Orally Active 1,2,4-Trioxanes: Synthesis and Antimalarial Assessment of a New Series of 9-Functionalized 3-(1-Arylvinyl)-1,2,5-trioxaspiro[5.5]undecanes against Multi-Drug-Resistant *Plasmodium yoelii nigeriensis* in Mice[1]

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Using easily accessible keto-trioxanes **7a**−**g** as the starting materials, a series of new variously functionalized 1,2,4-trioxanes **10**−**36** have been prepared and evaluated for antimalarial activity against multi-drug-resistant *Plasmodium yoelii nigeriensis* in mice in the dose range of 24 mg/kg × 4 days to 96 mg/kg × 4 days by oral route. Trioxanes **10**, **12**, **14**, **16**, **18**, **20**, and **22** have shown promising antimalarial activity. Trioxanes **14** and **18**, the two most active compounds of the series, provide 100% and 60% protection at 48 mg/kg × 4 days and 24 mg/kg × 4 days, respectively. In this model β-arteether provides 100% and 20% protection at 48 mg/kg × 4 days and 24 mg/kg × 4 days, respectively.

Malaria is a major parasitic disease affecting over 100 countries of the tropical and subtropical regions of the world including India. Around 300−500 million clinical cases of malaria are reported every year of which around 2−3 million die due to complicated cases of malaria.[2] Situation is getting worse with the emergence of multi-drug-resistant parasites. Against this background, isolation of artemisinin **1** by the Chinese as the antimalarial principle of *Artemisia annua* has been a major breakthrough in malaria chemotherapy. Artemisinin is active against both chloroquine-sensitive and chloroquine-resistant malaria.[3]

Artemisinin derivatives such as artemether **2**, arteether **3**, and artesunic acid **4** (Figure 1) have better solubility and activity profile than the parent compound and are increasingly finding use either alone or in combination with other drugs for the treatment of malaria caused by multi-drug-resistant *P. falciparum*.[4] The peroxide group present in the form of 1,2,4-trioxane is essential for the antimalarial activity of artemisinin and its derivatives. Several synthetic trioxanes originating from different laboratories including our group have shown promising antimalarial activity both in vitro and in vivo.[5,6]

Earlier we have shown that β-hydroxyhydroperoxides prepared by photooxygenation of allylic alcohols[6a,7] react with 1,4-cyclohexanedione to give keto-functionalized 1,2,4-trioxanes (Scheme 1), and that these trioxanes undergo facile reductive amination with various amines to give amino-functionalized 1,2,4-trioxanes (prototype **8** and **9**) (Figure 2).[8,9] Some of these amino-functionalized 1,2,4-trioxanes have shown high order of activity against multi-drug-resistant *Plasmodium yoelii nigeriensis* in mice.[9]

We have further explored the chemistry of the carbonyl group of these keto-trioxanes with the twin objectives (i) to assess the stability of the trioxane moiety under conditions of variety of organic reactions and (ii) to generate a library of new trioxanes with different functional groups. In the event these keto-trioxanes were found to be stable under conditions of reduction with $NaBH_4$, Wadsworth−Emmons reaction with triethylphosphonacetate and triethylphosphon-2-propionate, Reformatsky reaction with $BrCH_2COOEt$/Zn, and Grignard reaction with MeMgBr and PhMgBr. In the process, we have prepared series of variously functionalized 1,2,4-trioxanes **10**−**36** and assessed their antimalarial activity against multi-drug-resistant *P. yoelii nigeriensis* in mice. Some of these trioxanes have shown high order of antimalarial activity comparable with that of the β-arteether, by oral route. In this paper we describe the details of the study.[10]

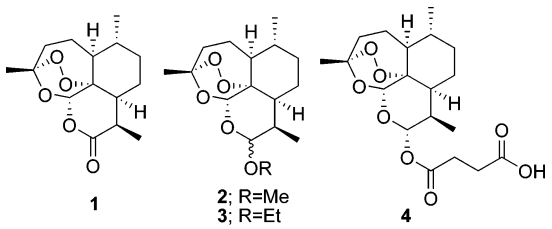
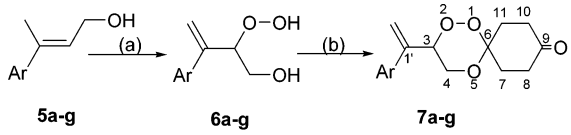


Figure 1. Artemisinin and its derivatives.

Scheme 1[a]



(**a**, Ar = Ph; **b**, Ar = 4-PhC_6H_4; **c**, Ar = 4-ClC_6H_4; **d,** 4-$OMeC_6H_4$; **e**, 4-MeC_6H_4, **f**, 4-cyclohexylPh; **g**, 2-naphthyl)

[a] Reagents and reaction conditions: (a) *hν*, O_2, methylene blue, MeCN, −10 to 0 °C; (b) 1,4-cyclohexanedione, concd HCl, 5 °C.

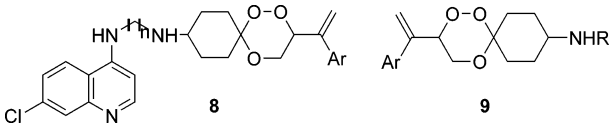
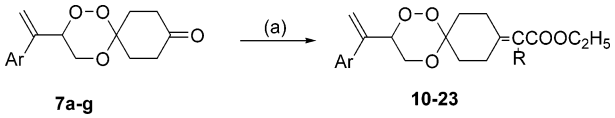


Figure 2. Prototypes of amino-functionalized 1,2,4-trioxanes.

Scheme 2[a]



[a] Reagents and reaction conditions: (a) $(OEt)_2P(O)CH_2CO_2Et$/$(OEt)_2P(O)CH(CH_3)CO_2Et$, NaH, DME/ THF, 0 °C to room temperature, 2−3 h.

Chemistry. β-Hydroxyhydroperoxides **6a**−**g** prepared by photooxygenation of allylic alcohols **5a**−**g** were condensed with 1,4-cyclohexanedione in the presence of concd HCl to furnish keto-trioxanes **7a**−**g** in 28−51% yields (based on allylic

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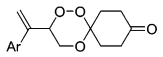
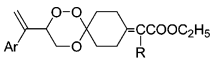
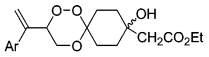
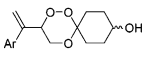
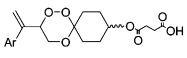
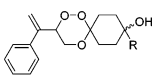
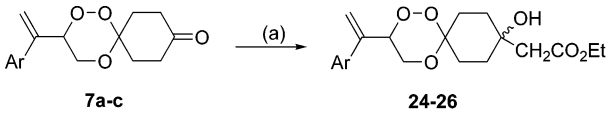
Table 1. Yields of Functionalized 1,2,4-Trioxanes **10**−**36**

General Structure	Compound	Substituents	Yield (%)[a]
	**7a**	Ar = Ph	51
	7b	Ar = 4-PhC_6H_4	42
	7c	Ar = 4-ClC_6H_4	38
	7d	Ar = 4-OMeC_6H_4	28
	7e	Ar = 4-MeC_6H_4	32
	7f	Ar = 4-cyclohexylPh	32
	7g	Ar = 2-naphthyl	33
	**10**	Ar = Ph, R = H	93
	11	Ar = Ph, R = CH_3	83
	12	Ar = 4-PhC_6H_4, R =H	93
	13	Ar = 4-PhC_6H_4, R = CH_3	84
	14	Ar = 4-ClC_6H_4, R = H	91
	15	Ar = 4-ClC_6H_4, R = CH_3	85
	16	Ar = 4-OMeC_6H_4, R = H	91
	17	Ar = 4-OMeC_6H_4, R = CH_3	84
	18	Ar = 4-MeC_6H_4, R = H	91
	19	Ar = 4-MeC_6H_4, R = CH_3	86
	20	Ar = 4-cyclohexylPh, R = H	90
	21	Ar = 4-cyclohexylPh, R = CH_3	82
	22	Ar = 2-naphthyl, R = H	92
	23	Ar = 2-naphthyl, R = CH_3	82
	**24a and 24b**	Ar = Ph	83
	25a and 25b	Ar = 4-PhC_6H_4	88
	26a and 26b	Ar = 4-ClC_6H_4	84
	**27**	Ar = Ph	96
	28	Ar = 4-PhC_6H_4	94
	29	Ar = 4-ClC_6H_4	93
	30	Ar = 4-MeC_6H_4	95
	**31**	Ar = Ph	91
	32	Ar = 4-PhC_6H_4	95
	33	Ar = 4-ClC_6H_4	91
	34	Ar = 4-MeC_6H_4	93
	**35a and 35b**	R = CH_3	54
	36a and 36b	R = C_6H_5	57

[a] Yield in each case refers to the single preparation of the target compound.

alcohol). Reaction of keto-trioxanes **7a**−**g** with triethylphosphonacetate in the presence of NaH in dimethoxyethane furnished α,*β*-unsaturated esters **10**, **12**, **14**, **16**, **18**, **20**, and **22** as inseparable mixtures of geometrical isomers in 90−93% yields (Scheme 2, Table 1). ^{1}H NMR of these trioxanes show characteristics signals of 1,2,4-trioxane moiety: 5-H_e appears around *δ* 3.80 (dd, *J* = 11.8, 3.0 Hz), 5-H_a around *δ* 3.98 (dd, *J* = 11.8, 10.0 Hz), and 6-H around *δ* 5.26 (dd, *J* = 10.0, 3.0 Hz). The isomeric pairs show identical ^{1}H NMR except the signal for 5-H_e appears at different places. Similar reaction of keto-trioxanes **7a**−**g** with triethylphosphon-2-propionate under similar conditions furnished α,*β*-unsaturated esters **11**, **13**, **15**, **17**, **19**, **21**, and **23** as inseparable mixtures of geometrical isomers in 82−86% yields (Scheme 2, Table 1). ^{1}H NMR of

Scheme 3[a]



7a-c → **24-26**

7a Ar = phenyl
7b Ar = 4-biphenyl
7c Ar = 4-chlorophenyl

24a Ar = phenyl (higher R_f)
24b Ar = phenyl (lower R_f)
25a Ar = 4-bihenyl (higher R_f)
25b Ar = 4-biphenyl (lower R_f)
26a Ar = 4-chlorophenyl (higher R_f)
26b Ar = 4-chlorophenyl (lower R_f)

[a] Reagents and conditions: (a) Zn/$BrCH_2CO_2Et$, benzene, 50 °C, 4 h.

the isomeric pairs differ only for the signals for OCH_2CH_3; they have identical δ values for 5-H_e, 5-H_a, and 6-H.

