198. Synthesis, Structure, and Antimalarial Activity of Tricyclic 1,2,4-Trioxanes Related to Artemisinin

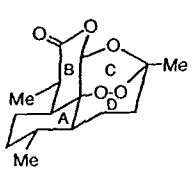
by **Charles W. Jefford***, **Javier A. Velarde**, **Gérald Bernardinelli**[a]), **Dorothy H. Bray**, **David C. Warhurst**[b]), and **Wilbur K. Milhous**[c])

[a]) Department of Organic Chemistry, University of Geneva, CH–1211 Geneva 4
[b]) PHLS Malaria Reference Laboratory, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK
[c]) Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, D.C. 20307-5100, USA

(3. VIII. 93)

Two sets of tricyclic 1,2,4-trioxanes containing the ABC (**10**, **11**) and ACD ring portions (**21**, **22**, **32**, **33**, **37**, and **38**) of artemisinin (**1**) were synthesized by successive photo-oxygenation of appropriate enol-ether precursors to 1,2-dioxanes and inter- and intramolecular reaction with a carbonyl compound or oxo-substituted side-chain. The structures of **10**, **21**, and **22** were determined by X-ray analysis. The anti-malarial activity of all trioxanes, except **37** and **38**, was evaluated *in vitro* against chloroquine-sensitive and chloroquine-resistant *Plasmodium falciparum* parasites. Trioxanes **11** and **21** were as active as artemisinin (**1**). It was found that neither the lactone function nor rings B and D of **1** were essential for activity. A possible pharmacophore for artemisinin-like activity, which embodies a spirocyclopentane group attached to C(3) of 1,2,4-trioxane, was proposed.

Introduction. – The worldwide spread of the resistance of *Plasmodium falciparum* to existing antimalarial agents together with the incidence of cross-resistance to structurally related derivatives makes the search for new drugs a matter of high priority [1]. The discovery that a naturally occurring sesquiterpenic 1,2,4-trioxane, artemisinin (**1**), is endowed with potent antimalarial properties has provided a providential lead for the development of improved versatile analogues [2]. However, this opportunity has not been exploited so far. Instead, derivatives of **1**, namely arteether (**2**), artemether (**3**), sodium artesunate (**4**), and sodium artelinate (**5**) were chosen for clinical trials, despite difficulties in administration arising from poor solubility and stability [3] [4]. It occurred to us that the first step in designing better drugs based on **1** was to determine which parts of the skeleton were essential for the high activity characteristic of the parent structure. It is



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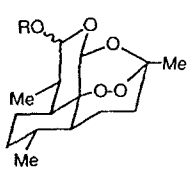
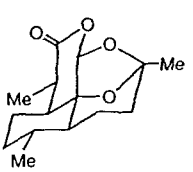


2 R = Et
3 R = Me
4 R = $NaO_2C(CH_2)_2C(O)$
5 R = 4-NaO_2C–$C_6H_4CH_2$



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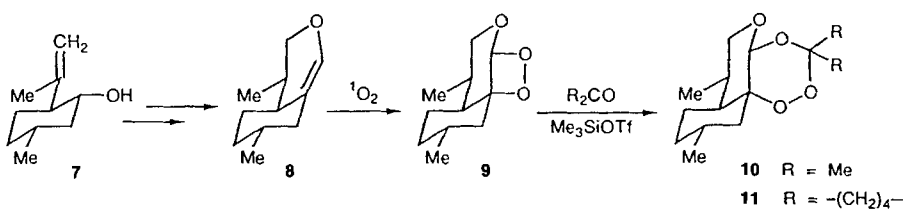
already known that the endoperoxide bridge in **1** is a key structural element, because the metabolite **6**, where only an ether bridge remains, is devoid of activity [5]. Moreover, recent studies on cyclic peroxides and tetrahydrobenzopyran-derived 1,2,4-trioxanes demonstrated that neither the peroxide function nor the 1,2,4-trioxane ring alone are sufficient to confer significant antimalarial activity [6]. Consequently, in an attempt towards defining the structure-activity relationship, we synthesized several 1,2,4-trioxanes structurally resembling artemisinin and hereby report on their antimalarial activity *in vitro* against *Plasmodium falciparum*.

Chemistry. – Artemisinin (**1**) is a tetracyclic molecule composed of a cyclohexane, a δ-lactone, a 1,2,4-trioxane, and a 1,2-dioxepane moiety designated A, B, C, and D, respectively. We decided to synthesize two sets of tricyclic artemisinin-like compounds which embody just three of these cyclic features.

The ABC ring portion of artemisinin (**1**) was constructed by taking (−)-isopulegol (**7**) as the homochiral starting material or A ring component (*Scheme 1*). The B ring was assembled in five steps to give dihydropyran derivative **8** [7]. Photo-oxygenation of the double bond was face-specific. The resulting *exo*-1,2-dioxetane **9** was then enlarged into the two 1,2,4-trioxanes **10** and **11** by the inclusion of acetone and cyclopentanone, respectively, on catalysis with trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf). The

Scheme 1



structures of **10** and **11** embody the precise configurational features of artemisinin (**1**) as the ABC rings possess the same chirality. However, the X-ray analysis of **10** showed that the trioxane ring, unlike that in **1**, adopts a chair conformation in the solid state. There may be a conformational bias towards a boat in the corresponding spirocyclopentane derivative **11**.

To prepare derivatives containing the ACD ring, an intramolecular variant of the above-mentioned process was undertaken. The point of departure was 3-(2-oxocyclohexyl)propanenitrile (**12**; *Scheme 2*)[1]). Application of the *Horner-Wittig* reaction to **12** by using diphenyl(methoxymethyl)phosphine oxide [8] afforded the (*E*)- and (*Z*)-isomers **13** and **14**, respectively, in a 1:1 ratio. After chromatographic separation, the identity of each was established by recourse to ^{1}H- and ^{13}C-NMR spectroscopy.

Each isomer can adopt one of two chair conformations in which the side chain occupies either an equatorial (e) or an axial (a) position. The (*E*)-isomer **13** prefers the former, while the (*Z*)-isomer **14** favors the latter owing to the operation of $A^{1,3}$ strain [9]. Accordingly, the (*E*)- and (*Z*)-isomers are readily distinguishable from each other by the characteristic chemical-shift differences of C(2), C(6), and the attached H-atoms (*Table 1*). The proton

[1]) For the sake of clarity, racemic mixtures are represented as single enantiomers in *Schemes 2–7*.

Scheme 2[1])

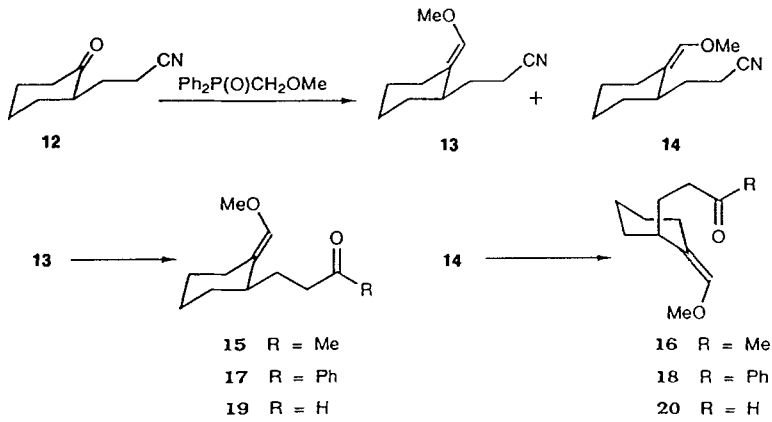
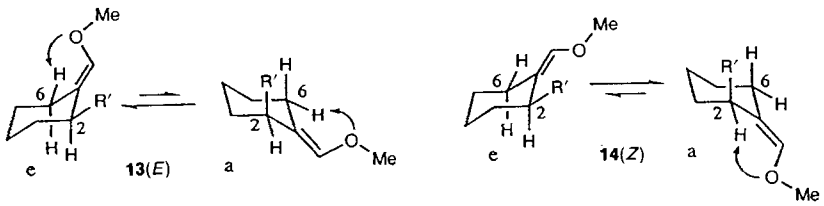


