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Facile construction of 6-carbomethoxymethyl-3-methoxy-1,2-dioxane, a core structure of spongean anti-malarial peroxides

Nobutoshi Murakami,[a] Motoyuki Kawanishi,[a] Sawako Itagaki,[b] Toshihiro Horii[b] and Motomasa Kobayashi[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan*
[b]*Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka 565-0871, Japan*

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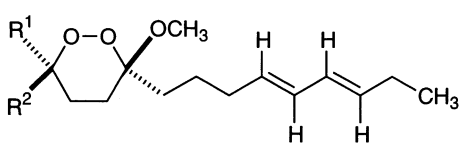
Abstract—Facile construction of 6-carbomethoxymethyl-3-methoxy-1,2-dioxane, the core structure of spongean anti-malarial peroxides, has been developed by combination of $Sc(OTf)_3$-mediated peroxyhemiacetalization of keto-ester and Michael addition of the resultant peroxyhemiacetal in the fluorinated alcohol.

Currently, problems of parasite resistance to all commercially available anti-malarials have seriously weakened therapeutic control and threatened to cause a global resurgence of malaria.[1] Urgently, alternative chemotherapeutic strategies are needed. During the course of our program aiming at new anti-malarial substances from natural sources,[2] we found the methyl esters (**1** and **2**) of peroxyplakoric acids A_3 and B_3[3] isolated from a marine sponge of *Plakortis* sp. to exhibit anti-malarial activity (Fig. 1). Both substances showed similar anti-malarial potency against *Plasmodium falciparum* (IC_{50}, **1**: 1.5×10^{-7} M; **2**: 1.2×10^{-7} M) along with high selective toxicity index (**1**: 140; **2**: 250) between parasites and human epidermoid carcinoma KB 3-1 cells. From the structural comparison with the known anti-malarial peroxides such as artemisinin[4] and yingzhaosu A analogues,[5] the 6-carbomethoxymethyl-3-methoxy-1,2-dioxane portion in **1** and **2** is strongly suggested to be related to their anti-malarial activity. We presumed that this core structure could be constructed by intramolecular Michael addition of a peroxyhemiacetal group, which would be built up from a ketonic carbonyl residue to an α,β-unsaturated ester moiety. Although this strategy was adopted to prepare several endoperoxides with the 3-alkoxy-1,2-dioxane moiety, the reported yield of the desired peroxides was about 30% yield.[6] On the other hand, introduction of a peroxyhemiacetal function to a ketonic carbonyl residue has been achieved by Wittig reaction followed by ozonolysis of a resultant enol ether.[7] Similarly, the conversion yield for these two steps was too low to be applicable to this procedure. In this context, we



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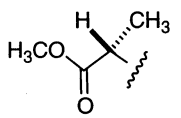
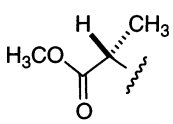
1	H	
2		H

Figure 1. Chemical structures of methyl esters (**1** and **2**) of peroxyplakoric acids A_3 and B_3.

Keywords: anti-malarials; marine metabolites; peroxyhemiacetal; Michael addition; peroxides.
* Corresponding author. Fax: 81-6-6879-8219; e-mail: kobayasi@phs.osaka-u.ac.jp