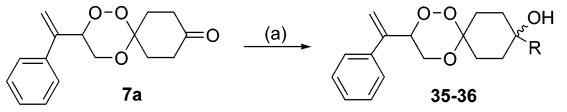
Reformatsky reaction of **7a** with $BrCH_2COOEt$/Zn in dry benzene furnished β-hydroxyesters **24a** and **24b** as a mixture of diastereomers in 83% yield, which were separated by column chromatography. 5H_e in both these isomers show similar δ values; (δ 3.67 for **24a** and δ 3.77 for **24b**) whereas 5H_a of **24b** appears downfield as compared to that of **24a**; (δ 3.78 for **24a** and δ 4.03 for **24b)**. Keto-trioxanes **7b** and **7c** under similar reaction conditions furnished esters **25a** and **25b**, and **26a** and **26b** as a diastereomeric mixture in 88% and 84% yields, respectively. Pure isomers **25a** and **25b**, and **26a** and **26b**, were obtained by column chromatography (Scheme 3, Table 1). A similar difference in δ values of 5H_a in **25a** and **25b**, and **26a** and **26b**, was observed.

Reduction of **7a**−**c** and **7e** with $NaBH_4$ in MeOH furnished alcohols **27**−**30** in 93−96% yields as inseparable mixtures of diastereomers, which on reaction with succinic anhydride and triethylamine in CH_2Cl_2 at room temperature gave hemisuccinates **31**−**34** in 91−94% yields, again as inseparable mixtures of diastereomers (Scheme 4, Table 1).

Reaction of keto-trioxane **7a** with MeMgBr in dry diethyl ether furnished a diastereomeric mixture of alcohols **35a** and **35b** in 54% yield. These two isomers were separated by column chromatography. Similar reaction of **7a** with PhMgBr furnished trioxanes **36a** and **36b** as a mixture of diastereomers in 57% yield. These isomers were separated by column chromatography and characterized separately, while they were screened as mixture for biological activity (Scheme 5, Table 1).[11] Here also isomeric pairs show similar δ for 5H_e but downfield shift in the δ value of 5H_a.

Antimalarial Activity. Parent trioxanes **7a**−**g** and their derivatives **10**−**36** were assessed for antimalarial activity against multi-drug-resistant *P. yoelii nigeriensis* in mice by oral route using Peters's procedure.[13a] In this model β-arteether shows 100% clearance of parasitemia at 48 mg/kg × 4 days and all the treated mice survive beyond day 28. At 24 mg/kg × 4 days β-arteether provides only 20% protection to the treated mice. Therefore all the trioxanes were initially tested at 96 mg/kg × 4 days orally, double the effective dose of β-arteether. Trioxanes **10**, **12**, **14**, **18**, and **22** which provided 100% protection at this dose were further tested at 48 mg/kg × 4 days and 24 mg/kg × 4 days.[13b] Trioxanes **16** and **20** which provided 80% and 60% protection, respectively at 96 mg/kg × 4 days, were also evaluated at 48 mg/kg × 4 days. Results are summarized in Table 2.

Scheme 5[a]



7a → **35-36**

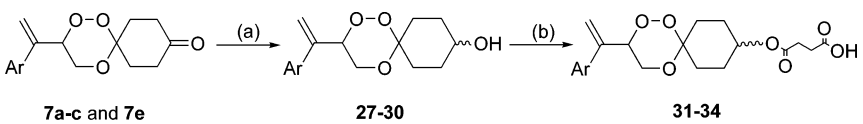
35a R = CH_3 (higher R_f)
35b R = CH_3 (lower R_f)
36a R = C_6H_5 (higher R_f)
36b R = C_6H_5 (lower R_f)

[a] Reagents and reaction conditions: (a) CH_3MgI/C_6H_5MgBr, 0 °C, 1 h.

Results and Discussion

As can be seen from Table 2, except for trioxane **7f**, which protects 60% of the treated mice, none of the parent keto-trioxanes **7a**−**g** provides significant protection. Similarly, none of their $NaBH_4$-reduced products **27**−**30** and their hemisuccinates **31**−**34** show significant activity. Wadsworth−Emmons reaction products **10**, **12**, **14**, **16**, **18**, **20**, and **22** show very promising activity. The most active compounds of the series are **14** and **18**, both of which show 100% protection at 48 mg/kg. Even at 24 mg/kg, these trioxanes provide 60% protection to the treated mice. These two compounds have an edge over β-arteether which shows only 20% protection at 24 mg/kg. Trioxanes **10** and **22** also provide 100% protection at 48 mg/kg. At 24 mg/kg both **10** and **22**, however, show complete clearance of parasitemia on day 4 but none of the treated mice survive till day 28. Trioxane **12** provides 100% protection at 96 mg/kg only. At 48 mg/kg it shows more than 90% suppression of parasitemia on day 4 but none of the treated mice is protected. Trioxanes **16** and **20** provide 80% and 60% protection, respectively, at 96 mg/kg. Even at 48 mg/kg both these compound show 100% clearance of parasitemia on day 4 and 40% of the treated mice survive beyond day 28. Surprisingly, none of the Wadsworth−Emmons products **11**, **13**, **15**, **17**, **19**, **21**, and **23**, which have only an extra methyl group at the double bond, show significant protection, indicating that the spatial requirement in this part of the molecule is very stringent and even an extra methyl group is not tolerated. This is further reflected in the Reformatsky reaction products **24**−**26** and Grignard reaction products **35** and **36**, none of which show any activity. Among the active trioxanes **10**, **12**, **14**, **16**, **18**, **20**, and **22**, there is clear correlation between antimalarial activity and hydrophobicity. Trioxanes **10**, **14**, **18**, and **22** which have log *p* values between 3.79 and 4.79 show a better activity profile than those which have either lower log *p* values (trioxane **16**, log *p* = 3.66) or higher log *p* values (trioxane **12**, log *p* = 5.46, trioxane **20**, log *p* = 5.78). The log *p* value of β-arteether also lies within this range (log *p* = 3.84). Comparatively poor antimalarial activity of trioxanes **12** and **20** are in conformity with Lipinski's rule of five.[14] However, in the rest of the series, there are several trioxanes having log *p* values which range

Scheme 4[a]



7a-c and **7e** → **27-30** → **31-34**

7a Ar = phenyl
7b Ar = 4-biphenyl
7c Ar = 4-chlorophenyl
7e Ar = 4-methylphenyl

27 Ar = phenyl
28 Ar = 4-biphenyl
29 Ar = 4-chlorophenyl
30 Ar = 4-methylphenyl

31 Ar = phenyl
32 Ar = 4-biphenyl
33 Ar = 4-chlorophenyl
34 Ar = 4-methylphenyl

[a] Reagents and reaction conditions: (a) $NaBH_4$, MeOH, 0°, 0.5 h; (b) succinic anhydride, triethylamine, CH_2Cl_2, rt, 1 h.

Table 2. In Vivo Antimalarial Activity of 1,2,4-Trioxanes **10**−**36** against *P. yoelii* in Swiss Mice

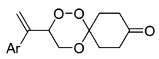
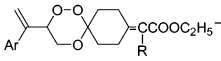
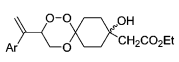
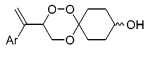
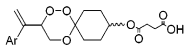
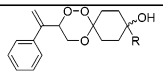
General Structure	Compound	Substituents	Log *p*	Dose (mg/kg /day)	% Suppression on Day-4[a, b]	Mice alive on day-28
	**7a**	Ar = Ph	2.94	96	7	0/5
	7b	Ar = 4-PhC_6H_4	4.62	96	92	0/5
	7c	Ar = 4-ClC_6H_4	3.50	96	18	0/5
	7d	Ar = 4-OMeC_6H_4	2.82	96	32	0/5
	7e	Ar = 4-MeC_6H_4	3.43	96	7	0/5
	7f	Ar = 4-cyclohexylPh	4.93	96	100	3/5
	7g	Ar = 2-naphthyl	3.94	96	15	0/5
	**10**	Ar = Ph, R = H	3.79	96 48 24	100 100 99	5/5 5/5 0/5
	11	Ar = Ph, R = CH_3	4.14	96	39	0/5
	12	Ar = 4-PhC_6H_4, R =H	5.46	96 48	100 93	5/5 0/5
	13	Ar = 4-PhC_6H_4, R = CH_3	5.81	96 48	100 100	2/5 0/5
	14	Ar = 4-ClC_6H_4, R = H	4.35	96 48 24	100 100 100	5/5 5/5 3/5
	15	Ar = 4-ClC_6H_4, R = CH_3	4.70	96	87	0/5
	16	Ar = 4-OMeC_6H_4, R = H	3.66	96 48	100 100	4/5 2/5
	17	Ar = 4-OMeC_6H_4, R = CH_3	4.01	96	18	0/5
	18	Ar = 4-MeC_6H_4, R = H	4.28	96 48 24	100 100 100	5/5 5/5 3/5
	19	Ar = 4-MeC_6H_4, R = CH_3	4.62	96	100	0/5
	20	Ar = 4-cyclohexylPh, R = H	5.78	96 48	100 100	3/5 2/5
	21	Ar = 4-cyclohexylPh, R = CH_3	6.13	96	100	2/5
	22	Ar = 2-naphthyl, R = H	4.79	96 48 24	100 100 100	5/5 5/5 0/5
	23	Ar = 2-naphthyl, R = CH_3	5.14	96	97	0/5
	**24a (higher R_f)**	Ar = Ph	2.83	96	87	0/5
	24b (lower R_f)	Ar = Ph	2.83	96	37	0/5
	25a (higher R_f)	Ar = 4-PhC_6H_4	4.50	96	93	0/5
	25b (lower R_f)	Ar = 4-PhC_6H_4	4.50	96	97	0/5
	26a (higher R_f)	Ar = 4-ClC_6H_4	3.39	96	31	0/5
	26b (lower R_f)	Ar = 4-ClC_6H_4	3.39	96	74	0/5