Table 1. *^{13}C- and ^{1}H-NMR Chemical Shifts* (δ in ppm) *of compounds* **13** *and* **14** *in* $CDCl_3$



	H–C(2)	*H*–C(6)	C(2)	C(6)
13	2.10	2.36	37.54	21.88
14	2.82	1.82	32.55	26.31

contiguous to the MeO group is deshielded relative to the same proton in the other isomer [10]; this is the H_e–C(6) (Δ 0.54 ppm) in either the equatorial or axial conformation of **13** and the H_e–C(2) (Δ 0.72 ppm) in the axial conformation of **14**. This correlation is corroborated by the complementary but opposite shift differences, which are observed in the ^{13}C-NMR spectra, the so-called γ-effect [11]. When the MeO group lies close to C(2) or C(6), shielding occurs. In the (*E*)-isomer **13**, the resonance of C(6) appears upfield (Δ 4.43 ppm) from that of the (*Z*)-isomer **14**. Similarly, the (*Z*)-isomer **14** exhibits its C(2) resonance upfield (Δ 4.99 ppm) relative to that of the (*E*)-isomer 13.

Having established the geometric configurations of **13** and **14**, they were converted by standard procedures into the corresponding 3′-oxobutyl, 3′-oxo-3′-phenylpropyl, and 3′-oxopropyl derivatives of the (*E*)- (**15**, **17**, and **19**) and (*Z*)-series (**16**, **18**, and **20**; *Scheme 2*).

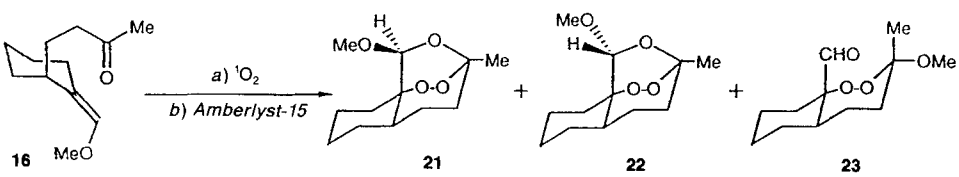
Next, oxygenative cyclization was accomplished as before in two steps. First, the photo-oxygenation of **16** was assayed at low temperatures in different solvents to find the best conditions. The resulting solution was then treated with *Amberlyst-15* (*Table 2*). In each case, just three products (**21**–**23**) were isolated as colorless crystalline solids by chromatography (*Scheme 3*). Although elemental analysis indicated that they had all incorporated one molecule of O_2, their structures could not be determined by NMR spectroscopy. Fortunately, recourse to X-ray analysis revealed that two were a pair of

Table 2. *Oxygenated Cyclic Products* (**21–23**) *Obtained by Photo-oxygenation*[a]) *of (Z)-4-[2-(Methoxymethylidene)cyclohexyl]butan-2-one* (**16**) *and Isomerization*[b]) *of the Intermediate 1,2-Dioxetane* (**24**)[c])

Solvents		Catalyst	Products		
A[a])	*B*[b])		**21**	**22**	**23**
MeOH	CH_2Cl_2	*Amberlyst-15*	10	10	17
MeCN[d])	MeCN	*Amberlyst-15*	28	10	36
CH_2Cl_2	CH_2Cl_2	*Amberlyst-15*	48	19	30
CH_2Cl_2	CH_2Cl_2	$AlCl_3$	39	17	0
CH_2Cl_2	CH_2Cl_2	Me_3SiOTf	16.6	10	0

[a]) Photo-oxygenation was carried out in solvent *A* at −78°, except where noted. [b]) Catalyzed isomerization was carried out in solvent *B* at 0°. [c]) For further details, consult *Exper. Part.* [d]) Photo-oxygenation at −30°.

Scheme 3[1])



'*endo*'- and '*exo*'-methoxy-1,2,4-trioxanes (**21** and **22**; *Fig. 1*), and that the third was a formyl peroxide (**23**; *Fig. 2*). The trioxane ring in the '*endo*'- and '*exo*'-epimers **21** and **22** exists in a twisted-boat conformation just like that observed in artemisinin (**1**) [12]. Furthermore, ring D, the dioxepane portion, adopts a twist-chair conformation which has a pseudo-C_2 axis passing through the O(1) atom [13]. In the bicyclic peroxide **23**, the dioxepane ring still keeps the twist-chair conformation with the pseudo-C_2 axis cutting through the C(1) atom, and has the particularity of bearing *trans*-disposed CHO and MeOH substituents. The yield and proportions of the trioxanes and peroxide **21–23** depend crucially on the solvent and the catalysts used (*Table 2*). In MeOH, apart from **21–23**, which were formed in minor amounts, a complex mixture of non-identifiable polar products was formed. On passing to the non-polar solvents MeCN and CH_2Cl_2, a net improvement occurred giving **21–23** in high yield. The use of $AlCl_3$ was superior to Me_3SiOTf as catalyst. Both had the advantage of not giving the undesired peroxide **23**.

On following the photo-oxygenation of **16** by TLC, it was noticed that the '*endo*'-epimer **21** formed first and that the '*exo*'-epimer **22** and peroxide **23** appeared later. This behavior suggests that **22** and **23** arise from **21**, which, in fact, they do. In an independent experiment, **21** alone in CH_2Cl_2 was treated with *Amberlyst-15* at −10° for 5 h. It was transformed completely into the '*exo*'-trioxane **22** and the peroxide **23**.

When the photo-oxygenation of **16** was repeated in CH_2Cl_2 or $CDCl_3$ at −78°, but in the absence of acid catalyst, a single product was formed which appeared from its NMR spectrum to be 1,2-dioxetane **24** (*Scheme 4*). On warming the solution to room temperature, 2-(3′-oxobutyl)cyclohexanone (**25**), the scission product of **24**, was obtained. This latter finding provides a rationale for the formation of trioxane **21**. The structure postulated for **24** arises by attack of $^1O_2$ on the least hindered side of the double bond of **16**

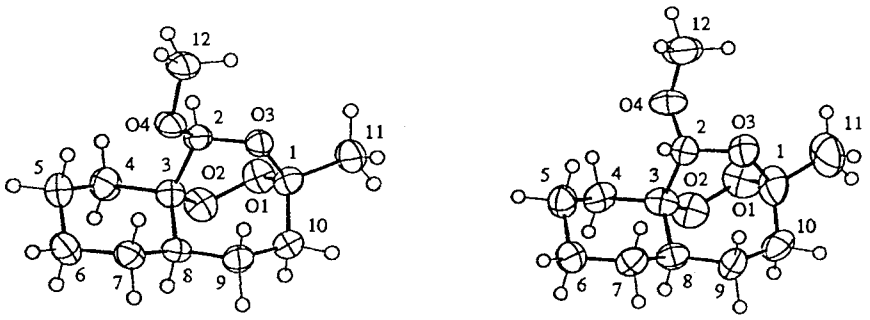


Fig. 1. *Perspective drawings of the crystal structures of the* 'endo'- *and* 'exo'-*methoxy-1,2,4-trioxanes* **21** *and* **22**, *respectively, with atomic numbering* (arbitrary). Ellipsoids are represented with 40% probability.

