215. Mechanistic and Synthetic Studies on the Formation of 1,2,4-Trioxanes Related to Arteannuin. Photooxygenation of a Bicyclic Dihydropyran

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Dedicated to Dr. *Edward C. Taylor* on the occasion of his 65th birthday

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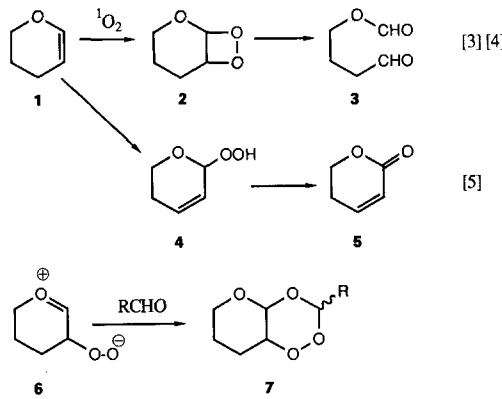
The photooxygenation of (4*R*,4a*S*,7*R*)-4,4a,5,6,7,8-hexahydro-4,7-dimethyl-3*H*-2-benzopyran (**16**) was performed in *i*) MeOH, *ii*) acetaldehyde, and *iii*) acetone at −78°. The products obtained respectively were *i*) (2*R*)-2-[(1*S*,4*R*)-4-methyl-2-oxocyclohexyl]propyl formate (**17**; 72% yield), *ii*) **17** (54.5%), (1*R*,4*R*,4a*S*,7*R*)-3,4,4a,5,6,7-hexahydro-4,7-dimethyl-1*H*-2-benzopyran-2-yl hydroperoxide (**19**; 16.7%), a 12:1 ratio of (3*R*,4a*R*,7*R*,7a*S*,10*R*,11a*R*)-7,7a,8,9,10,11-hexahydro-3,7,10-trimethyl-6*H*-[2]benzopyrano[1,8a-*e*]-1,2,4-trioxane (**20**) and its C(3)-epimer **21** (17%), together with evidence for the 1,2-dioxetane (**22**) originating from the addition of dioxygen to the *re-re* face of the double bond of **16**, and *iii*) unidentified products and traces of **22**. Addition of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) to the acetone solution of **16** after photooxygenation afforded (4a*R*,7*R*,7a*S*,10*R*,11a*R*)-7,7a,8,9,10,11-hexahydro-3,3,7,10-tetramethyl-6*H*-[2]benzopyrano[1,8a-*e*]-1,2,4-trioxane (**23**, 40%). The photooxygenation of **16** in CH_2Cl_2 at −78° followed by addition of acetone and Me_3SiOTf afforded **17** (11%), **23** (59%), and (4a*R*,7*R*,7a*S*,10*R*,11a*R*)-7,7a,8,9,10,11-hexahydro-3,3,7,10-tetramethyl-6*H*-[2]benzopyrano[8a,1-*e*]-1,2,4-trioxane (**24**; 5%). Repetition of the last experiment, but replacing acetone by cyclopentanone, gave **17** (16%), (4'a*R*,7'*R*,7'a*S*,10'*R*,11'a*R*)-7',7'a,8',9',10',11'-hexahydro-7',10'-dimethylspiro[cyclopentane-1,3'-6'*H*-[2]benzopyrano[1,8a-*e*]-1,2,4-trioxane] (**25**; 61%), and (4'a*R*,7'*R*,7'a*S*,10'*R*,11'a*R*)-7',7'a,8',9',10',11'-hexahydro-7',10'-dimethylspiro[cyclopentane-1,3'-6'*H*-[2]benzopyrano[8a,1-*e*]-1,2,4-trioxane] (**26**, 4%). The X-ray analysis of **23** was performed, which together with the NMR data, established the structure of the trioxanes **20**, **21**, **24**, **25**, and **26**. Mechanistic and synthetic aspects of these reactions were discussed in relation to the construction of the 1,2,4-trioxane ring in arteannuin and similar molecules.

Introduction. – The photooxygenation of olefins forms a substantial, but controversial chapter in organic chemistry [1]. A long-standing question concerns the nature of the primary intermediates formed from the reaction of singlet oxygen ($^1O_2$) with olefins [2]. Depending upon the circumstances, monoolefins can follow different mechanisms producing hydroperoxides, 1,2-dioxetanes, or both. An apt example is provided by 3,4-dihydro-2*H*-pyran (**1**) [3]. Polar solvents favor the formation of the formyl formate **3**, arising from the cleavage of the nonisolated intermediate dioxetane **2**, whereas in nonpolar solvents, hydroperoxide **4** prevails, ultimately undergoing dehydration to the α,β-unsaturated ketone **5**. The effect of solvent on these competing reaction courses has been rationalized in terms of the involvement of the ring O-atom in stabilizing charge development in the transition state [4]. Normally, the resulting zwitterionic peroxide **6** would imperceptibly close to the dioxetane **2**. However, on the basis of precedent, proof for the existence of such an intermediate could be secured by trapping it with aldehyde [5] whereupon a trioxane **7** would be formed *(Scheme 1)*.

