Synthesis of 1,2,4-trioxanes and 1,2,4-trioxepanes by *N*-halogenosuccinimide-mediated cyclisations of unsaturated hydroperoxyacetals

Yoshihiro Ushigoe, Yoshihiro Kano and Masatomo Nojima *

Department of Material Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

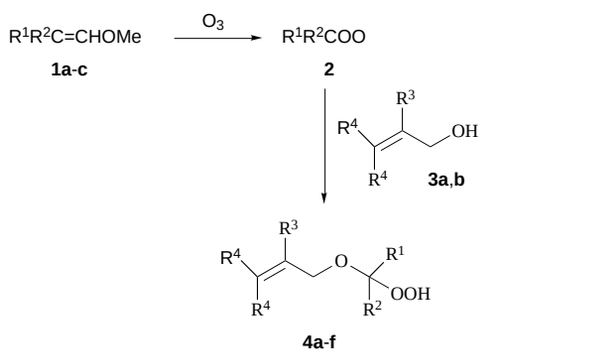
Ozonolyses of vinyl ethers 1a–c in CH_2Cl_2 in the presence of allylic and homoallylic alcohols 3a–c give in each case the corresponding unsaturated hydroperoxy acetals 4a–h, derived from capture of the carbonyl oxides 2a–c by the unsaturated alcohols. *N*-Halogenosuccinimide-mediated cyclisations of the hydroperoxides give the corresponding 1,2,4-trioxanes and/or 1,2,4-trioxepanes, depending on the structure of the hydroperoxides and the identity of the *N*-halogenosuccinimides.

The discovery of pharmacologically active six- and seven-membered ring peroxides has given rise to renewed interest in the development of new syntheses of such structures.[1] Although several methods have been developed for the synthesis of 1,2,4-trioxanes,[2] in the case of 1,2,4-trioxepanes only one reliable method is known. Adam and Duran[3] reported that the acid-catalysed cyclocondensation of 3-hydroxypropyl hydroperoxides and ketones provides the corresponding 1,2,4-trioxepanes. As a new synthetic method for 1,2,4-trioxanes and 1,2,4-trioxepanes, we considered that electrophilic cyclisation of unsaturated hydroperoxy acetals might be promising,[4] an expectation which has been independently confirmed recently by Dussault and Davies.[5] In their work they used an I_2/base system to initiate the cyclisation of unsaturated hydroperoxy acetals, in which the peroxy anion plays a key role. We report herein our own results for the *N*-halogenosuccinimide-mediated synthesis of 1,2,4-trioxanes and 1,2,4-trioxepanes.

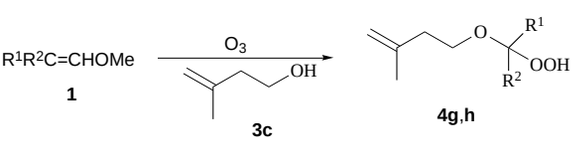
Results and discussion

Preparation of unsaturated hydroperoxy acetals

Ozonolysis of 1-phenyl-2-methoxyethene **1a** in CH_2Cl_2 in the presence of 2-methylprop-2-en-1-ol **3a** (10 equiv.) at −70 °C, followed by column chromatography on silica gel, gave the expected unsaturated hydroperoxy acetal **4a** (47%). This implies that electron-deficient ozone reacts selectively with the electron-rich vinyl ether **1a** to afford benzaldehyde oxide **2a** which, in turn, is efficiently captured by the allylic alcohol **3a**.[6] Also, ozonolyses of the vinyl ethers **1a**–**c** in the presence of 2-methylprop-2-en-1-ol **3a** or 3-methylbut-2-en-1-ol **3b** gave, in each case, the corresponding unsaturated hydroperoxy acetals **4b**–**f** in moderate yields (Scheme 1). From the ozonolyses of the vinyl ethers **1a**,**c** in the presence of 3-methylbut-3-en-1-ol **3c**, were obtained the 1-(3-methylbut-3-enyloxy)alkyl hydroperoxides **4g**,**h** (Scheme 1). Thus, treatment of a mixture of a vinyl ether and an unsaturated alcohol with ozone seems to be an efficient method for the preparation of the unsaturated hydroperoxy acetals. The ^{1}H and ^{13}C NMR spectra, together with the elemental analyses, supported the structure. As additional confirmation, treatment of the unsaturated hydroperoxide **4d** with PhNCO in the presence of a catalytic amount of pyridine gave the expected ester **5d** [eqn. (1)].

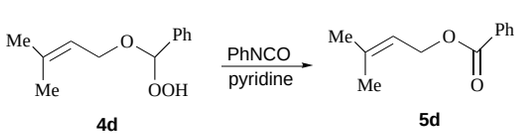


	R^1	R^2	R^3	R^4	**4**, % yield
a	Ph	H	Me	H	47
b	C_7H_{15}	H	Me	H	72
c	-$(CH_2)_5$-		Me	H	64
d	Ph	H	H	Me	59
e	C_7H_{15}	H	H	Me	62
f	-$(CH_2)_5$-		H	Me	65



	R^1	R^2	**4**, % yield
g	Ph	H	58
h	-$(CH_2)_5$-		45

Scheme1

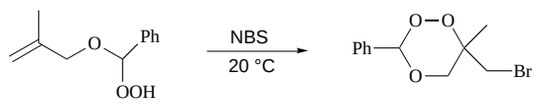


(1)

Synthesis of 1,2,4-trioxanes and 1,2,4-trioxepanes

With the unsaturated hydroperoxy acetals **4a**–**h** to hand, we then conducted *N*-halogenosuccinimide-mediated cyclisations. Treatment of the hydroperoxide **4a** with *N*-bromosuccinimide

(NBS) in CH_2Cl_2 gave the corresponding 1,2,4-trioxane **6a**, together with a complex mixture of unidentified, highly polar products. The physical properties of the unidentified products imply that oligomerisation of the hydroperoxide **4a** and/or dehydration may compete with the desired cyclisation process. There was no evidence for the formation of the corresponding 1,2,4-trioxepane. In attempting to optimise the conditions for this reaction, we repeated it under a variety of conditions and found that the reaction with 2 equiv. of NBS in CH_2Cl_2 in the presence of $NaHCO_3$ for 15 h is most satisfactory (Scheme 2).

