# *CIS*-FUSED DIHYDROFURANO-1,2,4-TRIOXANES

Charles W. Jefford,* Shu-juan Jin, Jean-Claude Rossier,
Shigeo Kohmoto, and Gérald Bernardinelli

Department of Organic Chemistry and Laboratory of Crystallography,
University of Geneva, 1211 Geneva 4, Switzerland

*Abstract* - The endoperoxide obtained from 2,5-diphenylfuran at -30°C on catalysis with trimethylsilyl trifluoromethanesulfonate condenses with pivalaldehyde, acetone and cyclohexanone to give the corresponding *cis*-fused dihydrofurano-1,2,4-trioxanes (**20**, **21**, **22** and **23**) respectively in yields not greater than 27%. The reaction of pivalaldehyde with the endoperoxide derived from 1,4-diphenyl-1,3-cyclopentadiene gives the *cis* and *trans*-3-*tert*-butyl substituted *cis*-fused cyclopenteno-1,2,4-trioxanes (**26** and **27**) in 75% yield. The structures of **22**, **23**, **26** and **27** are determined by X-ray.

## INTRODUCTION

The discovery that qinghaosu or artemisinin (**1**), a tetracyclic peroxide isolated from the shrub, *Artemisia annua*, and its lactol derivatives, ß-artemether and ß-arteether (**2** and **3**), are active against chloroquine-resistant strains of *Plasmodium falciparum*, has opened a new era in the chemotherapy of malaria.[1] Consequently, much effort has been devoted to developing new methods for the economical synthesis of structurally simpler 1,2,4-trioxanes which still retain or even exceed the potency of **1**-**3**. We have shown that the 1,4-endoperoxides of readily available dienes, such as 1,4-disubstituted derivatives of naphthalene, 1,3-cyclohexadiene, and 1,3-cyclopentadiene, on acid-catalysis, react with aldehydes and ketones to afford the corresponding *cis*-fused bicyclic trioxanes in high yield.[2] A pertinent illustration[3] is provided by the

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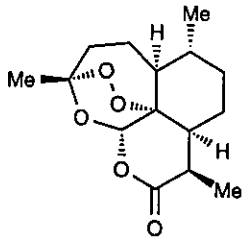
Dedicated to Professor Shigeru Oae on the occasion of his 77th birthday.



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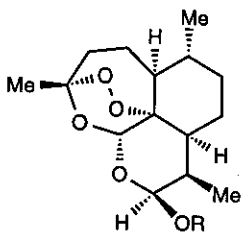
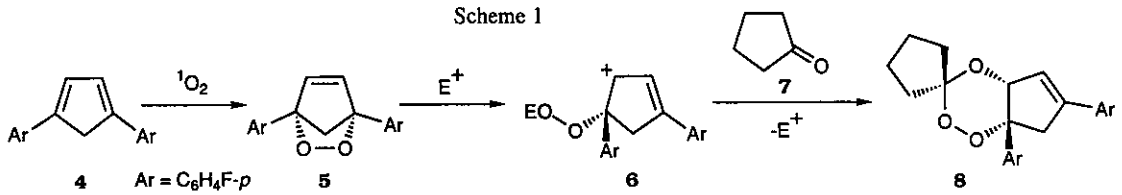


2 R = Me
3 R = Et

synthesis of the extremely active antimalarial, cyclopenteno-1,2,4-trioxane (**8**), which is obtained by the dye-sensitized photo-oxygenation of 1,4-di(4-fluorophenyl)-1,3-cyclopentadiene (**4**) and the condensation of the resulting endoperoxide (**5**) with cyclopentanone (**7**) (Scheme 1).

Scheme 1



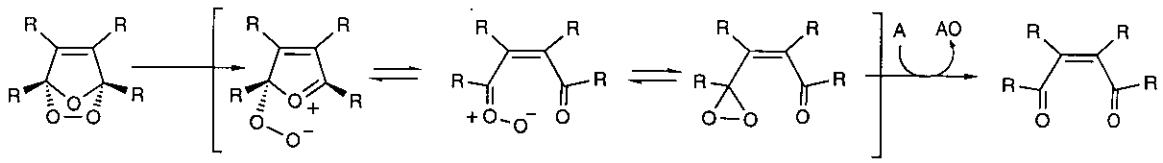
**4** Ar = $C_6H_4F$-*p* **5** **6** **8**

The first step is believed to entail the addition of Lewis acid ($E^+$) to the peroxide element of **5** so forming the peroxy allylic cation (**6**). Thereafter, **6** cyclizes across the carbonyl function of **7** in the expected electronic sense to give **8**. Because **5** is symmetrical, it also reacts to give the enantiomer of **8**, thereby affording a racemic mixture.