Scheme 1

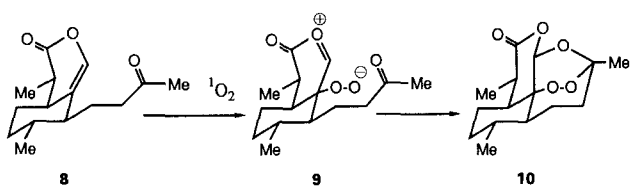


[3] [4]

[5]

Apart from mechanistic considerations, this trapping reaction is of synthetic potential in view of the importance of arteannuin (**10**). Not only is arteannuin an extremely potent antimalarial agent, but it is the only 1,2,4-trioxane found in nature [6]. Furthermore, although its synthesis has been accomplished [7], uncertainty surrounds the crucial step, the construction of the trioxane ring. A recently attempted synthesis of **10** has been based precisely on the aforementioned trapping reaction [8]. The pentenolide **8**, obtained from artemisinic acid, was expected to give the zwitterionic peroxide **9** which then should add across the pendent ketone group to create the arteannuin edifice **10** *(Scheme 2)*. In fact,

Scheme 2



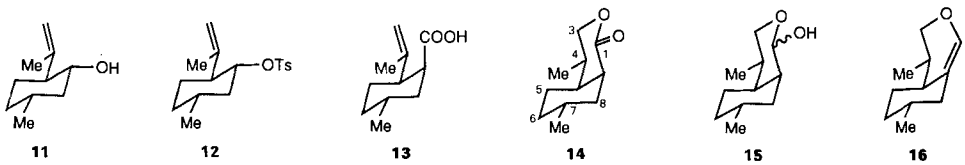
[8]

the photooxygenation of **8** was unsuccessful. The reason for failure was attributed to electron withdrawal by the lactone grouping so preventing the formation of the key peroxide **9**. Another invalidating possibility, which was not considered at the time, could have been hydroperoxidation. Finally, the conditions used may have been at fault since irradiation with a high-pressure mercury arc lamp is not appropriate for producing $^1O_2$. Consequently, we judged in worthwhile to examine a simpler bicyclic dihydropyran model in which the potentially troublesome lactone and ketone functions were omitted.

We now describe experiments with the bicyclic dihydropyran **16** in order to ascertain the best conditions for the photooxygenation in the desired sense. Acetaldehyde, acetone, and cyclopentanone are used as external traps.

Results. – Commercially available (–)-isopulegol (**11**) was used for the preparation of **16**. It was converted *via* its *p*-toluenesulfonate **12** into the known 2-isopropenyl-5-methylcyclohexanecarboxylic acid (**13**; *Scheme 3*). Oxidative hydroboration furnished the lac-

Scheme 3

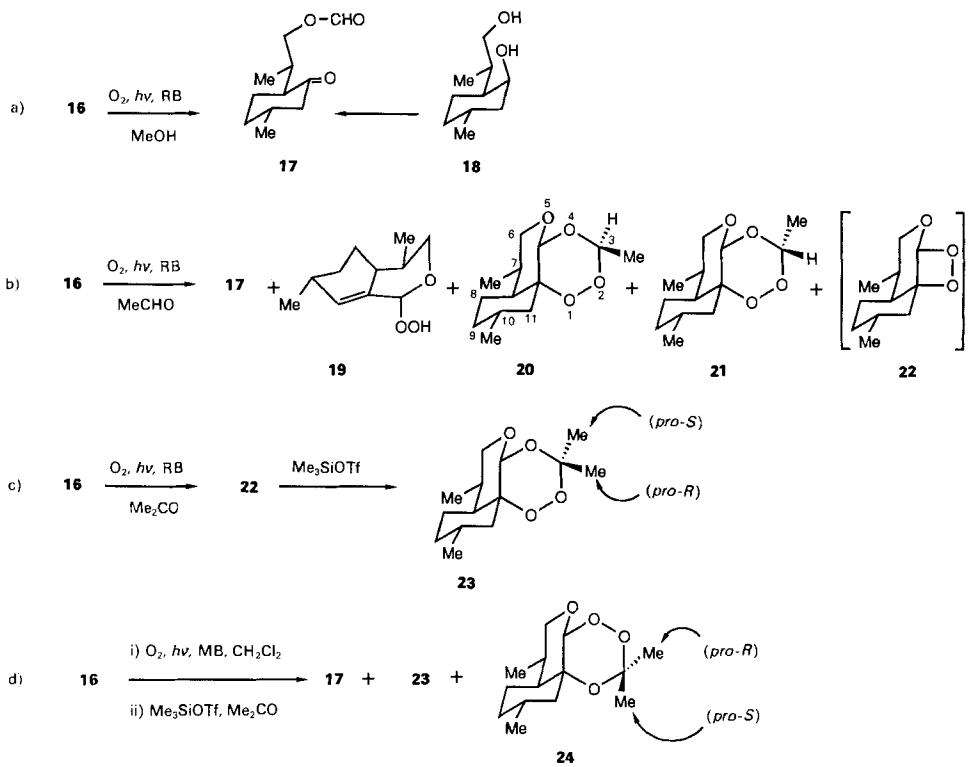


tone **14** which, on reduction to the lactol **15**, provided the dihydropyran **16** on dehydration. The overall yield for **11**→**16** was 41%. These modifications are controlled by the chirality of the starting material so that **16** possesses three chiral centers which are the same as those in arteannuin.

Singlet oxygen was generated and allowed to react with **16** under different sets of conditions. Firstly, photooxygenation was tried at −78° using rose bengal (RB) as sensitizer and MeOH as solvent. A single product was obtained in 72% yield, the oxo formate **17**, whose identity was confirmed by independent synthesis from the enantiomerically pure diol **18** *(Scheme 4, a)*.

Secondly, the photooxygenation was performed under the previous conditions, but using excess acetaldehyde as solvent. This time, in addition to the oxo formate **17**

Scheme 4



(54.5%), the allylic hydroperoxide **19** (16.7%) was obtained, together with a pair of epimeric 1,2,4-trioxanes **20** and **21** in a 12:1 ratio (17%) in which a molecule of acetaldehyde had been incorporated *(Scheme 4, b)*. The NMR spectrum of the reaction mixture also revealed the presence of a 1,2-dioxetane, probably **22**.