Table 2. (Continued)

General Structure	Compound	Substituents	Log *p*	Dose (mg/kg /day)	% Suppression on Day-4[a, b]	Mice alive on day-28
	**27**	Ar = Ph	4.46	96	78	0/5
	28	Ar = 4-PhC_6H_4	2.79	96	91	2/5
	29	Ar = 4-ClC_6H_4	3.35	96	74	0/5
	30	Ar = 4-MeC_6H_4	3.27	96	37	0/5
	**31**	Ar = Ph	2.69	96	82	0/5
	32	Ar = 4-PhC_6H_4	4.36	96	99	0/5
	33	Ar = 4-ClC_6H_4	3.24	96	39	0/5
	34	Ar = 4-MeC_6H_4	3.17	96	97	0/5
	**35a and 35b**	R = CH_3	3.01	96	92	0/5
	36a and 36b	R = C_6H_5	4.40	96	95	0/5
β-Arteether		-	3.84	48	100	5/5
		-		24	100	1/5
Chloroquine				100	100	0/5
				30	100	0/5
Mefloquine				100	100	3/5
				30	100	1/5
Halofantrine				100	100	2/5
				30	100	0/5
Vehicle Control		-		-	-	0/15

[a] Percent suppression = [(C − T)/C] × 100; where C = Parasitemia in control group, and T = Parasitemia in treated group. [b] 100% suppression of parasitemia means, number of parasites if at all present, are below the detection limit.[13]

between 3.79 and 4.79 but none of them show significant activity, indicating therefore that minor structural differences can override the hydrophobicity criterion.

Conclusions

In conclusion, in our efforts to assess the behavior of 1,2,4-trioxane moiety toward variety of reaction conditions we have prepared a new series of functionalized trioxanes using the chemistry of carbonyl group of trioxanes **7a**−**g**. Several of these trioxanes show a better activity profile than the parent trioxanes **7a**−**g**. The activity profiles of trioxanes **14** and **18**, the most active compounds of the series, are better than that of the clinically used drug, *β*-arteether. Trioxanes **10** and **22** also show high order of antimalarial activity, which is very close to that of *β*-arteether.

Experimental Section

All glass apparatus were oven dried prior to use. Melting points were determined on COMPLAB melting point apparatus and are 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 (operating at 200 MHz for ^{1}H and at 50 MHz for ^{13}C) or DRX-300 (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C) spectrometers using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Fast atom bombardment mass spectra (FAB-MS) were obtained on a 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 C H N S analyzer (Germany). High-resolution electron impact mass spectra (HR-EIMS) were obtained on a JEOL MS route 600H instrument. 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 aqueous 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) using freshly distilled solvents. All chemicals and reagents were obtained from Aldrich (Milwaukee, WI), 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 wires overnight prior to use. Log *p* values of the compounds were calculated using Chem Draw Ultra 6.0.

3-(1-Phenyl-vinyl)-1,2,5-trioxaspiro[5.5]undec-9-one (7a). A solution of allylic alcohol **5a (**1 g, 6.75 mmol) and methylene blue (30 mg) in acetonitrile (100 mL) was irradiated with a 500 W tungsten−halogen lamp at −10 to 0 °C while oxygen was bubbled slowly into the reaction mixture for 4 h. 1,4-Cyclohexanedione (1.15 g, 10.13 mmol) and concd HCl (0.2 mL) were added, and the reaction mixture was left at 5 °C for 18 h. Usual workup followed by chromatography over silica gel furnished trioxane **7a** (0.94 g, 51% yield, based on allylic alcohol **5a**); mp 70−71 °C; IR (KBr, cm^{-1}) 1717; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05 (t, 2H, J = 7.06 Hz), 2.32−2.67 (m, 6H), 3.85 (dd, 1H, J = 11.8, 2.9 Hz), 3.96

(dd, 1H, $J = 11.8, 10.1$ Hz), 5.31 (dd, 1H, $J = 10.1, 2.9$ Hz), 5.36 and 5.53 (2 × s, 2H), 7.32−7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.79 (t), 33.57 (t), 36.79 (t), 36.95 (t), 63.72 (t), 80.83 (d), 101.50 (s), 117.10 (t), 126.81 (d, integrating for two carbons), 128.72 (d), 129.05 (d, integrating for two carbons), 138.84 (s), 143.59 (s), 210.00 (s); FAB-MS (*m*/*z*) 275 $[M + H]^+$; Anal. Calcd for $C_{16}H_{18}O_4$: C 70.06%, H 6.61%; found: C 69.77%, H 6.86%.

Compounds **7b**−**g** were prepared by the above procedure.

3-(1-Biphenyl-4yl-vinyl)-1,2,5-trioxaspiro[5.5]undec-9-one (7b). Yield 42%; mp 104−105 °C; IR (KBr, cm^{-1}) 1711; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.07 (t, 2H, $J = 7.06$ Hz), 2.33−2.69 (m, 6H), 3.91 (dd, 1H, $J = 12.0, 3.5$ Hz), 4.02 (dd, 1H, $J = 12.0, 9.7$ Hz), 5.38 (dd, 1H, $J = 9.7, 3.5$ Hz), 5.41 and 5.59 (2 × s, 2H), 7.31−7.62 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.85 (t), 33.61 (t), 36.83 (t), 36.99 (t), 63.76 (t), 80.77 (d), 101.56 (s), 117.01 (t), 127.20 (d, integrating for two carbons), 127.42 (d, integrating for two carbons), 127.53 (d, integrating for two carbons), 127.98 (d), 129.26 (d, integrating for two carbons), 137.65 (s), 140.76 (s), 141.62 (s), 143.11 (s), 210.08 (s); FAB-MS (*m*/*z*) 351 $[M + H]^+$; Anal. Calcd for $C_{22}H_{22}O_4$: C 75.41%, H 6.33%; found: C 75.41%, H 6.68%.

3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undecan-9-one (7c). Yield 38%; mp 72−74 °C; IR (KBr, cm^{-1}) 1715; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05 (t, 2H, $J = 7.1$ Hz), 2.35−2.69 (m, 6H), 3.86 (dd, 1H, $J = 11.9, 3.2$ Hz), 3.97 (dd, 1H, $J = 11.9, 10.0$ Hz), 5.26 (dd, 1H, $J = 10.0, 3.2$ Hz), 5.36 and 5.52 (2 × s, 2H), 7.27−7.32 (m, 4H); FAB-MS (*m*/*z*) 309 and 311 $[M + H]^+$; Anal. Calcd for $C_{16}H_{17}ClO_4$: C 62.24%, H 5.55%; found: C 62.51%, H 5.46%.

3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undecan-9-one (7d). Yield 28%; viscous oil; IR (neat, cm^{-1}) 1716; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05 (t, 2H, $J = 7.0$ Hz), 2.32−2.70 (m, 6H), 3.75−3.89 (m, 1H), 3.81 (s, 3H, OCH_3), 3.97 (dd,,1H, $J = 11.9, 10.0$ Hz), 5.30 (dd, 1H, $J = 10.0, 2.9$ Hz), 5.24 and 5.45 (2 × s, 2H), 6.88 (d, 2H, $J = 8.0$ Hz), 7.33 (d, 2H, $J = 8.0$ Hz); FAB-MS (*m*/*z*) 305 $[M + H]^+$; Anal. Calcd for $C_{17}H_{20}O_5$: C 67.09%, H 6.62%; found: C 66.92%, H 6.72%.

3-(1-*p*-Tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-one (7e). Yield 32%; mp 66−68 °C; IR (KBr, cm^{-1}) 1718; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.04 (t, 2H, $J = 7.0$ Hz), 2.31−2.66 (m, 6H), 2.34 (s, 3H), 3.86 (dd, 1H, $J = 12.1, 3.7$ Hz), 3.95 (dd, 1H, $J = 12.1, 10.2$ Hz), 5.31 (dd, 1H, $J = 10.2, 3.7$ Hz), 5.28 and 5.49 (2 × s, 2H), 7.15 (d, 2H, $J = 8.0$ Hz), 7.28 (d, 2H, $J = 8.0$ Hz); FAB-MS (*m*/*z*) 289 $[M + H]^+$; Anal. Calcd for $C_{17}H_{20}O_4$: C 70.81%, H 6.99%; found: C 70.54%, H 6.77%.

3-[1-(4-Cyclohexyl-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undecan-9-one (7f). Yield 32%; mp 62−64 °C; IR (KBr, cm^{-1}) 1719; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.47 (m, 5H), 1.73−1.85 (m, 5H), 2.05 (t, 2H, $J = 7.2$ Hz), 2.35−2.67 (m, 7H), 3.87 (dd, 1H, $J = 12.0, 3.3$ Hz), 3.97 (dd, 1H, $J = 12.0, 10.2$ Hz), 5.28 (s, 1H), 5.40 (dd, 1H, $J = 10.2, 3.3$ Hz), 5.51 (s, 1H), 7.20 (d, 2H, $J = 8.2$ Hz), 7.32 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.51 (t), 27.24 (t, integrating for two carbons), 27.79 (t), 33.66 (t), 34.75 (t, integrating for two carbons), 36.85 (t), 37.02 (t), 44.64 (d), 63.91 (t), 80.81 (d), 101.46 (s), 116.19 (t), 126.63 (d, integrating for two carbons), 127.51 (d, integrating for two carbons), 136.18 (s), 143.34 (s), 148.81 (s), 210.18 (s); FAB-MS (*m*/*z*) 357 $[M + H]^+$; HR-EIMS calc for $C_{22}H_{28}O_4$ 356.1988 found 356.2008.