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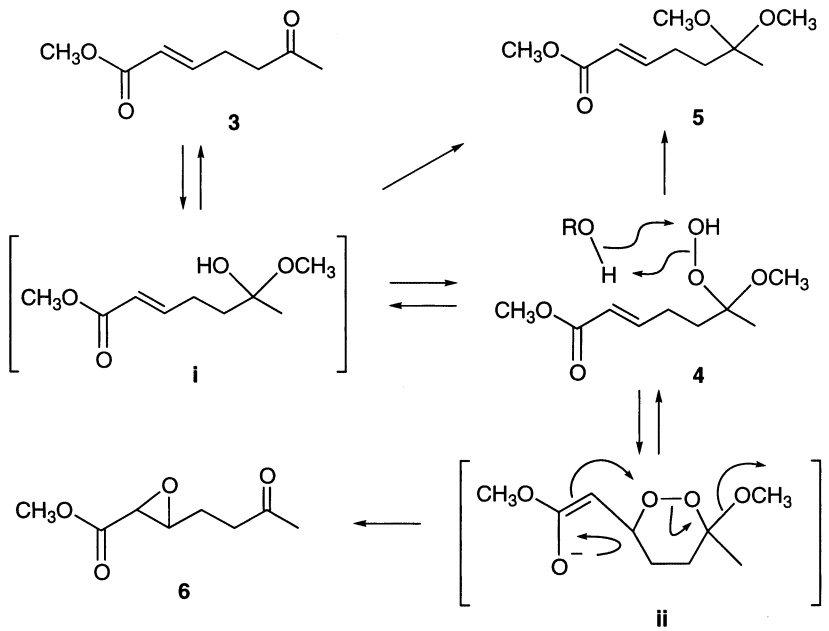
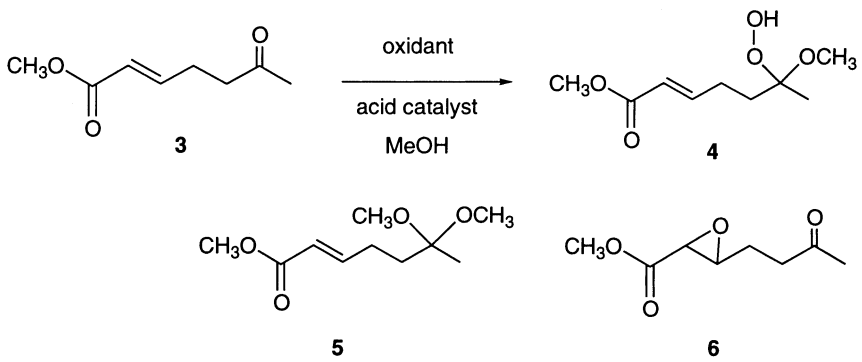
devoted ourselves to develop a new practical method for constructing the core peroxide structure. This communication deals with a facile construction method of 6-carbomethoxymethyl-3-methoxy-1,2-dioxane by an ingenious combination of $Sc(OTf)_3$-mediated peroxyhemiacetalization to a ketonic carbonyl residue and intramolecular Michael addition of a peroxyhemiacetal group in the fluorinated alcohol.



Scheme 1. Plausible reaction pathway in peroxyhemiacetalization of **3**.

Table 1. Introduction of peroxyhemiacetal function to **3**



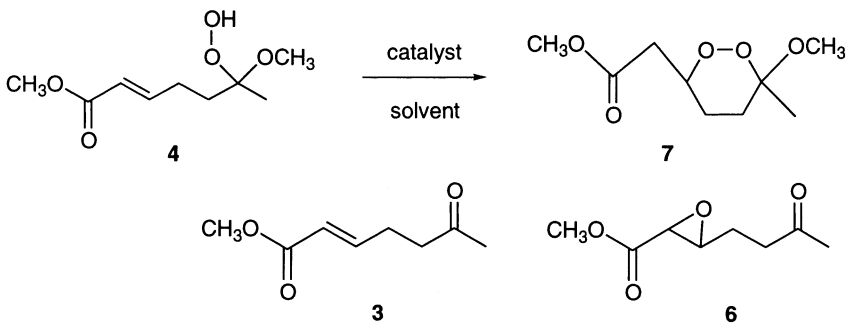
Entry	**3** (M)	$H_2O_2 \cdot H_2NCONH_2$ (equiv.)	Acid	Conc. of acid (M)	Yield (%)			
					3	**4**	**5**	**6**
1	0.5	1.0[a]	Conc. H_2SO_4	0.03	37	10	0	43
2	0.5	2.5	TsOH	0.03	16	35	12	28
3	0.5	10	TsOH	0.03	13	24	11	44
4[b]	0.5	2.5	TsOH	0.03	42	37	13	0
5[b]	0.5	10	TsOH	0.03	38	45	8	0
6	0.025	20	TsOH	0.03	9	72	6	7
7	0.025	20	$SnCl_4$	0.03	27	30	22	10
8	0.025	20	TMSOTf	0.03	26	31	28	7
9	0.025	20	$Sc(OTf)_3$	0.03	9	29	12	45
10	0.025	20	$Yb(OTf)_3$	0.03	61	10	13	8
11	0.025	20	$La(OTf)_3$	0.03	52	17	16	7
12	0.025	20	$Sc(OTf)_3$	0.003	14	57	11	16
13	0.025	7.5	$Sc(OTf)_3$	0.003	6	83	7	0

[a] In this reaction, 30% H_2O_2 was used.
[b] 3 Å MS (20 mg/1.0 mL) was added.