Thirdly, photooxygenation was repeated just as before, but using excess acetone as solvent. No trace of product containing entrapped acetone was found. Instead, TLC of the crude material again revealed the formation of an unstable compound, assumed to be **22**, since it gave a positive reaction when treated with a starch/KI solution. When trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) was subsequently added to the mixture at −78°, 1,2,4-trioxane **23** incorporating one molecule of acetone was obtained in 40% yield as well as other unidentified products *(Scheme 4, c)*.

Fourthly, in order to corroborate the formation of the acetone product, the photooxygenation of **16** was optimized by using methylene blue (MB) in CH_2Cl_2 at −78°. To the resulting cold mixture, excess acetone and Me_3SiOTf were added. Workup afforded the oxo formate **17** in 11% yield and two isomeric products incorporating a molecule of acetone, **23** and **24**, in yields of 59 and 5% *(Scheme 4, d)*. Fortunately, the major isomer **23** provided a crystal suitable for X-ray. Its structure was determined to be a 1,2,4-trioxane having the same absolute configuration as the corresponding part of arteannuin *(Fig.)*.

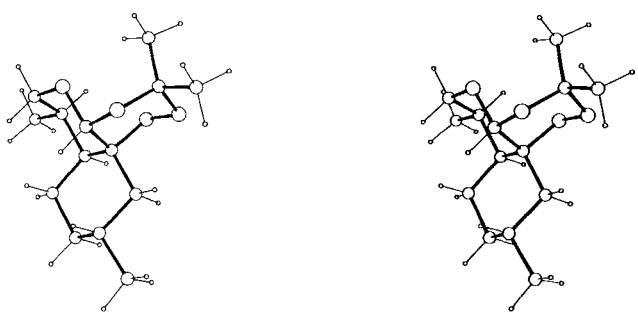
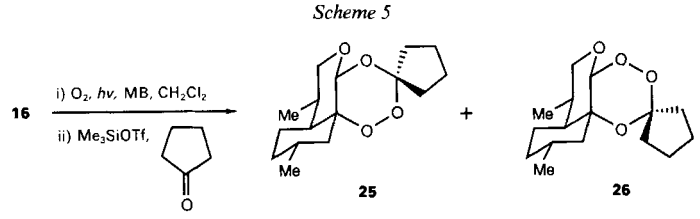


Figure. *Stereoscopic view of the structure of compound* **23**

By comparison of the NMR spectra, which were very similar, the gross structure of the minor isomer **24** was deduced as being the same as **23** except that the sequence of O-atoms was reversed.

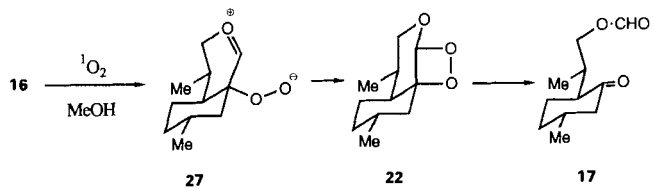
The two aforementioned events, photooxygenation and condensation, proceeded equally well with cyclopentanone. Again, two 1,2,4-trioxanes, the spirocyclic isomers **25** and **26**, were formed in 61 and 8% yield, respectively *(Scheme 5)*.

Scheme 5



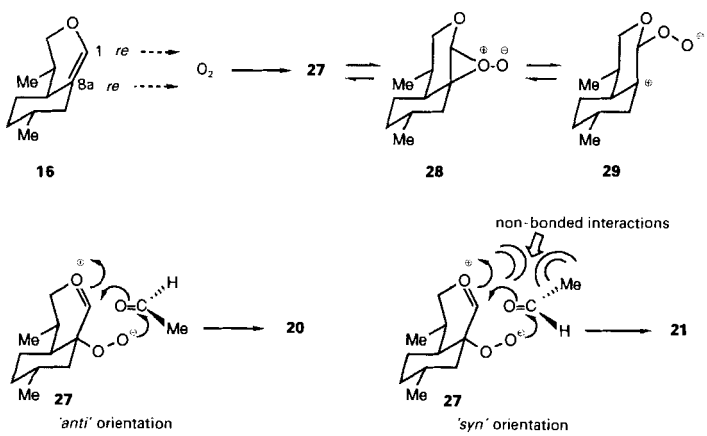
Discussion. – The present results resemble those obtained from molecules sharing similar structural features such as 3,4-dihydro-2*H*-pyrans [3] and enol ethers [9][10], in that the product composition is a reflection of solvent polarity. However, there are important differences *(vide infra)*. In MeOH, which is polar and chemically inert under the conditions of photooxygenation, the bicyclic pyran **16** behaves typically. Only the cleavage product **17** is produced offering proof for the finite existence of the dioxetane **22**, presumably resulting from the zwitterionic peroxide **27** *(Scheme 6)*. No hydroperoxide is detected, although it might have been expected to be a minor reaction component.

Scheme 6



On performing the photooxygenation in pure acetaldehyde, evidence for the presumed precursor to the dioxetane **22**, namely the zwitterionic peroxide **27** or its operational equivalent, is provided by the formation, albeit to a minor extent, of the epimeric trimethyl-1,2,4-trioxanes **20** and **21**. The overall structure and the assignment of configuration at the C(3) atoms of **20** and **21** follow from the characteristic chemical shifts of the Me groups taken together with the absolute configuration of the tetramethyl analogue **23** which was determined by X-ray *(vide infra)*. Hence $^1O_2$ only attacks the *re-re* face of the double bond of **16**. In principle, the O_2 molecule could attach itself either to the C(8a) or C(1) atoms or even to both, thereby generating the isomeric dihydropyranium peroxides **27**, **29**, and the perepoxide **28** *(Scheme 7)*. As all three zwitterionic species are interconvertible, their reality can only be defined in terms of their capture. Acetaldehyde is probably sufficiently electrophilic to trap any of them, but discriminates in favor of **27**.