3-(1-Naphthalen-2-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-one (7 g). Yield 33%; mp 58−60 °C; IR (KBr, cm^{-1}) 1714; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.06 (t, 2H, $J = 7.0$ Hz), 2.32−2.70 (m, 6H), 3.93 (dd, 1H, $J = 11.9, 3.0$ Hz), 4.00 (dd, 1H, $J = 11.9, 9.9$ Hz), 5.46 (dd, 1H, $J = 9.9, 3.0$ Hz), 5.42 and 5.65 (2 × s, 2H), 7.45−7.53 (m, 3H), 7.79−7.83 (m, 4H); FAB-MS (*m*/*z*) 325 $[M + H]^+$; Anal. Calcd for $C_{20}H_{20}O_4$: C 74.06%, H 6.21%; found: C 74.12%, H 6.28%.

[3-(1-Phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-ylidene]-acetic Acid Ethyl Ester (10). In an oven dried three-necked flask (100 mL), equipped with a magnetic stirrer, was placed NaH (50% suspension in mineral oil; 0.20 g, 8.39 mmol) and washed with dry hexane (20 mL). Dry DME (20 mL) was added, the slurry was cooled to 0 °C, and a solution of triethylphosphonoacetate (1.35 g, 6.04 mmol) in dry DME (10 mL) was added dropwise with stirring. After the addition was complete, the resulting solution was stirred for an additional 1 h. To the yellow solution thus obtained was added dropwise a solution of trioxane **7a** (1 g, 3.64 mmol) in dry DME (15 mL), while maintaining the temperature of the flask at 0 °C. After the addition was complete the resulting solution was stirred for additional 0.5 h at 0 °C. Reaction mixture was diluted with water (40 mL) and extracted with diethyl ether (2 × 75 mL). The combined organic layer was washed successively with water (2 × 15 mL) and brine (10 mL), dried over anhyd Na_2SO_4, and concentrated to obtain crude product which was purified by column chromatography over silica gel using AcOEt−hexane (1:49) as eluant to furnish spiro trioxane **10** (viscous oil, 1.16 g, 93% yield) as an inseparable mixture of geometrical isomers. IR (neat, cm^{-1}) 1711; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, 3H, $J = 7.1$ Hz), 1.77−1.84 (m, 2H), 2.08−2.19 (m, 1H), 2.27−2.45 (m, 3H), 2.84−3.13 (m, 2H), 3.79 (dd, 1H, $J = 12.1, 2.9$ Hz), 3.94 and 3.96 (2 × dd, 1H, $J = 12.1, 10.0$ Hz, together integrating for 1H), 4.14 (q, 2H, $J = 7.1$ Hz), 5.28 (dd, 1H, $J = 10.0, 2.9$ Hz), 5.33 and 5.50 (2 × s, 2H), 5.68 (s, 1H), 7.30−7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.69 (q), 24.82 and 24.97 (t), 29.18 and 29.90 (t), 33.06 and 33.28 (t), 34.82 and 35.46 (t), 60.04 (t), 63.41 (t), 80.77 (d), 102.14 (s), 115.08 (d), 116.85 and 117.00 (t), 126.80 (d, integrating for two carbons), 128.62 (d), 128.99 (d, integrating for two carbons), 138.96 (s), 143.78 (s), 159.97 (s), 166.78 (s); FAB-MS (*m*/*z*) 345 $[M + H]^+$; HR-EIMS calc for $C_{20}H_{24}O_5$ 344.1624 found 344.1625.

Compounds **11**−**23** were also prepared by the same procedure.

2-[3-(1-Phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-ylidene]-propionic Acid Ethyl Ester (11). Yield 83%, viscous oil: IR (neat, cm^{-1}) 1709; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 and 1.30 (2 × t, 3H, $J = 7.2$ Hz, together integrating for 3H), 1.72−1.78 (m, 2H), 1.89 (s, 3H), 2.00−2.16 (m, 1H), 2.28−2.43 (m, 3H), 2.51−2.71 (m, 2H), 3.79 (dd, 1H, $J = 11.7, 3.1$ Hz), 3.96 (dd, 1H, $J = 11.7, 10.8$ Hz), 4.19 and 4.20 (2 × q, 2H, $J = 7.2$ Hz, together integrating for 2H), 5.28 (dd, 1H, $J = 10.8, 3.1$ Hz), 5.33 and 5.50 (2 × s, 2H), 7.28−7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.64 (q), 15.72 (q), 26.40 and 26.58 (t), 27.18 and 27.37 (t), 29.16 and 29.70 (t), 34.78 and 35.29 (t), 60.66 (t), 61.43 (t), 80.80 (d), 102.59 (s), 116.88 and 116.96 (t), 122.05 (s), 126.82 (d, integrating for two carbons), 128.58 (d), 128.97 (d, integrating for two carbons), 138.99 (s), 143.82 (s), 145.04 and 145.15 (s), 170.38 (s); FAB-MS (*m*/*z*) 359 $[M + H]^+$; HR-EIMS calc for $C_{21}H_{26}O_5$ 358.1780 found 358.1780.

[3-(1-Biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-ylidene]-acetic Acid Ethyl Ester (12). Yield 93%, mp 143−145 °C; IR (KBr, cm^{-1}) 1707; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J = 7.1$ Hz), 1.79−1.86 (m, 2H), 2.08−2.45 (m, 4H), 2.81−3.14 (m, 2H), 3.84 (dd, 1H, $J = 11.7, 3.3$ Hz), 3.97 and 3.99 (2 × dd, 1H, $J = 11.7, 10.2$ Hz, together integrating for 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 5.32 (dd, 1H, $J = 10.2, 3.3$ Hz), 5.35 and 5.57 (2 × s, 2H), 5.69 (s, 1H), 7.34−7.60 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.74 (q), 25.01 (t), 29.94 and 30.15 (t), 33.12 and 33.33 (t), 34.86 and 35.50 (t), 60.13 (t), 63.48 (t), 80.72 (d), 102.26 (s), 115.07 (d), 116.94 (t), 127.21 (d, integrating for two carbons), 127.43 (d, integrating for two carbons), 127.72 (d, integrating for two carbons), 127.95 (d), 129.27 (d, integrating for two carbons), 137.78 (s), 140.80 (s), 141.49 (s), 143.19 (s), 160.10 (s), 166.87 (s); FAB-MS (*m*/*z*) 421 $[M + H]^+$; Anal. Calcd for $C_{26}H_{28}O_5$: C 74.26%, H 6.71%; found: C 74.37%, H 6.82%.

2-[3-(1-Biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-ylidene]-propionic Acid Ethyl Ester (13). Yield 84%, mp 68−70 °C; IR (KBr, cm^{-1}) 1705; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 and 1.30 (2 × t, 3H, $J = 7.0$ Hz, together integrating for 3H), 1.75−1.82 (m, 2H), 1.89 (s, 3H), 2.06−2.13 (m, 1H), 2.33−2.46 (m, 3H), 2.56−2.68 (m, 2H), 3.83 (dd, 1H, $J = 11.7, 3.1$ Hz), 4.00 (dd, 1H, $J = 11.7, 10.3$ Hz), 4.19 and 4.20 (2 × q, 2H, $J = 7.0$ Hz, together integrating for 2H), 5.30 (dd, 1H, $J = 10.3, 3.1$ Hz), 5.35 and 5.57 (2 × s, 2H), 7.30−7.60 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.71 (q), 15.80 (q), 26.46 and 26.64 (t), 27.23 and 27.43 (t), 29.22 and 29.76 (t), 34.83 and 35.34 (t), 60.72 (t), 63.46 (t),

80.69 and 80.73 (d), 102.65 (s), 116.82 and 116.90 (t), 122.09 (s), 127.22 (d, integrating for two carbons), 127.43 (d, integrating for two carbons), 127.70 (d, integrating for two carbons), 127.95 (d), 129.27 (d, integrating for two carbons), 137.81 (s), 140.81 (s), 141.47 (s), 143.31 (s), 145.11 and 145.24 (s), 170.40 (s); FAB-MS (*m*/*z*) 435 $[M + H]^+$; Anal. Calcd for $C_{27}H_{30}O_5$: C 74.63%, H 6.96%; found: C 74.84%, H 6.82%.

{**3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-ylidene**}**-acetic Acid Ethyl Ester (14).** Yield 91%; mp 78−80 °C; IR (KBr, cm^{-1}) 1710; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J = 7.1$ Hz), 1.78−1.84 (m, 2H), 2.08−2.18 (m, 1H), 2.28−2.43 (m, 3H), 2.83−3.09 (m, 2H), 3.79 (dd, 1H, $J = 11.9$, 2.7 Hz), 3.95 and 3.97 (2 × dd, 1H, $J = 11.9$, 10.0 Hz, together integrating for 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 5.22 (dd, 1H, $J = 10.0$, 2.7 Hz), 5.34 and 5.36 (2 × s, 1H), 5.50 and 5.51 (2 × s, 1H), 5.68 (s, 1H), 7.32 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.67 (q), 24.79 and 24.93 (t), 29.20 and 29.93 (t), 33.02 and 33.22 (t), 34.71 and 35.36 (t), 60.06 (t), 63.11 (t), 80.61 (d), 102.23 (s), 115.13 (d), 117.56 and 117.65 (t), 128.18 (d, integrating for two carbons), 129.17 (d, integrating for two carbons), 134.61 (s), 137.40 (s), 142.66 (s), 159.81 (s), 166.70 (s); FAB-MS (*m*/*z*) 379 and 381 $[M + H]^+$; Anal. Calcd for $C_{20}H_{23}ClO_5$: C 63.41%, H 6.12%; found: C 63.56%, H 6.17%.