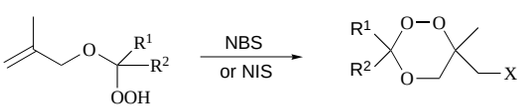


4a **6a**

Entry	NBS ratio	Additive	Solvent	Reaction time/h	**6a** % yield
1	1	—	CH_2Cl_2	2	8[a]
2	2	—	CH_2Cl_2	4	25
3	2	—	CH_2Cl_2	6	31
4	4	—	CH_2Cl_2	4	23
5	2	$NaHCO_3$	CH_2Cl_2	6	31
6	2	$NaHCO_3$	CH_2Cl_2	15	36
7	2	$NaHCO_3$	$ClCH_2CH_2Cl$	6	30

[a] Unchanged **4a** was recovered in 40%.

Scheme 2



4a,**b** **6a-d**

	R^1	R^2	X	**6**, % yield
a	Ph	H	Br	36
b	C_7H_{15}	H	Br	25
c	Ph	H	I	18
d	C_7H_{15}	H	I	15

Scheme 3

The results from the peroxyhalogenation of the unsaturated hydroperoxy acetals **4a**,**b** are summarised in Scheme 3. The reaction with NBS gave 6-bromomethyl-6-methyl-1,2,4-trioxanes **6a**,**b** in isolated yields of 25–36%. From the reactions of **4a**,**b** with *N*-iodosuccinimide (NIS), the iodo-1,2,4-trioxanes **6c**,**d** were obtained, albeit in poorer yields (15–18%). It should be noticed that for the synthesis of 1,2,4-trioxanes, this method has a complementary relationship with the halogenocyclisation of the hemiperacetals derived from 2,3-dimethylbut-3-en-2-yl hydroperoxide and aliphatic aldehydes reported by Bloodworth and Shah.[4b]

Reaction of the hydroperoxide **4c** with NBS or NIS was found to be sluggish and gave (^{1}H NMR) only the corresponding trioxanes. However, column chromatography on silica gel results in peroxide decomposition, the reason for which is obscure.

For the trioxanes **6a**–**d**, two stereoisomers are possible and these were obtained as *ca*. 4:1 mixtures. However, only the major isomer was isolated in a pure state by repeated column chromatography on silica gel and/or recrystallisation. To confirm the structure of the major isomer of the trioxane **6c**, NOE measurements were undertaken. As shown in Fig. 1, the 3-phenyl group and the 6-iodomethyl group were confirmed as having a *cis* relationship. In this connection, Dussault and Davies[5] have reported that the I_2/base-mediated cyclisations of α-(prop-2-enyloxy)octyl hydroperoxide gives 3-heptyl-6-iodomethyl-1,2,4-trioxane (*ca*. 20%) as a mixture of two stereoisomers, the base-dependent ratio of which is 4:1–10:1. Interestingly, the *cis* isomer is the major product.

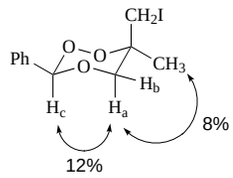
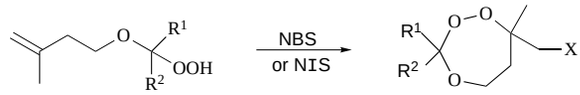


Fig. 1 The NOE in the 1,2,4-trioxane **6c**

From the reaction of the hydroperoxide **4g** with NBS was obtained the 1,2,4-trioxepane **7a** as a *ca*. 3:2 mixture of two stereoisomers (18% yield) (Scheme 4). The reaction of the hydroperoxide **4h** with NBS gave the trioxepane **7b** (one isomer). Iodo trioxepane **7c** was also obtained from the reaction of the hydroperoxide **4h** with NIS (32%). In contrast, the hydroperoxide **4g** reacted with NIS to give a complex mixture of unidentified products. In this connection, Dussault and Davies[5] have reported that the expected trioxepane, 7-iodomethyl-3-heptyl-1,2,4-trioxepane, cannot be isolated from the reaction of α-(but-3-enyloxy)octyl hydroperoxide with I_2/Bu^{t}OK in the presence of 18-crown-6, although the hydroperoxy acetal is consumed under the reaction conditions.



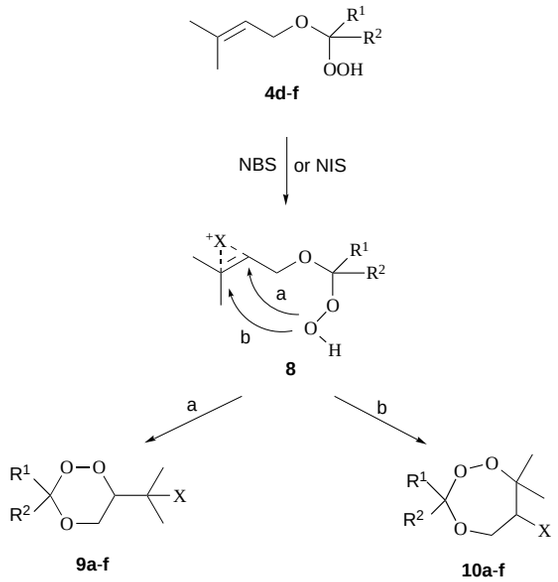
4g,**h** **7a-c**

	R^1	R^2	X	**7**, % yield
a	Ph	H	Br	18
b	-$(CH_2)_5$-		Br	18
c	-$(CH_2)_5$-		I	32

Scheme 4

Treatment of the hydroperoxides **4d**,**e** with NBS gave mixtures of the two isomeric cyclic peroxides, **9a**,**b** and **10a**,**b**, the structures of which were determined on the basis of their DEPT spectra (see Experimental section).[7] The relatively large difference in the chemical shifts between the two geminal methyl groups in the trioxepane **10** was also characteristic. Judged from the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture, only one isomer was produced for each of the cyclic peroxides. From the reaction of the hydroperoxide **4f**, only the 1,2,4-trioxepane **10c** was obtained (34%) (Scheme 5). In contrast, NIS seems to favour the production of the 1,2,4-trioxane. Thus, the reaction of the hydroperoxides **4d**,**e** gave exclusively the corresponding 1,2,4-trioxanes **9d**,**e**, while a mixture of the two isomeric peroxides, **9f** and **10f**, was obtained from the hydroperoxide **4f**.