In principle, the aforementioned reaction should be applicable to other kinds of endoperoxides and thus provide a means of enlarging the number and variety of candidates for evaluation as antimalarials. It occurred to us that the analogous course with furan endoperoxides should be equally feasible and furnish dihydrofurano-1,2,4-trioxanes. However, it should be stated at the outset that furan peroxides are much less stable than their 1,3-cyclopentadiene-derived counterparts and can only be characterized in solution or isolated at low temperatures.[4,5] Moreover, since structurally speaking they are secondary ozonides, furan endoperoxides are prone to hydrolysis[6] and rearrangement.[7,9] They are also capable of transferring an oxygen atom to acceptors (A), such as olefins, sulfides and even adamantanone.[10] An illustration is provided by **9** (Scheme 2). Its oxidizing power has been attributed to the intermediacy of the carbonyl oxide (**11**) or its dioxirane equivalent (**12**), which are supposed to be in equilibrium with the zwitterionic peroxide (**10**) stemming from **9** by scission. Abstraction of an oxygen atom from **11** or **12** would account for the formation of the oxygenated acceptor (AO) and diketone (**13**). Despite the plausibility of this scheme, attempts to trap **11** or **12** with aldehydes and ketones have failed so far.[11] Clearly, these possible

mechanistic diversions might vitiate the avowed aim of preparing furano-trioxanes. We now describe experiments performed with 2,5-diphenylfuran (**14**) as a representative furan because its endoperoxide (**15**) is known to be perfectly stable at temperatures between -30 and -15°C provided that strictly aprotic conditions are observed.[12] The aim was to appraise its synthetic potential and at the same time to address the aforementioned mechanistic questions.