2-{**3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-ylidene**}**-propionic Acid Ethyl Ester (15).** Yield 85%; viscous oil; IR (neat, cm^{-1}) 1707; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 and 1.30 (2 × t, 1H, $J = 6.6$ Hz each), 1.77−1.78 (m, 2H), 1.88 (s, 3H), 2.06−2.09 (m, 1H), 2.36 (m, 3H), 2.50−2.68 (m, 2H), 3.78 (dd, 1H, $J = 11.7$, 2.8 Hz), 3.96 (dd, 1H, $J = 11.7$, 10.8 Hz), 4.19 and 4.20 (2 × q, 2H, $J = 6.6$ Hz, together integrating for 2H), 5.21 (dd, 1H, $J = 10.8$, 2.8 Hz), 5.35 and 5.51 (2 × s, 2H), 7.32 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.66 (q), 15.74 (q), 26.39 and 26.56 (t), 27.15 and 27.34 (t), 29.20 and 29.73 (t), 34.70 and 35.20 (t), 60.67 (t), 63.10 (t), 80.56 (d), 102.65 (s), 117.62 (t), 122.10 (s), 128.19 (d, integrating for two carbons), 129.16 (d, integrating for two carbons), 134.56 (s), 137.42 (s), 142.71 (s), 145.09 (s), 170.34 (s); FAB-MS (*m*/*z*) 393 and 395 $[M + H]^+$; Anal. Calcd for $C_{21}H_{25}ClO_5$: C 64.20%, H 6.41%; found: C 64.34%, H 6.37%.

{**3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-ylidene**}**-acetic Acid Ethyl Ester (16).** Yield 91%; viscous oil; IR (neat, cm^{-1}) 1712; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J = 7.1$ Hz), 1.66−1.85 (m, 2H), 2.10−2.17 (m, 1H), 2.28−2.44 (m, 3H), 2.87−3.10 (m, 2H), 3.79 (dd, 1H, $J = 11.8$, 3.1 Hz), 3.81 (s, 3H), 3.95 and 3.97 (2 × dd, 1H, $J = 11.8$, 10.4 Hz, together integrating for 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 5.23−5.28 (m, 2H), 5.44 (s, 1H), 5.68 (s, 1H), 6.87 (d, 2H, $J = 8.6$ Hz), 7.33 (d, 2H, $J = 8.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.68 (q), 24.82 and 24.97 (t), 29.16 and 29.87 (t), 33.08 and 33.29 (t), 34.86 and 35.50 (t), 55.69 (q), 60.08 (t), 63.50 (t), 80.91 (d), 102.16 (s), 114.37 (d, integrating for two carbons), 115.01 (d), 115.29 and 115.47 (t), 127.97 (d, integrating for two carbons), 131.33 (s), 143.03 (s), 160.06 (s), 166.85 (s); FAB-MS (*m*/*z*) 375 $[M + H]^+$; HR-EIMS calc for $C_{21}H_{26}O_6$ 374.1721 found 374.1701.

2-{**3-[1-(4-Methoxy-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-ylidene**}**-propionic Acid Ethyl Ester (17).** Yield 84%; viscous oil; IR (neat, cm^{-1}) 1710; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 and 1.30 (2 × t, 3H, $J = 7.0$ Hz, together integrating for 3H), 1.76−1.80 (m, 2H), 1.88 (s, 3H), 2.04−2.11 (m, 1H), 2.32−2.45 (m, 3H), 2.51−2.66 (m, 2H), 3.78 (dd, 1H, $J = 11.8$, 2.8 Hz), 3.81 (s, 3H), 3.95 (dd, 1H, $J = 11.8$, 10.3 Hz), 4.19 and 4.20 (2 × q, 2H, $J = 7.0$ Hz, together integrating for 2H), 5.23 (s, 1H), 5.26 (dd, 1H, $J = 10.3$, 2.8 Hz), 5.43 (s, 1H), 6.87 (d, 2H, $J = 8.6$ Hz), 7.33 (d, 2H, $J = 8.6$ Hz); FAB-MS (*m*/*z*) 389 $[M + H]^+$; HR-EIMS calc for $C_{22}H_{28}O_6$ 388.1886 found 388.1914.

[3-(1-*p*-Tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-ylidene]-acetic Acid Ethyl Ester (18). Yield 91%; mp 64−66 °C; IR (KBr, cm^{-1}) 1711; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J = 7.1$ Hz), 1.75−1.84 (m, 2H), 2.12−2.16 (m, 1H), 2.29−2.44 (m, 3H), 2.34 (s, 3H), 2.90−3.05 (m, 2H), 3.79 (dd, 1H, $J = 11.8$, 2.9 Hz), 3.94 and 3.95 (2 × dd, 1H, $J = 11.8$, 10.3 Hz, together integrating for 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 5.26 (dd, 1H, $J = 10.3$, 2.9 Hz), 5.28 and 5.48 (2 × s, 2H), 5.68 (s, 1H), 7.15 (d, 2H, $J = 8.2$ Hz), 7.28 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.71 (q), 21.51 (q), 24.83 and 24.98 (t), 29.18 and 29.89 (t), 33.09 and 33.30 (t), 34.87 and 35.51 (t), 60.07 (t), 63.51 (t), 80.82 (d), 102.13 (s), 115.03 (d), 116.01 and 116.17 (t), 126.65 (d, integrating for two carbons), 129.69 (d, integrating for two carbons), 136.02 (s), 138.49 (s), 143.54 (s), 160.05 (s), 166.81 (s); FAB-MS (*m*/*z*) 359 $[M + H]^+$; Anal. Calcd for $C_{21}H_{26}O_5$: C 70.37%, H 7.31%; found: C 70.46%, H 7.45%.

2-[3-(1-*p*-Tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-ylidene]-propionic Acid Ethyl Ester (19). Yield 86%; viscous oil: IR (neat, cm^{-1}) 1711; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 and 1.30 (2 × t, 3H, $J = 7.0$ Hz each), 1.66−1.80 (m, 2H), 1.88 (s, 3H), 2.04−2.11 (m, 1H), 2.34 (s, 3H), 2.37−2.41 (m, 2H), 2.55−2.66 (m, 2H), 3.78 (dd, 1H, $J = 11.5$, 2.6 Hz), 3.95 (dd, 1H, $J = 11.5$, 10.4 Hz), 4.18 and 4.19 (2 × q, 2H, $J = 7.0$ Hz, together integrating for 2H), 5.25 (dd, 1H, $J = 10.4$, 2.6 Hz), 5.27 and 5.47 (2 × s, 2H), 7.15 (d, 2H, $J = 8.0$ Hz), 7.28 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.66 (q), 15.75 (q), 21.53 (q), 26.41 and 26.58 (t), 27.19 and 27.39 (t), 29.14 and 29.68 (t), 34.82 and 35.32 (t), 60.69 (t), 63.52 (t), 80.81 (d), 102.56 (s), 116.14 (t), 122.03 (s), 126.65 (d, integrating for two carbons), 129.68 (d, integrating for two carbons), 136.03 (s), 138.50 (s), 143.58 (s), 145.06 and 145.18 (s), 170.47 (s); FAB-MS (*m*/*z*) 373 $[M + H]^+$; Anal. Calcd for $C_{22}H_{28}O_5$: C 70.94%; H 7.58%; found: C 71.04%, H 7.66%.

{**3-[1-(4-Cyclohexyl-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-ylidene**}**-acetic Acid Ethyl Ester (20).** Yield 90%; viscous oil: IR (neat, cm^{-1}) 1713; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J = 7.1$ Hz), 1.34−1.45 (m, 4H), 1.71−1.84 (m, 8H), 2.09−2.17 (m, 1H), 2.28−2.45 (m, 4H), 2.83−3.09 (m, 2H), 3.81 (dd, 1H, $J = 12.1$, 2.9 Hz), 3.95 and 3.97 (2 × dd, 1H, $J = 12.1$, 10.8 Hz, together integrating for 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 5.27 (dd, 1H, $J = 10.8$, 2.9 Hz), 5.30 and 5.49 (2 × s, 2H), 5.68 (s, 1H), 7.18 (d, 2H, $J = 8.1$ Hz), 7.31 (d, 2H, $J = 8.1$ Hz); FAB-MS (*m*/*z*) 427 $[M + H]^+$; Anal. Calcd for $C_{26}H_{34}O_5$: C 73.21%; H 8.03%; found: C 73.38%, H 8.14%.

2-{**3-[1-(4-Cyclohexyl-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]-undec-9-ylidene**}**-propionic Acid Ethyl Ester (21).** This was obtained in 82% yield as an oil: IR (neat, cm^{-1}) 1712; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, 3H, $J = 7.2$ Hz), 1.39−1.50 (m, 4H), 1.73−1.95 (m, 8H), 2.02−2.14 (m, 1H), 2.32−2.76 (m, 6H), 3.79 (dd, 1H, $J = 11.8$, 2.8 Hz), 3.96 (dd, 1H, $J = 11.8$, 10.5 Hz), 4.19 and 4.20 (2 × q, 2H, $J = 7.2$ Hz, together integrating for 2H), 5.27 (dd, 1H, $J = 10.5$, 2.8 Hz), 5.30 and 5.49 (2 × s, 2H), 7.18 (d, 2H, $J = 8.0$ Hz), 7.32 (d, 2H, $J = 8.0$ Hz); FAB-MS (*m*/*z*) 441 $[M + H]^+$; Anal. Calcd for $C_{27}H_{36}O_5$: C 73.61%; H 8.24%; found: C 73.72%, H 8.37%.

