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AN UNSUCCESSFUL APPROACH TO THE FRAMEWORK OF THE ANTIMALARIAL, ARTEETHER

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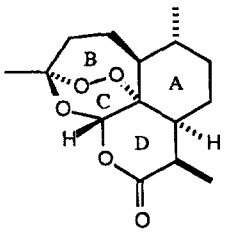
Summary: The hexahydrobenzopyran **7a**, prepared using the *new acetone anion equivalent* **17**, reacted with singlet oxygen to produce mixtures containing the dioxetane **6**, but *in situ* treatment with acid failed to generate detectable amounts of **4**, an analogue of the antimalarial arteether **3**.

Although the use of the Chinese herb 'Qinghao' (*Artemisia annua* L.) for the treatment of malaria was first recorded over 1600 years ago,[1] it was not until 1972 that the active principle of this plant was isolated and identified as (+)-artemisinin **1**,[2,3] a sesquiterpene of the cadalane (amorphane) type. The antimalarial activity of this unusual compound, especially against the *Plasmodium falciparum* strains responsible for the most severe forms of the disease, provided a major lead in an area where resistance to existing drug treatments is increasing alarmingly. Extensive studies in China revealed that derivatives of dihydroartemisinin **2** were considerably more potent than the parent compound **1**,[4] and following a research programme coordinated by the World Health Organisation, the ethyl acetal **3**, known as β-arteether, was selected for clinical development as an antimalarial.[5]



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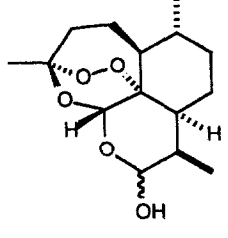

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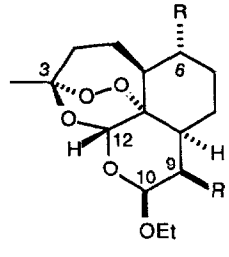
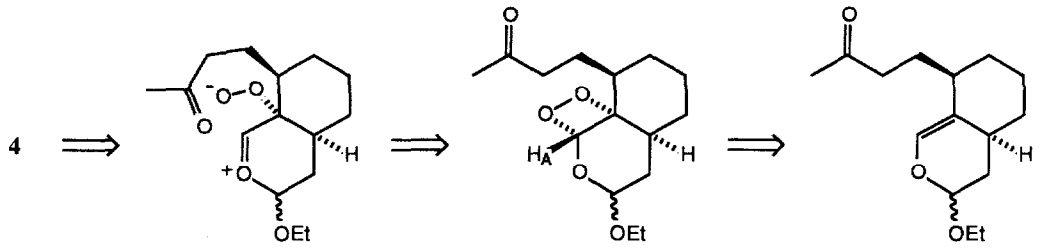


3 R = Me
4 R = H

The novel structure, activity, and low natural yield of artemisinin **1** have prompted three total syntheses,[6-8] an attempted semi-synthesis,[9] the preparation of an analogue,[10] and model studies aimed at securing routes to the biologically crucial 1,2,4-trioxane component of the molecule.[11,12] Our own efforts have been directed towards β-arteether **3**, currently available only *via* artemisinin **1**, and we describe here an attempt to generate the tetracyclic skeleton of **3** directly as the 6,9-bis(demethyl) homologue **4**. Disconnection of the BC portion of **4** reveals that a zwitterionic peroxide **5**, set up for intramolecular capture by the pendant carbonyl group, could function as its immediate precursor (Scheme 1). We therefore sought to prepare the dioxetane **6**, which might give **5** [or an equivalent] directly or under the influence of acid, *via* singlet oxygenation of the bicyclic acetal **7**.