A plausible mechanism for the described reaction is illustrated in Scheme 5. The first step may involve formation of the halogenium ion intermediate **8**, which is followed by attack of the hydroperoxy group on the electron-deficient carbon to yield



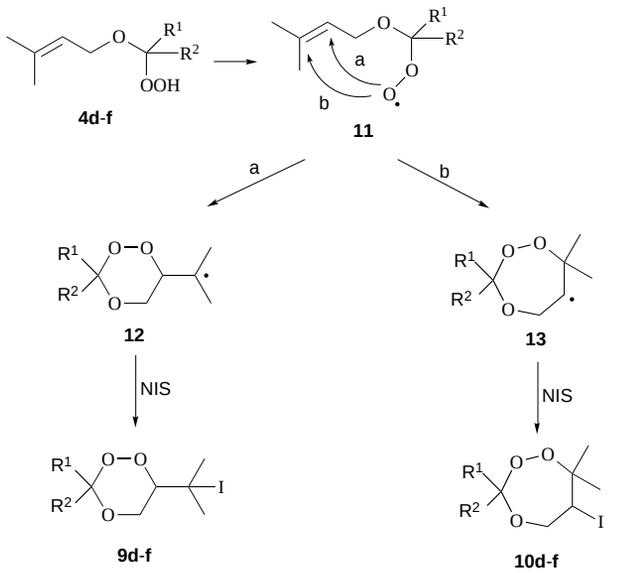
				% yield	
	R^1	R^2	X	**9**	**10**
a	Ph	H	Br	27	14
b	C_7H_{15}	H	Br	31	16
c	-$(CH_2)_5$-		Br		34
d	Ph	H	I	27	
e	C_7H_{15}	H	I	38	
f	-$(CH_2)_5$-		I	28	10

Scheme 5

either the 1,2,4-trioxane **9** (path a) or the 1,2,4-trioxepane **10** (path b). The former pathway is favoured in terms of the entropy of the cyclisation, while the latter may provide significant contribution, if the stability of the carbocation controls the regiochemistry of the cyclisation. The observed composition of the two cyclic peroxides, **9** and **10**, suggests that several factors including the structure of the unsaturated hydroperoxy acetals **4** and the identity of the *N*-halogenosuccinimides affect the mode of the cyclisation in a complicated fashion. It is noted, however, that selective formation of the 1,2,4-trioxanes **6a**–**d** from the hydroperoxides **4a**,**b** and of the 1,2,4-trioxepanes **7a**–**c** from the hydroperoxides **4g**,**h** would be understandable in the framework of a mechanism involving the corresponding halogenium ion intermediates.

Alternatively, the cyclisation may proceed by a free-radical chain mechanism with the propagation steps in Scheme 6. Initiation, which probably involves electron transfer from the hydroperoxide **4** to *N*-halogenosuccinimide,[4a] provides the peroxyl radical **11** which is known to cyclise to an alkyl radical. On the basis of non-stereospecificity in the cyclisation of *E*- and *Z*-hex-3-enyl hydroperoxides, Bloodworth and Curtis[4a] have proposed the significance of a similar free-radical mechanism particularly in the *N*-iodosuccinimide-mediated reaction. If consideration is given to (i) the more favourable disposition of the 6-*exo* over the 7-*endo* mode of cyclisation in the unsaturated alkyl and peroxy radicals[8] and (ii) the relative stability between two peroxy radical intermediates, **12** and **13**, the 1,2,4-trioxepane **10f** from the hydroperoxide **4f** does not seem likely to be produced by the radical chain mechanism.

The question is then, whether the radical chain mechanism is operative or not in the reactions of the hydroperoxides **4d**,**e** with NIS, since in these cases the 1,2,4-trioxanes **9d**,**e** were the sole isolable cyclic peroxides. To confirm the possibility of the

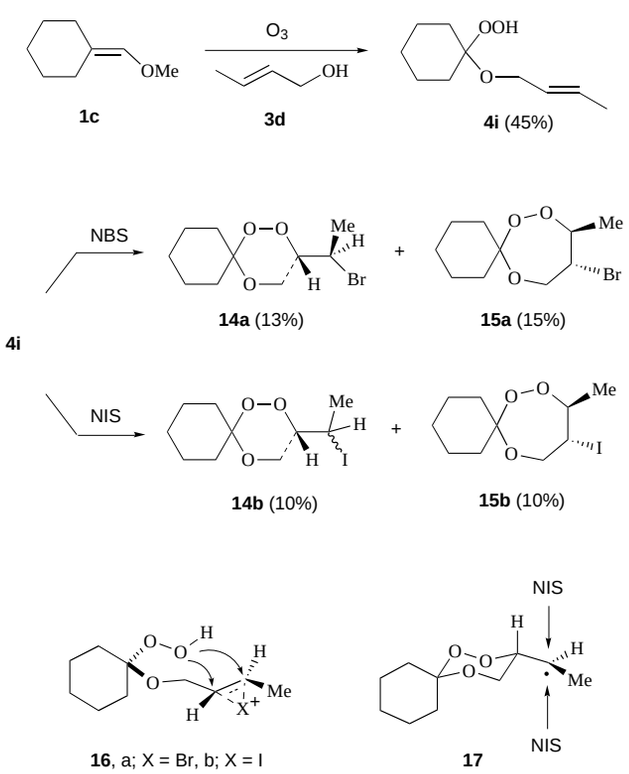


Scheme 6

participation of the free-radical chain mechanism, the *N*-halogenosuccinimide-mediated cyclisation of the hydroperoxide **4i**, derived from capture of the carbonyl oxide **2c** with *E*-but-2-en-1-ol **3d**, was undertaken.

Stereochemistry of the cyclisation

Ozonolysis of methoxymethylenecyclohexane **1c** in CH_2Cl_2 in the presence of *E*-but-2-en-1-ol **3d** gave the unsaturated hydroperoxy acetal **4i** (45%). Treatment with NBS then gave a mixture of the trioxane **14a** and the trioxepane **15a**, only one isomer being obtained for each product (Scheme 7). When the



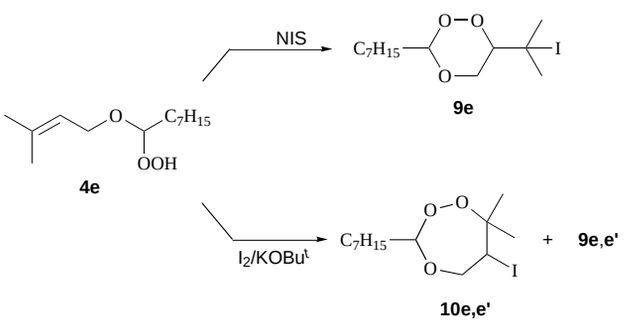
Scheme 7

same reaction was repeated with NIS, however, the trioxane **14b** was obtained as a *ca*. 2:1 mixture of two stereoisomers, whereas the trioxepane **15b** was isolated as a single isomer.

