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SYNTHESIS OF TRICYCLIC ARTEANNUIN-LIKE COMPOUNDS

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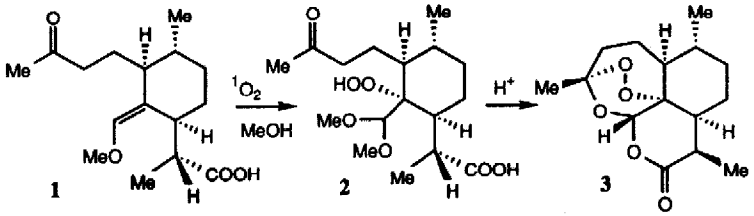
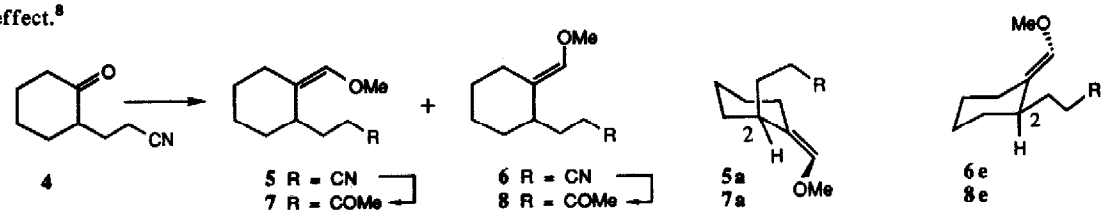
Summary. Methylene blue-sensitized photo-oxygenation of Z-2-(3'-oxobutyl)methoxymethylidenecyclohexane (7)in CH_2Cl_2 at -78°, followed by catalysis with Amberlyst-15, gave an epimeric pair of methoxy-1,2,4-trioxanes (9 and 10) and an isomeric peroxide (11) in 67 and 30% yields. The E-isomer (8) under the same conditions also gave 9-11 (48%) and 2-formyl-3-(3'-oxobutyl)cyclohexene (30%). Trioxanes are formed by cyclization of an initially formed 1,2-dioxetane.

Two recent syntheses[1] of arteannuin (3), an unusual, sesquiterpenic 1,2,4-trioxane endowed with antimalarial properties,[2] have depended on the photo-oxygenation of an enol ether in methanol, exemplified by 1 and the acid-catalyzed transformation of the resulting hydroperoxide 2 to 3. The nature of these steps remains problematical.[3] As part of our program of developing new technology for preparing 1,2,4-trioxane analogues of improved antimalarial activity,[4] we now describe the synthesis of two new arteannuin-like molecules in which the aforementioned reactions are clarified.

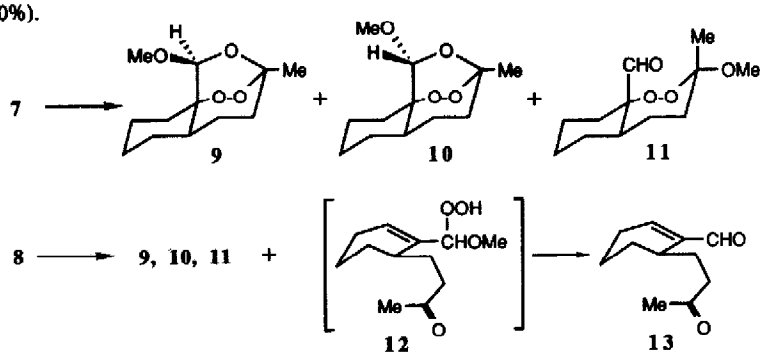


The starting point was 2-(2-cyanoethyl)cyclohexanone (4)[5] which, on treatment with diphenylmethoxymethylphosphine oxide,[6] gave a 1:1 mixture of the Z and E methoxymethylidenes (5 and 6). Each isomer was separated by chromatography and converted with lithiummethyl to the corresponding 3-oxobutyl derivatives 7 and 8. The Z and E configurations were assigned from the characteristic ^1H and ^{13}C-NMR spectra of 5 and 6. The side-chain in the E isomer 6 prefers the equatorial disposition (6e). In contrast, the Z isomer 5, on account of $A^{1,3}$ strain,[7] adopts the chair conformation in which the side-chain occupies an axial position (5a). Consequently, the proximity of the methoxy substituent to the C2-H grouping provides the essential clue to geometry. The C2 proton is deshielded in 5a compared to 6e. Conversely, the C2 carbon atom is shielded in 5a relative to 6e thanks to the γ-effect.[8]