Scheme 2




**9** **10** **11** **12** **13**

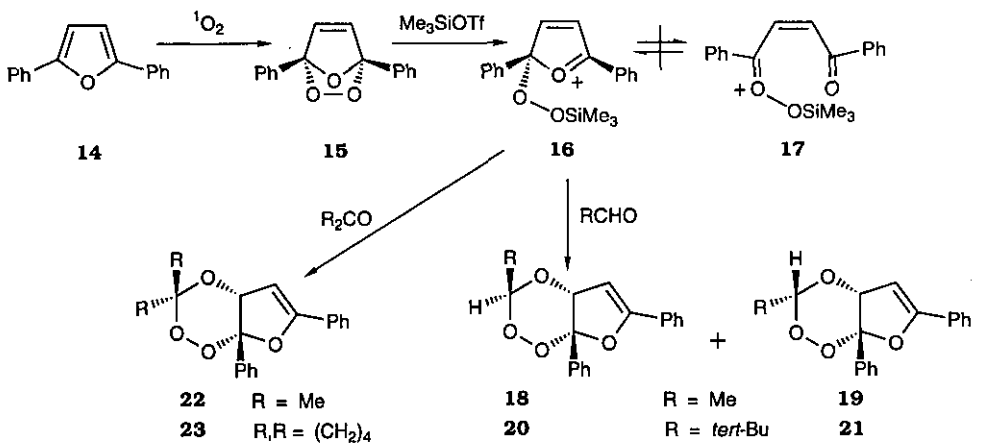
## RESULTS AND DISCUSSION

First, the endoperoxide (**15**) was produced *in situ* by the dye-sensitized photo-oxygenation of **14** at -30°C. Thereafter, an equivalent of acetaldehyde was added with stirring to the reaction mixture together with an equivalent of trimethylsilyl trifluoromethanesulfonate ($Me_3SiOTf$) and a few drops of 2,6-di-*tert*-butylpyridine (DTBP). Examination of the nmr spectrum of the crude oily product suggested that the *trans*-epimer of the *cis*-fused bicyclic trioxane (**19**) had formed, but not the *cis*-epimer (**18**) (Scheme 3). Unfortunately, **19** was far too unstable to be separated by chromatography. Repeating the experiment with pivalaldehyde instead led to the formation of both the *cis*- and *trans-tert*-butyldihydrofurano-1,2,4-trioxanes (**20** and **21**) in a ratio of 1:2, but only in 16% yield. Although **21** was isolated as a pure substance, chromatographic purification of **20** was not possible as it was inextricably mixed with a small amount of what appears to be the dioxolane analogue of **21**, *viz.* **20a**.

Encouraged by these results, the previous experiment was repeated with acetone as the carbonyl partner in the reaction with pre-formed **15** (Scheme 3). The 1,2,4-trioxane (**22**) was isolated in 27% yield. Cyclohexanone reacted similarly, but less efficiently with **15** to give the spirocyclic trioxane (**23**) in 14% yield. Fortunately, **22** and **23** were obtained as colorless, crystalline solids, which enabled their structures to be analysed by X-ray. However, only that of **22** could be determined with acceptable precision (Figure 1). Apart from confirming its constitution, X-ray shows that the furan and trioxane rings are *cis*-fused and that the latter adopts a twist-boat conformation. Refinement of the structure of **23** revealed the same *cis*-fusion and the same twist-boat conformation for the trioxane ring. The peroxyacetal grouping abutting C(7a) in **22** and **23** is noteworthy and constitutes a feature not been seen in trioxanes prepared so far.

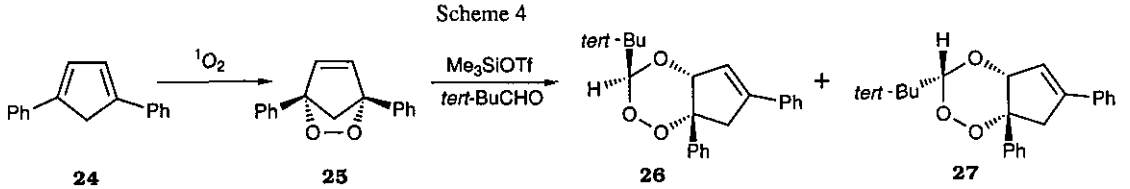
Surprisingly, attempts to incorporate other apparently reactive carbonyl compounds, such as adamantanone, cyclopentanone, tetrahydro-4*H*-pyran-4-one, and benzaldehyde, with **15** were unsuccessful. It was also discovered that the photo-oxygenation of **14** in the presence of effective electrophiles such as acetaldehyde was equally without success. It can therefore be deduced that singlet oxygen undergoes concerted [4 + 2] addtion to the diene moiety in **14** to give **15** directly without passing through the peroxy zwitterionic intermediate corresponding to **10** (Scheme 2).

Scheme 3




By way of comparison, 1,4-diphenyl-1,3-cyclopentadiene (**24**) was photo-oxygenated and the resulting peroxide (**25**) treated with pivalaldehyde exactly under the same conditions as those used for **15** (Scheme 4). The result was dramatically different. The *cis*- and *trans-tert*-butyl-cyclopenteno-1,2,4-trioxanes (**26** and **27**) were readily obtained in a ratio of 5:6 in 75% yield. After purification by chromatography and recrystallization from acetonitrile, both trioxanes afforded crystals suitable for X-ray analysis. As expected, it was found that the bicyclic entity in both cases is *cis*-fused, but the trioxane ring, owing to the possible anchoring effect of the *tert*-butyl group, is disposed in a chair conformation (Figure 1). As a bonus, the unambiguous configurations of **26** and **27** served to confirm the structures previously assigned to the oxacyclic analogues (**20** and **21**) by correlation of the $^1$H-nmr spectral data of both sets of compounds.