The stereoselectively in the NBS-mediated cyclisation suggests that the reaction proceeds *via* the bromonium ion inter-

mediate **16a** and thereby leads to stereospecific cyclisation (*trans* addition); this probably yields the *erythro* isomer for the trioxane **14a** and the *trans* isomer for the trioxepane **15a**.[4a] In the case of iodocyclisation, the stereochemistry implies that the stereospecific *trans*-addition *via* the iodonium ion **16b** competes with the free-radical chain process *via* the peroxyl-radical intermediate **17**, the former predominating for the formation of the trioxepane **15b**, while the latter would be important for the formation of the trioxane derivative **14b**.

Perhaps in accordance with this, I_2/KOBu^t-mediated cyclisation, which is most likely to proceed *via* the iodonium ion intermediate **8e**,[5] gave mainly two stereoisomeric 1,2,4-trioxepanes **10e**,**e**′ (36%) together with two isomeric trioxanes **9e**,**e**′ (13%) (Scheme 8). It should be noticed that the reaction



Scheme 8

with NIS resulted in exclusive formation of the 1,2,4-trioxane **9e**, suggesting that a minor change in the reaction conditions may affect significantly the reaction course, and thus lead to a change in the product composition.

Experimental

General

^{1}H (270 MHz) and ^{13}C NMR (67.5 MHz) spectra were obtained in $CDCl_3$ with $SiMe_4$ as standard; *J* values are given in Hz. The method of ozonolysis has been described earlier.[9] 1-Phenyl-2-methoxyethene **1a**, 1-methoxynon-1-ene **1b**, and methoxymethylenecyclohexane **1c** were prepared by a reported method.[10]

Caution

Since organic peroxides are potentially hazardous compounds, they must be handled with due care; avoid exposure to strong heat or light, or mechanical shock, or oxidizable organic materials, or transition metal ions. No particular difficulties were experienced in handling any of the new peroxides synthesised in this work using the reaction scales and procedures described below together with the safeguards mentioned above.

Ozonolysis of a vinyl ether in the presence of an unsaturated alcohol

Ozonolysis of 1-phenyl-2-methoxyethene **1a** in the presence of 2-methylprop-2-en-1-ol **3a** is representative. A slow stream of ozone (3.20 mmol) was passed through a CH_2Cl_2 solution (15 cm^3) of the vinyl ether **1a** (430 mg, 3.20 mmol) and 2-methylprop-2-en-1-ol **3a** (2 cm^3, 30 mmol) at −70 °C. After adding diethyl ether (70 cm^3) to the reaction mixture, the organic layer was separated, washed with ice-cold aqueous potassium dihydrogen phosphate and saturated brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was separated by column chromatography on silica gel. Elution with diethyl ether–hexane (1:4) gave the hydroperoxide **4a** (293 mg, 47%).

α-(2-Methylprop-2-enyloxy)benzyl hydroperoxide 4a. Oil (Found: C, 68.4; H, 7.2. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%); δ_H 1.94 (3 H, s), 4.37 (1 H, d, *J* 12.9), 4.49 (1 H, d, *J* 12.9), 5.12 (1 H, s), 5.25 (1 H, s), 6.05 (1 H, s), 7.5–7.7 (5 H, m) and 9.46 (1 H, s); δ_C 19.28, 72.47, 105.63, 112.44, 126.77, 128.07, 128.91, 135.51 and 141.38.

1-(2-Methylprop-2-enyloxy)octyl hydroperoxide 4b. Oil (Found: C, 66.0; H, 11.2. $C_{12}H_{24}O_3$ requires C, 66.6; H, 11.2%); δ_H 0.88 (3 H, t, *J* 6.4), 1.2–1.7 (12 H, m), 1.76 (3 H, s), 4.08 (1 H, d, *J* 12.9), 4.24 (1 H, d, *J* 12.9), 4.85 (1 H, t, *J* 5.8), 4.91 (1 H, s), 5.02 (1 H, s) and 9.02 (1 H, s); δ_C 13.91, 19.37, 22.48, 24.55, 29.02, 29.20, 31.63, 72.44, 106.99, 112.22 and 141.83.

1-(2-Methylprop-2-enyloxy)cyclohexyl hydroperoxide 4c. Oil (Found: C, 64.4; H, 9.8. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%); δ_H 1.3–1.8 (10 H, m), 1.78 (3 H, s), 3.96 (2 H, s), 4.87 (1 H, s), 5.07 (1 H, s) and 8.33 (1 H, s); δ_C 19.37, 22.39, 25.16, 31.29, 63.85, 105.23, 110.62 and 142.73.

α-(3-Methylbut-2-enyloxy)benzyl hydroperoxide 4d. Oil (Found: C, 68.8; H, 7.8. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%); δ_H 1.68 (3 H, s), 1.75 (3 H, s), 4.2–4.3 (2 H, m), 5.42 (1 H, t, *J* 6.3), 5.84 (1 H, s), 7.3–7.5 (5 H, m) and 8.87 (s, 1 H); δ_C 18.10, 25.80, 65.16, 105.27, 120.09, 127.01, 128.30, 129.09, 135.90 and 138.36. One drop of pyridine was added to a benzene solution (15 cm^3) of the hydroperoxide **4d** (312 mg, 1.50 mmol) and phenyl isocyanate (357 mg, 3.00 mmol) and the mixture was stirred at room temp. for 15 h. The reaction mixture was then poured into water and extracted with diethyl ether. After the extract had been dried and concentrated, the products were separated by column chromatography on silica gel. Elution with diethyl ether–hexane (1:9) gave 3-methylbut-3-enyl benzoate **5d**, an oil (Found: C, 75.5; H, 7.5. $C_{12}H_{14}O_2$ requires C, 75.8; H, 7.4%); δ_H 1.76 (3 H, s), 1.78 (3 H, s), 4.81 (2 H, d, *J* 6.3), 5.47 (1 H, t, *J* 6.3), 7.3–7.5 (3 H, m) and 8.04 (2 H, d, *J* 16.5); δ_C 18.10, 25.80, 61.85, 118.69, 128.28, 129.58, 130.46, 132.79, 139.12 and 166.63.