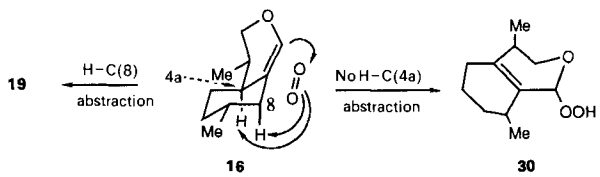
Scheme 7



Union of the two molecules occurs through two limiting orientations, designated as *'anti'* and *'syn'*, which lead to the 3,5-*trans*- and 3,5-*cis*-trioxanes **20** and **21** (trioxane numbering), respectively *(Scheme 7)*. The 12:1 ratio observed is undoubtedly dictated by the unfavorable 1,3-diaxial non-bonded interactions experienced in the transition state arising from the *'syn'* orientation. Despite the intervention of acetaldehyde as reactant, most of **27** manages to escape, but suffers its usual fate, closure to dioxetane **22** and scission to the oxo formate **17**. It is worth noting that the formation and capture of **27** from **16**, a 3,4-dihydro-2*H*-pyran, finds an exact parallel in the behavior of the enol ethers 2-methoxy-8,9,10-trinorborn-2-ene and 2-(methoxymethylidene)adamantane [11].

Equally important is the polarity of acetaldehyde which should be similar to that of acetone, a solvent conducive to the 'ene' reaction. Appropriately enough, a minor amount of hydroperoxide **19** is formed. However, it is not the right isomer. In general, trisubstituted monoolefins react with $^1O_2$ on the more crowded side [12]. Accordingly, although both the axial H–C(4a) and H–C(8) bonds are properly aligned for efficient overlap with the π-system of the double bond, only the former bond would be expected to break. However, none of the intracyclic olefinic hydroperoxide **30** is detected and thus constitutes an important exception to the rule *(Scheme 8)*. The reason for the formation of the wrong isomer **19** may reside in the equatorial nature of the developing O–C bond which means that the other atom of the O_2 molecule can only reach the closer axial H–C(8). Even if the less well stabilized zwitterionic peroxide **29** is initially formed, the same argument still holds as the only difference is the timing of the making and breaking of bonds.

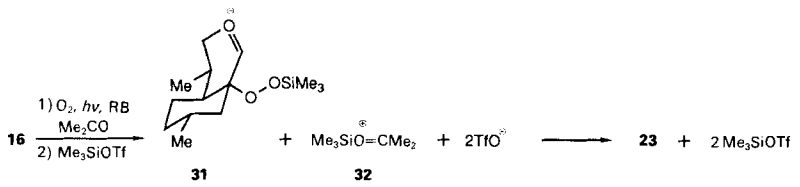
Scheme 8



In acetone, both dioxetane and hydroperoxide pathways are possible. However, the products were not identified directly. Evidently, the zwitterionic peroxide **27** is first formed, but the absence of trioxane adduct indicates that acetone is simply not electrophilic enough to capture it. This result has been observed for other enol ethers, the zwitterionic peroxides of which similarly differentiate between aldehydes and ketones [13]. Furthermore, it is entirely compatible with the general rule that tetrasubstituted olefines on ozonation do not yield secondary ozonides, or rather that carbonyl oxides, which are, after all, homologues of zwitterionic peroxides, do not add to ketones [14]. Subsequent addition of Me_3SiOTf to the photooxygenated acetone solution activates either the dioxetane **22** contained therein or the acetone molecule or even both through creation of the silyl cationic species **31** and **32** to bring about the assembly of the trioxane entity **23** *(Scheme 9)*.

The photooxygenation step is substantially improved by using CH_2Cl_2 as solvent, which on account of its polarity strongly promotes the generation of zwitterionic peroxides and the resulting dioxetane **22**. Subsequent addition of acetone with catalysis by

Scheme 9

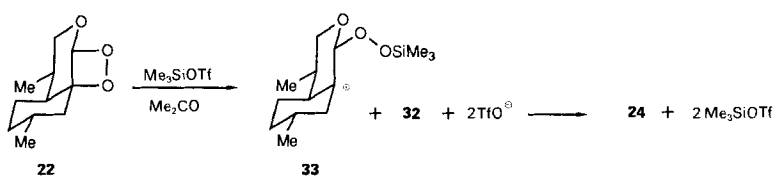


Me_3SiOTf gives not a single 1,2,4-trioxane as anticipated, but two isomers **23** and **24**. Nevertheless, some 11% of dioxethane **22** eludes capture through cleavage to **17**.

As the absolute configuration of **23** is established by X-ray, it serves as the structural yardstick for the other trioxanes. The three six-membered rings in **23** are all disposed as chairs. The same arrangement can be assumed for the othe trioxanes. The prochiral Me groups located at C(3) in **23** are easy to distinguish. The (*pro-S*)-Me group is *'syn'*-axial and close to the pyran O-atom and therefore deshielded [15] (1.73 ppm) with respect to the (*pro-R*)-Me group (1.29 ppm) which lies in an uncrowded equatorial position *(Scheme 4, c)*. These chemical shifts are markers for the epimeric trimethyl trioxanes **20** and **21** where the configurations at C(3) are assigned by analogy. The similar values for the chemical shifts of the geminal Me groups of the minor tetramethyltrioxane isomer **24** (1.37 and 1.47 ppm) are explicable by the reverse O-atom order which now places the (*pro-S*)-Me group *'syn'*-axial to the nonpolar, and therefore ineffectual, ring CH_2 group *(Scheme 4, d)*. The correctness of the overall structure of **24** is also corroborated by the almost identical values of the chemical shift for the proton of the O–CH–O group of **24** and **23** (5.12 and 4.95 ppm, resp.). The origin of **24** must arise from the alternative mode of opening of the dioxetane ring in **22** by Me_3SiOTf to give the silyl derivative **33** of the peroxide **29** which then condenses with acetone in the logical electronic sense *(Scheme 10)*. The formation of this odd trioxane is reminiscent of the behavior of 1,3-dimethylindole on photooxygenation in the presence of acetaldehyde [16].

