH_2-)	92-95°C	44
23.	Trioxane belonging to norcamphor group(**8c** R = cycloheptyl)	65-68°C	38.6
24.	Trioxane belonging to adamantane group (**9c** R = cycloheptyl)	oil	50.6
25.	3-ethyl-3-methyl-6-[(4'-cyclooctylphenyl) vinyl]-1,2,4-trioxane (compound **7da**, formula 7, R = cyclooctyl)	oil	28.7
26.	3-[(4'-cyclooctylphenyl)vinyl]-1,2,5-trioxaspiro-(5,5)-undecane (trioxane **7db**, formula 7, R = cyclooctyl; R_1 R_2 = -$CH_2CH_2CH_2CH_2CH_2$-)	58-60°C	47.8
27.	3-[(4'-cyclooctylphenyl)vinyl]-1,2,5-trioxaspiro-(6,5)-dodecane (trioxane **7dc**, formula 7, R = cyclooctyl; R_1 R_2 = -$CH_2CH_2CH_2CH_2CH_2CH_2$-)	oil	28.3
28.	Trioxane **7dd**, formula 7, R = cyclooctyl, R_1R_2 = CH_2-CH_2-CH(Ph)-CH_2-CH_2-)	95-97°C	39.5
29.	8-[(4'-cyclooctylphenyl)vinyl]-6,7,10-trioxaspiro(4,5)undecane (**7de**, formula 7, R = cycloheptyl, R_1R_2 = CH_2-CH_2-CH_2-CH_2-)	Oil	45.5
30.	Trioxane **7df**, formula 7, R= cyclooctyl, R_1R_2 = CH_2-CH_2-CH($C(CH_3)_2CH_2CH_3$)-CH_2CH_2-	89-91°C	51.7
31.	Trioxane belonging to norcamphor group(**8d** R = cyclooctyl)	oil	47.5
32.	Trioxane belonging to adamantane group (**9d** R = cyclooctyl)	oil	44.4
33.	6-[([1,1'-biphenyl]-4yl)vinyl]-3-phenyl-1,2,4-trioxane (**7ea**, formula 7, R=Ph, R_1,R_2 = H, Ph).	110-112°C	70
34.	8-[([1,1'-biphenyl]-4yl)vinyl]-6,7,10-trioxaspiro (4,5) decane (**7eb**, formula 7, R=Ph, R_1R_2 =-$CH_2CH_2CH_2CH_2$-)	102-104°C	45.1
35.	3-[([1,1'-biphenyl]-4yl)vinyl]-1,2,5-trioxaspiro (5,5) undecane (**7ec**, formula 7, R=Ph, R_1R_2 = -$CH_2CH_2CH_2CH_2CH_2$-)	96-98°C	46.1
36.	3-Decyl-3-Methyl-6-[([1,1'-biphenyl]-4-yl)-vinyl]-1,2,4-trioxane (**7ed**, formula 7, R=Ph; R_1, R_2=CH_3, -$CH_2(CH_2)_8CH_3$)	86-90°C	27