The photo-oxygenation and subsequent acid treatment of the Z and E isomeric 3-oxobutyl derivatives proved equally distinctive.[9] The Z isomer 7 in CH_2Cl_2, at -78°, using methylene blue as sensitizer, followed by addition of Amberlyst-15, afforded two epimeric 1,2,4-trioxanes (9 and 10) and the peroxide 11 in yields of 48, 19, and 30% respectively. Compounds 9-11 were separated by column chromatography over silica gel using CH_2Cl_2 as eluant.[10] As the NMR spectra were insufficiently informative, their structures were elucidated by X-ray analysis of single crystals[11] (Fig.). The same sequence of photo-oxygenation and acid treatment of the E isomer 8 also delivered 9, 10, and 11, but in diminished yields of 17, 17, and 14% respectively as they were compensated by the formylcyclohexene 13[12] in 30% yield, which undoubtedly arose from the competing formation of the hydroperoxide 12.

It should be emphasized that the correct choice of conditions was crucial for success. Temperatures higher than -78°, solvents such as MeOH, and catalysts like trimethylsilyl trifluoromethanesulfonate resulted in inferior yields of 9-11 (<40%).



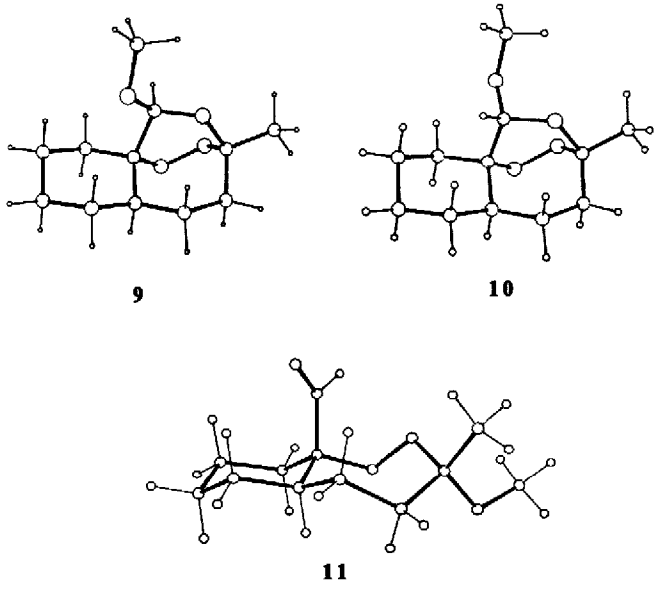
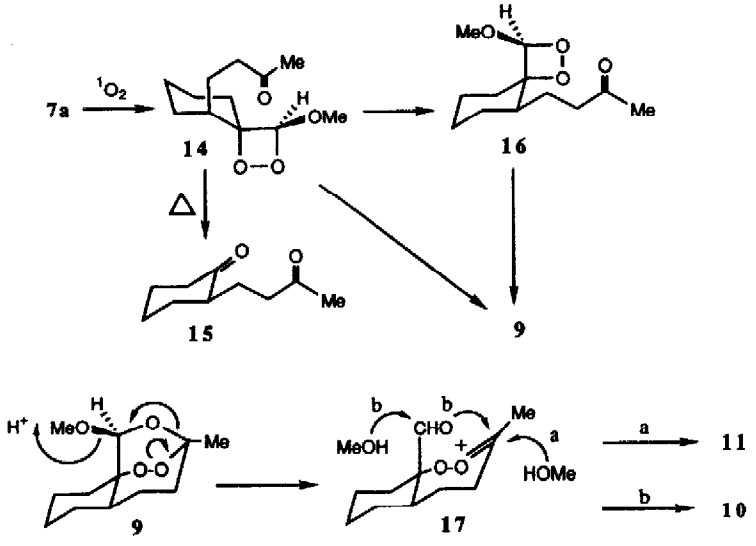