1-(3-Methylbut-2-enyloxy)octyl hydroperoxide 4e. Oil (Found: C, 67.7; H, 11.3. $C_{13}H_{26}O_3$ requires C, 67.8; H, 11.4%); δ_H 0.88 (3 H, t, *J* 6.3), 1.2–1.6 (12 H, m), 1.69 (3 H, s), 1.76 (3 H, s), 4.1–4.3 (2 H, m), 4.84 (1 H, t, *J* 5.8), 5.37 (1 H, t, *J* 6.4) and 9.17 (1 H, s); δ_C 17.74, 22.43, 24.51, 25.52, 28.97, 29.13, 31.57, 31.60, 65.02, 106.54, 120.40 and 137.38.

1-(3-Methylbut-2-enyloxy)cyclohexyl hydroperoxide 4f. Oil (Found: C, 65.2; H, 10.0. $C_{11}H_{20}O_3$ requires C, 65.9; H, 10.1%); δ_H 1.2–1.6 (10 H, m), 1.61 (3 H, s), 1.66 (3 H, s), 3.99 (2 H, d, *J* 5.8), 5.31 (1 H, t, *J* 5.8) and 8.77 (s, 1 H); δ_C 17.27, 22.19, 24.97, 25.14, 56.79, 104.70, 121.10 and 135.57.

α-(3-Methylbut-3-enyloxy)benzyl hydroperoxide 4g. Oil (Found: C, 69.4; H, 7.8. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%); δ_H 1.79 (3 H, s), 2.42 (2 H, t, *J* 6.6), 3.7–3.8 (1 H, m), 3.9–4.0 (1 H, m), 4.86 (2 H, t, *J* 6.9), 5.83 (1 H, s), 7.2–7.5 (5 H, m) and 8.59 (1 H, s); δ_C 22.59, 37.81, 66.87, 106.42, 112.13, 126.90, 128.28, 129.11, 135.62 and 143.00.

1-(3-Methylbut-3-enyloxy)cyclohexyl hydroperoxide 4h. Oil (Found: C, 66.4; H, 10.3. $C_{11}H_{20}O_3$ requires C, 66.0; H, 10.1%); δ_H 1.3–1.8 (10 H, m), 1.81 (3 H, s), 2.31 (2 H, t, *J* 6.4), 3.63 (2 H, t, *J* 6.4), 4.85 (2 H, s) and 8.20 (1 H, s); δ_C 22.55, 22.73, 25.29, 31.36, 37.86, 58.76, 105.34, 111.90 and 144.26.

1-(But-2-enyloxy)cyclohexyl hydroperoxide 4i. Oil (Found: C, 64.5; H, 9.6. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%); δ_H 1.2–2.0 (10 H, m), 1.72 (3 H, d, *J* 6.1), 4.00 (2 H, d, *J* 6.3), 5.6–5.9 (2 H, m) and 8.80 (1 H, s); δ_C 17.68, 22.57, 25.30, 31.50, 61.35, 105.54, 127.75 and 129.18.

Reaction of the hydroperoxides 4a–c with *N*-halogenosuccinimide

Reaction of the hydroperoxide **4a** with NBS is representative. To a CH_2Cl_2 solution (15 cm^3) of the hydroperoxide **4a** (380 mg, 2.0 mmol) was added NBS (697 mg, 4.0 mmol) and then $NaHCO_3$ (165 mg, 2.0 mmol). The mixture was stirred at room temp. in a flask covered by aluminum foil for 15 h and then diluted with hexane (30 cm^3). The precipitated succinimide was filtered off, washed with hexane (3 × 5 cm^3) and the combined filtrate and washings were concentrated by rotary evaporator to leave an oily residue. This was separated by column chromatography on silica gel. Elution with diethyl ether–hexane (95:5)

gave the trioxane **6a** (196 mg, 36%) whilst a subsequent elution with diethyl ether–hexane (30:70) gave an unidentified polar product as an oil (52 mg); δ_H 1.3–1.9 (m), 3.5–4.8 (m), 5.3–5.4 (m), 5.9–6.4 (m) and 7.3–7.7 (m), the ratio of the peak areas being 4:6:2:1:10; δ_C 33.14, 68.57, 105.91, 117.59 and 126.9–130.0; ν_{max}/cm^{-1} 3400, 3050, 2950, 1710, 1495, 1450, 1280, 1090, 755 and 700; *m*/*z* (CI) 339 (1%), 337 (4), 335 (2), 293 (2), 291 (8), 289 (7), 275 (10), 273 (11), 257 (80), 255 (80), 175 (95) and 105 (100). Elution with diethyl ether–hexane (40:60) then gave a different unidentified product (67 mg) as an oil (Found: C, 48.5; H, 4.7; Br, 29.3. $C_{11}H_{13}BrO_3$ requires C, 48.4; H, 4.8; Br, 29.3%); δ_H 1.46 (3 H, s), 3.58 (2 H, dd, *J* 10.6 and 15.2), 4.39 (2 H, dd, 11.6 and 15.5), 7.45 (1 H, br s), 7.5–7.7 (3 H, m) and 8.05 (2 H, d, *J* 6.9); δ_C 23.13, 40.52, 68.90, 71.03, 128.52, 129.67, 133.39 and 166.31; ν_{max}/cm^{-1} 3470, 2950, 1720 and 1295; *m*/*z* (CI) 275 (37), 273 (37), 257 (100) and 255 (100).

6-Bromomethyl-6-methyl-3-phenyl-1,2,4-trioxane 6a. Mp 50–52 °C (from ethyl acetate–hexane) (Found: C, 48.3; H, 4.8; Br, 29.1. $C_{11}H_{13}BrO_3$ requires C, 48.4; H, 4.8; Br, 29.3%); δ_H 1.28 (3 H, s), 3.84 (1 H, d, *J* 10.2), 3.87 (1 H, d, *J* 11.4), 4.07 (1 H, d, *J* 10.2), 4.35 (1 H, d, *J* 11.4 Hz), 6.08 (1 H, s) and 7.3–7.5 (5 H, m); δ_C 19.89, 34.61, 69.74, 78.49, 104.00, 126.92, 128.50, 130.15 and 133.69.

