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A new type of 1,2,4-trioxanes structurally related antimalarial artemisinin

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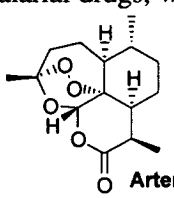
Abstract

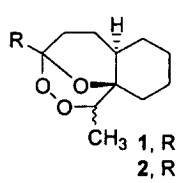
Co(II)-catalyzed triethylsilylperoxygenations of allylic alcohols **5** followed by acid catalyzed desilylative cyclizations with a pendant keto group furnished new types of 1,2,4-trioxanes **1–3** under very mild conditions in moderate yields.

Keywords: 1,2,4-trioxane; artemisinin; peroxide; oxygenation; cyclization; malaria.

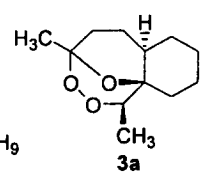
The discovery of artemisinin, an active principle of the Chinese medicinal plant qinghao, was an important milestone in antimalarial chemotherapy.[1] Several classes of peroxides related to artemisinin and even synthetic 1,2,4-trioxanes were found to have potent antimalarial activities.[2] Many synthetic methods for 1,2,4-trioxanes have been known, such as copper(II) catalyzed cyclization of vicinal hydroxy hydroperoxide,[3] acid-catalyzed cyclization of hydroperoxy acetals with olefins[4] or epoxides,[5] 1,2-dioxetane with ketones or aldehydes,[6] peroxyaldehyde with ketones or aldehydes,[7] and cationic ring expansion of ozonides.[8] Recently, we reported several bicyclic 1,2,4-trioxanes, which were synthesized from Co(II)-catalyzed oxygenation of cinnamyl alcohol followed by acid-catalyzed cyclization with various aldehydes or ketones.[9] In continuing work on the synthesis of 1,2,4-trioxanes in the search for new antimalarial drugs, we wish to report new types of 1,2,4-trioxanes **1–3**.



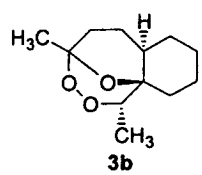
Artemisinin



1, R = *n*-C_4H_9
2, R = C_6H_5



3a



3b

Pyrrolidine enamine of cyclohexanone was alkylated with acrylonitrile and then hydrolyzed to give 3-(2-oxo-cyclohexyl)propanenitrile (**4**). Addition of vinylmagnesium bromide to the ketone **4** gave 3-(2-hydroxy-2-vinylcyclohexyl)propanenitrile in a 5:1 *trans*:*cis* ratio. Then the nitrile was converted to the ketones **5a**, **5b** and **5c** in 56, 39 and 62% yields, respectively (Scheme 1).[10]

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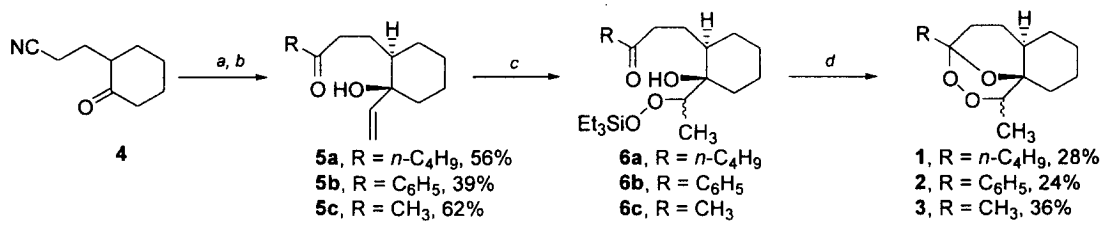
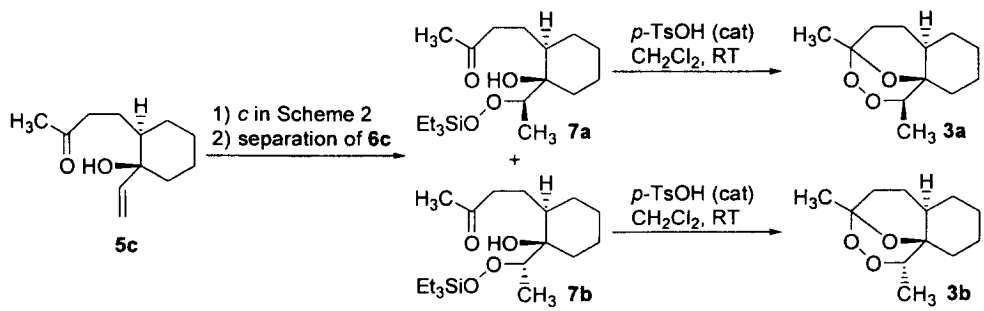