[3-(1-Naphthalen-2-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-ylidene]-acetic Acid Ethyl Ester (22). Yield 92%; mp 54−56 °C; IR (KBr, cm^{-1}) 1706; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J = 7.1$ Hz), 1.65−1.87 (m, 2H), 2.08−2.20 (m, 1H), 2.29−2.49 (m, 3H), 2.86−3.14 (m, 2H), 3.86 (dd, 1H, $J = 11.8$, 2.4 Hz), 4.00 and 4.02 (2 × dd, 1H, $J = 11.8$, 10.3 Hz, together integrating for 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 5.42 (dd, 1H, $J = 11.8$, 2.4 Hz), 5.44 and 5.65 (2 × s, 2H), 5.69 (s, 1H), 7.45−7.54 (m, 3H), 7.79−7.84 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.75 (q), 24.86 and 25.01 (t), 29.25 and 29.95 (t), 33.10 and 33.31 (t), 34.87 and 35.51 (t), 60.10 (t), 63.53 (t), 80.79 (d), 102.24 (s), 115.14 (d), 117.30 and 117.45 (t), 124.80 (d), 125.75 (d), 126.79 (d), 126.89 (d), 128.02 (d), 128.67 (d), 128.75 (d), 133.48 and 133.69 (s), 136.19 (s), 143.65 (s), 159.99 (s), 166.81 (s); FAB-MS (*m*/*z*) 395 $[M + H]^+$; HR-EIMS calc for $C_{24}H_{26}O_5$ 394.1780 found 394.1763.

2-[3-(1-Naphthalen-2-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-ylidene]-propionic Acid Ethyl Ester (23). Yield 82%; viscous oil: IR (neat, cm^{-1}) 1700; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 and 1.30 (2 × t, 3H, $J = 7.0$ Hz, together integrating for 3H), 1.63−1.83 (m, 2H), 1.89 (s, 3H), 2.04−2.16 (m, 1H), 2.33−2.48 (m, 3H), 2.57−2.71 (m, 2H), 3.85 (dd, 1H, $J = 11.9$, 2.8 Hz), 4.01 (dd, 1H, $J = 11.9$, 10.3 Hz), 4.19 and 4.20 (2 × q, 2H, $J = 7.0$ Hz, together integrating for 2H), 5.42 (dd, 1H, $J = 10.3$, 2.8 Hz),

5.43 and 5.65 (2 × s, 2H), 7.46−7.55 (m, 3H), 7.80−7.84 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.69 (q), 15.78 (q), 26.44 and 26.61 (t), 27.22 and 27.41 (t), 29.20 and 29.74 (t), 34.82 and 35.33 (t), 60.72 (t), 63.56 (t), 80.81 (d), 102.67 (s), 117.34 and 117.42 (t), 122.09 (s), 124.82 (d), 125.75 (d), 126.76 (d), 126.87 (d), 128.01 (d), 128.65 (d), 128.72 (d), 133.45 and 133.67 (s), 136.21 (s), 143.68 (s), 145.05 and 145.17 (s), 170.42 (s); FAB-MS (*m*/*z*) 409 [M + H]$^+$; HR-EIMS calc for $C_{25}H_{28}O_5$ 408.1937 found 408.1961.

9-Hydroxy-3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-acetic Acid Ethyl Ester (24). To a refluxing mixture of Zn dust (0.57 g, 8.75 mmol) and I_2 (3−4 crystals) in benzene (50 mL) was added ethyl bromoacetate (1.4 g, 8.75 mmol) dissolved in benzene (20 mL) over 30 min. Reaction mixture was refluxed for 3 h and then cooled to 50 °C. A solution of trioxane **7a** (0.60 g, 2.18 mmol) in benzene (15 mL) was added dropwise, and the reaction mixture was stirred at the same temperature for 4 h, when it was cooled to 0 °C and treated with 5% aq H_2SO_4 (20 mL). The organic layer was separated, washed successively with 5% aq $NaHCO_3$ (20 mL) and brine (10 mL), and dried over anhyd Na_2SO_4, solvent was removed, and the crude product, consisting of a mixture of diastereomers, was purified by column chromatography over silica gel using AcOEt−hexane (1:9) as eluant to furnish **24a** (higher R_f) and **24b** (lower R_f) in combined yield of 83% as viscous oil.

9-Hydroxy-3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-acetic Acid Ethyl Ester (24a, higher R_f). viscous oil; IR (neat, cm^{-1}) 1730, 3515; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7.1 Hz), 1.47−2.01 (m, 7H), 2.39 (s, 2H), 2.45−2.48 (m, 1H), 3.41 (s, 1H, OH), 3.67 (dd, 1H. J = 11.9, 3.4 Hz), 3.78 (dd, 1H, J = 11.9, 9.8 Hz), 4.11 (q, 2H, J = 7.1 Hz), 5.17 (dd, 1H, J = 9.8, 3.4 Hz), 5.24 and 5.41 (2 × s, 2H), 7.21−7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.57 (q), 29.93 (t), 30.10 (t), 33.36 (t), 33.62 (t), 45.55 (t), 61.14 (t), 63.35 (t), 69.46 (s), 80.76 (d), 102.61 (s), 116.86 (t), 126.82 (d, integrating for two carbons), 128.57 (d), 128.96 (d, integrating for two carbons), 138.99 (s), 143.85 (s), 173.22 (s); FAB-MS (*m*/*z*) 363 [M + H]$^+$; Anal. Calcd for $C_{20}H_{26}O_6$: C 66.28%, H 7.23%; found: C 66.34%, H 7.25%.

9-Hydroxy-3-(1-phenl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl]-acetic Acid Ethyl Ester (24b, lower R_f). viscous oil: IR (neat, cm^{-1}) 1714, 3512; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.1 Hz), 1.53−2.12 (m, 7H), 2.46 (s, 2H), 2.62−2.70 (m, 1H), 3.53 (s, 1H, OH), 3.77 (dd, 1H, J = 11.9, 2.9 Hz), 4.03 (dd, 1H, J = 11.9, 10.3 Hz), 4.17 (q, 2H, J = 7.1 Hz), 5.25 (dd, 1H, J = 10.3, 2.9 Hz), 5.31 and 5.50 (2 × s, 2H), 7.31−7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.56 (q), 30.10 (t), 30.56 (t), 33.48 (t), 33.71 (t), 45.67 (t), 61.14 (t), 63.29 (t), 69.37 (s), 80.74 (d), 102.58 (s), 116.79 (t), 126.77 (d, integrating for two carbons), 128.59 (d), 128.98 (d, integrating for two carbons), 139.01 (s), 143.80 (s), 173.39 (s); FAB-MS (*m*/*z*) 363 [M + H]$^+$; Anal. Calcd for $C_{20}H_{26}O_6$: C 66.28%, H 7.23%; found: C 66.41%, H 7.33%.

Compounds **25** and **26** were also prepared by the same procedure.

[3-(1-Biphenyl-4-yl-vinyl)-9-hydroxy-1,2,5-trioxa-spiro[5.5]-undec-9-yl]-acetic Acid Ethyl Ester (25). This was obtained as a white solid in 88% yield as a mixture of diastereomers **25a** and **25b** which were separated by column chromatography.

[3-(1-Biphenyl-4-yl-vinyl)-9-hydroxy-1,2,5-trioxa-spiro[5.5]-undec-9-yl]-acetic Acid Ethyl Ester (25a, higher R_f). mp 140−141 °C; IR (KBr, cm^{-1}) 1713, 3510; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.1 Hz), 1.49−2.15 (m, 7H), 2.45 (s, 2H), 2.49−2.57 (m, 1H), 3.44 (s, 1H, OH), 3.80 (dd, 1H, J = 11.9, 3.5 Hz), 3.90 (dd, 1H, J = 11.9, 9.7 Hz), 4.17 (q, 2H, J = 7.1 Hz), 5.29 (dd, 1H, J = 9.7, 3.5 Hz), 5.35 and 5.56 (2 × s, 2H), 7.34−7.60 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.60 (q), 24.31 (t), 29.96 (t), 33.40 (t), 33.67 (t), 45.60 (t), 61.15 (t), 63.35 (t), 69.49 (s), 80.69 (d), 102.67 (s), 116.79 (t), 127.22 (d, integrating for two carbons), 127.41 (d, integrating for two carbons), 127.66 (d, integrating for two carbons), 127.92 (d), 129.24 (d, integrating for two carbons), 137.84 (s), 140.82 (s), 141.43 (s), 143.40 (s), 173.20 (s); FAB-MS (*m*/*z*) 439 [M + H]$^+$; Anal. Calcd for $C_{26}H_{30}O_6$: C 71.21%, H 6.90%; found: C 71.43%, H 6.94%.

[3-(1-Biphenyl-4-yl-vinyl)-9-hydroxy-1,2,5-trioxa-spiro[5.5]-undec-9-yl]-acetic Acid Ethyl Ester (25b, lower R_f). mp 124−125 °C; IR (KBr, cm^{-1}) 1700, 3515; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.1 Hz), 1.54−2.09 (m, 7H), 2.46 (s, 2H), 2.67 (dd, 1H, J = 13.4, 2.4 Hz), 3.51 (s, 1H, OH), 3.82 (dd, 1H, J = 11.9, 2.9 Hz), 4.06 (dd, 1H, J = 11.9, 10.2 Hz), 4.17 (q, 2H, J = 7.1 Hz), 5.28 (dd, 1H, J = 10.2, 2.9 Hz), 5.33 and 5.56 (2 × s, 2H), 7.34−7.61 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.57 (q), 24.50 (t), 30.57 (t), 33.50 (t), 33.73 (t), 45.69 (t), 61.16 (t), 63.29 (t), 69.37 (s), 80.63 (d), 102.64 (s), 116.69 (t), 127.15 (d, integrating for two carbons), 127.43 (d, integrating for two carbons), 127.69 (d, integrating for two carbons), 127.91 (d), 129.23 (d, integrating for two carbons), 137.85 (s), 140.83 (s), 141.47 (s), 143.31 (s), 173.40 (s); FAB-MS (*m*/*z*) 439 [M + H]$^+$; Anal. Calcd for $C_{26}H_{30}O_6$: C 71.21%, H 6.90%; found: C 70.89%, H 6.97%.