6-Bromomethyl-6-methyl-3-heptyl-1,2,4-trioxane 6b. Oil (Found: C, 49.3; H, 8.0. $C_{12}H_{23}BrO_3$ requires C, 48.8; H, 8.0%); δ_H 0.8–1.8 (18 H, m), 3.65 (1 H, d, *J* 11.9), 3.77 (1 H, d, *J* 10.4), 3.91 (1 H, d, *J* 10.4), 4.11 (1 H, d, *J* 11.9) and 5.10 (1 H, t, *J* 5.4); δ_C 14.04, 19.75, 22.55, 23.56, 28.99, 29.24, 31.63, 31.77, 34.72, 69.20, 78.17 and 104.57.

6-Iodomethyl-6-methyl-3-phenyl-1,2,4-trioxane 6c. Mp 84 °C (from ethyl acetate–hexane) (Found: C, 41.3; H, 4.0; I, 39.7. $C_{11}H_{13}IO_3$ requires C, 41.3; H, 4.1; I, 39.6%); δ_H 1.29 (3 H, s), 3.84 (2 H, s), 3.95 (1 H, d, *J* 11.9), 4.35 (1 H, d, *J* 11.9), 6.05 (1 H, s) and 7.3–7.5 (5 H, m); δ_C 9.89, 21.64, 69.79, 77.68, 103.90, 126.86, 128.45, 130.10 and 133.59.

3-Heptyl-6-iodomethyl-6-methyl-1,2,4-trioxane 6d. Oil (Found: C, 42.2; H, 6.9. $C_{12}H_{23}IO_3$ requires C, 42.1; H, 6.9%); δ_H 0.87 (3 H, t, *J* 6.4), 1.19 (3 H, s), 1.2–1.8 (12 H, m), 3.68 (1 H, d, *J* 10.1), 3.72 (1 H, d, *J* 11.9), 3.76 (1 H, d, *J* 10.1), 4.12 (1 H, d, *J* 11.9) and 5.08 (1 H, t, *J* 5.1); δ_C 10.19, 14.05, 21.58, 22.55, 23.56, 29.00, 29.26, 31.65, 31.77, 69.31, 76.39 and 104.57.

Reaction of the hydroperoxides 4g,h with *N*-halogenosuccinimide

Reaction of the hydroperoxide **4g** with NBS is representative. A mixture of the hydroperoxide **4g** (447 mg, 2.15 mmol), NBS (767 mg, 4.30 mmol) and $NaHCO_3$ (181 mg, 2.15 mmol) in CH_2Cl_2 (20 cm^3) was stirred at room temp. for 15 h. Work-up as described above gave the crude products which were separated by column chromatography on silica gel. Elution with benzene–hexane (3:7) gave the trioxepane **7a** (109 mg, 18%).

7-Bromomethyl-7-methyl-3-phenyl-1,2,4-trioxepane 7a. Oil (a 3:2 mixture of two isomers) (Found: C, 50.5; H, 5.1. $C_{12}H_{15}BrO_3$ requires C, 50.2; H, 5.2%); δ_H 1.30 (1.8 H, s), 1.46 (1.2 H, s), 2.0–2.5 (2 H, m), 3.41 (1.2 H, s), 3.52 (0.4 H, d, *J* 10.6), 3.65 (0.4 H, d, *J* 10.6), 4.0–4.2 (2 H, m), 6.04 (0.4 H, s), 6.08 (0.6 H, s) and 7.2–7.5 (5 H, m); δ_C 22.19, 24.71, 37.06, 39.37, 41.03, 41.39, 64.91, 65.05, 83.27, 83.92, 106.94, 107.71, 126.70, 128.23, 129.18, 129.36, 134.77 and 135.29.

9-Bromomethyl-9-methyl-7,8,12-trioxaspiro[5.6]dodecane 7b. Oil (Found: C, 46.9; H, 6.7. $C_{11}H_{19}BrO_3$ requires C, 47.3; H, 6.9%); δ_H 1.26 (3 H, s), 1.3–2.2 (12 H, m) and 3.6–4.0 (4 H, m); δ_C 22.54, 22.93, 23.56 (CH_3), 25.36, 32.24, 32.40, 37.61, 40.27, 58.40 (OCH_2), 82.50 (OOC) and 106.54 (OCOO).

9-Iodomethyl-9-methyl-7,8,12-trioxaspiro[5.6]dodecane 7c. Oil (Found: C, 40.9; H, 6.0. $C_{11}H_{19}IO_3$ requires C, 40.5; H, 5.9%); δ_H 1.27 (3 H, s), 1.4–2.2 (12 H, m), 3.49 (1 H, d, *J* 10.2), 3.62 (1 H, d, *J* 10.2) and 3.7–3.9 (2 H, m); δ_C 13.46, 22.55, 22.95, 25.38, 25.47 (CH_3), 32.24, 32.46, 40.52, 58.53 (OCH_2), 81.71 (OOC) and 106.47 (OCOO).

Reaction of the hydroperoxides 4d–f with *N*-halogenosuccinimide

Reaction of the hydroperoxide **4d** with NBS is representative. A mixture of the hydroperoxide **4d** (610 mg, 2.93 mmol), NBS (1044 mg, 5.86 mmol) and $NaHCO_3$ (246 mg, 2.93 mmol) in CH_2Cl_2 (20 cm^3) was stirred at room temp. for 15 h. Work-up as described above gave the crude products which were separated by column chromatography on silica gel. Elution with benzene–hexane (1:4) gave the trioxane **9a** (115 mg, 14%). Subsequent elution with benzene–hexane (3:7) gave the 1,2,4-trioxepane **10a** (115 mg, 14%).

6-(1-Bromo-1-methylethyl)-3-phenyl-1,2,4-trioxane 9a. Oil (Found: C, 50.2; H, 5.4. $C_{12}H_{15}BrO_3$ requires C, 50.2; H, 5.3%); δ_H 1.44 (3 H, s), 1.46 (3 H, s), 4.2–4.4 (3 H, m), 5.98 (1 H, s) and 7.2–7.5 (5 H, m); δ_C 25.07, 55.96, 69.49, 85.01, 105.64, 126.72, 128.32, 129.38 and 135.10.

6-Bromo-7,7-dimethyl-3-phenyl-1,2,4-trioxepane 10a. Oil (Found: C, 49.9; H, 5.3. $C_{12}H_{15}BrO_3$ requires C, 50.2; H, 5.3%); δ_H 1.42 (3 H, s), 1.53 (3 H, s), 4.0–4.3 (3 H, m), 6.20 (1 H, s) and 7.2–7.5 (5 H, m); δ_C 21.10, 25.25, 56.53, 64.94, 84.44, 103.27, 126.45, 128.54, 129.29 and 134.99.