In the first instance, we explored a transformation method of a ketonic carbonyl residue into a peroxyhemiacetal function (Scheme 1). As shown in Table 1, the reported procedure (entry 1),[8] in which peroxyhemiacetal was not isolated, afforded a small amount of the desired product **4** together with significant recovery of **3**[9] and formation of an epoxy-ketone **6**. The epoxy-ketone **6** is believed to generate from the intramolecular Michael addition and subsequent cleavage of the O–O bond with elimination of the methoxyl anion, as shown in Scheme 1. Under this condition, a hemiacetal **i** precursory to **4** would be easily converted to **3** by acid treatment. Thus, dehydrated urea-hydrogen peroxide ($H_2O_2{\cdot}H_2NCONH_2$) and *p*-toluenesulfonic acid were applied to this conversion (entry 2). While this condition increased the yield of **4**, a dimethylacetal **5** was newly provided as a side-product. Addition of a further amount of $H_2O_2{\cdot}H_2NCONH_2$ resulted in increasing the formation of **6** rather than **4** (entry 3). Removal of H_2O, which would be formed from $H_2O_2{\cdot}H_2NCONH_2$ in the oxidation step of the intermediary hemiacetal **i**, using 3 Å MS completely suppressed formation of **6** (entries 4 and 5). This evidence suggested that Michael addition by the hydroperoxyl group in **4** was terminated by the anhydrous condition. Nevertheless, nearly a half amount of the keto-ester **3** remained in the absence of H_2O. Based on these findings, a slight amount of H_2O apparently promotes formation of **i**. On the contrary, generation of the epoxy-ketone **6** via Michael addition of the hydroperoxyl group in **4** was stimulated in the presence of an excess amount of H_2O. When the reaction was carried out with a twenty-fold volume of MeOH in order to suppress the participation of H_2O, the yield of the desired **4** was improved up to 72% (entry 6). A Lewis acid catalyst such as $SnCl_4$ and TMSOTf had no influence on the yield of **4**, as shown in entries 7 and 8.

The above-described outcome of transformation from **3** into **4** indicates a plausible reaction pathway, as illustrated in Scheme 1. First of all, the keto-ester **3** would be subjected to acetalization with MeOH under acidic conditions to give the hemiacetal intermediate **i**, which would be further converted by oxidation with $H_2O_2{\cdot}H_2NCONH_2$ or substitution of the hydroxyl group by the hydroperoxyl group to furnish the peroxyhemiacetal **4**. Alternatively, subsequent acetalization of **i** would concomitantly provide the dimethylacetal **5**. Intramolecular Michael addition of the hydroperoxyl group in **4** followed by epoxidation involving O–O bond cleavage also afforded the undesired epoxy-ketone **6**. During this transformation, there would be an equilibrium between **3** and **4** through hydrolysis of the peroxyhemiacetal **4**. Additionally, the treatment of **4** in MeOH with *p*-TsOH under anhydrous condition afforded **3** exclusively, which indicates that **4** would also act as an oxidizing agent of alcohol and water to revert to the hemiacetal **i**. These findings showed us that either protection of the hydroperoxyl group in the peroxyhemiacetal **4** or suppression of hydrolysis of **4** would lead to enhancement of the yield of **4**.