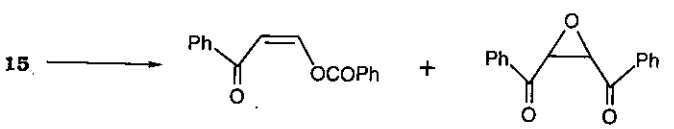
Scheme 4



## CONCLUSION

The foregoing results demonstrate that a certain mechanistic parallel exists between the endoperoxides of furan and 1,3-cyclopentadiene. The formation of 1,2,4-trioxanes (**21**, **22**, and **23**) from **15** obviously stems from the silylperoxy cation (**16**) which incorporates pivalaldehyde or ketone into a *cis*-fused six-membered ring just like its analogue (**6**); the alternative cyclization to the *trans*-fused bicyclic system being precluded for steric reasons. However, the yields are markedly lower for **15**, which could be due to either the diminished reactivity of the presumed peroxy cation (**16**) towards the carbonyl partner or to spontaneous decomposition of **15**, or reversion to **14**. Although carbonyl oxides have been presumed[8] to arise by cleavage of the furan ring in **15** and its congeners, most of the evidence for them has been indirect. In fact, thermolysis of **15** typically gives ring-opened products,[9] namely, the Baeyer-Villiger product (**28**) and the epoxide (**29**) (Scheme 5). In other words, **15** because of its secondary ozonide structure, unlike the 1,2-dioxetanes of enol ethers[13]and dihydropyrans[14] which condense efficiently with aldehydes, gets easily diverted towards other avenues of reaction.

Scheme 5




**28** **29**

The preceding examples of capture of the silylperoxy cation (**16**) by the electrophilic species pivalaldehyde and acetone, rather than its carbonyl oxide tautomer (**17**) (Scheme 3), tends to militate against the existence of the latter, at least in the present context. Finally, it must be admitted that furan endoperoxides do not appear to be good candidates for synthetic purposes in view of the poor yields although they do appear to react to a certain degree according to the already established mechanistic principles required for 1,2,4-trioxane formation.[15]

## ACKNOWLEDGMENTS

We are indebted to the Swiss National Science Foundation (grant No. 20-38 939.93) and the Canton of Geneva for the support of this research. Thanks are also extended to Messieurs A. Pinto and J.P. Saulnier for the nmr measurements, and Professors A. Buchs and F. Gülaçar for the acquisition of the mass spectral data. We also thank Ms. D. Jaggi for technical assistance.

## EXPERIMENTAL PART

General. All solvents were distilled and glassware flame-dried prior to use. Tlc: silica gel 60 $F_{254}$ (Merck, thickness 5 mm) or aluminum oxide $F_{254}$ Fluka. Column Chromatography: silica gel 60 (230-400 mesh ASTM Merck); florisil (100-200 mesh, Fluka). mp: Reichert hot-stage microscope (uncorrected). $^1$H and $^{13}$C-Nmr: Varian-XL-200 or Bruker-AMX-400 spectrometer, resp.; chemical shifts (δ) in ppm relative to internal TMS ( = 0 ppm), coupling constants (J) in Hz; commercial $CDCl_3$ was used without purification unless otherwise indicated; $^{13}$C-Nmr spectra were recorded by using APT and assigned as o (odd) for C-atoms with 1 or 3 attached H-atoms and e (even) for C-atoms with no or 2 attached H-atoms. Ms: m/z (intensities in % rel. to base peak); Vacuum-Generators VG-7070, CH-4 MAT and Finnigan GC/MS-4023 using the INCOS data collection system. Elemental analyses were performed by Dr. H.J. Eder, Service de Microchimie, Institut de Chimie Pharmaceutique, Université de Genève.