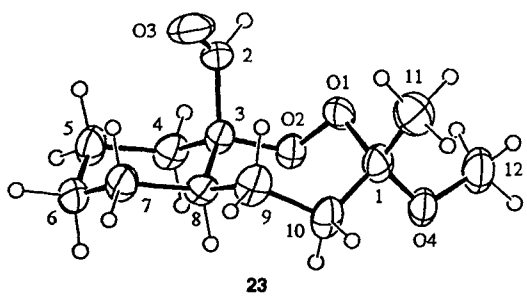
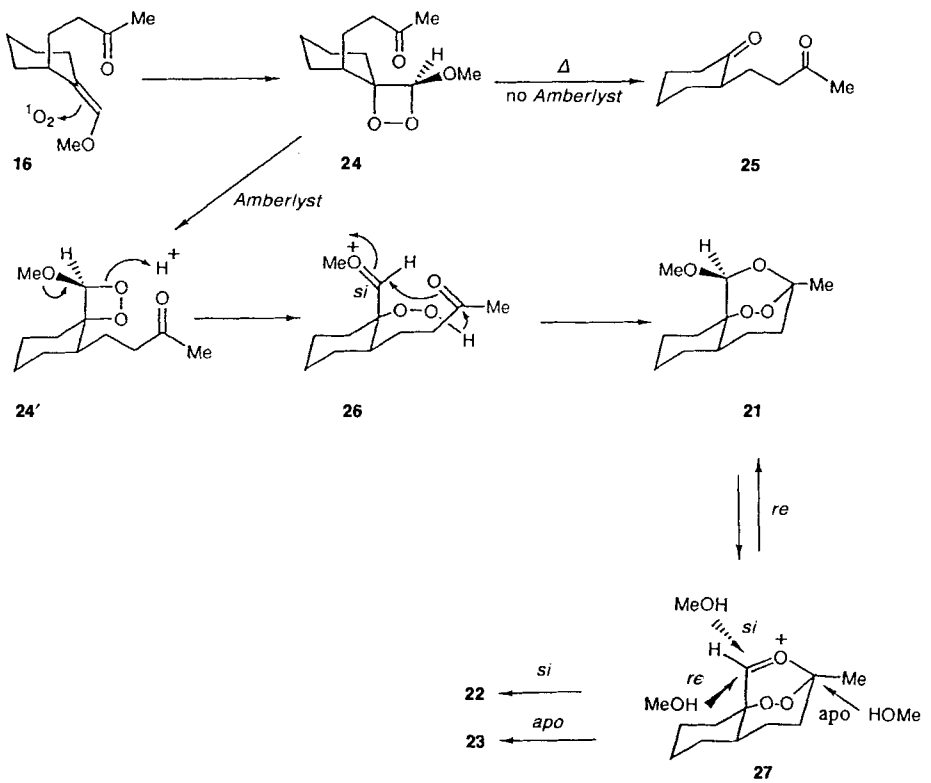


Fig. 2. *Perspective drawings of the crystal structure of peroxide* **23** *with atomic numbering* (arbitrary). Ellipsoids are represented with 40% probability.

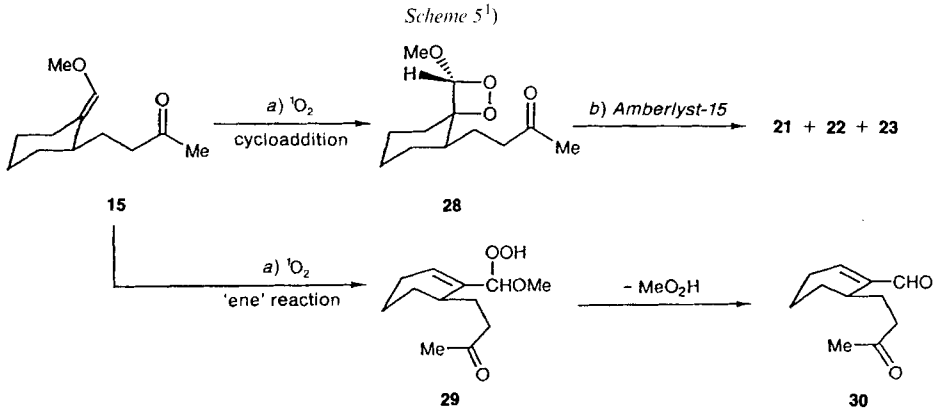
which, for purposes of discussion, is shown as the (*R*)-enantiomer (*Scheme 4*). Conformational inversion places the side chain close to the dioxetane grouping, the future reactive site (**24**→**24′**). Protonation and opening of the dioxetane ring in **24′** creates **26**, the methylideneoxonium moiety of which is immediately attacked on its *si* face by the pendent carbonyl function. The latter is simultaneously attacked by the newly formed hydroperoxy group thereby completing the bicyclic closure and producing the kinetic product, the '*endo*'-epimer **21**. Subsequent protonation of **21** affords the tricyclic cation **27** and a molecule of MeOH which have the chance of recombining on the *re* or *si* faces of the methylideneoxonium moiety, thereby accounting for the equilibration of the '*endo*'- and '*exo*'-epimers **21** and **22** (*Scheme 4*). However, a third avenue is possible. *Apo*-attack cleaves the trioxane ring with *Walden* inversion to place the entering MeO substituent uniquely *trans* to the newly formed aldehyde group (**27**→**23**). Interestingly, when non-protic catalysts were used, the peroxide **23** was not observed (*Table 2*). This result could mean that the *Lewis* acid tightly binds to the MeO group and the site from whence it came so preventing the more complicated maneuver required for ring cleavage.

Scheme 4[1])



The same sequence of photo-oxygenation and acid catalysis was carried out with the (*E*)-isomer **15**. By choosing nonpolar solvents, the yields of products were better than 65%, but in addition to **21**–**23**, cyclohexenecarbaldehyde **30** appeared as the major product (*Scheme 5*). The provenance of **30** is a consequence of the preferred equatorial

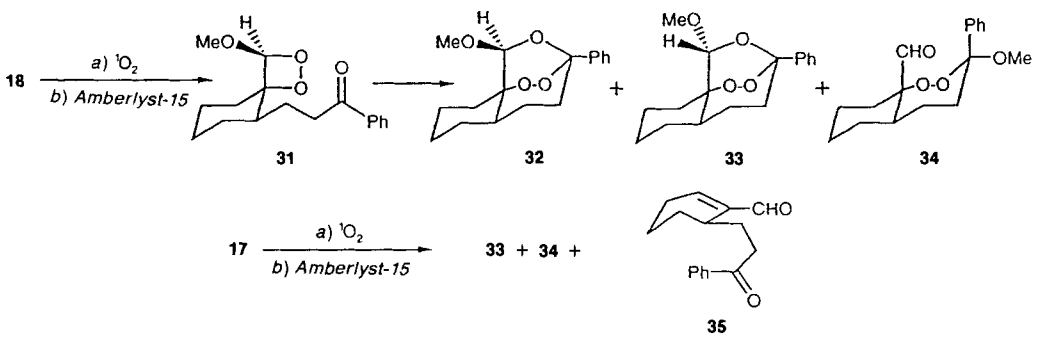
Scheme 5[1])



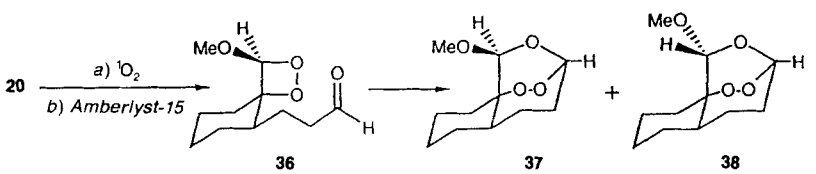
conformation of **15** which, unlike **16**, has axial allylic H-atoms available for a competing ene reaction. Attack by $^1O_2$ on the least hindered face, therefore, follows two courses. Cycloaddition as before is expected to give dioxetane **28**. Subsequent acid-catalyzed isomerization implicating the keto side-chain would logically give the '*exo*'-methoxy epimer **22** as the kinetic product, but this point was not verified experimentally. Thereafter, the '*endo*'-methoxy epimer **21** and peroxide **23** would arise by acid-catalyzed equilibration. The incoming molecule of $^1O_2$ as it approaches the double bond of **15** also experiences the '*syn*'-effect exerted by the MeO group [14]. The ene reaction supervenes and the axial H-atom at the least substituted adjacent center is abstracted to give hydroperoxide **29** and eventually **30** by hydrolysis during the workup.