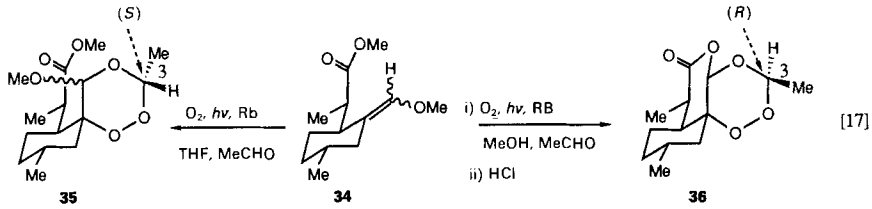
Cyclopentanone displays the same mechanistic pattern as acetone with respect to **16** and requires no particular comment.

Scheme 10



However, comment is necessary on the enol ether **34**, which has features in common with **16**. Photooxygenation of **34** using RB in THF solution containing acetaldehyde [17] was reported to give a pair of epimeric methoxy-1,2,4-trioxanes **35** having the (*S*) configuration at C(3) in a combined yield of 35% *(Scheme 11)*. In contrast, photooxygenation in MeOH and acetaldehyde followed by acidification gave a 15% yield of the deethano-arteannuin **36** in which the C(3) atom has the *(R)* configuration. From previous experience [18] a pair of diastereoisomers would be expected for **35**, but epimeric

Scheme 11



[17]

at C(3). The primary event would have been formation of the zwitterionic peroxide corresponding to **34** and its capture by acetaldehyde in the *'anti'* and *'syn'* orientations. Interestingly, trioxane **36** is the oxo analogue of the major trioxane **20** obtained from **16**. In both cases, the C(3) atom has the (*R*) configuration. Clearly, **36** was obtained from either the zwitterionic peroxide or the protonated dioxetane derived from **34** followed by addition of acetaldehyde in the *'anti'* orientation *(cf. Scheme 7)*.

Conclusion. – These results demonstrate that the formation of the 1,2,4-trioxane ring depends critically on the conditions of photooxygenation, namely the choice of solvent, temperature, and catalyst. In the particular instance of the bicyclic pyran **16**, which constitutes an essential part of the arteannuin molecule, a convenient procedure has been devised for the adjunction of a molecule of O_2 with aldehydes and ketones which will provide a range of deethano-arteannuin derivatives in good yield.

Other examples of the present technology for constructing the 1,2,4-trioxane ring in arteannuin-like molecules as well as arteannuin itself will be reported elsewhere.

We are indebted to the *Swiss National Science Foundation* (grant No. 2.632-0.87) for partial support of this work.

Experimental Part

1. General. All solvents were distilled prior to use. TLC: silica gel, *60 F254 (Merck)*. Column chromatography: silica gel *60* (230–400 mesh, *Merck*). *Reichert* hot-stage microscope; uncorrected. IR spectra (in cm^{-1}): *Perkin-Elmer-681* spectrometer. ^{1}H-NMR spectra: *Bruker-WH-360* spectrometer; chemical shifts in ppm relative to internal TMS (= 0 ppm, coupling constants *J* in Hz. MS (in m/*z* (rel. %)): *Finnigan GC/MS 4023* using the INCOS data system. Elemental analyses were carried out by Dr. *H.J. Eder*, Service de Microchimie, Institut de Chimie Pharmaceutique, University of Geneva.

Procedure for Photooxygenation. The soln. to be photooxygenated was cooled to −78° by a dry ice/acetone bath and irradiated by a 500-W *Sylvania-FFX* halogen-tungsten filament lamp screened with a UV cut-off filter (> 418 nm) while O_2 was passed through the soln. (TLC monitoring).

2. *(+)-(4*R*,4a*S*,7*R*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-4,7-dimethyl-1*H*-2-benzopyran-1-one* (**14**). To a soln. of 2-(isopropenyl)-5-methylcyclohexane-1-carboxylic acid (**13**; 1.95 g, 10.7 mmol; prepared from the *p*-toluenesulfonate **12** of (−)-isopulegol (**11**) [19]). in THF (100 ml) was added dropwise 9-borabicyclo[3.3.1]nonane (9-BBN) (*Aldrich*, 0.5M in hexane; 45 ml, 22.5 mmol) under N_2. After stirring for 24 h, NaOH (6N, 10 ml) was added portionwise followed by slow addition of H_2O_2 (30%, 10 ml). The mixture was stirred at 50° for 1.5 h and diluted with Et_2O. The org. layer was washed twice with dil. brine. Next the aq. layers were combined, acidified, and extracted with Et_2O. The Et_2O soln. was stirred overnight with a few crystals of $TsOH \cdot H_2O$. Evaporation followed by chromatography of the crude oil on silica gel gave **14** as a colorless oil (1.87 g, 95%), which crystallized on standing. M.p. 48–50°. $[\alpha]^{20} = +23.4$ (*c* = 0.07, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 4.35 (*dd*, *J* = 11, 4.2, 1 H); 4.08 (*dd*, *J* = 11, 3.8, 1 H); 2.30 (*dm*, *J* = 13, 1 H); 2.17 (*dt*, *J* = 12, 3.5, 1 H); 2.02 (*m*, 1 H); 1.75 (*dm*, 1 H); 1.67 (*m*, 2 H); 1.40

(*m*, 1 H); 1.26 (*dq*, *J* = 13, 3.8, 1 H); 1.0–0.85 (*m*, 2 H); 0.99 (*d*, *J* = 7.5, 3 H); 0.91 (*d*, *J* = 6.5, 3 H). IR ($CHCl_3$): 1725*s*. MS: 182 (100, M^+), 167, 152, 140, 123, 109, 96, 81, 68. Anal. calc. for $C_{11}H_{18}O_2$: C 72.49, H 9.95; found: C 72.53, H 10.01.