{**3-[1-(4-Chloro-phenyl)-vinyl]-9-hydroxy-1,2,5-trioxa-spiro-[5.5]undec-9-yl**}**-acetic Acid Ethyl Ester (26).** This was obtained as a white solid in 84% yield as a mixture of diastereomers **26a** and **26b** which were separated by column chromatography.

{**3-[1-(4-Chloro-phenyl)-vinyl]-9-hydroxy-1,2,5-trioxa-spiro-[5.5]undec-9-yl**}**-acetic-Acid Ethyl Ester (26a, higher R_f).** mp 104−105 °C; IR (KBr, cm^{-1}) 1712, 3445; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.1 Hz), 1.42−1.78 (m, 5H), 1.88−2.12 (m, 2H), 2.47 (s, 2H), 2.51−2.57 (m, 1H), 3.47 (s, 1H, OH), 3.74 (dd, 1H, J = 11.8, 3.2 Hz), 3.85 (dd, 1H, J = 11.8, 9.8 Hz), 4.17 (q, 2H, J = 7.1 Hz), 5.18 (dd, 1H, J = 9.8, 3.2 Hz), 5.34 and 5.48 (2 × s, 2H), 7.29−7.31 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.56 (q), 24.29 (t), 29.83 (t), 33.35 (t), 33.61 (t), 45.57 (t), 61.13 (t), 63.02 (t), 69.42 (s), 80.59 (d), 102.68 (s), 117.56 (t), 128.20 (d, integrating for two carbons), 129.13 (d, integrating for two carbons), 134.53 (s), 137.45 (s), 142.79 (s), 173.15 (s); FAB-MS (*m*/*z*) 397 and 399 [M + H]$^+$; Anal. Calcd for $C_{20}H_{25}ClO_6$: C 60.53%, H 6.35%; found: C 60.64%, H 6.42%.

{**3-[1-(4-Chloro-phenyl)-vinyl]-9-hydroxy-1,2,5-trioxa-spiro-[5.5]undec-9-yl**}**-acetic Acid Ethyl Ester (26b, lower R_f).** This was obtained as a white solid: mp 96−97 °C; IR (KBr, cm^{-1}) 1703, 3497; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz), 1.52−1.71 (m, 5H), 1.89−2.12 (m, 2H), 2.46 (s, 2H), 2.62 (dd, 1H, J = 13.4, 2.5 Hz), 3.53 (bs, 1H, OH), 3.77 (dd, 1H, J = 11.8, 2.9 Hz), 4.02 (dd, 1H, J = 11.8, 10.3 Hz), 4.17 (q, 2H, J = 7.2 Hz), 5.18 (dd, 1H, J = 10.3, 2.9 Hz), 5.33 and 5.49 (2 × s, 2H), 7.30−7.31 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.55 (q), 24.52 (t), 30.47 (t), 33.48 (t), 33.70 (t), 45.68 (t), 61.12 (t), 62.98 (t), 69.32 (s), 80.55 (d), 102.67 (s), 117.44 (t), 128.14 (d, integrating for two carbons), 129.16 (d, integrating for two carbons), 134.57 (s), 137.48 (s), 142.74 (s), 173.33 (s); FAB-MS (*m*/*z*) 397 and 399 [M + H]$^+$; Anal. Calcd for $C_{20}H_{25}ClO_6$: C 60.53%, H 6.35%; found: C 60.68%, H 6.39%.

3-(1-Phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-ol (27). To a magnetically stirred ice cooled solution of **7a** (0.50 g, 1.82 mmol) in MeOH (20 mL) was added powdered $NaBH_4$ (0.07 g, 1.82 mmol) over 10 min. The reaction mixture was stirred at 0 °C for 0.5 h. The mixture was neutralized with glacial acetic acid, diluted with water, and extracted with diethyl ether (2 × 30 mL). The combined organic layer was washed with brine (10 mL), dried over anhyd Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography over silica gel using AcOEt−hexane (3:7) as eluant to furnish **27** as an inseparable mixture of diastereomers (0.48 g, 96%) as a white solid. mp 68−70 °C; IR (KBr, cm^{-1}) 3394; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57−2.12 (m, 7H), 2.36−2.45 and 2.54−2.64 (m, 1H), 3.77−4.03 (m, 3H), 5.25 (dd, 1H, J = 10.1, 3.3 Hz), 5.32 and 5.50 (2 × s, 2H), 7.31−7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.32 and 25.80 (t), 30.41 and 30.58 (t), 30.83 and 30.95 (t), 31.17 and 31.85 (t), 63.17 and 63.53 (t), 68.28 and 68.79 (d), 80.72 and 80.77 (d), 102.26 and 102.37 (s), 116.84 and 116.88 (t), 126.79 (d, integrating for two carbons), 128.60 (d), 128.99 (d, integrating for two carbons), 139.00 (s), 143.79 (s); FAB-MS (*m*/*z*) 277 [M + H]$^+$; Anal. Calcd for $C_{16}H_{20}O_4$: C 69.54%, H 7.30%; found: C 69.47%, H 7.36%.

Compounds **28**−**30** were also prepared by the same procedure.

Biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-ol (28).

Yield 94%; mp 106−108 °C; IR (KBr, cm^{-1}) 3426; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43−2.11 (m, 7H), 2.37−2.48 and 2.57−2.65 (2 × bm, 1H), 3.77−4.03 (m, 3H), 5.30 (dd, 1H, J = 10.7, 3.2 Hz), 5.34 and 5.57 (2 × s, 2H), 7.31−7.66 (m, 9H); FAB-MS (*m*/*z*) 353 $[M + H]^+$; Anal. Calcd for $C_{22}H_{24}O_4$: C 74.98%, H 6.86%; found: C 74.82%, H 6.72%.

3-[1-(4-Chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undecan-9-ol (29). Yield 93%; mp 108−110 °C; IR (KBr, cm^{-1}) 3387; ^1H NMR (200 MHz, $CDCl_3$) δ 1.50−2.01 (m, 7H), 2.26−2.32 and 2.48−2.54 (2 × bm, 1H), 3.72−3.95 (m, 3H), 5.18 (dd, 1H, J = 10.1, 3.1 Hz), 5.33 and 5.49 (2 × s, 2H), 7.28−7.31 (m, 4H); FAB-MS (*m*/*z*) 311 and 313 $[M + H]^+$; Anal. Calcd for $C_{16}H_{19}ClO_4$: C 61.84%, H 6.16%; found: C 61.76%, H 6.22%.

3-(1-*p*-Tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-ol (30). Yield 95%; mp 70−72 °C; IR (KBr, cm^{-1}) 3426; ^1H NMR (200 MHz, $CDCl_3$) δ 1.51−2.09 (m, 7H), 2.34 (s, 3H), 2.55−2.65 (bm, 1H), 3.72−4.00 (m, 3H), 5.25 (dd, 1H, J = 11.9, 3.2 Hz), 5.30 and 5.47 (2 × s, 2H), 7.15 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz); FAB-MS (*m*/*z*) 291 $[M + H]^+$; Anal. Calcd for $C_{17}H_{22}O_4$: C 70.32%, H 7.64%; found: C 70.46%, H 7.69%.

Succinic Acid Mono-[3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]-undec-9-yl] Ester (31). To a solution of alcohol **27** (0.40 g, 1.44 mmol), triethylamine (0.22 g, 2.18 mmol), and DMAP (5 mg) in CH_2Cl_2 (20 mL) was added succinic anhydride (0.29 g, 2.89 mmol) at room temperature. After 1h the solvent was removed under vacuum, and the residue was taken up in water and was extracted with diethyl ether (2 × 25 mL). The combined organic layer was washed with brine (10 mL), dried over anhyd Na_2SO_4, and evaporated to dryness. The crude product was purified by column chromatography over silica gel using AcOEt−hexane (5:5) as eluant to furnish **31** as an inseparable mixture of diastereomers, (0.58 g, 91% yield), mp 60−62 °C; IR (KBr, cm^{-1}) 1729; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63−1.86 (m, 6H), 2.02−2.15 (m, 1H), 2.30−2.39 (m, 1H), 2.62−2.67 (m, 4H), 3.77 and 3.79 (2 × dd, 1H, J = 11.7, 3.6 Hz, together integrating for 1H), 3.91 and 3.97 (2 × dd, 1H, J = 11.7, 10.2 Hz, together integrating for 1H), 4.92−4.94 (bm, 1H), 5.26 (dd, 1H, J = 10.2, 3.6 Hz), 5.32 and 5.50 (2 × s, 2H), 7.28−7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.08 and 25.34 (t), 26.99 and 27.11 (t, integrating for two carbons), 29.38 and 29.70 (t, integrating for two carbons), 30.64 and 30.86 (t), 63.14 and 63.40 (t), 70.84 and 71.20 (d), 80.71 (d), 102.04 and 102.11 (s), 116.91 (t), 126.77 (d, integrating for two carbons), 128.61 (d), 128.99 (d, integrating for two carbons), 138.93 (s), 143.71 (s), 172.10 (s), 177.81 (s); FAB-MS (*m*/*z*) 377 $[M + H]^+$; Anal. Calcd for $C_{20}H_{24}O_7$: C 63.82%, H 6.43%; found: C 64.12%, H 6.34%.

Compounds **32**−**34** were prepared by the same procedure.

