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An unexpected product in the photooxygenation of a cyclic enol ether

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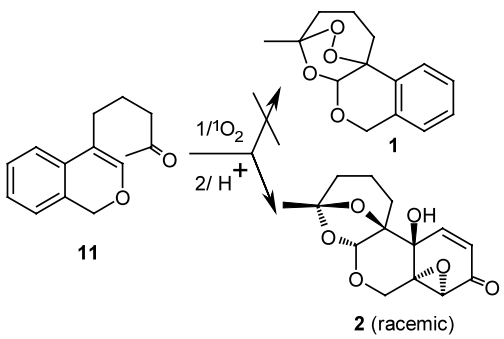
Abstract—The photooxygenation product of a cyclic enol ether conjugated with an *o*-phenylene ring is a novel epoxy compound instead of a 1,2,4-trioxane analogue. The structure of the compound was elucidated by X-ray analysis.

Artemisinin and its derivatives are currently used in clinical practice as effective antimalarial drugs. As the 1,2,4-trioxane ring is considered to be a structural requirement for significant activity, a number of tricyclic 1,2,4-trioxanes have been prepared as potential antimalarial agents.[1–7] Here, we would like to report a synthesis aimed at compound **1** and identification of an unexpected product **2**.

Photooxygenation of cyclic enol ethers has been known as a reliable synthetic method for the transformation of deoxoartemisinin analogues.[8–10] 4-(4-Oxo)-pentyl-2-benzopyran **11** was chosen as a cyclic enol ether which was expected to yield C-nor-5,10-phenylene ring deoxoartemisinin analogue **1** by standard photooxygenation (Scheme 1).



Scheme 1.

5-Bromo-2,2-dioxolane ketal pentane **5** was prepared in 64% yield from acetylbutyrolactone **3** by nucleophilic substitution–decarboxylation in boiling 34% HBr solution[11] and ketalization with ethyleneglycol in refluxing benzene solution containing *p*-TsOH.

Chlorination of *o*-xylene **6** according to the literature,[12] followed by nucleophilic substitution with sodium cyanide in refluxing acetonitrile afforded *o*-methylbenzyl cyanide **7** in 90% yield.[13] The alkylation of **7** with **5** in the presence of sodium hydride in HMPA provided **8** in 80% yield,[14] which was hydrolyzed in boiling potassium hydroxide/ethylene glycol solution to give 2-(2-methyl)-phenyl-6-oxo-hepta-noic acid **9** in 84% yield. Compound **9** was converted into **10** in 80% yield by bromination with NBS–benzoyl peroxide–CCl_4, cyclization in triethylamine–acetone and ketalization with ethyleneglycol–*p*-TsOH in benzene. Reduction of **10** in toluene by DIBAL-H at −78°C and dehydration in acetone–*p*-TsOH at room temperature gave the desired cyclic enol ether **11** in 57% yield.[15] Compound **11** was photooxygenized in methylene chloride in the presence of methylene blue at −78°C under a bubbling stream of oxygen to provide racemic **2** in 30% yield (Scheme 2)[16].

It has been demonstrated by NMR, IR and elemental analysis that compound **2** has a molecular formula of $C_{14}H_{16}O_6$ and comprises a hydroxyl group, a carbon–carbon double bond, a carbonyl and an epoxide moiety. The proton and carbon chemical shift assignments for compound **2** are shown in Table 1. The H–H COSY spectrum showed the relative positions of

Keywords: epoxy compound; 1,2,4-trioxane; cyclic enol ether; photooxygenation.

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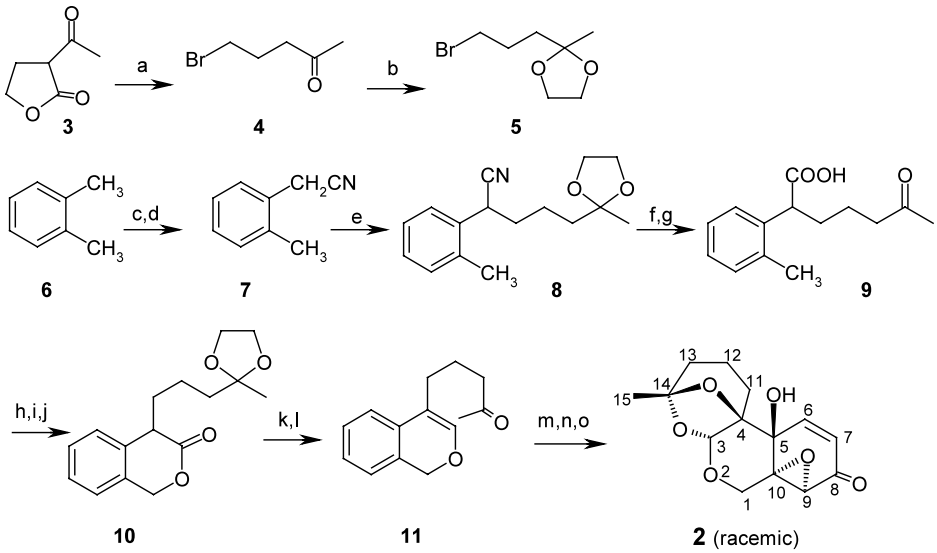