Scheme 1. Reagents: (a) CH_2=CHMgBr, THF, 0°C; (b) RLi, ether, rt; (c) $Co(acac)_2$ (0.1 equiv.), Et_3SiH (1.5 equiv.), ethanol, under O_2; (d) *p*-TsOH (cat.), CH_2Cl_2

Then Co(II)-catalyzed oxygenations with the double bonds of the compounds **5a–c** in the presence of triethylsilane yielded a 1:1 diastereomeric mixture of the triethylsilylperoxy alcohols **6a–c**, respectively. The triethylsilylperoxy alcohols **6a** and **6b** were cyclized by adding a catalytic amount of *p*-toluenesulfonic acid to give a 1:1 diastereomeric mixture of the corresponding 1,2,4-trioxanes **1** and **2** in 28 and 24% yields from the keto-allylic alcohols **5a** and **5b**, respectively. Since the two diastereomers of the **6c** have relatively different polarities, we were able to separate them using silica gel chromatography to give the isomers **7a** and **7b** in almost 1:1 ratio.[11] Both diastereomers **7a** and **7b** were independently cyclized to give the 1,2,4-trioxanes **3a** and **3b** in 20 and 16% yields, respectively, as shown in Scheme 2. Note that all these 1,2,4-trioxanes **1–3** were structurally unique, in which two alkyl groups were substituted at both 3- and 6-positions of the 1,2,4-trioxane ring.

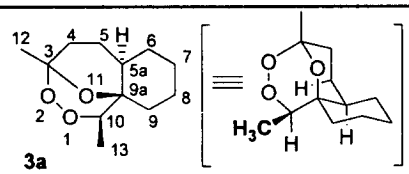


Scheme 2.

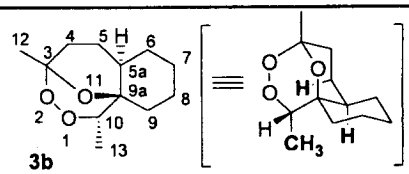
We have studied 2D NMR experiments to accomplish ^1H and ^{13}C NMR signal assignments and to confirm relative stereochemistry of the trioxanes **3a** and **3b** (Table 1). Proton J-networks and proton–carbon connectivities exhibiting overall covalent linkages of **3a** and **3b** were confirmed by ^1H, ^{13}C NMR, DEPT, and HETCOR COSY and TOCSY experiments. The relative stereochemistry was finally confirmed by temperature dependent (–60 to 30°C) NOESY experiments with 150, 200, 250 ms mixing times. Direct NOE enhancements for **3b** were found between H^{13} and H^{5a} and between H^{13} and H^5, while no such NOE for **3a** was found.

In summary, new 1,2,4-trioxanes **1–3**, structurally related to antimalarial artemisinin, were synthesized by employing Co(II)-catalyzed triethylsilylperoxygenation and then acid catalyzed desilylative cyclization with a pendant keto group under very mild conditions in moderate yields. In view of the increasing demand for effective antimalarial 1,2,4-trioxanes, the present strategy would be of high value in searching for new antimalarials structurally related to artemisinin.