37.	3,3-Dimethyl-6-[([1,1'-biphenyl]-4yl)vinyl]-1,2,4-trioxane (**7ee**, formula 7, R=Ph, R_1, R_2 = CH_3,CH_3)	90-92^{0}C	37.2
38.	Trioxane **7ef**, formula 7, R=Ph, R_1 R_2 = -$CH_2CH_2CH(Ph)CH_2CH_2$-	150-154^{0}C	81
39.	Trioxane **7eg**, formula 7, R=Ph, R_1R_2 = CH_2-CH_2-CH($C(CH_3)_2CH_2CH_3$)-CH_2CH_2-)	94-98^{0}C	85.5
40.	3[([1,1'-biphenyl]-4yl)vinyl]-1,2,5-trioxaspiro(5,6)dodecane (**7eh**, formula 7, R=Ph, R_1 R_2 = $CH_2CH_2CH_2CH_2CH_2$ CH_2-)	90-92^{0}C	24.6
41.	Trioxane belonging to norcamphor group(**8e** R=Ph)	86-90^{0}C	45.1
42.	Trioxane belonging to adamantane group (**9e** R=Ph)	94-96^{0}C	71.04
43.	3,3-Dimethyl-6-[(4'-bromo-[1,1'-biphenyl]-4-yl)- vinyl]-1,2,4-trioxane (**7fa**, formula 7, R = *p*-Br-C_6H_4; R_1, R_2=CH_3, CH_3)	92-95^{0}C	69.7
44.	3-Ethyl-3-methly-6-[(4'-bromo-[1,1'-biphenyl]-4-yl)- vinyl]-1,2,4-trioxane (**7fb**, formula 7, R = *p*-Br-C_6H_4; R_1, R_2=CH_3, CH_2CH_3)	82-85^{0}C	37.5
45.	3-[(4'-bromo-[1,1'-biphenyl]-4-yl)-vinyl]-1,2,5-trioxaspiro (5,5) undecane (**7fc** , formula 7, R = *p*-Br-C_6H_4; R_1 R_2=$CH_2CH_2CH_2CH_2CH_2$-)	118-120^{0}C	47
46.	Trioxane **7fd**,formula 7, R = *p*-Br-C_6H_4, R_1 R_2 = =-CH_2-CH_2-CH[$C(CH_3)_2CH_2CH_3$]-CH_2-CH_2-	122-124^{0}C	60
47.	8-[(4'-bromo-[1,1'-biphenyl]-4yl)vinyl]-6,7,10-trioxaspiro (4,5) decane (**7fe**, formuma 7, R = *p*-Br-C_6H_4, R_1 R_2 =-CH_2-CH_2-CH_2-CH_2-)	104-106°C	66.6
48.	Trioxane **7ff**, formula 7, R = *p*-Br-C_6H_4, R_1 R_2 = CH_2-CH_2-CH(Ph)-CH_2-CH_2-	104-106°C	66.6
49.	Trioxane belonging to norcamphor group(**8f** R = *p*-Br-C_6H_4)	122-124^{0}C	42.8
50.	Trioxane belonging to adamantane group (**9f** R = *p*-Br-C_6H_4)	118^{0}C	63.6
51.	8-[(4'-chloro-[1,1'-biphenyl]-4yl)vinyl]-6,7,10-trioxaspiro (4,5) decane (**7ga**, formula 7, R = *p*-Cl-C_6H_4, R_1R_2 =-$CH_2CH_2CH_2CH_2$-)	105-107°C	33.8
52	3-[(4'-chloro-[1,1'-biphenyl]-4-yl)-vinyl]-1,2,5-trioxaspiro (5,5) undecane (**7gb** , formula 7, R = *p*-Cl-C_6H_4; R_1 R_2=$CH_2CH_2CH_2CH_2CH_2$-)	109-111°C	50

53.	Trioxane **7gc**, formula 7, R = *p*-Cl-C_6H_4, R_1 R_2 = $CH_2CH_2CH(Ph)CH_2CH_2$-)	145-148^{0}C	24.4
54.	Trioxane **7gd**, formula 7, *p*-Cl-C_6H_4, R_1R_2 = CH_2-CH_2-CH[$C(CH_3)_2CH_2CH_3$]-CH_2CH_2-	115-118^{0}C	35.3
55.	3-Ethyl-3-methyl-6-[(4'-chloro-[1,1'-biphenyl]-4yl)vinyl]-1,2,4-trioxane (**7ge**, formula 7, R = *p*-Cl-C_6H_4, R_1, R_2 = CH_3,CH_2CH_3)	70-72^{0}C	67.7
56.	Trioxane belonging to norcamphor group(**8g**, R = *p*-Cl-C_6H_4)	122-124°C	64.6
57.	Trioxane belonging to adamantane group (**9g**, R = *p*-Cl-C_6H_4)	112-115°C	69.14

ANTIMALARIAL ACTIVITY

The antimalarial activity of the test compounds was evaluated in rodent using multidrug resistant strain of *Plasmodium yoelii Nigeriensis* in swiss mice.

General Procedure: Random bred swiss mice of either sex (20±2gm) were inoculated intraperitoneally with $1x10^5$ *P. yoelli* (MDR) parasites on day zero. The treatments with test compounds were administered to group of 5 mice each at different dose levels ranging between 24-96 mg/kg/day. The treatment was administered via intramuscular route for 4 consecutive days (day 0-3).