Scheme 2. *Reagents and conditions*: (a) 34% HBr, boiling, 80%; (b) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, reflux-H_2O, 80%; (c) SO_2Cl_2, BPO, reflux, 50%; (d) NaCN, PEG-400, CH_3CN, reflux, 90%; (e) 50% NaH, **5**, HMPA, 80%; (f) KOH, $(CH_2OH)_2$, reflux; (g) 10% HCl, 84% from **8**; (h) NBS, BPO, CCl_4, reflux; (i) Et_3N, acetone, rt; (j) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, reflux-H_2O, 80% from **9**; (k) DIBAL-H, toluene, −78°C; (l) acetone, *p*-TsOH, rt, 57% from **10**; (m) methylene blue, O_2, *hv*, CH_2Cl_2, −78°C; (n) TMSOTf; (o) Et_3N, 30% from **11**.

Table 1. Proton and carbon chemical shift assignments for **2**

No.	^{1}H (ppm)	^{13}C (ppm)	No.	^{1}H (ppm)	^{13}C (ppm)
1	4.68 (d, J=12.1 Hz, 1H)	65.66	8		191.82
1	3.51 (d, J=12.1 Hz, 1H)		9	3.43 (d, J=1.8 Hz, 1H)	54.89
3	5.30 (s, 1H)	99.97	10		63.20
4		84.60	11	1.75 (m, 2H)	33.56
5		67.62	12	1.59 (m, 2H)	17.03
5-OH	3.94 (s, 1H)		13	1.77 (m, 2H)	26.67
6	6.61 (d, J=10.6 Hz, 1H)	143.01	14		112.42
7	5.98 (dd, J=10.6, 1.8 Hz, 1H)	125.85	15	1.64 (s, 3H)	24.34

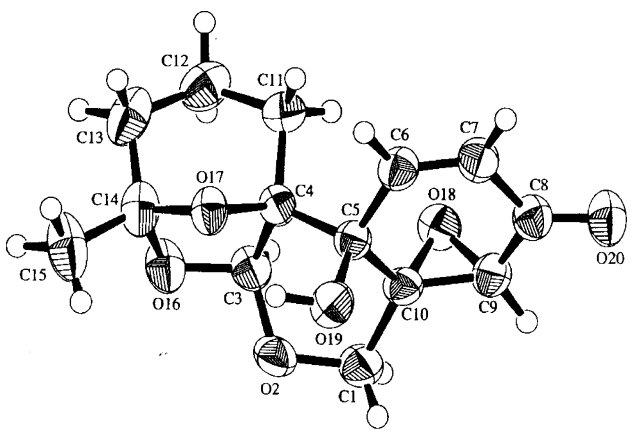

Figure 1. X-Ray structure of **2**.

H atoms. The relative stereochemistry (Fig. 1) was finally confirmed by X-ray diffraction analysis.[17,18]

The novel epoxide **2** shows moderate cytotoxicity against P388 (IC_{50} <10^{-6} mol/L) and other bioactivities in primary in vitro examinations. Further work is in progress.[18]