Submission of the phenyl-substituted (*Z*)- and (*E*)-enol ethers **18** and **17** to photooxygenation and *Amberlyst*-catalyzed rearrangement also resulted in capture of an O_2 molecule, but less efficiently (*Scheme 6*). The (*Z*)-isomer **18** gave the '*endo*'- and '*exo*'-methoxy-1,2,4-trioxanes **32** and **33**, accompanied by the peroxide **34**. Evidence for the intermediate 1,2-dioxetane **31** was also secured. Only the '*endo*'-epimer **33** and its cleavage product **34**, together with aldehyde **35** arising from the ene reaction, were obtained from the (*E*)-epimer **17**.

Scheme 6[1])



Scheme 7[1])



Lastly, the 3′-oxopropyl-substituted (*Z*)-enol derivative **20** was photo-oxygenated directly without prior purification in view of its instability (*Scheme 7*). Once again, evidence for the 1,2-dioxetane **36** was obtained. Acid catalysis converted it to the '*endo*'- and '*exo*'-methoxy epimers **37** and **38** in 22 and 30% yield, respectively. No trace of the corresponding bicyclic peroxide was detected. Similar treatment of the (*E*)-isomer **19** was disappointing: no trioxanes were isolated, and only extensive decomposition of the reaction mixture was observed.

***In vitro* Antimalarial Activity.** – Samples of the synthetic tricyclic 1,2,4-trioxanes and appropriate reference compounds were tested *in vitro* against *Plasmodium falciparum* clones and strains by using the method developed by *Desjardins* and coworkers, and subsequently modified by *Milhous* and other authors [15] [16]. Unfortunately, the ACD derivatives **37** and **38** were not sufficiently stable to be tested.

The effectiveness of the sample in inhibiting nucleic-acid synthesis as measured by the incorporation of tritiated hypoxanthine in the clones and strains was determined. Inhibitory concentrations (*IC*) are expressed in nanogram/ml. The Indochina W2 clone is resistant to chloroquine, quinine, pyrimethamine, and sulfadoxine but susceptible to mefloquine, whereas the Sierra Leone D6 clone is susceptible to chloroquine, quinine, pyrimethamine, and sulfadoxine but resistant to mefloquine. The Kanchanaburi K1 strain is resistant to chloroquine and pyrimethamine [17] and the CDCI Honduras strain is sensitive to chloroquine and resistant to pyrimethamine [18].

Table 3. In vitro *Antimalarial Activity of Some Artemisinin Analogues Against* P. falciparum *Clones*

	W2 clone		D6 clone	
	IC_{50} [ng/ml]	IC_{90} [ng/ml]	IC_{50} [ng/ml]	IC_{90} [ng/ml]
1	1.1	–	2.2	–
10	6.2	25.8	28.7	59.8
11	2.0	3.3	2.3	30.4
21	1.8	3.9	16.5	11.5
22	9.7	16.9	754	875
23	1837	8132	2608	7547
Quinine	9.6	–	2.1	–
Chloroquine	23.4	–	0.9	–
Mefloquine	0.8	–	4.6	–
Pyrimethamine	5.5	–	0.01	–
Sulfadoxine	2060	–	35	–

Table 4. In vitro *Antimalarial Activity of Some Artemisinin Analogues Against* P. falciparum *Strains*

	K1-strain		Honduras strain	
	IC_{50} [ng/ml]	IC_{90} [ng/ml]	IC_{50} [ng/ml]	IC_{90} [ng/ml]
1	1.6 (1.3–1.9)	4.0 (3.3–4.9)	1.1 (0.6–1.8)	3.4 (2.0–5.6)
21	3.6 (2.7–4.7)	22.0 (16.6–29.3)	6.4 (4.6–8.8)	51.8 (38.0–71.7)
22	40.5 (38.6–42.6)	103.2 (98.3–108.4)	49.5 (35.9–68.1)	236.3 (171.6–325.8)
32	4.0 (2.0–8.0)	18.2 (9.0–36.5)	9.2 (7.2–11.7)	32.3 (25.4–41.1)
33	9.6 (6.8–13.4)	34.0 (24.2–47.6)	10.5 (7.9–14.0)	39.6 (29.8–52.7)
Chloroquine	87.1 (69.6–109.5)	221.4 (176.4–277.9)	5.7 (5.0–6.5)	10.2 (8.9–11.8)

The IC_{50} and IC_{90} values determined in these assays (*Tables 3* and *4*) provide a measure of the efficacy of a particular compound with respect to a panel of conventional quinoline- and sulfonamide-based drugs.

Discussion. – It is no surprise that the synthetic trioxanes which display high activities are those (**10** and **11**) possessing a part of the molecular architecture of artemisinin (**1**) (*Table 3*). Their extraordinarily small IC_{50} and IC_{90} values confirm that ring D and a lactone function are not essential for activity. The difference in activity between **10** and **11**, although not great, appears to be significant. Clearly, the Me_2C grouping in **10** serves as a substitute for the ethane bridge in ring D of **1**. However, its replacement by the spirocyclopentane group is even more effective (see **11**) and probably springs from the conformational constraint or compression that it exerts on the attached trioxane ring causing it to buckle into a boat-like form.

Remarkably high activities are also exhibited by the pair of epimers **21** and **22**. The very small IC_{50} and IC_{90} values confirm again that the lactone ring is not part of the pharmacophore and that even ring B is not necessary for artemisinin-like activity. It is worth noting that although the tetrahydropyran ring, *e.g.* ring B in **10** and **11**, can be dispensed with, a fourth O-atom is still required. In **21** and **22**, the MeO substituent fulfills this requirement. Paradoxically, the '*exo*'-methoxy substituent in **22**, which mimics the orientation of the O-atom in the B ring of artemisinin (**1**) and the *seco*artemisinins **10** and **11**, confers less activity than its '*endo*'-epimer **21**.

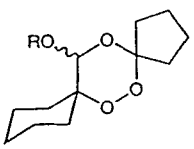
The large IC_{50} and IC_{90} values for **23** demonstrate that an intact trioxane ring is a *sine qua non* and that the cyclic peroxide function alone is insufficient for antimalarial activity. This result also suggests that the aforementioned difference in efficacy between the '*endo*'- and '*exo*'-epimers **21** and **22**, respectively, might be due to the decomposition of **22** to **23** by traces of acid.

The synthetic 1,2,4-trioxanes follow the same trend as that of artemisinin in being more effective against the chloroquine-resistant W2 clone. The most potent trioxanes are **11** and **21** in that they have the smallest IC_{50} and IC_{90} values. In addition, the activities of **21** and **22** compare well with that of the chiral natural product, artemisinin, especially when it is remembered that they are not only fully synthetic but racemic mixtures.