3. *(4R,4aS,7R)-4,4a,5,6,7,8-Hexahydro-4,7-dimethyl-3H-2-benzopyran* (**16**). A soln. of **14** (500 mg, 2.75 mmol) in toluene (100 ml) was reduced to 90 ml by distillation and then cooled to −70°. DIBAL (1M in hexane; 6.8 ml, 2.5 equiv.) was added dropwise under N_2. The reaction was usually complete within 2 h as shown by TLC. The resulting mixture was poured into 2N H_2SO_4/ice and extracted with Et_2O. Drying (Na_2SO_4) and evaporation gave a residue which was dissolved in benzene (100 ml). The soln. was heated under reflux with $TsOH \cdot H_2O$ (15 mg) to remove H_2O azeotropically from the intermediate lactol **15** (TLC monitoring). After 3 h, the soln. was cooled and passed over a column of silica gel (10 g). Evaporation gave pure **16** as a colorless oil which solidified on standing (442 mg, 97%). A sample for analysis was obtained by short-path evaporation (40°/0.02 Torr). M.p. 35–37°. IR ($CDCl_3$): 1675*m*. ^{1}H-NMR ($CDCl_3$): 6.2 (*m*, 1 H); 3.72 (*dd*, *J* = 10, 3, 1 H); 3.52 (*dd*, *J* = 10, 8.5, 1 H); 2.07 (*m*, 3 H); 1.95 (*m*, 1 H); 1.77 (*m*, 1 H); 1.68 (*m*, 1 H); 1.50 (*tm*, *J* = 11, 1 H); 1.34 (*m*, 1 H); 1.13–0.85 (*m*, 3 H); 0.87 (*d*, *J* = 4.5, 6 H). MS: 166 (100, M^+), 151, 137, 124, 109, 95, 81, 67. Anal. calc. for $C_{11}H_{16}O$: C 79.47, H 10.91; found: C 79.27, H 10.88.

4. *Photooxygenation of* **16**. 4.1. *In the Presence of MeOH*. A soln. of **16** (50 mg, 0.3 mmol) in dry MeOH (20 ml) containing rose bengal (RB; 5 mg) was cooled and photooxygenated for 5 h. After allowing the mixture to warm to 0°, MeOH was evaporated and the residue purified by chromatography on a silica-gel column (hexane/AcOEt 9:1); 43 mg (72%) of *(2R)-2-[(1S,4R)-4-methyl-2-oxocyclohexyl]propyl formate* (**17**) as a colorless oil. IR ($CDCl_3$): 3020*w*, 1720*s*, 1185*s*, 910*m*. ^{1}H-NMR ($CDCl_3$): 8.04 (*d*, *J* = 1, CHO); 4.14 (*ddd*, *J* = 11, 5, 1 H); 4.05 (*ddd*, *J* = 11, 6.5, 1 H); 2.37 (*dm*, 1 H); 1.00 (*d*, *J* = 6.5, 3 H); 0.99 (*d*, *J* = 7, 3 H). MS: 198 (M^+), 137, 112 (100), 97, 84, 69. Anal. calc. for $C_{11}H_{18}O_3$: C 66.64, H, 9.15; found: C 66.47, H 9.10.

4.2. *In the Presence of Acetaldehyde*. A soln. of **16** (80 mg, 0.48 mmol) and RB (5 mg) in freshly distilled acetaldehyde (25 ml) was photooxygenated for 4 h (TLC monitoring). The soln. was evaporated, the residue diluted with CH_2Cl_2/pentane 1:1 (4 ml), filtered, and evaporated. The ^{1}H-NMR ($CDCl_3$) of the crude product revealed the presence of the dioxetane **22** (characteristic signals: 5.83 (*s*, 1 H); 4.11 (*dd*, *J* = 10.0, 7.5, 1 H); 3.99 (*dd*, *J* = 11.5, 10.0, 1 H)) **19**, and **20/21**. Chromatography on a silica-gel column with hexane/AcOEt 20:1 permitted the isolation of **17** (52 mg, 54.5%), **19** (16 mg, 16.7%), and **20/21** (inseparable 12:1 mixture, similar R_f values; 20 mg, 17%). The hydroperoxide nature of **19** was confirmed by a positive reaction on spraying a sample with an aq. soln. of starch/KI.

(1R,4R,4aS,7R)-3,4,4a,5,6,7-Hexahydro-4,7-dimethyl-1H-2-benzopyran-1-yl Hydroperoxide (**19**). ^{1}H-NMR ($CDCl_3$): 8.78 (br. *s*, 1 H); 5.74 (*s*, 1 H); 5.68 (*s*, 1 H); 4.14 (*dd*, *J* = 112, 3, 1 H); 3.55 (*dd*, *J* = 11, 2, 1 H); 0.90 (*d*, *J* = 7, 3 H); 0.88 (*d*, *J* = 7, 3 H).