Table 1
Proton and carbon chemical shift assignments for **3a** and **3b**



3a



3b

	^{1}H (ppm)	^{13}C (ppm)	^{1}H (ppm)	^{13}C (ppm)
3		101.5		102.0
4	1.92 (m)	30.45	1.93 (m)	30.02
5	1.35, 2.92	27.98	1.28, 2.68	26.43
5a	1.51 (m)	37.78	1.47 (m)	31.56
6	0.97, 1.67	34.11	1.22, 1.48	33.52
7	1.58, 1.75	29.51	1.35, 1.76	28.25
8	1.54	20.76	1.54	20.16
9	1.74	25.89	1.72	25.65
9a		70.84		72.05
10	3.70 (q, J = 6.4 Hz)	82.01	4.19 (q, J = 6.8 Hz)	83.75
12	1.25 (s)	25.49	1.26 (s)	25.62
13	1.44 (d, J = 6.4 Hz)	14.53	1.11 (d, J = 6.8 Hz)	13.13

Acknowledgements

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11. Spectral data for **1** (1:1 diastereomeric mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (q, J=6.4 Hz, 1H for one isomer) and 3.57 (q, J=6.8 Hz, 1H for the other), 2.20–2.04 (m, 1H), 1.75–1.51 (m, 10H), 1.50–1.09 (m, 8H), 1.26 (d, J=6.8 Hz, 3H for one isomer) and 1.02 (d, J=6.4 Hz, 3H for the other), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.7, 108.6, 82.17, 81.88, 81.61, 78.65, 39.13, 38.22, 38.19, 33.43, 32.38, 30.72, 30.14, 29.68, 28.80, 28.14, 25.95, 25.72, 25.45, 25.33, 24.60, 24.31, 23.15, 23.11, 22.68, 22.49, 18.14, 14.22, 14.20, 13.54; FT-IR (neat, cm^{-1}) 2931, 2865, 1458, 1377, 1251, 1094, 972; HRMS (CI, CH_4) calcd for $C_{16}H_{31}O_3$(M+CH_5^+): 271.2273; found: 271.2272. Spectral data for **2** (1:1 diastereomeric mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.36–7.25 (m, 3H), 4.23 (q, J=6.4 Hz,

1H for one isomer) and 3.76 (q, J=6.8 Hz, 1H for the other), 2.38–2.22 (m, 1H), 2.06–1.91 (m, 1H), 1.90–1.70 (m, 4H), 1.70–1.50 (m, 3H), 1.50–1.38 (m, 1H), 1.35–1.16 (m, 3H), 1.35 (d, J=6.8 Hz, 3H for one isomer) and 1.02 (d, J=6.4 Hz, 3H for the other); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 142.0, 129.7, 128.1, 128.0, 126.7, 125.3, 125.2, 107.7, 107.5, 85.80, 82.75, 81.90, 79.33, 38.70, 33.02, 32.28, 31.38, 31.32, 30.64, 28.72, 28.06, 25.81, 25.59, 24.83, 24.51, 22.51, 22.35, 18.11, 13.33; FT-IR (neat, cm^{-1}) 2929, 2860, 1496, 1450, 1284, 1092; HRMS (CI, CH_4) calcd for $C_{18}H_{27}O_3(M+CH_5^+)$: 291.1960; found: 291.1962. Experimental procedure for the 1,2,4-trioxane **3a** and **3b**: To a solution of **5c** (98.1 mg, 0.50 mmol) and $Co(acac)_2$ (17.8 mg, 0.050 mmol) in ethanol (10 mL) were added triethylsilane (120 μL, 0.75 mmol) at 0°C under oxygen atmosphere. The resulting solution was purged twice with an oxygen stream for 10 min and stirred under a slightly positive pressure of oxygen. After being stirred at room temperature for 10 h, the reaction solution was concentrated and then separated by silica gel chromatography with a 20:80 mixture of ethyl acetate and hexane to afford the two isomers (**7a**, nonpolar, 42 mg; **7b**, polar, 35 mg, combined 45% yield). The isomers **7a** and **7b** were treated with *p*-toluenesulfonic acid (1.0 mg) in dichloromethane (10 mL) and stirred at room temperature for 2 h. Each reaction mixture was concentrated and chromatographed to afford the corresponding 1,2,4-trioxanes **3a** (19.6 mg, 20%) and **3b** (15.7 mg, 16%), respectively. Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) data are summarized in Table 1; FT-IR (neat, cm^{-1}) 2932, 2867, 1451, 1375, 1103. Compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) data are summarized in Table 1; FT-IR (neat, cm^{-1}) 2931, 2863, 1457, 1376, 1246, 1109; HRMS (CI, CH_4) calcd for $C_{12}H_{21}O_3(M+H^+)$: 213.1491; found: 213.1497.