Blood smears from experimental mice were observed on day 4 and 7, day 10 and thereafter at regular intervals till day 28 or death of the animal. The parasitaemia level on day 4 was compared with the vehicle control group and the present suppression of parasitaemia in treated groups was calculated.

For determining the curative dose of a compound the treated mice were observed till day 28. The dose at which no parasitaemia develop during the observation period has been reported as the curative dose. The anti-malarial data is summarized in **table 7**.

Table 7: ANTIMALARIAL ACTIVITY OF TRIOXANES AGAINST *P.yoelii* IN MICE

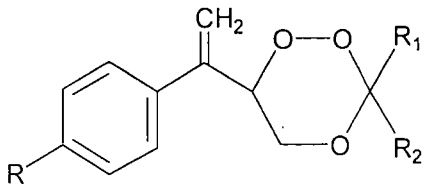
Compd. No.	Route	Dose Mg/kg	No. Of Animals	% Suppression on Day 4	Cured/treated
7aa	i.m.	96	5	100	0/5
	oral	96	5	100	5/5
7ab	i.m.	96	5	77.56	0/5
	oral	96	5	100	0/5

7ac	i.m.	96	5	84.94	0/5
	oral	96	5	100	5/5
7ad	i.m.	96	5	48	0/5
	oral	96	5	88.68	0/5
7ae	i.m.	96	5	43.58	0/5
	oral	96	5	100	0/5
7ba	i.m.	96	5	71.26	0/5
	oral	96	5	100	0/5
7bc	i.m.	96	5	41.98	0/5
	oral	96	5	95.64	0/5
7bd	i.m.	96	5	71.73	0/5
	oral	96	5	100	5/5
7be	i.m.	96	5	91.6	0/5
	oral	48	5	100	5/5
7bf	i.m.	96	5	71.26	0/5
	oral	96	5	100	0/5
7bh	i.m.	96	4	100	1/4
	oral	96	4	100	4/4
7bi	i.m.	96	5	53.01	0/5
	oral	96	5	100	5/5
7ca	i.m.	96	5	62.18	0/5
	oral	96	5	100	1/5
7cb	i.m.	96	5	86.31	0/5
	oral	96	5	100	5/5
7cd	i.m.	96	5	58.17	0/5
	oral	96	5	100	2/5
7db	i.m.	96	5	9.5	0/5
	oral	96	5	100	5/5
7dd	i.m.	96	5	73.81	0/5
	oral	96	5	100	4/5
7de	i.m.	96	5	57.4	0/5
	oral	96	5	100	3/5
7df	i.m.	96	5	0	0/5
	oral	96	5	100	3/5
7eb	i.m.	96	6	100	6/6
	oral	96	5	100	0/5
7ec	i.m.	96	4	100	0/4
	oral	96	4	100	4/4
7ee	i.m.	96	5	60.9	0/5
	oral	96	5	96.8	0/5
7ef	i.m.	96	5	42.7	0/5
	oral	96	5	100	2/5
7eg	i.m.	96	5	87.6	0/5
	oral	96	5	100	3/5
7eh	i.m.	96	5	92	0/5
	oral	96	5	100	4/5
7fa	i.m.	96	5	83.7	0/5
	oral	96	5	died	-
7fb	i.m.	96	4	51.41	0/5
	oral	96	4	100	0/5

7fc	i.m.	96	5	46.4	1/5
	oral	96	5	100	5/5
7fd	i.m.	48	5	51.09	0/5
	oral	96	5	88.39	0/5
7fe	i.m.	96	4	89.4	0/5
	oral	96	4	100	3/5
7ff	i.m.	96	4	46.1	0/5
	oral	96	4	100	2/5
8a	i.m.	96	5	81.23	0/5
	oral	96	5	100	5/5
8b	i.m.	96	5	100	3/5
	oral	48	6	100	6/6
8c	i.m.	96	5	43.55	0/5
	oral	96	5	100	3/5
8e	i.m.	96	4	100	1/4
	oral	96	4	100	4/4
8f	i.m.	96	5	100	0/5
	oral	96	5	100	5/5
9a	i.m.	96	5	81.23	0/5
	oral	96	5	100	5/5
9b	i.m.	96	5	82.16	0/5
	oral	96	5	100	5/5
9c	i.m.	96	5	74.57	0/5
	oral	96	5	100	5/5
9d	i.m.	96	5	60.12	0/5
	oral	96	5	100	5/5
9e	i.m.	96	6	100	0/6
	oral	96	6	100	6/6
9f	i.m.	96	5	92.4	2/5
	oral	48	5	100	5/5
9g	i.m.	96	5	100	-
	oral	96	5	100	3/5