The relative activities of **21** and **22** against the *P. falciparum* clones were confirmed in the K1 and Honduras strains (*Table 4*). Replacement of the bridgehead Me group by the Ph substituent improved antimalarial action. Comparison of the '*endo*'-epimers **21** and **32** shows that they have about the same activity against the K1 and Honduras strains. More importantly, the difference between the Ph-substituted '*endo*'- and '*exo*'-methoxy epimers (**32** *vs.* **33**) is in the same sense as that seen for the Me analogues (**21** and **22**). Moreover, the Ph-substituted '*exo*'-methoxy trioxane **33** is superior in activity to its Me homologue **22**. Once again, the trioxanes are more effective against the chloroquine-resistant than the sensitive strain.

In general, all new trioxanes performed better than the traditional N-containing drugs, with the exception of mefloquine. Similar results as those reported for **21** and **32** here and earlier [19] were also obtained with related hydroxyethyl derivatives [20]. However, in these experiments, only the '*endo*'-methoxy epimers were isolated and tested. Equilibration of the '*endo*'- to the '*exo*'-epimers and eventually to the cleaved peroxide products was not reported. Furthermore, two methylated lactone analogues of **10** were reported to have comparable *in vitro* activity [21].

The present findings indicate that possible pharmacophores for high artemisinin-like activity may be represented by the hypothetical doubly spirocyclic trioxane **39** and the *cis*-fused bicyclic entity **40**. It is also to be noted that a Ph substituent, although not part



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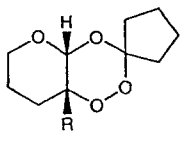

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of the pharmacophore, but attached to the trioxane ring, is beneficial for activity. Apart from these structural requirements, chemical stability, particularly towards acid, is also a prerequisite for a candidate antimalarial drug. The homochiral ABC compounds **10** and **11** are certainly stable enough, but are relatively inaccessible as their syntheses entail many steps. On the other hand, the easily prepared racemic ACD derivatives **21**, **22**, **32**, and **33** are potentially disadvantaged by their equilibration to less active isomers when acids are present. Studies such as those described here have played an important part in the design of simple *cis*-fused bicyclic 1,2,4-trioxanes which are stable and potent antimalarial drug candidates [22].

We gratefully acknowledge the *UNDP/World Bank/WHO* Special Programme for Research and Training in Tropical Diseases for partial support of this research. We also thank Messrs *J. P. Saulnier* and *A. Pinto* for the NMR measurements, and Mrs *C. Clément* for the MS measurements.

Experimental Part

General. Solvents were purchased from *Fluka AG* and *Aldrich AG*; when necessary, they were dried and purified before use. TLC: plates coated with silica gel *60* (F_{254} *Merck*). Flash column chromatography (FC): silica gel *60* (230–400 mesh, *Merck*); CC = column chromatography. M.p. (uncorrected): *Reichert* hot-plate instrument. IR Spectra: *Perkin-Elmer-681* and *FT-M-Polaris* spectrometers; in $CHCl_3$. NMR Spectra: *Varian-XL-200* and *Bruker-WH-360* instruments; in $CDCl_3$; chemical shifts (δ) in ppm with reference to Me_4Si; signal intensities are normalized to 1 H; coupling constants *J* in Hz. MS: *Finnigan-4000* and *VG-70-70E* spectrometers. Elemental analyses were performed by Dr. *H. J. Eder*, Service de Microchimie, Département de Chimie Pharmaceutique, University of Geneva.

Procedure for photo-oxygenation: A soln. of the reactant was cooled to −78° with a dry-ice/acetone bath or a *Huber-TC-50* cryostat for other temperatures, while O_2 was passed. Irradiation was effected with a tungsten filament lamp (*Sylvania FFX*), cooled by a jet of compressed air, and screened with a *Spindler* and *Hoyer GG 475* filter to cut off UV light.

1. *(E)- and (Z)-3-[2-(Methoxymethylidene)cyclohexyl]propanenitrile* (**13** and **14**, resp.). A soln. of (methoxymethyl)diphenylphosphine oxide (12.3 g, 50 mmol) [8] in THF (300 ml) was stirred at 0° for 20 min with lithium diisopropylamide (LDA) prepared from $(i\text{-}Pr)_2NH$ (5.05 g, 50 mmol) and 1.6M BuLi/hexane (31.25 ml) in THF (60 ml). The soln. was cooled to −70°, and 3-(2-oxocyclohexyl)propanenitrile (**12**; 7.55 g, 50 mmol) in THF (50 ml) was added dropwise [23]. The resulting mixture was allowed to warm to 20° and then stirred further for 24 h. Next, hexane (100 ml) was added. Removal of the precipitated diphenylphosphinite by filtration over *Celite* gave a soln. which was dried ($MgSO_4$) and evaporated. The oily residue was purified by CC (silica gel, 20% AcOEt/pentane): **13** (R_f 0.37; 2.68 g, 30%) and **14** (R_f 0.42; 2.7 g, 30%). Colorless oils.

13: IR: 2938*s*, 2830*m*, 2820*w*, 2245*m*, 1125*s*. ^{1}H-NMR: 1.0–1.9 (*m*, 9 H); 2.0 (*m*, 1 H); 2.1 (*m*, 2 H); 2.3 (*dt*, 1 H); 3.48 (*s*, 3 H); 5.75 (*s*, 1 H). ^{13}C-NMR: 140.37; 119.91; 117.47; 59.38; 37.54; 32.74; 27.01; 26.91; 22.38; 21.88; 15.29. Anal. calc. for $C_{11}H_{17}NO$: C 73.69, H 9.56, N 7.82; found: C 71.89, H 9.21, N 7.52.

14: IR: 2940*s*, 2860*m*, 2840*w*, 2245*m*, 1680*m*, 1125*s*. ^{1}H-NMR: 1.2–2.3 (*m*, 12 H); 2.9 (*m*, 1 H); 3.52 (*s*, 3 H); 5.86 (*s*, 1 H). ^{13}C-NMR: 141.37; 120.53; 116.9; 59.22; 32.55; 31.31; 28.02; 27.57; 26.31; 21.70; 15.21. Anal. calc. for $C_{11}H_{17}NO$: C 73.69, H 9.56, N 7.82; found: C 71.54, H 9.18, N 7.72.

δ(H) and δ(C) of H–C(2) and H–C(6) of **13** and **14** were assigned unambiguously by means of DEPT and hetero-COSY experiments (see *Table 1*).

2. *(E)- and (Z)-4-[2-(Methoxymethylidene)cyclohexyl]butan-2-one* (**15** and **16**, resp.). A soln. of **13** (200 mg, 1.11 mmol) in dry Et_2O (20 ml) was stirred at 0° under N_2 to which 1.6M MeLi/Et_2O (1.4 ml) was added dropwise. The mixture was stirred for further 6 h. Thereafter, a sat. aq. soln. of NH_4Cl (10 ml) was added dropwise with stirring. Next, the org. layer was separated, the aq. phase extracted with Et_2O (2 × 10 ml), and the combined org. layer washed (H_2O), dried ($MgSO_4$), and evaporated. CC (SiO_2, 2% AcOEt/pentane) gave **15** (200 mg, 91%). Yellow oil. R_f 0.35. IR: 3000*w*, 2936*s*, 2860*m*, 1720*s*, 1680*m*, 1125*s*, 1095*w*. ^{1}H-NMR: 1.2–2.0 (*m*, 10 H); 2.1 (*s*, 3 H); 2.35 (*m*, 3 H); 3.45 (*s*, 3 H); 5.72 (*s*, 1 H). Anal. calc. for $C_{12}H_{20}O_2$: C 73.41, H 10.28; found: C 73.19, H 10.30.