6-(1-Bromo-1-methylethyl)-3-heptyl-1,2,4-trioxane 9b. Oil (Found: C, 50.2; H, 8.1; Br, 25.7. $C_{13}H_{25}BrO_3$ requires C, 50.5; H, 8.1; Br, 25.8%); δ_H 0.87 (3 H, t, *J* 6.6), 1.2–1.8 (12 H, m), 1.37 (3 H, s), 1.44 (3 H, s), 4.0–4.1 (3 H, m) and 4.97 (1 H, t, *J* 5.6); δ_C 14.07, 22.10, 22.59, 24.35, 25.03, 29.08, 29.27, 31.07, 32.11, 56.10, 69.15, 84.60 and 106.88.

6-Bromo-7,7-dimethyl-3-heptyl-1,2,4-trioxepane 10b. Oil (Found: C, 50.5; H, 8.2; Br, 25.7. $C_{13}H_{25}BrO_3$ requires C, 50.5; H, 8.1; Br, 25.8%); δ_H 0.88 (3 H, t, *J* 6.4), 1.2–1.6 (12 H, m), 1.35 (3 H, s), 1.52 (3 H, s), 3.8–4.1 (3 H, m) and 5.17 (1 H, t, *J* 5.6); δ_C 14.07, 20.83, 22.59, 24.46, 25.23, 29.06, 29.26, 30.95, 31.68, 56.71, 63.76, 83.99 and 104.39.

9,9-Dimethyl-10-bromo-7,8,12-trioxaspiro[5.6]dodecane 10c. Oil (Found: C, 47.65; H, 7.0. $C_{11}H_{19}BrO_3$ requires C, 47.3; H, 6.9%); δ_H 1.2–1.7 (10 H, m), 1.33 (3 H, s), 1.52 (3 H, s) and 3.7–4.0 (3 H, m); δ_C 19.66 (CH_3), 22.54, 22.91, 25.20, 25.25 (CH_3), 33.11, 33.61, 55.89 (CHBr), 63.51 (OCH_2), 83.27 (COO) and 105.27 (OCOO).

6-(1-Iodo-1-methylethyl)-3-phenyl-1,2,4-trioxane 9d. Oil (Found: C, 43.4; H, 4.5. $C_{12}H_{15}IO_3$ requires C, 43.1; H, 4.5%); δ_H 2.20 (3 H, s), 2.31 (3 H, s), 4.27 (1 H, d, *J* 4.5), 4.35 (1 H, dd, *J* 11.9 and 4.5), 4.82 (1 H, d, *J* 11.9), 6.15 (1 H, s) and 7.3–7.5 (5 H, m); δ_C 35.55 (CH_3), 36.08 (CH_3), 52.08 (CHI), 64.04 (OCH_2), 84.91 (OOCH), 103.81 (OCHOO), 127.03, 128.46, 129.94 and 134.21.

3-Heptyl-6-(1-iodo-1-methylethyl)-1,2,4-trioxane 9e. Oil (Found: C, 44.0; H, 7.1; I, 35.0. $C_{13}H_{25}IO_3$ requires C, 43.8; H, 7.1; I, 35.6%); δ_H 0.87 (3 H, t, *J* 6.4), 1.2–1.9 (12 H, m), 1.95 (3 H, s), 1.96 (3 H, s), 3.7–4.3 (3 H, m) and 5.18 (1 H, t, *J* 5.2); δ_C 14.07 (CH_3), 22.61, 23.74, 29.02, 29.29, 31.65, 34.05 (CH_3), 34.38 (CH_3), 39.97 (CI), 68.38 (OCH_2), 85.70 (OOCH) and 104.42 (OCHOO).

3-(1-Iodo-1-methylethyl)-1,2,5-trioxaspiro[5.5]undecane 9f. Mp 63 °C (from ethyl acetate–hexane) (Found: C, 40.5; H, 5.8; I, 38.8. $C_{11}H_{19}IO_3$ requires C, 40.5; H, 5.9; I, 38.9%); δ_H 1.4–2.2 (10 H, m), 1.98 (3 H, s), 2.05 (3 H, s), 3.58 (1 H, dd, *J* 3.4 and 9.7), 3.97 (1 H, dd, *J* 11.6 and 3.4) and 4.07 (1 H, dd, *J* 11.6 and 9.7); δ_C 22.23, 25.39, 29.54, 34.05 (CH_3), 34.27 (CH_3), 41.48 (CI), 61.83 (OCH_2), 85.32 (OOCH) and 102.50 (OCOO).

9,9-Dimethyl-10-iodo-7,8,12-trioxaspiro[5.6]dodecane 10f. Oil (Found: C, 40.7; H, 5.7. $C_{11}H_{19}IO_3$ requires C, 40.5; H, 5.9%); δ_H 1.3–1.7 (10 H, m), 1.31 (3 H, s), 1.55 (3 H, s) and 3.8–4.0 (3 H, m); δ_C 21.89 (CH_3), 22.57, 22.95, 25.21, 26.04 (CH_3), 31.20, 33.77, 38.10 (CHI), 65.64 (OCH_2), 83.36 (OOC) and 105.89 (OCOO).

Reaction of the hydroperoxide 4i with *N*-halogenosuccinimide

The reaction of the hydroperoxide **4i** with NIS is representative. A mixture of the hydroperoxide **4i** (372 mg, 2.00 mmol), NIS (900 mg, 4.00 mmol) and $NaHCO_3$ (168 mg, 2.00 mmol) in

CH_2Cl_2 (20 cm^3) was stirred at room temp. for 15 h. Work-up as described above gave the crude products which were separated by column chromatography on silica gel. Elution with diethyl ether–hexane (3:97) gave the trioxepane **15b** (64 mg, 10%, single isomer). The second fraction (elution with diethyl ether–hexane, 1:9) gave the 1,2,4-trioxane **14b** (63 mg, 10%, a mixture of two stereoisomers). The structures of the trioxane **14a**,**b** and the trioxepane **15a**,**b** were determined by comparison of the ^{1}H and ^{13}C NMR spectra with those of the relevant trioxane **9f** and the trioxepane **10f**; (i) in the ^{13}C NMR spectra only three signals were observed for the highly symmetrical cyclohexane ring of the trioxane **14a**,**b**, while in the case of the trioxepane **15a**,**b** six signals were observed, and (ii) in the ^{1}H NMR spectra the methyl signal of the trioxepane **15b** responded at a relatively higher field.