Succinic Acid Mono-[3-(1-biphenyl-4-yl-vinyl)-1,2,5-trioxa-spiro[5.5]undec-9-yl] Ester (32). Yield 95%; mp 104−106 °C; IR (KBr, cm^{-1}) 1727; ^1H NMR (200 MHz, $CDCl_3$) δ 1.67−1.83 (m, 6H), 2.04−2.16 (m, 1H), 2.32−2.38 (m, 1H), 2.59−2.70 (m, 4H), 3.81 and 3.83 (2 × dd, 1H, J = 11.9, 3.3 Hz, together integrating for 1H), 3.95 and 4.01 (2 × dd, 1H, J = 11.9, 10.2 Hz, together integrating for 1H), 4.92−4.94 (bm, 1H), 5.29 (dd, 1H, J = 10.2, 3.3 Hz), 5.34 and 5.57 (2 × s, 2H), 7.34−7.60 (m, 9H); FAB-MS (*m*/*z*) 453 $[M + H]^+$; Anal. Calcd for $C_{26}H_{28}O_7$: C 69.01%, H 6.24%; found: C 69.14%, H 6.27%.

Succinic Acid Mono-{3-[1-(4-chloro-phenyl)-vinyl]-1,2,5-trioxa-spiro[5.5]undec-9-yl} Ester (33). Yield 91%; mp 72−74 °C; IR (KBr, cm^{-1}) 1725; ^1H NMR (200 MHz, $CDCl_3$) δ 1.65−1.87 (m, 6H), 2.04−2.11 (m, 1H), 2.28−2.34 (m, 1H), 2.59−2.70 (m, 4H), 3.76 and 3.78 (2 × dd, 1H, J = 11.8, 3.2 Hz, together integrating for 1H), 3.91 and 3.97 (2 × dd, 1H, J = 11.8, 10.0 Hz, together integrating for 1H), 4.91−4.93 (bm, 1H), 5.19 (dd, 1H, J = 10.0, 3.2 Hz), 5.34 and 5.50 (2 × s, 2H), 7.31 (s, 4H); FAB-MS (*m*/*z*) 411 and 413 $[M + H]^+$; Anal. Calcd for $C_{20}H_{23}ClO_7$: C 58.47%, H 5.64%; found: C 58.32%, H 5.46%.

Succinic Acid Mono-[3-(1-*p*-tolyl-vinyl)-1,2,5-trioxa-spiro[5.5]-undec-9-yl] Ester (34). Yield 93%; mp 64−66 °C; IR (KBr, cm^{-1}) 1731; ^1H NMR (200 MHz, $CDCl_3$) δ 1.65−1.87 (m, 6H), 2.02−2.19 (m, 2H), 2.34 (s, 3H), 2.62−2.72 (m, 4H), 3.76 and 3.77 (2 × dd, 1H, J = 11.8, 3.1 Hz, together integrating for 1H), 3.90 and 3.96 (2 × dd, 1H, J = 11.8, 10.4 Hz, together integrating for 1H), 4.90−4.93 (bm, 1H), 5.23 (dd, 1H, J = 11.8, 3.1 Hz), 5.26 and 5.47 (2 × s, 2H), 7.14 (d, 2H, J = 7.9 Hz), 7.27 (d, 2H, J = 7.9 Hz); FAB-MS (*m*/*z*) 391$[M + H]^+$; Anal. Calcd for $C_{21}H_{26}O_7$: C 64.60%, H 6.71%; found: C 64.46%, H 6.37%.

9-Methyl-3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-ol (35). To an ice cold solution of MeMgBr (prepared from 0.18 g of Mg and 1.8 g of MeI) in ether was added a solution of **7a** (0.70 g, 2.55 mmol) in anhydrous ether, and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was cooled and quenched with water (7 mL). Usual workup followed by chromatography furnished **35a** (higher R_f) and **35b** (lower R_f) in combined yield of 54%.

9-Methyl-3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-ol (35a, higher R_f). viscous oil: IR (neat, cm^{-1}) 3419; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.63−1.93 (m, 6H), 2.03−2.18 (m, 1H), 2.37−2.44 (m, 1H), 3.76 (dd, 1H, J = 11.6, 3.1 Hz), 3.88 (dd, 1H, J = 11.6, 10.1 Hz), 5.25 (dd, 1H, J = 10.1, 3.1 Hz), 5.33 and 5.50 (2 × s, 2H), 7.31−7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.94 (t), 30.08 (q), 30.68 (t), 35.31 (t), 35.60 (t), 63.36 (t), 69.56 (s), 80.76 (d), 102.73 (s), 116.83 (t), 126.43 (d, integrating for two carbons), 127.65 (d), 128.57 (d, integrating for two carbons), 139.02 (s), 143.87 (s); ES-MS (ES^++Na) 313; Anal. Calcd for $C_{17}H_{22}O_4$: C 70.32%, H 7.64%; found: C 70.37%, H 7.24%.

9-Methyl-3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-ol (35b, lower R_f). viscous oil: IR (neat, cm^{-1}) 3381; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.58−2.03 (m, 7H), 2.58 (dd, 1H, J = 6.2, 2.2 Hz), 3.77 (dd, 1H, J = 11.9, 2.9 Hz), 4.01 (dd, 1H, J = 11.9, 10.3 Hz), 5.25 (dd, 1H, J = 10.3, 2.9 Hz), 5.31 and 5.50 (2 × s, 2H), 7.29−7.48 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.04 (t), 30.48 (q), 31.13 (t), 35.35 (t), 35.51 (t), 63.27 (t), 69.44 (s), 80.72 (d), 102.71 (s), 116.79 (t), 126.78 (d, integrating for two carbons), 128.58 (d), 128.98 (d, integrating for two carbons), 139.04 (s), 143.82 (s); ES-MS (ES^++Na) 313; Anal. Calcd for $C_{17}H_{22}O_4$: C 70.32%, H 7.64%; found: C 70.66%, H 7.36%.

Compound **36** was prepared by the same procedure.

9-Phenyl-3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-ol (36). This was obtained as a white solid in 57% yield as a mixture of diastereomers **36a** and **36b** which were separated by column chromatography.

9-Phenyl-3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-ol (36a, higher R_f). mp 96−98 °C; IR (KBr, cm^{-1}) 3448; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70−1.78 (m, 4H), 1.95−2.26 (m, 3H), 2.71 (d, 1H, J = 12.0 Hz), 3.80 (dd, 1H, J = 12.0, 3.0 Hz), 3.91 (dd, 1H, J = 12.0, 9.9 Hz), 5.28 (dd, 1H, J = 9.9, 3.0 Hz), 5.34 and 5.50 (2 × s, 2H), 7.23−7.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3 (t), 29.9 (t), 34.5 (t), 35.0 (t), 62.9 (t), 72.5 (s), 80.3 (d), 102.1 (s), 116.4 (t), 124.5 (d, integrating for two carbons), 126.4 (d, integrating for two carbons), 127.0 (d), 128.1 (d), 128.3 (d, integrating for two carbons), 128.5 (d, integrating for two carbons), 138.5 (s), 143.3 (s), 148.0 (s); FAB-MS (*m*/*z*) 353 $[M + H]^+$; Anal. Calcd for $C_{22}H_{24}O_4$: C 74.98%, H 6.86%; found: C 74.66%, H 6.71%.

9-Phenyl-3-(1-phenyl-vinyl)-1,2,5-trioxa-spiro[5.5]undecan-9-ol (36b, lower R_f). mp 104−106 °C; IR (KBr, cm^{-1}) 3449; ^1H NMR (200 MHz, $CDCl_3$) δ 1.69−2.21 (m, 7H), 2.84 (d, 1H, J = 12.5 Hz), 3.81 (dd, 1H, J = 11.9, 2.8 Hz), 4.07 (dd, 1H, J = 11.9, 10.4 Hz), 5.29 (dd, 1H, J = 10.4, 2.8 Hz), 5.34 and 5.52 (2×s, 2H), 7.28−7.52 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.11 (t), 31.25 (t), 35.49 (t, integrating for two carbons), 63.39 (t), 73.46 (s), 80.78 (d), 102.50 (s), 116.92 (t), 124.91 (d, integrating for two carbons), 126.81 (d, integrating for two carbons), 127.46 (d), 128.67 (d), 128.76 (d, integrating for two carbons), 129.05 (d, integrating for two carbons), 139.04 (s), 143.78 (s), 148.66 (s); FAB-MS (*m*/*z*) 353 $[M + H]^+$; Anal. Calcd for $C_{22}H_{24}O_4$: C 74.98%, H 6.86%; found: C 74.72%, H 6.53%.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **10**, **11**, **12**, **13**, **14**, **15**, **16**, **18**, **19**, **22**, **23**, **24a**, **24b**, **25a**, **25b**, **27**, **31**, **35a**, **35b**, **36a**, and **36b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We have not been able to assign the relative stereochemistry to the pairs of the diastereomers **24a** and **24b**, **25a** and **25b**, **26a** and **26b**, **35a** and **35b**, and **36a** and **36b**. For the sake of clarity these isomers have been differentiated on the basis of their behaviour on TLC.; faster moving (higher R_f) and slower moving (lower R_f).

(12) (a) Peters, W. Techniques for the study of drug response in experimental malaria. In *Chemotherapy and drug resistance in malaria*; Academic Press: London, 1970; pp 64−136. (b) In vivo test procedure: The colony bred Swiss mice (25 ± 1 g) 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 of compounds **10**−**30**, **35**, and **36** were prepared in groundnut oil while hemisuccinates **31**−**34** were dissolved in 5% $NaHCO_3$ 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 orally for each dose. Parasitemia levels were recorded from thin blood smears between day 4−28.[15] The treated mice surviving beyond day 28 were recorded as the mice protected by the drug. Mice treated with β-arteether served as positive controls.

(13) (a) 100% suppression of parasitemia means, number of parasites if at all present, are below the detection limit. The parasites present below the detection limit can multiply and eventually can be detected. In such cases though the drug is providing near 100% suppression of the parasitemia but will not provide full protection to the treated mice. Multi-drug-resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine and halofantrine. (b) 100% protection means all the treated mice survive till day 28. Similarly 60% protection means only 60% of the treated survive till day 28.

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