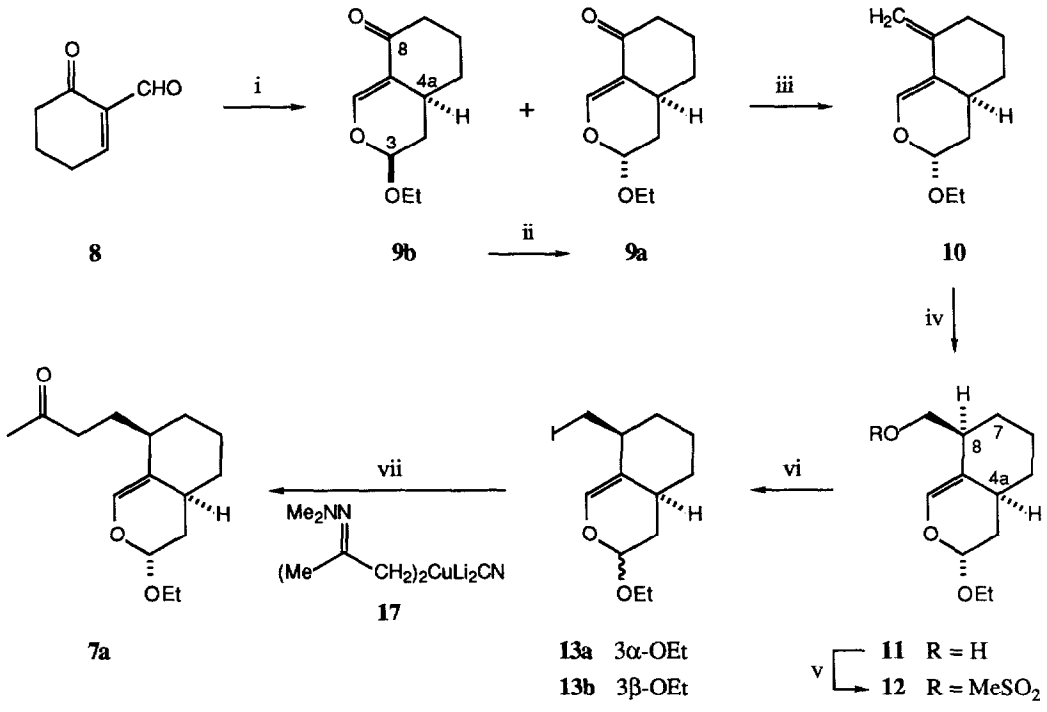
5 **6** **7**

Scheme 1

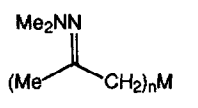
The approach used to prepare the acetal **7** is summarised in Scheme 2.[13] Heterodiene cycloaddition of ethoxyethene to 2-formylcyclohex-2-en-1-one **8**[14] gave the *exo* and *endo*-cycloadducts **9a** and **9b** (ratio 1:6) in 91% yield, and the kinetic product **9b** was converted into the thermodynamically more stable isomer **9a** by equilibration with acid. Methylenation of **9a** using Lombardo's reagent[15] gave the unstable diene **10**, which on hydroboration gave the hydroxymethyl compound **11** stereospecifically. The structure of **11** was deduced from the high field ^{1}H n.m.r. spectrum of the derived mesylate **12**, which indicated that two of the three vicinal coupling constants associated with the axial H-7 were large (13 Hz) and that H-8 must therefore be axial.

The forcing conditions needed to effect the displacement of the hindered mesylate **12** with iodide ion caused some epimerisation, yielding a mixture of **13a** and **13b** (*ca.* 4:1) and serving a warning that the introduction of the remainder of the side chain would require the use of a particularly reactive acetone anion equivalent. And so it proved. Treatment of **13** with the lithiated acetone hydrazone **14**[16] elicited no reaction at all, while use of the cuprates **15**[17] and **16**[18] gave only traces of the desired product. A reagent with a higher operating temperature was required and, exploiting the principles established by Lipshutz,[19] we prepared the higher order cyanocuprate **17**, which proved stable over an extended period at around 0 °C. Treatment of **17** with the mixture of iodides **13** and unmasking of the carbonyl group using copper(II) chloride[20] thus afforded a workable yield of **7a**.

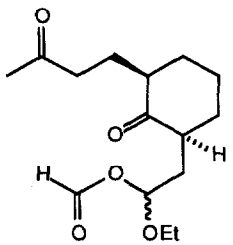
Photo-oxygenation (Methylene Blue sensitiser) of the ketone **7a** was slow in methanol at -78 °C, conditions known to favour the formation of dioxetanes from enol ethers,[12,21] but was conveniently rapid in CD_3OD, in which the lifetime of singlet oxygen is enhanced.[22] The starting material gave way to a complex mixture of products whose ^{1}H n.m.r. spectrum included signals in the region expected for H_A of the dioxetane **6** (*ca.* 6 ppm). Treatment of the mixture with acids (formic, Amberlyst® 15) gave new polar products, but the methyl ketone unit from the starting material **7a** was obviously intact (δ >2.0, compared to 1.41 in arteether) both before and after the acid treatment. Evidence that the initial products included the dioxetane **6** was obtained on repeating the reaction in acetonitrile at -40 °C, which gave a mixture from which two of the previously observed products were recovered. The less polar of these was assigned the structure **18** [δ 8.16 (HCO_2R), 5.0 (CHOEt)], since it decomposed on standing overnight in $CDCl_3$ into the more polar **19** [δ 10.0 (CHO); m/z 211 (*M* + 1, 82%), 210 (M^+, 69), 193 (*M* - OH, 100), 180 (*M* - HCHO, 17)], an authentic sample of which is in preparation. The formate **18** is an anticipated[23] thermal scission product of the dioxetane **6**. Treating mixtures presumed to contain the dioxetane **6** with Lewis acids in various solvents gave traces of **18** and **19** as the only recognisable components of complex mixtures. We conclude that photo-oxygenation of the ketone **7a** produces the dioxetane **6**, but that the conversion of the latter into the tetracycle **4** is impracticable from a synthetic point of view.