A soln. of **14** was treated with MeI in exactly the same way as **13**: **16** (198 mg, 90%). Oil. R_f 0.32. IR: 3000*w*, 2940*s*, 2860*m*, 2840*w*, 1710*s*, 1680*m*, 1125*s*, 1095*m*. ^{1}H-NMR: 1.2–2.0 (*m*, 10 H); 2.12 (*s*, 3 H); 2.4 (*m*, 2 H); 2.8 (*m*, 1 H); 3.5 (*s*, 3 H); 5.8 (*s*, 1 H). Anal. calc. for $C_{12}H_{20}O_2$: C 73.41, H 10.28; found: C 73.21, H 10.28.

3. *(E)- and (Z)-3-[2-(Methoxymethylidene)cyclohexyl]-3-phenylpropan-1-one* (**17** and **18**). The enol ethers **13** and **14** (400 mg, 2.22 mmol) were dissolved separately in Et_2O (30 ml) at 0°, and each was treated as described below. PhLi (2.2 ml, 2.0M in benzene/Et_2O; 2 equiv.) was the added dropwise under N_2, the mixture stirred for 3 h at 0°, and sat. aq. NH_4Cl soln. (20 ml) added. The aq. layer was then extracted with Et_2O, the Et_2O layer washed, dried ($MgSO_4$), and evaporated, and the residue submitted to FC (SiO_2, CH_2Cl_2) [24]: **17** (450 mg, 78%: R_f 0.39) and **18** (500 mg, 86%: R_f 0.41).

17: IR: 3000*w*, 2930*s*, 2860*m*, 1680*s*, 1600*w*, 1120*s*. ^{1}H-NMR: 1.3–2.1 (*m*, 10 H); 2.35 (*m*, 1 H); 3.0 (*t*, ^3J = 7, 2 H); 3.56 (*s*, 3 H); 5.8 (*s*, 1 H); 7.5 (*m*, 3 H); 8.0 (*m*, 2 H). Anal. calc. for $C_{17}H_{22}O_2$: C 79.02, H 8.59; found: C 78.85, H 8.42.

18: IR: 3000*w*, 2940*s*, 2860*m*, 2840*w*, 1680*s*, 1600*w*, 1125*s*. ^{1}H-NMR: 1.0–2.1 (*m*, 10 H); 2.95 (*m*, 1 H); 3.0 (*t*, ^3J = 7, 2 H); 3.48 (*s*, 3 H); 5.84 (*d*, ^4J = 1.5, 1 H); 7.5 (*m*, 3 H); 8.0 (*m*, 2 H). Anal. calc. for $C_{17}H_{22}O_2$: C 79.02, H 8.59; found: C 78.59, H 8.77.

4. *(E)- and (Z)-3-[2-(Methoxymethylidene)cyclohexyl]propanal* (**19** and **20**, resp.). To solns. of **13** and **14** (100 mg, 0.56 mmol), dissolved separately in THF (10 ml) at −78°, was added 2M AlH(i-Bu)$_2$/hexane (0.8 ml, 1.5 equiv.). The resulting soln. was allowed first to warm to 20° and then stirred for 12 h. Next, a sat. aq. soln. of NH_4Cl was added, the aq. phase extracted with Et_2O, and the combined Et_2O extract washed, dried ($MgSO_4$), and evaporated. The ^{1}H-NMR and IR spectra of the residue revealed the formation of **19** (80 mg, 79%) and **20** (85 mg, 85%).

19: R_f 0.67 (10% AcOEt/CH_2Cl_2). IR: 2920*s*, 2860*m*, 1725*s*, 1680*m*, 1125*s*, 1100*w*. ^{1}H-NMR: 1.0–2.2 (*m*, 13 H); 3.52 (*s*, 3 H); 5.78 (br. *s*, 1 H); 9.82 (*t*, ^3J = 2, 1 H).

20: R_f 0.65 (10% AcOEt/CH_2Cl_2). IR: 2925*s*, 2860*m*, 1720*s*, 1680*m*, 1120*s*, 1095*w*. ^{1}H-NMR: 1.0–2.1 (*m*, 12 H); 2.9 (*m*, 1 H); 3.5 (*s*, 3 H); 5.8 (br. *s*, 1 H); 9.8 (*t*, ^3J = 2, 1 H).

5. *Photo-oxygenation of* **16**. 5.1. *In MeOH*. A soln. of **16** (100 mg, 0.51 mmol) and methylene blue (MB; 5 mg) in MeOH (10 ml) was photo-oxygenated at −78° for 2 h. TLC (5% AcOEt/CH_2Cl_2): 1 product spot. R_f 0.32. The MeOH was evaporated *in vacuo* at −30° and the residue taken up in CH_2Cl_2 at −50°. *Amberlyst-15* (200 mg) was added and the mixture stirred for 10 h at 0°. Removal of the catalyst by filtration and separation by CC (SiO_2, CH_2Cl_2) afforded **21** (12 mg, 10%). **22** (12 mg, 10%), and **23** (20 mg, 17%) as crystalline colorless solids.

5.2. *In MeCN*. A soln. of **16** (100 mg, 0.51 mmol) and MB (5 mg) in MeCN (10 ml) was photo-oxygenated at −30° for 1 h. *Amberlyst-15* (100 mg) was added to the soln. which was then stirred for 5 h at 0°. The previous workup was followed to give **21** (32 mg, 28%), **22** (12 mg, 10.5%), and **23** (42 mg, 36%).

5.3. *In CH_2Cl_2*. A soln. of **16** (100 mg, 0.51 mmol) and MB (5 mg) in CH_2Cl_2 (10 ml) was photo-oxygenated at −78° for 1 h, after which time *Amberlyst-15* (100 mg) was added. The mixture was stirred at 0° for 10 h and submitted to the usual workup to give **21** (56 mg, 48%), **22** (22 mg, 19%), and **23** (35 mg, 30%).

5.4. *Without Acid Catalyst*. The photo-oxygenation as described in *5.3* was repeated with **16** (20 mg, 0.1 mmol) in CH_2Cl_2 (10 ml). After stirring the mixture for 1 h, a portion was examined by TLC (25% AcOEt/CH_2Cl_2): 1 product spot, R_f 0.5. The solvent was then evaporated to give *(2RS)-2-(3'-oxobutyl)cyclohexanone* (**25**; 15.5 mg, 90%) as colorless liquid [25].

5.5. *In $CDCl_3$*. The same procedure was followed as in *5.3*, but in $CDCl_3$ as solvent. The NMR spectrum of the mixture at −35° gave ^{1}H-NMR signals characteristic of dioxetane **24**.

5.6. *Catalysis with $AlCl_3$ and Me_3SiOTf*. Photo-oxygenation of **16** was performed as in *5.3*. $AlCl_3$ (50 mg) was added to the soln. at 0°, followed by neutralization with a few drops of Et_3N. Workup gave **21** (48 mg, 39%) and **22** (20 mg, 17%). The same procedure but using Me_3SiOTf (0.1 ml) as the *Lewis* acid also gave **21** (20 mg, 17%) and **22** (12 mg, 10%).

4-[(3RS,4RS,5SR)-3-Methoxy-1,2-dioxaspiro[3.5]nonan-5-yl]butan-2-one (**24**): ^{1}H-NMR: 1.0–2.6 (*m*, 13 H); 2.2 (br. *s*, 3 H); 3.41 (*s*, 3 H); 5.25 (br. *s*, 1 H).