(3R,4aR,7R,7aS,10R,11aR)-7,7a,8,9,10,11-Hexahydro-3,7,10-trimethyl-6H-[2]benzopyrano[1,8a-e]-1,2,4-trioxane (**20**; major isomer). ^{1}H-NMR ($CDCl_3$): 5.93 (*q*, *J* = 5, 1 H); 4.97 (*s*, 1 H); 3.68 (*ddd*, *J* = 11.4, 1 H); 3.55 (*dd*, *J* = 11, 11, 1 H); 2.79 (*ddd*, *J* = 13.4, 2, 1 H); 2.35 (*m*, 1 H); 1.75 (*m*, 1 H); 1.55–1.33 (*m*, 3 H); 1.21 (*d*, *J* = 5, 3 H); 1.02 (*dd*, *J* = 13, 13, 1 H); 0.98–0.82 (*m*, 1 H); 0.90 (*d*, *J* = 6.5, 3 H); 0.67 (*d*, *J* = 7, 1 H).

(3S,4aR,7R,7aS,10R,11aR)-7,7a,8,9,10,11-Hexahydro-3,7,10-trimethyl-6H-[2]benzopyrano[1,8a-e]-1,2,4-trioxane (**21**; minor isomer). ^{1}H-NMR ($CDCl_3$): 5.31 (*q*, *J* = 6, 1 H); 4.90 (*s*, 1 H); 3.75 (*dd*, 1 H); 3.42 (*dd*, *J* = 10, 10, 1 H); 2.63 (*ddd*, *J* = 14.4, 1, 1 H); 1.75 (*d*, *J* = 6, 3 H); 0.90 (*d*, 3 H); 0.75 (*d*, *J* = 7, 3 H).

4.3. *In the Presence of Acetone*. Photooxygenation was repeated exactly as in *4.2*, but in pure acetone (25 ml). A portion of the soln. was evaporated and the residue taken up in $CDCl_3$. Examination of the ^{1}H-NMR revealed signals at 5.83, 4.11, and 3.99 ppm consistent with the dioxetane **22**. Other products were present, but could not be identified; no trioxane was formed. To the remaining soln., Me_3SiOTf (0.065 ml) was added with stirring for 30 min, followed by addition of Et_3N (0.5 ml). H_2O (45 ml) was next added. Extraction with Et_2O (25 ml), drying (Na_2SO_4), and evaporation gave **23** (48 mg, 40% from **16**). Data: see *4.4*.

4.4. *In the Presence of* CH_2Cl_2. 4.4.1. A soln. of **16** (52 mg, 0.31 mmol) and methylene blue (MB; 5 mg) in dry CH_2Cl_2 (25 ml) was cooled and photooxygenated for 2.5 h. Next, acetone (1 ml) was added dropwise, followed by Me_3SiOTf (0.065 ml). After stirring for 30 min, Et_3N (0.5 ml) was added. The resulting soln. was poured into H_2O and diluted with CH_2Cl_2 (20 ml). The org. layer was washed with H_2O (3 × 10 ml) and dried (Na_2SO_4). After evaporation, the residue was purified on a silica-gel column with hexane/AcOEt 9:1 to give **23** (47 mg, 59%), **24** (4.1 mg, 5%), and **17** (6.5 mg, 11%).

(4aR,7R,7aS,10R,11aR)-7,7a,8,9,10,11-Hexahydro-3,3,7,10-tetramethyl-6H-[2]benzopyrano[1,8a-e]-1,2,4-trioxane (**23**; major isomer). Colorless crystals. M.p. 77–78° (pentane). $[\alpha]_D^{20} = -132$ (*c* = 0.06, $CHCl_3$). IR ($CDCl_3$): 3000, 2970, 2940, 2880, 1460, 1385, 1375, 1075. ^{1}H-NMR ($CDCl_3$): 4.95 (*s*, 1 H); 3.63 (*ddd*, *J* = 11, 4.5, 1,

1 H); 3.43 (*dd*, J = 11, 11, 1 H); 2.67 (*ddd*, J = 13.5, 3.5, 2, 1 H); 2.34 (*m*, 1 H); 1.73 (*s*, 3 H); 1.72–1.55 (*m*, 3 H); 1.45–1.26 (*m*, 2 H); 1.29 (*s*, 3 H); 1.03 (*dd*, J = 13, 13, 1 H); 0.95–0.78 (*m*, 1 H); 0.90 (*d*, J = 6.5, 3 H); 0.68 (*d*, J = 7, 3 H). MS: 238 (M^+), 191, 167 (100), 149, 123, 109, 95, 81, 69, 55. Anal. calc. for $C_{14}H_{24}O_4$: C 65.60, H 9.44; found: C 65.67, H 9.53.

Crystallographic Data of **23.** As the crystals of **23** decomposed rapidly on X-ray bombardment, they were placed in a glass capillary and sealed under Ar. Cell parameters and reflection intensities were measured at 165 K on a *Philips-PW1100* diffractometer with graphite monochromated Mo-$K\alpha$ radiation. Owing to the decrease in the diffracted intensities during data collection, two crystals were measured and all intensities corrected for this drift. The structure was solved by direct methods [20] and refined by full-matrix least-squares [21] with two scale factors. A summary of crystal data, intensity measurements, and structure refinement is given in the *Table*. All crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre*, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

Table. *Crystal Data, Intensity Measurement and Structure Refinement for* **23**

Formula	$C_{14}H_{24}O_4$	$(\sin\Theta/\lambda)_{max}$ [Å^{-1}]	0.51
Molecular weight	256.3	No. of measured reflections	939
Crystal system	Orthorhombic	No. of observed reflections	728
Space group	$P2_12_12_1$	Criterion for observed	$\lvert F_o\rvert > 4\sigma(F_o)$ and $\lvert F_o\rvert > 8$
Temperature [K]	165	No. of parameters	164
a [Å]	6.0759(7)	Refinement (on F)	full-matrix
b [Å]	9.2369(16)	Weighting scheme	$\omega = 1$
c [Å]	25.730(5)	H-atoms	calculated
V [Å^3]	1444.1(2)	Max. and average Δ/σ	0.017, 0.004
Z	4	Max. and min. $\Delta\rho$ [eÅ^{-3}]	0.34, −0.32
D_c [g·cm^{-3}]	1.18	S	3.98
F_{000}	560	R [%]	5.3
μ [mm^{-1}]	0.079		