1. Reaction of 1,4-diphenyl-2,3,7-trioxabicyclo[2.2.1]hept-5-ene (**15**) with acetaldehyde. A solution of 2,5-diphenylfuran (**14**)[16] (168 mg, 0.76 mmol) and methylene blue (0.5 mg) in $CH_2Cl_2$ (5 ml) was photo-oxygenated at -30°C under irradiation of a 500 W Osram Nitrophot tungsten lamp. When all of **14** had been consumed (tlc, 2-4 h), the solution was cooled to -78°C. 2,6-Di-*tert*-butylpyridine (8 mg, 0.045 mmol) and acetaldehyde (334 mg, 7.6 mmol) and $Me_3SiOTf$ (171 mg, 0.77 mmol) were then successively added dropwise and the mixture stirred at -78°C for 1.5 h. The reaction was quenched with $Et_3N$ (0.15 ml) and the solution washed (3 x $H_2O$) and dried ($MgSO_4$). The sensitizer was removed by filtration and excess solvent evaporated. Examination of the crude oil by $^1$H-Nmr spectroscopy revealed the presence of (3R*,4aR*,7aR*)-3,4a,7,7a-tetrahydro-3-methyl-6,7a-diphenyl-7-oxacyclopenta[1,2-*e*][1,2,4]trioxin (**19**), acetaldehyde trimer, and possible the *cis*-epimer (**18**). Column chromatography on silica gel ($CH_2Cl_2$:hexane, 1:5) gave a pure sample of **19**. $^1$H-Nmr: δ 1.21 (d, J = 5, 3H), 4.89 (d, J =3, 1H), 5.59 (d, J = 3, 1H), 5.74 (q, J = 5, 1H), 7.35-7.85 (m, 10H).

2. The previous experiment was repeated, except that pivalaldehyde (656 mg, 76 mmol) was used instead of acetaldehyde. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give a mixture of three products (37.9 mg, 16%) in a ratio of 6:3:2 as determined by $^1$H-Nmr. Further chromatographic separation afforded the *trans*-epimer (**21**) as a single product, and a mixture of the *cis*-epimer (**20**) and another product, tentatively assigned as the *trans*-epimeric dioxolane (**20a**).

(3R*,4aR*,7aR*)-3-*tert*-Butyl-3,4a,7,7a-tetrahydro-6,7a-diphenyl-7-oxacyclopenta[1,2-*e*][1,2,4]trioxin (**21**). Colorless oil. $^1$H-nmr (400 MHz): δ 0.93 (s, 9H), 4.84 (d, J = 2.8, 1H), 5.17 (s, 1H), 5.50 (d, J = 2.8, 1H), 7.28-7.40 (m, 6H), 7.50-7.77 (m, 4H). $^{13}$C-Nmr (100 MHz): δ 24.9 (o), 35.2 (e), 77.2 (o), 97.1 (o), 105.6 (o), 109.7 (e), 125.9 (o), 127.3 (o), 128.6 (o), 128.6 (o), 129.8 (o), 129.9 (o), 137.0 (e), 159.1 (e), 159.1 (e). Ms: 338 (0.35, $M^+$), 122 (70), 105 (100), 77 (96), 74 (14), 51 (86).

(3S*,4aR*,7aR*)-3-*tert*-Butyl-3,4a,7,7a-tetrahydro-6,7a-diphenyl-7-oxacyclopenta[1,2-*e*][1,2,4]trioxin (**20**) and (2R*,3aS*,6aR*)-2-*tert*-butyl-2,3a,4,6a-tetrahydro-3a-phenyl-4-oxacyclopenta[2,1-*d*][1,3]-dioxole (**20a**). Colorless oil. $^1$H-Nmr (400 MHz): δ **20**: 0.97 (s, 9H), 4.92 (s, 1H), 5.32 (d, J = 2.0, 1H), 5.49 (d, J = 2.0, 1H), 7.25-7.40 (m, 6H), 7.48-7.72 (m, 4H). **20a**: 1.00 (s, 9H), 4.88 (s 1H), 5.21 (d, J = 2.4, 1H), 5.37 (d, J = 2.4, 1H), 7.25-7.40 (m, 6H), 7.48-7.72 (m, 4H). $^{13}$C-Nmr (100 MHz): 24.7 (o), 24.8 (o), 33.67 (e), 34.73 (e), 80.91 (o), 90.00 (o), 92.87 (o), 94.31 (o), 104.65 (o), 108.84 (o), 109.25 (e), 109.25 (e), 125.53 (o), 125.92 (o), 125.92 (o), 126.10 (o), 128.41 (o), 128.41 (o), 128.50 (o), 128.57 (o), 128.81 (o), 129.62 (o), 129.79 (o), 129.79 (o), 133.23 (e), 134.11 (e), 137.56 (e), 138.97 (e), 158.46 (e), 161.49 (e). Ms: No $M^+$, 105 (100), 77 (55), 57 (42), 51 (27).