(1RS,6SR,9SR,12RS)-12-Methoxy-9-methyl-10,11,13-trioxatricyclo[7.2.2.0^{1,6}]tridecane (**21**): M.p. 74–75° (from pentane). R_f 0.5. IR: 3000*w*, 2940*s*, 2860*m*, 1450*m*, 1140*s*, 1120*s*, 1030*s*. ^{1}H-NMR: 1.25 (*m*, 5 H); 1.65–1.85 (*m*, 8 H); 2.05 (*ddd*, ^2J = 15, ^3J = 4, 3, 1 H); 2.3 (*ddd*, ^2J = 15, ^3J = 14, 4, 2 H); 3.53 (*s*, 3 H); 4.93 (*s*, 1 H). MS: no M^+, 196 (0.8), 168 (3.4), 150 (2.0), 138 (9), 125 (100), 111 (20), 98 (22), 81 (23), 55 (95). Anal. calc. for $C_{12}H_{20}O_4$: C 63.12, H 8.84; found: C 62.99, H 8.93.

(1RS,6SR,9SR,12SR)-12-Methoxy-9-methyl-10,11,13-trioxatricyclo[7.2.2.0^{1,6}]tridecane (**22**): M.p. 63° (from hexane). R_f 0.19. IR: 3000*w*, 2945*s*, 2860*m*, 1450*m*, 1145*s*, 1120*s*, 1025*s*. ^{1}H-NMR: 1.2 (*m*, 5 H); 1.4 (*s*, 3 H); 1.7 (*m*, 4 H); 1.85 (*m*, 1 H); 2.0 (*m*, 1 H); 2.4 (*m*, 2 H); 3.5 (*s*, 3 H); 4.95 (*s*, 1 H). MS: no M^+, 196 (10), 168 (17), 138 (50), 125 (98), 111 (42), 98 (42), 55 (100). Anal. calc. for $C_{12}H_{20}O_4$: C 63.12, H 8.84; found: C 63.38, H 8.99.

(3RS,5aSR,9aRS)-3,4,5,5a,6,7,8,9-Octahydro-3-methoxy-3-methyl-9aH-1,2-benzodioxepine-9a-carbaldehyde (**23**): M.p. 80° (from hexane). R_f 0.3. IR: 3000*w*, 2940*s*, 2860*m*, 1740*s*, 1450*m*. ^{1}H-NMR: 1.2 (*s*, 3 H); 1.21–2.1 (*m*, 13 H); 3.35 (*s*, 3 H); 9.55 (*d*, 1 H). Anal. calc. for $C_{12}H_{20}O_4$: C 63.12, H 8.84; found: C 63.07, H 8.87.

Crystallographic Data for **21**–**23**. Cell parameters and diffracted intensities were measured at r.t. on a *Philips PW1100* diffractometer with graphite-monochromated Mo[$K\alpha$] radiation (λ = 0.71069 Å). Data were corrected for *Lorentz* and polarization effects, but not for absorption. During the data collections, the diffracted intensities decreased by *ca.* 2, 17, and 37% for **21**, **22**, and **23**, resp. All intensities were corrected for these drifts. The structures were solved by direct methods using MULTAN 80 [26], all other calculations used XRAY-76 [27] system and ORTEP [28] programs. All coordinates of the H-atoms were calculated. A summary of crystal data, intensity measurement, and structure refinement is givewn in *Table 5* and selected geometrical parameters are reported in *Table 6*. Crystallographic data were deposited with the *Cambridge Crystallographic Data Center*, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EW, England.

Table 5. *Summary of Crystal Data, Intensity Measurement, and Structure Refinement for* **21**–**23**

	21	**22**	**23**
Formula	$C_{12}H_{20}O_4$	$C_{12}H_{20}O_4$	$C_{12}H_{20}O_4$
Mol. wt.	228.3	228.3	228.3
Crystal system	triclinic	monoclinic	triclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
a [Å]	6.9908(8)	16.807(3)	6.462(3)
b [Å]	7.9224(6)	5.984(1)	10.393(1)
c [Å]	12.266(2)	13.092(2)	10.652(5)
α [°]	75.02(2)	90	63.15(4)
β [°]	84.71(2)	111.56(1)	81.18(4)
γ [°]	64.99(3)	90	75.19(2)
V [Å^3]	594.6(2)	1224.6(4)	616.5(5)
Z	2	4	2
F(000)	248	496	248
D_c [g·cm^{-3}]	1.28	1.24	1.23
μ(MoK_α) [mm^{-1}]	0.088	0.086	0.085
$((\sin\theta)/\lambda)_{max}$ [Å^{-1}]	0.53	0.51	0.51
No. measured reflections	1445	1528	1328
No. observed reflections	1231	759	874
Criterion for observed	$\lvert F_o\rvert > 4\sigma(F_o)$	$\lvert F_o\rvert > 4\sigma(F_o)$	$\lvert F_o\rvert > 4\sigma(F_o)$
Refinement (on F)	full-matrix	full-matrix	full-matrix
No. parameters	145	145	145
Weighting scheme	$\omega = 1$	$\omega = 1$	$\omega = 1$
Max. and average Δ/σ	0.0016, 0.0003	0.011, 0.02	0.0006, 0.0001
Max. and min. $\Delta\rho$ [e·Å^{-3}]	0.17, −0.31	0.35, −0.45	0.27, −0.35
S	7.8	5.7	4.6
R ($=\omega R$)	0.049	0.080	0.079

Table 6. *Selected Bond Lengths* [Å], *Bond Angles* [°] *and Torsional Angles* [°] *for* **21**–**23**

	21	**22**	**23**		**21**	**22**	**23**
C(1)–O(1)	1.417(5)	1.45(2)	1.44(1)	O(3)–C(1)–O(1)–O(2)	–71.5(3)	–73.4(8)	–
O(1)–O(2)	1.473(4)	1.47(1)	1.467(7)	C(1)–O(1)–O(2)–C(3)	39.9(3)	43(1)	108.6(8)
O(2)–C(3)	1.473(5)	1.48(1)	1.45(1)	O(1)–O(2)–C(3)–C(2)	23.0(3)	20(1)	44.2(8)
C(3)–C(2)	1.525(6)	1.50(1)	1.52(1)	O(2)–C(3)–C(2)–O(3)	–61.5(3)	–57(1)	–138.1(9)
C(2)–O(3)	1.427(4)	1.43 (1)	1.18(2)	C(3)–C(2)–O(3)–C(1)	32.8(4)	27(1)	–
O(3)–C(1)	1.424(5)	1.47(1)	–	C(2)–O(3)–C(1)–O(1)	32.1(3)	35(1)	–
O(4)–C(1)	–	–	1.41(1)	O(3)–C(2)–O(4)–C(12)	71.1(3)	–61(1)	–
O(4)–C(2)	1.391(5)	1.40(1)	–	C(3)–C(2)–O(4)–C(12)	–166.7(3)	173.0(9)	–
				O(1)–O(2)–C(3)–C(8)	–102.6(3)	–103.3(9)	–82.9(7)
O(3)–C(1)–O(1)	107.7(2)	106(1)	–	C(3)–C(8)–C(9)–C(10)	–41.9(5)	–40(1)	–72(1)
C(1)–O(1)–O(2)	110.1(2)	109.8(7)	111.5(6)	C(8)–C(9)–C(10)–C(1)	58.6(5)	57(1)	85(1)
O(1)–O(2)–C(3)	112.5(3)	111.6(7)	105.3(6)	C(9)–C(10)–C(1)–O(1)	–95.0(4)	–95(1)	–34(1)
O(2)–C(3)–C(2)	106.2(3)	109.7(7)	106.6(7)	C(10)–C(1)–O(1)–O(2)	50.8(3)	49(1)	–51(1)
C(3)–C(2)–O(3)	112.5(2)	113.7(8)	128(1)				
C(2)–O(3)–C(1)	113.3(3)	113.7(9)	–				
C(2)–O(4)–C(12)	113.0(3)	113.9(9)	–				

6. *Photo-oxygenation of* **15**. 6.1. *In MeCN*. A soln. of **15** (90 mg, 0.46 mol) and MB (5 mg) in MeCN (10 ml) was photo-oxygenated at –50° for 1 h. *Amberlyst-15* (50 mg) was then added and the mixture stirred at –20° for 5 h. On workup, **21** (12 mg, 11%), **22** (9 mg, 9%), and **23** (12 mg, 11%) were obtained, together with *6-(3'-oxobutyl)cyclohex-1-ene-1-carbaldehyde* (**30**) as a colorless oil.