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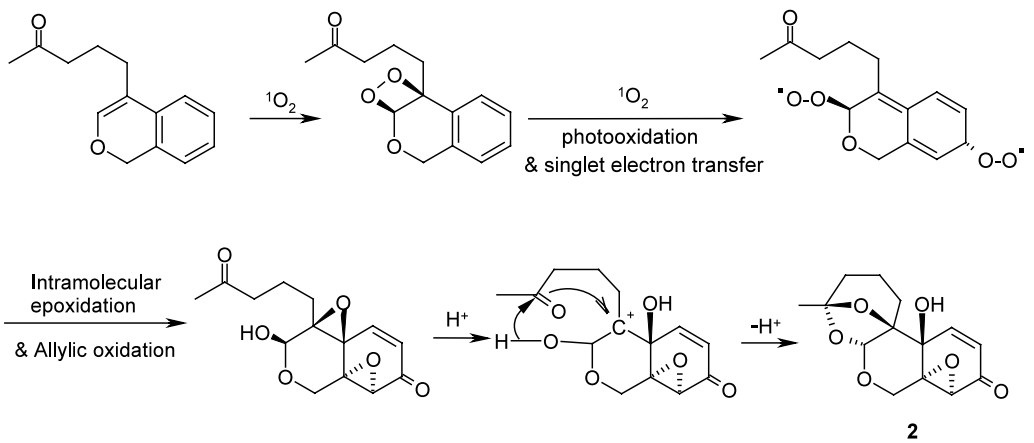
16. Data for **2**: mp 146–147°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.61 (d, $J=10.6$ Hz, 1H), 5.98 (dd, $J=10.6$, 1.8 Hz, 1H), 5.30 (s, 1H), 4.68 (d, $J=12.1$ Hz, 1H), 3.94 (s, 1H), 3.51 (d, $J=12.1$ Hz, 1H), 3.43 (d, $J=1.8$ Hz, 1H), 1.77 (m, 2H), 1.75 (m, 2H), 1.64 (s, 3H), 1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 191.82, 143.01, 125.85, 112.42, 99.97, 84.60, 67.62, 65.66, 63.20, 54.89, 33.56, 26.67, 24.34, 17.03; IR (cm^{-1}): 3479, 1687, 1443, 1387, 1319, 1246, 1213, 1078, 1051, 1036, 1009; anal. calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75; found: C, 59.93; H, 5.72. Data for **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, $J=6.8$ Hz, 1H), 7.20 (m, 3H), 3.95 (m, 5H), 2.34 (s, 3H), 1.95–1.54 (m, 6H), 1.32 (3H, s); IR (cm^{-1}): 2239, 1605, 1493, 1462, 1377, 1221, 1128, 1067; HRMS calcd for $C_{16}H_{21}NO_2$: 259.15723; found: 259.15767. Data for **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (m, 1H), 7.17 (m, 3H), 3.84 (t, $J=7.2$ Hz, 1H), 2.43 (t, $J=6.4$ Hz, 2H), 2.39 (s, 3H), 2.10 (m, 3H), 2.08 (br s, 1H), 1.73 (m, 2H), 1.56 (m, 2H); IR (cm^{-1}): 3400 (br), 1709, 1491, 1462, 1363, 1171; HRMS calcd for $C_{14}H_{18}O_3$: 234.12560; found: 234.12324. Data for **10**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.35–7.10 (m, 4H), 5.43 (d, $J=14.0$ Hz, 1H), 5.23 (d, $J=14.0$ Hz, 1H), 3.92 (m, 4H), 3.59 (t, $J=7.2$ Hz, 1H), 2.00 (m, 2H), 1.87 (m, 2H), 1.61 (m, 2H), 1.29 (s, 3H); IR (cm^{-1}): 1741, 1462, 1379, 1242, 1190, 1046; HRMS calcd for $C_{16}H_{20}O_4$: 276.13617; found: 276.1326. Data for **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (t, $J=7.3$ Hz, 1H), 7.18 (t, $J=7.3$ Hz, 1H), 7.17 (d, $J=7.3$ Hz, 1H), 7.03 (d, $J=7.3$ Hz, 1H), 6.46 (s, 1H), 4.98 (s, 2H), 2.50 (t, $J=7.3$ Hz, 2H), 2.35 (t, $J=7.3$ Hz, 2H), 2.15 (s, 3H), 1.82 (m, 2H); IR (cm^{-1}): 3392, 1714, 1491, 1452, 1360, 1248, 1209, 1155, 1072, 1047; HRMS calcd for $C_{14}H_{16}O_2$: 216.11504; found: 216.12053.
17. Single-crystal X-ray analysis of **2** (deposition number CCDC 164721): wavelength 0.71069 Å, temperature 293 K. Crystal system, space group = monoclinic, $P2_1/n$ (# 14). Crystal size 0.20×0.20×0.30 mm, $a=15.149$ (5), $b=10.602(1)$, $c=16.274(3)$ Å. Volume = 2607(1) Å^3. A total of 5310 reflections were collected in the range 25 (18.4–25.6°). The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 8.71989×10^{-7}). The structure was solved by direct method and expanded using Fourier techniques.
18. The formation of novel epoxide **2** must relate to a quite different mechanism. At this stage, it is hard to describe the exact mechanism without any further evidence, but three oxidations and two intramolecular epoxidations might be involved (Scheme 3).



Scheme 3.