Table 2. Michael addition of peroxyhemiacetal **4**



Entry	Reagent	Conc. of reagent (M)	Solvent	Yield (%)			
				3	**4**	**6**	**7**
1	NaOMe	0.1	MeOH	0	0	98	0
2	NaOMe	0.01	MeOH	0	0	89	8
3	NaOMe	0.001	MeOH	12	61	15	8
4	TsOH	0.005	CH_3CN	95	0	0	0
5	Et_2NH	0.01	MeOH	0	0	67	29
6[a]	Et_2NH		THF	0	0	98	0
7[a]	Et_2NH		CH_2Cl_2	0	0	100	0
8	Et_2NH	0.01	CF_3CH_2OH	0	0	44	53
9	Et_2NH	0.1	CF_3CH_2OH	0	0	67	31
10	Et_2NH	0.001	CF_3CH_2OH	8	48	20	22
11	Et_2NH	0.01	$(CF_3)_2CHOH$	24	0	2	72
12	Et_2NH	0.01	$(CF_3)_3COH$	88	0	5	0

[a] The reaction was conducted with 3 equiv. of Et_2NH.

Recently, rare earth metal triflates were found to be stable and capable of acting as a Lewis acid catalyst in aqueous media. In particular, lanthanoid(III) salts were applied to several chemical transformations and are regarded as being resistant to hydrolysis.[10] Therefore, formation of a coordination of **4** with the lanthanoid(III) salts might be anticipated to inhibit acetalization and/or Michael addition of the hydroperoxyl group in **4**. This assumption prompted us to utilize lanthanoid triflates for acid-catalyzed introduction of a peroxyhemiacetal function. While $Yb(OTf)_3$ and $La(OTf)_3$ did not stimulate peroxyhemiacetal formation, the recovered **3** was decreased in the case of $Sc(OTf)_3$ (entries 9–11). As a result of examining various reaction conditions, it was found $Sc(OTf)_3$ excellently mediated this conversion to furnish the desired **4** in 83% yield free from the successive Michael addition (entry 13). Comparison of entries 12 and 13 indicated that the increase in the yield of **4** might be related to the above-mentioned coordination formation between **4** and $Sc(OTf)_3$.

Next, construction of the 6-carbomethoxymethyl-3-methoxy-1,2-dioxane skeleton was investigated by intramolecular Michael addition, as demonstrated in Table 2. Previously reported procedures were unsuccessful for preparing the Michael adduct **7** (entries 1–4 in Table 2),[6] whereas a catalytic amount of Et_2NH in dry MeOH provided **7** in 29% yield (entry 5). In contrast, the reaction in the presence of a stoichiometric amount of Et_2NH in THF and CH_2Cl_2 afforded the epoxyketone **6** exclusively (entries 6 and 7).

Distribution of the products in this transformation suggested ready cleavage of the O–O bond in the plausible intermediate **ii** leading to elimination of the methoxyl anion, as shown in Scheme 1. Accordingly, protonation to the intermediate enolate **ii** would be expected to accelerate the formation of **7**. Thus, fluorinated alcohols with higher acidity than MeOH were tested in the conversion. In spite of an improvement of the yield of **7**[11] by the use of 2-trifluoroethanol, a fair amount of **6** was also obtained (entries 8–10). Notably, replacement of MeOH by 1,1,1,3,3,3-hexafluoropropan-2-ol brought about significant enhancement of the yield of **7** (72%), although the keto-ester **3** was obtained in 24% yield. Contrarily, application of 1,1,1,3,3,3-hexafluoro-2-trifluoromethylpropan-2-ol almost resulted in the formation of **3** (entry 12).

We have disclosed that two peroxides, the methyl esters of peroxyplakoric acid A_3 (**1**) and B_3 (**2**) isolated from a marine sponge of *Plakortis* sp., exhibit anti-malarial activity with high toxicity index. Then, in order to evaluate the anti-malarial activity of the core peroxide structure of **1** and **2**, we devoted ourselves to developing a new practical method for constructing a 6-carbomethoxymethyl-3-methoxy-1,2-dioxane structure. An ingenious combination of $Sc(OTf)_3$-mediated peroxyhemiacetalization of the keto-ester **3** and intramolecular Michael addition of the resultant hydroperoxyl group in **4** in $(CF_3)_2CHOH$ facilely constructed the 6-carbomethoxymethyl-3-methoxy-1,2-dioxane skeleton. Taking recovery of **3** in the latter conversion into account, it is noteworthy that the desired 6-carbomethoxymethyl-3-methoxy-1,2-dioxane **7** is furnished in 75% yield for two steps from an α,β-unsaturated ester **3**.[12,13] Current efforts are focused on a search for new anti-malarial peroxides by application of this synthetic protocol utilizing **4** as a scaffold and evaluation of their anti-malarial activity.