6.2. *In CH_2Cl_2*. The procedure in *6.1* was followed, except that CH_2Cl_2 was used as solvent and the temp. kept at –78°. On workup, **21** (18 mg, 17%), **22** (18 mg, 17%), **23** (15 mg, 14%), and **30** (27 mg, 30%) were obtained.

30: IR: 2940*s*, 2860*m*, 2320*m*, 1715*s*, 1685*s*. ^{1}H-NMR: 1.4–1.9 (*m*, 8 H); 2.15 (*s*, 3 H); 2.2–2.5 (*m*, 3 H); 6.8 (*t*, ^3J = 4, 1 H); 9.4 (*s*, 1 H).

7. *Photo-oxygenation of* **18**. A soln. of **18** (100 mg, 0.39 mmol) and MB (10 mg) in CH_2Cl_2 (20 ml) was photo-oxygenated at –78° for 45 min. TLC (10% AcOEt/CH_2Cl_2): presence of the corresponding 1,2-dioxetane **31**, R_f 0.06. *Amberlyst-15* (80 mg) was then added and the mixture stirred at 0° for 6 h. After workup, the crude product was subjected to FC [24] (SiO_2, 10% AcOEt/CH_2Cl_2): **32** (10 mg, 9%), **33** (18 mg, 16%), and **34** (14 mg, 12.5%) as a colorless oil, solid, and oil, resp.

(1RS,6SR,9RS,12RS)-12-Methoxy-9-phenyl-10,11,13-trioxatricyclo[7.2.2.0^{1,6}]tridecane (**32**): R_f 0.7. IR: 3100*w*, 2940*s*, 2860*m*, 1450*m*, 1100*s*, 1010*s*. ^{1}H-NMR: 1.25–2.2 (*m*, 11 H); 2.35 (*ddd*, ^2J = 10, ^3J = 5, 3.5, 1 H); 2.8 (*ddd*, ^2J = 15, ^3J = 13, 4, 1 H); 3.68 (*s*, 3 H); 5.15 (*d*, ^4J = 1.5, 1 H); 7.4 (*m*, 3 H); 7.6 (*m*, 2 H). Anal. calc. for $C_{17}H_{22}O_4$: C 70.31, H 7.64; found: C 70.18, H 7.63.

(1RS,6SR,9RS,12SR)-12-Methoxy-9-phenyl-10,11,13-trioxatricyclo[7.2.2.0^{1,6}]tridecane (**33**): M.p. 82°. R_f 0.5. IR: 3150*w*, 2935*s*, 2860*m*, 1450*m*, 1100*s*, 1015*s*. ^{1}H-NMR: 1.2–2.2 (*m*, 10 H); 2.3 (*m*, 1 H); 2.45 (*m*, 1 H); 2.9 (*ddd*, ^2J = 15, ^3J = 14, 4, 1 H); 3.65 (*s*, 3 H); 5.22 (*s*, 1 H); 7.4 (*m*, 3 H); 7.6 (*m*, 2 H). Anal. calc. for $C_{17}H_{22}O_4$: C 70.31, H 7.64; found: C 70.19, H 7.68.

(3RS,5aRS,9aSR)-3,4,5,5a,6,7,8,9-Octahydro-3-methoxy-3-phenyl-9aH-1,2-benzodioxepine-9a-carbaldehyde (**34**): R_f 0.61 (10% AcOEt/CH_2Cl_2). IR: 3030*w*, 2945*s*, 2860*m*, 1720*s*, 1280*s*, 1120*m*, 1100*m*, 1025*s*. ^{1}H-NMR: 1.2–2.2 (*m*, 11 H); 2.3 (*ddd*, ^2J = 14, ^3J = 7.5, 1.5, 1 H); 2.4 (*ddd*, ^2J = 14, ^3J = 11, 1.5, 1 H); 3.2 (*s*, 3 H); 7.34 (*m*, 4 H); 7.6 (*m*, 1 H). Anal. calc. for $C_{17}H_{22}O_4$: C 70.31, H 7.64; found: C 69.55, H 7.45.

8. *Photo-oxygenation of* **17**. The procedure and quantities adopted for **17** were exactly the same as those described in *Exper. 7*. FC [24] (10% AcOEt/CH_2Cl_2) gave **33** (8 mg, 7%), **34** (8 mg, 7%), and *6-(3'-oxo-3'-phenyl)-cyclohex-1-ene-1-carbaldehyde* (**35**; 33.8 mg, 36%).

35: Oil. R_f 0.25. IR: 3100*w*, 2940*s*, 2860*m*, 1705*vs*, 1685*vs*, 1580*w*, 1600*w*, 1450*m*. ^{1}H-NMR: 1.5–2.5 (*m*, 8 H); 2.7 (*m*, 1 H); 3.0 (*m*, 2 H); 6.8 (*t*, ^3J = 3.5, 1 H); 7.5 (*m*, 3 H); 8.0 (*m*, 2 H); 9.4 (*s*, 1 H).

9. *Photo-oxygenation of* **20**. A soln. of **20** (70 mg, 0.385 mmol) and MB (10 mg) in CH_2Cl_2 (20 ml) was photo-oxygenated at –78° for 1 h. TLC (10% AcOEt/CH_2Cl_2): 1,2-dioxetane **36** as the main product, R_f 0.6. Next,

Amberlyst-15 (15 mg) was added with stirring at −20° for 6 h (TLC: several products). Removal of the catalyst by filtration and submission of the filtrate to FC [24] (SiO_2, 3% AcOEt/CH_2Cl_2) furnished **37** (18 mg, 22%) and **38** (24 mg, 30%), together with other more polar, unidentified products.

(1RS,6SR,9SR,12RS)-12-Methoxy-10,11,13-trioxatricyclo[7.2.2.0^{1,6}]tridecane (**37**): R_f 0.56. IR: 2940*s*, 2860*w*, 1095*s*, 1030*m*, 950*m*. ^{1}H-NMR: 1.1–2.1 (*m*, 11 H); 2.2 (*m*, 2 H); 3.5 (*s*, 3 H); 4.95 (*s*, 1 H); 5.65 (*dd*, ^3J = 7.5, ^4J = 1.5, 1 H). Anal. calc. for $C_{11}H_{18}O_4$: C 61.65, H 8.45; found: C 61.96, H 8.75.

(1RS,6SR,9SR,12SR)-12-Methoxy-10,11,13-trioxatricyclo[7.2.2.0^{1,6}]tridecane (**38**): R_f 0.48. IR: 2935*s*, 2860*w*, 1100*s*, 1035*m*, 955*m*. ^{1}H-NMR: 1.1–2.5 (*m*, 11 H); 2.2 (*m*, 2 H); 3.55 (*s*, 3 H); 4.95 (*s*, 1 H); 5.6 (*d*, ^3J = 8.0, 1 H). Anal. calc. for $C_{11}H_{18}O_4$: C 61.65, H 8.47; found: C 60.96, H 8.76.

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