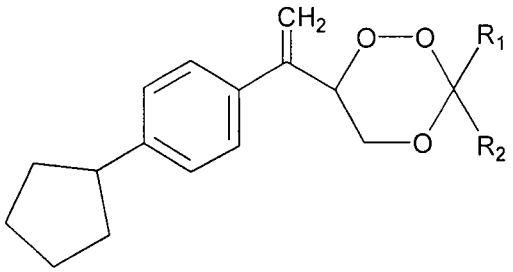
CLAIMS

1. Novel substituted 1,2,4-trioxanes of formula 7 having antimalarial activity, wherein R represents cycloalkyl groups selected from the groups consisting of cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl or aryl groups selected from phenyl, 4-bromophenyl and 4-chlorophenyl, R_1 and R_2 represent hydrogen, alkyl group selected from methyl, ethyl, propyl and decyl, aryl selected from phenyl, or part of a cyclic system such as cyclopentane, cyclohexane, substituted cyclohexane, cycloheptane, cyclo(2.2.1)heptane, adamantane.



7

2. Novel 1,2,4-trioxanes as claimed in claim 1 wherein the said compounds having the structural formula **7aa-ae** as shown below:



7aa $R_1 = R_2 = -CH_2\ CH_2\ CH_2\ CH_2-$

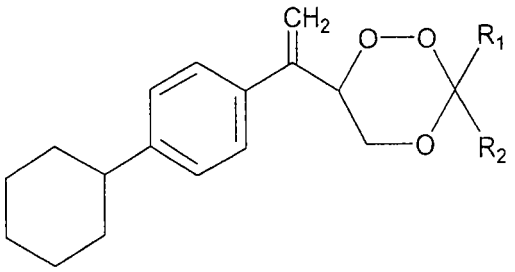
7ab $R_1 = R_2 = -CH_2\ CH_2\ CH\ (Ph)\ CH_2CH_2-$

7ac $R_1 = R_2 = -CH_2\ CH_2\ CH_2CH_2CH_2-$

7ad $R_1 = R_2 = -CH_2\ CH_2\ CH_2\ CH_2CH_2CH_2-$

7ae $R_1 = R_2 = -CH_2-CH_2-CH[C(CH_3)_2CH_2CH_3]-CH_2CH_2-$

3. Novel 1,2,4-trioxanes as claimed in claim 1-2 wherein the said compounds having the structural formula **7ba-bi** as shown below:



7ba $R_1 = R_2 = CH_3$

7bb $R_1 = CH_3$; R_2=-CH_2-(-CH_2)$_8$-CH_3

7bc R_1 = H; R_2= phenyl

7bd R_1 =R_2= -$CH_2CH_2CH_2CH_2CH_2$-

7be $R_1 = R_2$= -CH_2CH_2-CH(Ph)-CH_2CH_2-

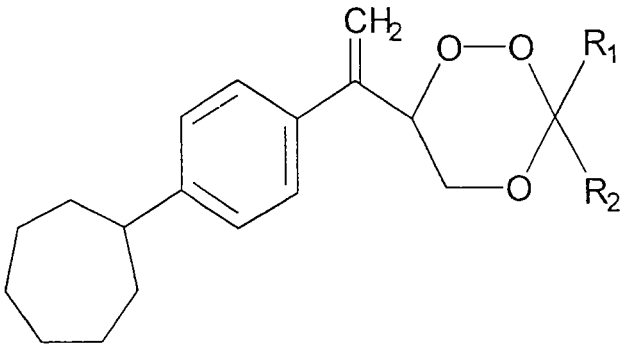
7bf $R_1 = CH_3$; R_2 =, CH_2CH_3

7bg $R_1 = CH_3$; R_2 = -$CH_2CH_2CH_3$

7bh $R_1 = R_2$= -$CH_2CH_2CH_2CH_2$-

7bi $R_1 = R_2$ = -CH_2-CH_2-CH[$C(CH_3)_2CH_2CH_3$]-CH_2CH_2-

4. Novel 1,2,4-trioxanes as claimed in claim 1-3 wherein the said compounds having the structural formula **7ca-cd** as shown below:



7ca $R_1 = R_2$ = -CH_2 -CH_2-CH_2-CH_2-CH_2-

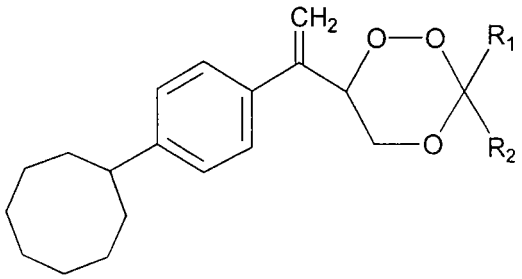
7cb $R_1 = R_2$ = -CH_2-CH_2-CH[$C(CH_3)_2CH_2CH_3$]-CH_2CH_2-

7cc $R_1 = R_2$ = -CH_2 -CH_2-CH_2-CH_2-

7cd $R_1 = R_2$= -CH_2CH_2-CH(Ph)-CH_2CH_2-

5. Novel 1,2,4-trioxanes as claimed in claim 1-4 wherein the said compounds having the structural formula **7da-df** as shown below:

14 AUG 2006



7da R_1, = CH_3; R_2= -CH_2CH_3

7db $R_1 = R_2$= -CH_2 -CH_2-CH_2-CH_2-CH_2-

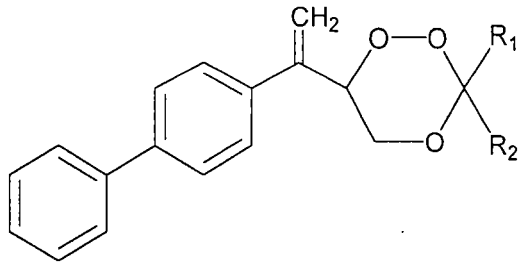
7dc $R_1 = R_2$=-CH_2-CH_2-CH_2-CH_2-CH_2-. CH_2-

7dd $R_1 = R_2$=-CH_2-CH_2 CH (Ph) CH_2CH_2-

7de $R_1 = R_2$= -$CH_2CH_2CH_2CH_2$-

7df $R_1 = R_2$ = -CH_2-CH_2-CH[$C(CH_3)_2CH_2CH_3$]-CH_2CH_2-

6. Novel 1,2,4-trioxanes as claimed in claim 1-5 wherein the said compounds having the structural formula **7ea-eh** as shown below:



7ea R_1 = H; R_2= phenyl

7eb $R_1 = R_2$ = -CH_2 CH_2 CH_2 CH_2-

7ec $R_1 = R_2$ = -CH_2 CH_2 $CH_2CH_2CH_2$-

7ed R_1 = CH_3; R_2 = -CH_2-(-CH_2)$_8$-CH_2-

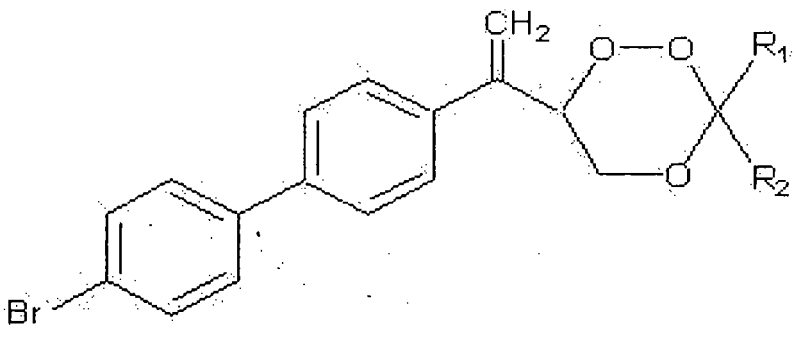
7ee $R_1 = R_2 = CH_3$

7ef $R_1 = R_2$ = -CH_2 CH_2 CH (Ph) CH_2CH_2-

7eg $R_1 = R_2$ = -CH_2-CH_2-CH[$C(CH_3)_2CH_2CH_3$]-CH_2CH_2-

7eh $R_1 = R_2$ = -CH_2 CH_2 CH_2 $CH_2CH_2CH_2$-

7. Novel 1,2,4-trioxanes as claimed in claim 1-6 wherein the said compounds having the structural formula **7fa-ff** as shown below:



7fa R_1, = R_2 = CH_3

7fb R_1 = CH_3 ; R_2 = CH_2CH_3

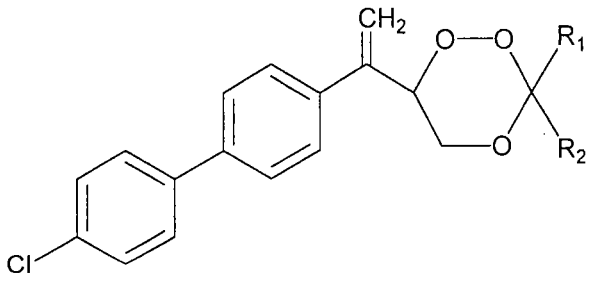
7fc R_1 = R_2= -$CH_2CH_2CH_2CH_2CH_2$-

7fd R_1 = R_2 = -CH_2-CH_2-CH[$C(CH_3)_2CH_2CH_3$]-CH_2CH_2-

7fe R_1 = R_2= -$CH_2CH_2CH_2CH_2$-

7ff R_1 = R_2= -CH_2CH_2-CH(Ph)-CH_2CH_2-

8. Novel trioxanes as claimed in claim 1-7 wherein the said compounds having the structural formulae **7ga-ge** as shown below:



7ga R_1 = R_2= -$CH_2CH_2CH_2CH_2$-

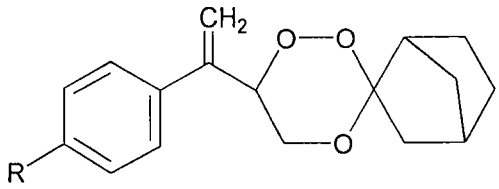
7gb R_1 = R_2= -$CH_2CH_2CH_2CH_2CH_2$-

7gc R_1 = R_2= -CH_2CH_2-CH(Ph)-CH_2CH_2-

7gd R_1 = R_2 = -CH_2-CH_2-CH[$C(CH_3)_2CH_2CH_3$]-CH_2CH_2-

7ge R_1 = CH_3 ; R_2 = -CH_2CH_3

9. Novel trioxanes as claimed in claim 1-7 wherein the said compounds having the structural formulae **8a-g** as shown below:



8a R= cyclopentyl

8b R= cyclohexyl

8c R= cycloheptyl

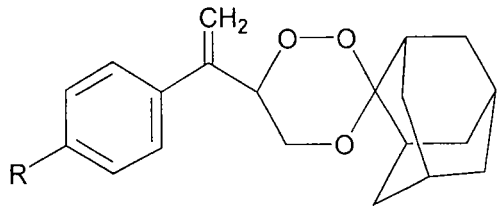
8d R=cyclooctyl

8e R= Phenyl

8f R= 4-Br-Phenyl

8g R= 4-Cl-Phenyl

10. Novel trioxanes as claimed in claim 1-9 wherein the said compounds having the structural formulae **9a-g** as shown below:



9a R= cyclopentyl

9b R= cyclohexyl

9c R= cycloheptyl

9d R=cyclooctyl

9e R= Phenyl

9f R= 4-Br-Phenyl

9g R= 4-Cl-Phenyl

11. A process for the preparation of substituted 1,2,4-trioxane of general formula (7), the said process comprising steps of:

(a) reacting aryl alkyl ketone of formula (1) with alkyl halo acetate of formula (2) in presence of zinc, catalytic amount of iodine in an aprotic organic solvent at a temperature ranging between 20°-120°C for a period of 2-8 hours,

(b) acidifying the reaction mixture of step (a) using aqueous 10% aqueous hydrochloric acid, separating the organic layer,

(c) washing the organic layer of step (b) with water, drying over anhydrous sodium sulphate, filtering, evaporating to obtain a residue,

(d) purifying the residue of step (c) over silica gel column, eluting with mixture of hexane: ethylacetate to obtain β-hydroxyester of general formula (2),

(e) dehydrating the β-hydroxyester of general formula (2) of step (d) with a dehydrating agent in an organic aprotic solvent at a temperature range of 20°-120°C for a period of 2-5 hours,

(f) diluting the reaction mixture of step (e) with saturated sodium bicarbonate solution, separating organic layer,