3-(1-Bromoethyl)-1,2,5-trioxaspiro[5.5]undecane 14a. Oil (Found: C, 45.5; H, 6.4. $C_{10}H_{17}BrO_3$ requires C, 45.3; H, 6.5%); δ_H 1.2–1.9 (10 H, m), 1.91 (3 H, d, *J* 6.6), 3.91 (1 H, dd, *J* 10.9 and 3.3), 4.12 (1 H, dd, *J* 10.9 and 4.0), 4.31 (1 H, ddd, *J* 4.0, 3.3 and 9.0) and 4.55 (1 H, qd, *J* 6.6 and 9.0); δ_C 22.52, 25.30, 31.25, 31.34, 48.56, 58.44, 63.61 and 105.72.

10-Bromo-9-methyl-7,8,12-trioxaspiro[5.6]dodecane 15a. Oil (Found: C, 45.8; H, 6.65); δ_H 1.2–1.8 (10 H, m), 1.35 (3 H, d, *J* 6.6), 3.63 (1 H, ddd, *J* 10.1, 10.6 and 4.0), 3.87 (1 H, dd, *J* 12.2 and 4.0), 4.01 (1 H, dd, *J* 10.6 and 12.2) and 4.22 (1 H, qd, *J* 6.6 and 9.9); δ_C 16.73, 22.54, 22.86, 25.18, 31.00, 33.44, 52.42, 64.87, 83.94 and 106.02.

3-(1-Iodoethyl)-1,2,5-trioxaspiro[5.5]undecane 14b. Oil (a *ca.* 2:1 mixture of two stereoisomers) (Found: C, 38.7; H, 5.6. $C_{10}H_{17}IO_3$ requires C, 38.5; H, 5.5%); δ_H 1.2–1.8 (10 H, m), 1.91 (0.9 H, d, *J* 6.3), 1.95 (2.1, H, d, *J* 6.3) and 3.8–4.2 (4 H, m); δ_C 17.39, 18.03, 22.21, 23.88, 24.23, 25.39, 29.92, 60.99, 67.80, 81.65, 81.92, 101.46 and 102.86.

10-Iodo-9-methyl-7,8,12-trioxaspiro[5.6]dodecane 15b. Mp 27–29 °C (Found: C, 38.6; H, 5.4); δ_H 1.3–1.8 (10 H, m), 1.42 (3 H, d, *J* 6.3), 3.79 (1 H, ddd, *J* 11.1, 10.6 and 3.9), 3.94 (1 H, dd, *J* 12.2 and 3.9), 4.05 (1 H, dd, *J* 12.2 and 11.1) and 4.33 (1 H, qd, *J* 6.3 and 10.6); δ_C 17.52, 22.52, 22.86, 25.20, 31.07, 33.61, 34.70, 66.74, 85.09 and 106.11.

Reaction of the hydroperoxide 4e with I_2/KOBu^t

To a benzene solution (20 cm^3) of the hydroperoxide **4e** (455 mg, 1.98 mmol), KOBu^t (222 mg, 1.98 mmol) and 18-crown-6 (523 mg, 1.98 mmol), was added I_2 (1005 mg, 3.96 mmol) during 5 min at 0 °C. The mixture was then stirred at room temp. for 12 h after which it was diluted with diethyl ether (70 cm^3). The organic layer was separated, washed with aqueous $NaHSO_3$ and saturated brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was separated by column chromatography on silica gel. Elution with benzene–hexane (15:85) gave a 7:3 mixture of the trioxepane **10e**′ and the trioxane **9e**′ (160 mg, 27%). Subsequent elution with benzene–hexane (1:4) gave a mixture of the diastereoisomeric trioxepane **10e** and trioxane **9e** (153 mg, 22%, **10e**:**9e** = 4:1). An attempt to separate the cyclic peroxides, **9e**′ and **10e**′, by repeated column chromatography on silica gel failed. Only the decomposition of a significant amount of the peroxides was observed. A similar trend was observed for the mixture of two peroxides, **9e** and **10e**.

7,7-Dimethyl-3-heptyl-6-iodo-1,2,4-trioxepane 10e′. This compound was mixed with 30% of the trioxane **9e**′. Oil (Found: C, 43.4; H, 7.0. $C_{13}H_{25}IO_3$ requires C, 43.8; H, 7.1%); δ_H 0.87 (3 H, t, *J* 6.9), 1.2–1.7 (12 H, m), 1.46 (3 H, s), 1.49 (3 H, s), 4.10 (1 H, dd, *J* 9.6 and 12.2), 4.18 (1 H, dd, *J* 2.3 and 12.2), 4.26 (1 H, dd, *J* 2.3 and 9.6) and 4.96 (1 H, t, *J* 5.6); δ_C 14.07, (CH_3), 22.61, 24.37, 25.14 (CH_3), 25.30 (CH_3), 29.09, 29.27, 31.70, 32.26, 36.84 (CHI), 71.38 (CH_2O), 84.69 (COO) and 106.90 (OCOO).

3-Heptyl-6-(1-iodo-1-methylethyl)-1,2,4-trioxane 9e′. This compound was mixted with 70% of **10e**′; only the characteristic signals in the NMR spectra are shown; δ_H 0.89 (3 H, t, *J* 6.3), 2.17 (3 H, s), 2.22 (3 H, s), 4.0–4.2 (2 H, m), 4.62 (1 H, dd, *J* 2.6 and 10.9) and 5.19 (1 H, t, *J* 5.3); δ_C 35.62 (CH_3), 36.12 (CH_3), 63.45 (CH_2O), 84.91 (COO) and 103.95 (OCOO).

7,7-Dimethyl-3-heptyl-6-iodo-1,2,4-trioxepane 10e. This compound was mixted with 20% of the trioxane **9e**. Oil (Found: C, 43.5; H, 7.0); δ_H 0.88 (3 H, t, *J* 6.9), 1.2–1.6 (12 H, m), 1.39 (3 H, s), 1.61 (3 H, s), 3.96 (1 H, dd, *J* 2.0 and 10.9), 4.0–4.1 (2 H, m) and 5.19 (1 H, t, *J* 5.9); δ_C 14.07 (CH_3), 22.57, 23.25 (CH_3), 24.46, 25.77 (CH_3), 29.04, 29.26, 30.98, 31.66, 38.60 (CHI), 65.70 (CH_2O), 83.90 (COO) and 104.39 (OCOO).

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