3. (4aR*,7aR*)-3,4a,7,7a-Tetrahydro-3,3-dimethyl-6,7a-diphenyl-7-oxacyclopenta[1,2-*e*][1,2,4]trioxin (**22**). Experiment 2 was repeated with **14** (126.6 mg, 0.57 mmol), acetone (4 ml), 2,6-di-*tert*-butylpyridine (8 mg, 0.045 mmol), and $Me_3SiOTf$ (127 mg, 0.57 mmol). The residue was purified by column chromatography on silica gel ($CH_2Cl_2$:hexane, 1:5) to give **22** (47.6 mg, 27%) as colorless crystals, mp 127-129°C (recrystallized from $CH_2Cl_2$). $^1$H-Nmr (400 MHz): δ 1.39 (s, 3H), 1.61 (s, 3H), 5.19 (d, J = 2.80, 1H), 5.47 (d, J = 2.80, 1H), 7.31-7.40 (m, 6H), 7.61-7.72 (m, 4H). $^{13}$C-Nmr (100 MHz): δ 25.53 (o), 26.47 (o), 79.54 (o), 96.60 (o), 103.54 (e), 110.72 (e), 125.72 (o), 125.78 (o), 128.42 (o), 128.58 (o), 129.52 (o), 129.71 (o), 137.11 (e), 157.74 (e), 157.96 (e). Ms: 310 (0.51, $M^+$), 105 (100), 51 (19). Anal. Calcd for $C_{19}H_{18}O_4$: C 73.53, H 5.85. Found: C 73.37, H 5.77.

4. (4aR*,7aR*)-3,3-Cyclohexyl-3,4a,7,7a-tetrahydro-6,7a-diphenyl-7-oxacyclopenta[1,2-*e*][1,2,4]trioxin (**23**). Experiment 3 was repeated with **14** (216.1 mg, 0.98 mmol), cyclohexanone (94.7 mg, 0.96 mmol), 2,6-di-*tert*-butylpyridine (8 mg, 0.045 mmol) and $Me_3SiOTf$ (276 mg, 0.98 mmol). Trioxane (**23**) was obtained (47 mg, 14%) as colorless crystals, mp 152-155°C (recrystallized from EtOH). $^1$H-Nmr (400 MHz): δ 1.50-2.50 (m, 10H), 5.19 (d, J = 2.8, 1H), 5.45 (d, J = 2.8, 1H), 7.29-7.39 (m, 6H), 7.62-7.71 (m, 4H). $^{13}$C-Nmr (100 MHz): δ 22.66 (e), 23.09 (e), 25.11 (e), 34.43 (e), 36.43 (e), 79.35 (o),

97.12 (o), 103.66 (e), 111.03 (e), 125.78 (o), 125.88 (o), 128.49 (o), 128.61 (o), 129.49 (o), 129.68 (o), 133.11 (e), 137.38 (e), 157.81 (e). Ms: No $M^+$, 236 (1), 220 (1), 105 (100), 77 (56), 55 (23), 51 (22). Anal. Calcd for $C_{22}H_{22}O_4$: C 75.41, H 6.33. Found: C 75.44, H 6.59.

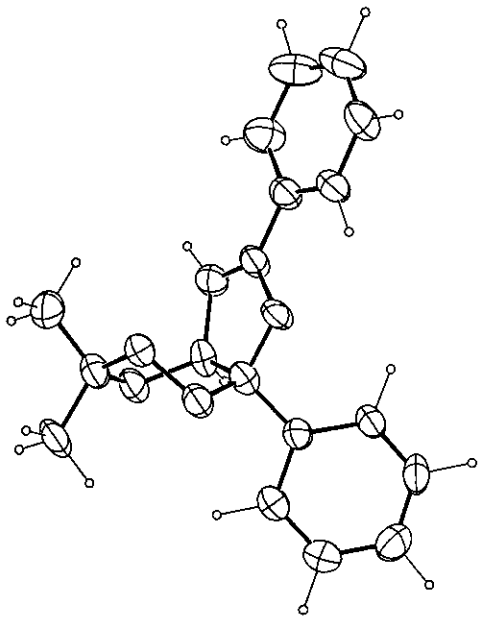
5. Reaction of 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]hept-5-ene (**25**) with pivalaldehyde. Experiment 2 was repeated with 1,4-diphenyl-1,3-cyclopentadiene (**24**)[17] (300 mg, 1.38 mmol) and pivalaldehyde (1.2 g, 14 mmol) and *Amberlyst-15* (300 mg). After filtration and evaporation of the solvent, the residue was purified by column chromatography on silica gel to give a mixture of two products (350 mg, 75%) in a ratio of 5:6 as determined by $^1$H-Nmr. Further chromatographic separation on silica gel ($CH_2Cl_2$) afforded the *cis* and *trans*-epimers (**26**) and (**27**) as pure products, which were recrystallized from acetonitrile.