Fig. Perspective drawings of the X-ray structures of 9, 10 and 11

These results are best rationalized by the initial attack of singlet oxygen on the least hindered face of the double bond. The Z isomer in its preferred conformation **7a**, having no axial allylic hydrogen atom available, produces solely the dioxetane **14**. In fact, proof for **14** was provided by carrying out the photo-oxygenation of **7** in $CDCl_3$ with methylene blue at -78°. A single new compound was formed and characterized by its NMR spectrum.[18] The same experiment conducted in CH_2Cl_2 followed by warming gave the diketone **15** in 90% yield arising by scission (**14**→**15**). The dioxetane **14** or its conformer **16** by acid catalysis could then undergo cyclization in two steps to **9**, which is the kinetic product since it is the first formed. Independent submission of **9** to acidic conditions caused its equilibration to **10** and **11**. It is noteworthy that the 6-membered ring in **9** breaks to create **11** preserving the peroxide link. Moreover, the *trans* placement of the methoxy group with respect to the aldehyde function is understandable in terms of the intermediacy of the oxonium ion **17**, which is attacked by the expelled methanol molecule on the least hindered side. Alternatively, methanol could add in tandem to the aldehyde group and cationic center in **17**, so accounting for the epimerization of **9** to **10**.



Similar mechanistic events are likely for the E isomer. However, since it exists preferentially as **8e**, axially disposed allylic hydrogen atoms enable singlet oxygen to undergo the "ene" reaction. Only the least substituted hydroperoxide is formed owing to *syn* selectivity.[14] Nonetheless, some dioxetane also forms which cyclizes to the trioxanes **9** and **10** as before.

Last, but by no means least, *in vitro* tests against *P. falciparum* clones have shown that **9** and **10**, but not **11**, possess commensurate activity with that of arteannuin.[15] Synthetic applications of the foregoing technology and detailed biological tests will be reported elsewhere.

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9. For the method used see: C.W. Jefford, Y. Wang, G. Bernardinelli, *Helv. Chim. Acta* **1988**, *71*, 2042.
10. Compounds **9-11** gave acceptable elemental analyses.
11. Crystallographic data: Data were collected on a Philips PW 1100 diffractometer (MoKα). Structures were solved by direct methods (MULTAN-80) and refined by full-matrix least-square analysis. Trioxane **9**, recrystallized from pentane, m.p. 74-75°. Triclinic crystals; space group P-1, a = 6.9908(8), b = 7.9224(6), c = 12.266(2) Å; α = 75.02(2); β = 84.71(2); γ = 64.99(3)°; Z = 2, d_c = 1.28 g · cm^{-3}. The final R-factor, based on 1231 observed reflections was 0.049. Trioxane **10**, recrystallized from hexane, m.p. 63°. Monoclinic; space group $P2_1/c$, a = 16.807(3), b = 5.9843(11), c = 13.092(2) Å; β = 111.56(1)°; Z = 4, d_c = 1.24 g · cm^{-3}. R-factor = 0.080, based on 759 observed reflections. Peroxide **11**, recrystallized (hexane, m.p. 80°). Triclinic; space group P-1, a = 6.462(3), b = 10.393(1), c = 10.652(5) Å; α = 63.15(4); β = 81.18(4); γ = 75.19(2)°; Z = 2, d_c = 1.23 g · cm^{-3}. R-factor = 0.079, based on 874 observed reflections. Details on all structures will be published in the full paper. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communications.
12. The substitution about the double bond in **13** was confirmed by the vinyl proton signal (6.8 ppm, t, ^3J = 4.0 Hz).
13. The configuration of **14** is assumed, but the signal at 5.25 ppm is typical for a trisubstituted 1,2-dioxetane (C.W. Jefford, C.G. Rimbault, *J. Am. Chem. Soc.* **1978**, *100*, 6437).
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15. We thank Dr. W. Milhous and his staff (Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, D.C. 20307-5100, USA) for performing the tests.

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