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9. The keto-ester **3** was quantitatively prepared from 4-hydroxypentan-1-ol for two steps, Swern oxidation followed by Wittig condensation with (carbethoxymethylene)-triphenylphosphorane.
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11. The resulting **7** was obtained as a mixture of two stereoisomers in a ratio of 4.8:1. The physicochemical properties of **7** are as follows. Colorless oil. IR (KBr) cm^{-1}: 1745. ^1H NMR (500 MHz, $CDCl_3$) major isomer: δ 1.26 (3H, s, 3-CH_3), 1.55–1.83 (4H, m, 4-H, 5-H), 2.32 (1H, dd, $J=15.9$, 5.5 Hz, 7-Ha), 2.44 (1H, dd, $J=15.9$, 7.9 Hz, 7-Hb), 3.24 (3H, s, 3-OCH_3), 3.63 (3H, s, CO_2CH_3), 4.47–4.55 (1H, m, 6-H); minor isomer: δ 1.29 (3H, s, 3-CH_3), 1.44–1.47, 1.55–1.83, 2.17–2.24 (4H, m, 4-H, 5-H), 2.54 (1H, dd, $J=15.3$, 6.1 Hz, 7-Ha), 2.93 (1H, dd, $J=15.3$, 7.9 Hz, 7-Hb), 3.27 (3H, s, 3-OCH_3), 3.64 (3H, s, CO_2CH_3), 4.47–4.55 (1H, dddd, $J=7.9$, 6.7, 6.1, 5.5 Hz, 6-H). FABMS: m/z 227 $(M+Na)^+$. FAB HRMS: obsd; m/z 227.0909. Calcd for $C_9H_{16}O_5Na$; m/z 227.0896 $(M+Na)^+$.
12. General procedure for preparing **4**: A solution of **3** (20 mg, 0.13 mmol) in anhydrous MeOH (5.2 mL) was treated with $Sc(OTf)_3$ (7.7 mg, 0.016 mmol) and $H_2O_2{\cdot}H_2NCONH_2$ (92 mg, 0.98 mmol) at room temperature for 48 h. The reaction mixture was diluted with CH_2Cl_2 (156 mL) and the resulting residue was removed by column packed with aluminum oxide 90 (neutral,

70–230 mesh, Merck Co. Ltd.). Removal of the solvent from the filtrate under reduced pressure gave a product, which was purified by SiO_2 column (*n*-hexane: $CHCl_3$:MeOH = 10:1:0.5) to furnish **4** (21.7 mg, 83%) together with **3** (1.2 mg, 6%) and **5** (1.8 mg, 7%).

4: Colorless oil. IR (KBr) cm^{-1}: 3381, 1719, 1657. ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (3H, s, 7-H), 1.78–1.90 (2H, m), 2.25–2.36 (2H, m), 3.29 (3H, s, 6-OCH_3), 3.70 (3H, s, CO_2CH_3), 5.82 (1H, d, J = 15.9 Hz, 2-H), 6.96 (1H, dt, J = 15.9, 6.7 Hz, 3-H), 7.74 (1H, br s, 6-OOH). FAB MS: m/z 227 $(M+Na)^+$. FAB HRMS: obsd; m/z 227.0921. Calcd for $C_9H_{16}O_5Na$; m/z 227.0896 $(M+Na)^+$.

13. General procedure for preparing **7**: A solution of Et_2NH (0.68 μL, 6.6 μmol) in $(CF_3)_2CHOH$ (60 μL) was added to a solution of **4** (22 mg, 0.11 mmol) in $(CF_3)_2CHOH$ (0.6 mL), then the whole mixture was stirred at room temperature for 8 h. Removal of the solvent from the whole mixture under reduced pressure gave a product, which was purified by SiO_2 column (*n*-hexane:EtOAc = 5:1) to furnish **7** (15.8 mg, 72%) along with **3** (4.1 mg, 24%) and **6** (0.4 mg, 2%).