(3S*,4aR*,7aR*)-3-*tert*-Butyl-3,4a,7,7a-tetrahydro-6,7a-diphenylcyclopenta[1,2-*e*][1,2,4]trioxin (**26**). Colorless crystals, mp 95-97°C. $^1$H-Nmr (400 MHz): δ 0.95 (s, 9H), 3.05 (br t, J = 1, 2H), 5.61 (s, 1H), 5.50 (d, J = 2.8, 1H), 5.23 (s, 1H), 7.25-7.75 (m, 10H).

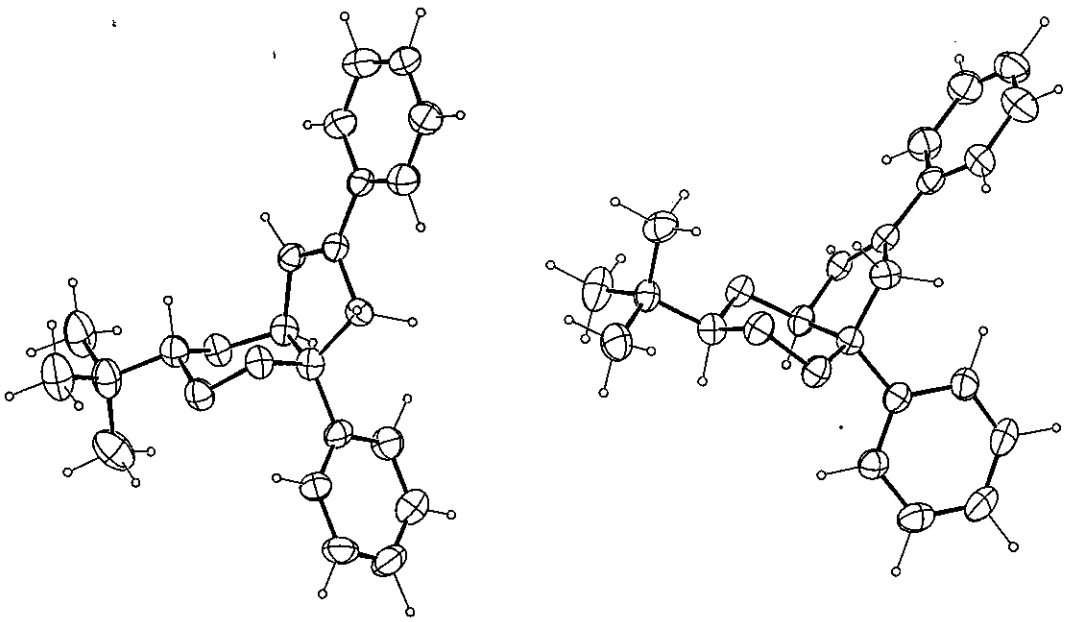
(3R*,4aR*,7aR*)-3-*tert*-Butyl-3,4a,7,7a-tetrahydro-6,7a-diphenylcyclopenta[1,2-*e*][1,2,4]trioxin (**27**). Colorless crystals, mp 115-118°C. $^1$H-Nmr (400 MHz): δ 1.04 (s, 9H), 3.14 (d, J = 15.5, 1H), 3.82 (dd, J = 15.5, 2.5, 1H), 4.64 (d, J = 3, 1H), 5.03 (s, 1H), 6.30 (t, J = 2.5, 1H), 7.25-7.75 (m, 10H).