(4aR,7R,7aS,10R,11aR)-7,7a,8,9,10,11-Hexahydro-3,3,7,10-tetramethyl-6H-[2]benzopyrano[8a,1-e]-1,2,4-trioxane (**24**; minor isomer). ^{1}H-NMR ($CDCl_3$): 5.12 (*s*, 1 H); 4.00 (*dd*, J = 11, 4.5, 1 H); 3.69 (*dd*, J = 11, 11, 1 H); 2.55 (*dm*, J = 13.5, 1 H); 2.45 (*m*, 1 H); 1.43 (*s*, 3 H); 1.37 (*s*, 3 H); 0.93 (*d*, J = 6.5, 3 H); 0.78 (*d*, J = 7, 3 H).

4.4.2. A soln. of **16** (100 mg, 0.6 mmol) in CH_2Cl_2 (50 ml) containing MB (7 mg) was cooled and photooxygenated for 3 h. Cyclopentanone (1.3 ml) was added slowly, followed by Me_3SiOTf (0.2 ml). The resulting soln. was stirred at −78° for 30 min. Et_3N (1 ml) was added, the soln. poured into H_2O and the mixture diluted with CH_2Cl_2. The org. layer was washed with H_2O (3 × 20 ml), dried ($NaSO_4$), and evaporated. The crude product was chromatographed on a silica-gel column with hexane/AcOEt 30:1 to give **25** (104 mg, 61%), **26** (14 mg, 8%), and **17** (19 mg, 16%).

(4'aR,7'R,7'aS,10'R,11'aR)-7',7'a,8',9',10',11'-Hexahydro-7',10'-dimethylspiro[cyclopentane-1,3'-6'H-[2]benzopyrano[1,8a-e]-1,2,4-trioxane] (**25**; major isomer). Colorless crystals from pentane. M.p. 83–85°. $[\alpha]_D^{20} = -148$ (c = 0.04, $CHCl_3$). IR ($CHCl_3$): 3000, 2980, 2930, 2880, 1455, 1330, 1075. ^{1}H-NMR ($CDCl_3$): 4.94 (*s*, 1 H); 3.63 (*ddd*, J = 13, 5, 1, 1 H); 3.44 (*dd*, J = 13, 13, 1 H); 2.75 (*ddd*, J = 14, 4, 2, 1 H); 2.64 (*m*, 1 H); 2.32 (*m*, 1 H); 1.94–1.50 (*m*, 10 H); 1.45–1.25 (*m*, 2 H); 1.02 (*dd*, J = 13, 13, 1 H); 0.94–0.80 (*m*, 1 H); 0.90 (*d*, J = 6.5, 3 H); 0.67 (*d*, J = 7, 3 H). MS: 166 ($M^{+\cdot} - O_2$ – cyclopentanone), 137, 112 (100), 97, 84, 69, 55. Anal. calc. for $C_{16}H_{26}O_4$: C 68.06, H 9.28; found: C 67.92, H 9.27.

(4'aR,7'R,7'aS,10'R,11'aR)-7',7'a,8',9',10',11'-Hexahydro-7',10'-dimethylspiro[cyclopentane-1,3'-6'H-[2]benzopyrano[8a,1-e]-1,2,4-trioxane] (**26**; minor isomer). ^{1}H-NMR ($CDCl_3$): 5.16 (*s*, 1 H); 4.00 (*dd*, J = 11, 6, 1 H); 3.56 (*dd*, J = 11, 10, 1 H); 2.54 (*ddd*, J = 14, 4, 2.5, 1 H); 2.35 (*m*, 1 H); 2.04 (*m*, 1 H); 0.92 (*d*, J = 6.5, 3 H); 0.77 (*d*, J = 7.5, 3 H).

5. *Conversion of (1S,2S,5R)-5-Methyl-2-[(1'R)-1'-methyl-2'-hydroxyethyl]cyclohexanol* (**18**) [22] *to* **17**. To a soln. of **18** (120 mg, 0.7 mmol) and dicyclohexylcarbodiimide (160 mg, 0.78 mmol) in CH_2Cl_2 (6 ml) and hexane (1 ml), HCOOH (150 mg, 3.3 mmol) was added dropwise at 0°. The mixture was stirred, allowed to warm to 25°, and stirred for another 3 h. Evaporation afforded a residue containing the primary monoformate, which was diluted with CH_2Cl_2 (3 ml) and used for the next step without further purification. The soln. of crude formate was

added to a soln. of pyridinium dichromate (PDC) prepared from Cr_2O_3 (900 mg, 9 mmol) and pyridine (1.4 ml) in CH_2Cl_2 (12 ml) at 0°. The formate remaining in the flask was washed into the PDC mixture with more CH_2Cl_2 (2 ml). The resulting mixture was stirred for 45 min, diluted with Et_2O/hexane 1:1, filtered, and evaporated. The residue was extracted several times with hexane and the soluble portion drained off. The hexane solns. were combined and evaporated to give crude **17**. Chromatography on a silica-gel column with hexane/AcOEt 9:1 gave pure **17** as a colorless oil (112 mg, 81% from **18**), identical in all respects to the cleavage product formed by photooxygenation (see *4.1*).

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