Scheme 2 *Reagents*: i, CH_2=CHOEt, 20 °C, 3 h (91%); ii, CF_3CO_2H, CH_2Cl_2, 10 °C, 72 h (75%); iii, CH_2Br_2, Zn, $TiCl_4$, CH_2Cl_2, 0 °C (33 - 43%); iv, 9-BBN, THF, then NaOH, H_2O_2 (99%); v, $MeSO_2Cl$, py (81%); vi, KI, 18-crown-6, THF, reflux, 4 d (69%); vii, **17**, THF, -20 to +10 °C, 72 h, then $CuCl_2$, H_2O, THF, pH 7, 6 h (40%).



	n	M
14	1	Li
15	1	(PhS)CuLi
16	2	CuLi



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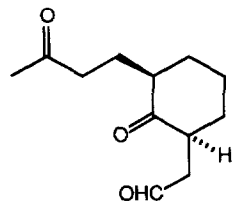

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13 Yields refer to (racemic) products, isolated by flash chromatography, with satisfactory i.r., ^{1}H n.m.r., and high resolution m.s. characteristics. Selected n.m.r. data ($CDCl_3$): **7a**, (300 MHz) 2.11 (3 H, s, MeCO), 4.85 (1 H, dd, *J* 2.5, 4.4 Hz, 3-H), 5.95 (1 H, br s, 1-H). **7b**, (300 MHz) 4.73 (1 H, dd, *J* 2.0, 8.1 Hz, 3-H), 5.99 (1 H, br s, 1-H). **9a**, (90 MHz) 5.19 (1 H, t, *J* 2 Hz, 3-H), 7.36 (1 H, d, *J* 2 Hz, 1-H). **9b**, (90 MHz) 5.06 (1 H, dd, *J* 2, 10 Hz, 3-H), 7.39 (1 H, d, *J* 2 Hz, 1-H). **10**, (90 MHz) 4.50 (1 H, t, *J* 2 Hz, 3-H), 4.77 (1 H, t, *J* 2.5 Hz, 9-H), 5.06 (1 H, t, *J* 2.5 Hz, 9'-H), 6.44 (1 H, d, *J* 2 Hz, 1-H). **11**, (80 MHz) 4.3 (1 H, br s, 9-H_2), 4.85 (1 H, m, 3-H), 6.0 (1 H, m, 1-H). **12**, (400 MHz) 1.04 (1 H, ddd, *J* 3.5, 13, 13 Hz, 5_{ax}-H), 1.08 (1 H, dddd, *J* 3.5, 13, 13, 13 Hz, 7_{ax}-H), 1.215 (3 H, t, *J* 7 Hz, Me), 1.22 (1 H, m, 5_{eq}-H), 1.54 (1 H, ddd, *J* 2.5, 9, 13.5 Hz, 4_{ax}-H), 2.00 (1 H, ddd, *J* 3.5, 6.5, 13.5 Hz, 4_{eq}-H), 2.15 (1 H, m, 4a-H), 2.38 (1 H, m, 8-H), 3.03 (3 H, s, $MeSO_2$), 3.45 - 3.6, 3.75 - 3.9 (total 2 H, m, OCH_2), 4.21 (1 H, dd, *J* 6.5, 9.5 Hz, 9-H), 4.39 (1 H, dd, *J* 5, 9.5 Hz, 9-H), 4.93 (1 H, dd, *J* 2.5, 3.5 Hz, 3-H), 5.97 (1 H, t, *J* 2 Hz, 1-H). **13a**, (80 MHz) 3.0 - 4.0 (4 H, m, OCH_2, 9-H_2), 4.85 (1 H, m, 3-H), 6.05 (1 H, m, 1-H); R_f (CCl_4 - toluene 1:1) 0.38 [**13b**, 0.31].

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