## CRYSTALLOGRAPHIC DATA

Trioxanes (**22**, **23**, **26** and **27**) gave single crystals suitable for X-ray. Cell parameters and intensities were measured at room temperature on a Philips PW 1100 diffractometer with graphite-monochromated Mo[Kα] radiation (λ = 0.71069 Å). Data were corrected for Lorentz and polarization effects, but not for absorption. The structures were solved by direct methods using MULTAN 87,[18] all other calculations used XTAL[19] and ORTEP[20] programs. All coordinates of the hydrogen atoms were calculated. A summary of crystal data, intensity measurements and structure refinements is given in Table 1. The refinement of **23** confirms that the trioxane ring has the same conformation as that found in **22**, but reveals substantial disorder for one of the phenyl substituents thereby precluding the acquisition of acceptable geometrical parameters. Consequently, data have not been deposited for **23**. Crystallographic data for the other three trioxanes have been deposited with the *Cambridge Crystallographic Data Centre*, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, England.



**22**



**26** **27**

Figure 1. Perspective views of the crystal structures of trioxanes (**22**, **26**, and **27**).

(ellipsoids are represented with 40% probability)

Table 1. Summary of crystal data, intensity measurements, and structure refinements for trioxanes (**22**, **23**, **26** and **27**).

| | **22** | **23** | **26** | **27** |
|---|---|---|---|---|
| Formula | $C_{19}H_{18}O_4$ | $C_{22}H_{22}O_4$ | $C_{22}H_{24}O_3$ | $C_{22}H_{24}O_3$ |
| Mol. wt. | 310.3 | 350.4 | 336.4 | 336.4 |
| Crystal system | Triclinic | Orthorhombic | Monoclinic | Monoclinic |
| Space Group | $P\bar{1}$ | $P2_12_12_1$ | $C2$ | $P2_1/n$ |
| a (Å) | 9.287 (1) | 5.551(1) | 22.812(4) | 6.421(2) |
| b (Å) | 9.552(1) | 18.290(5) | 6.162(1) | 9.530(2) |
| c (Å) | 9.656(1) | 17.589(6) | 13.541(3) | 30.292(12) |
| α (°) | 100.27(1) | 90 | 90 | 90 |
| β (°) | 95.13(1) | 90 | 91.64(1) | 92.23(2) |
| γ (°) | 106.98(1) | 90 | 90 | 90 |
| V (Å$^3$) | 2091.4(3) | 1785.8(8) | 1902.6(5) | 1852.3(5) |
| Z | 2 | 4 | 4 | 4 |
| F(000) | 328 | 744 | 720 | 720 |
| Dc gr.cm$^{-3}$ | 1.29 | 1.30 | 1.17 | 1.21 |
| μ(MoKα) mm$^{-1}$ | 0.084 | 0.083 | 0.072 | 0.074 |
| $((\sin\theta)/\lambda)_{max}$ (Å$^{-1}$) | 0.53 | 0.51 | 0.58 | 0.51 |
| No. measured reflc. | 1990 | 1208 | 1696 | 2195 |
| No. observed reflc. | 1467 | 775 | 1168 | 1483 |
| Criterion for observed | $\|Fo\| > 4\sigma(Fo)$ | $\|Fo\| > 4\sigma(Fo)$ | $\|Fo\| > 4\sigma(Fo)$ | $\|Fo\| > 4\sigma(Fo)$ |
| Refinement (on F) | Full-matrix | Full-matrix | Full-matrix | Full-matrix |
| No. parameters | 208 | 235 | 225 | 225 |
| Weighting scheme | $\omega = 1/\sigma^2(Fo)$ | $\omega = 1$ | $\omega = 1$ | $\omega = 1$ |
| Max. and min. Δρ (e.Å$^{-3}$) | 0.21 , -0.40 | 0.91 , -1.00 | 0.24 , -0.29 | 0.27 , -0.34 |
| R [a], ωR | 0.066 , 0.052 | 0.119 , 0.119 | 0.050 , 0.050 | 0.054 , 0.054 |

a) $R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo|$ ; $\omega R = [\, \Sigma \, (\omega |Fo| - |Fc|)^2 \, / \, \Sigma \, \omega |Fo|^2 \,]^{1/2}$

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