(g) washing the organic layer of step (f) with water, drying the organic layer over anhydrous sodium sulphate, filtering and evaporating to obtain a residue,

(h) purifying the residue of step (g) over silica gel columns to obtain the α,β-unsaturated ester of general formula (3),

(i) reducing the α, β-unsaturated ester of general formula (3) of step (h) with metal hydride in an anhydrous ethereal solvent at a temperature range of 0°-80°C for a period of 2-10 hours,

(j) quenching the reaction mixture of step (i), by adding water, further adding aqueous alkali hydroxide solution, separating the organic layer by filtering, washing the residue with the organic solvent to obtain combined organic solvent soluble fraction,

(k) evaporating the combined organic solvent soluble fraction of step (j) to dryness to obtain a product residue,

(l) purifying the residue of step (k) over silica gel column to obtain the allylic alcohol of general formula (4),

(m) dissolving the allylic alcohol of general formula (4) of step (l) in an organic solvent to obtain a solution,

(n) irradiating the solution of step (m) with a 250 watt tungsten halogen lamp, in presence of a sensitizer at a temperature range of –5° to –10°C for a period 3-10 hours,

(o) optionally adding water to the reaction mixture of step (n) separating organic layer, evaporating and crystallising the residue to obtain the required β-hydroxy-hydroperoxide compound of general formula (5),

(p) reacting the β-hydroxy hydroperoxide compound of general formula (5) with an aldehyde or ketone of formula (6) in an organic solvent in presence of an acid catalyst at room temperature for a period of 16 – 24 hours,

(q) adding water to the reaction mixture of step (p), separating organic layer, drying and evaporating the organic layer to obtain a residue,

(r) purifying by crystallising the residue of (q) to obtain the required substituted 1,2,4-trioxane analogues of general formula (7), and

(s) analogues of general formula (7) can also be obtained by performing steps (q) to (r) in the reaction mixture of step (n) .

12. A process as claimed in claim 11 wherein in step (a) alkyl group of the aryl alkyl ketone used is selected from a group consisting of cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

13. A process as claimed in claim 11 wherein in step (a) the aryl group of the aryl alkyl ketone used is selected from a group consisting of phenyl, 4-bromophenyl, or 4-chlorophenyl.

14. A process as claimed in claim 11 wherein in step (a) the alkyl halo acetate is selected from a group consisting of ethyl bromoacetate or ethyl chloroacetate.

15. A process as claimed in claim 11, wherein in step (a), the aprotic solvent is selected from a group consisting of diethyl ether, benzene, toluene or tetrahydrofuran.

16. A process as claimed in claim 11, wherein in step (e) the dehydrating agent used is selected from a group consisting of iodine, phosphorus pentoxide or p-toluene sulphonic acid.

17. A process as claimed in claim 11 wherein kin step (e) the organic solvent used is selected from a group consisting of dichloromethane, chloroform, benzene or toluene.

18. A process as claimed in claim 11 wherein in step (i) the metal hydride used is lithium aluminium hydride.

19. A process as claimed in claim 11 wherein in step (i) the anhydrous etheral solvent used is selected from a group consisting of diethylether or tetrahydrofuran.

20. A process as claimed in claim 11 wherein in step (m) the organic solvent used is selected from a group consisting of dichloromethane, benzene, acetonitrile or methanol.

21. A process as claimed in claim 11, wherein in step (n) the sensitizer used is a dye selected from a group consisting of methylene blue, Rose Bengal or tetraphenyl porphine.

22. A process as claimed in claim 11 wherein in step (p) the organic solvent used is selected from a group consisting of dichloromethane, chloroform, acetonitrile or benzene.

23. A process as claimed in claim 11 wherein in step (p) the acid catalyst used is selected from a group consisting of hydrochloric acid, sulphuric acid, p-toluene sulphoric acid or acidic resin.

24. A process as claimed in claim 11 wherein in step (p) the aldehyde or ketone used is selected from a group consisting of acetone, ethylmethyl ketone, methyl propyl ketone, decyl ketone, cyclopentanone, cyclohexanone, cycloheptanone, 4-phenyl cyclohexanone, 4-t-anyl cyclohexanone, cyclokeptanone, norcamphor, 2-alamantone, substituted or unsubstituted phenyl derivative.