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SYNTHESIS OF A NOVEL ARTEMISININ ANALOGUE HAVING POTENT ANTIMALARIAL ACTIVITY†

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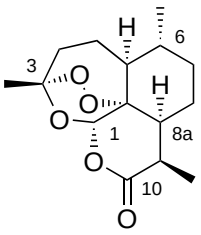
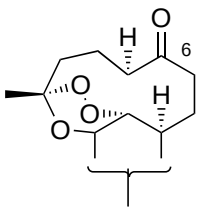
Abstract—An artemisinin analogue containing 1,2,4-trioxane structure was designed and synthesized. The compound exhibited significant and selective *in vitro* antimalarial activity.

Malaria is one of the most serious infectious diseases in tropical and subtropical area. Recently, development of a new class of antimalarial drugs is strongly required due to the problem of chloroquine-resistant *Plasmodium falciparum*, malaria parasite. Artemisinin (**1**, qinghaosu),[1] which contains an unusual cyclic peroxy structure, has become an important clinical drug for the treatment of the drug-resistant strains. Many of cyclic peroxy compounds as an artemisinin derivative have been synthesized or semi-synthesized, and some of them actually demonstrated effective antimalarial activities.[2,3] 1,2,4-Trioxane unit was recognized as the essential structure for high efficacy during the investigation of structure-activity relationships about the parent drug. We have designed a modified artemisinin derivative by the introduction of ketocarbonyl oxygen to the C(6) position shown in the partial structure (**2**) as a divergent scaffold for further structural derivation. Several methods for 1,2,4-trioxane framework construction have been reported,[4] for example, Roth reported the construction of 1,2,4-trioxane structure (**3**) from dehydrodecaline (**4**, artemisinic acid) by double oxidation using molecular oxygen.[4a] Hence, we



artemisinin (**1**)



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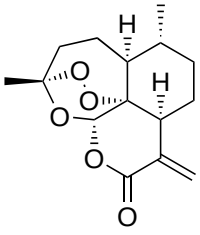

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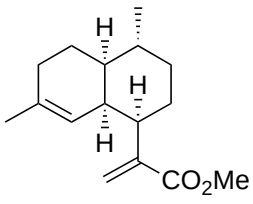


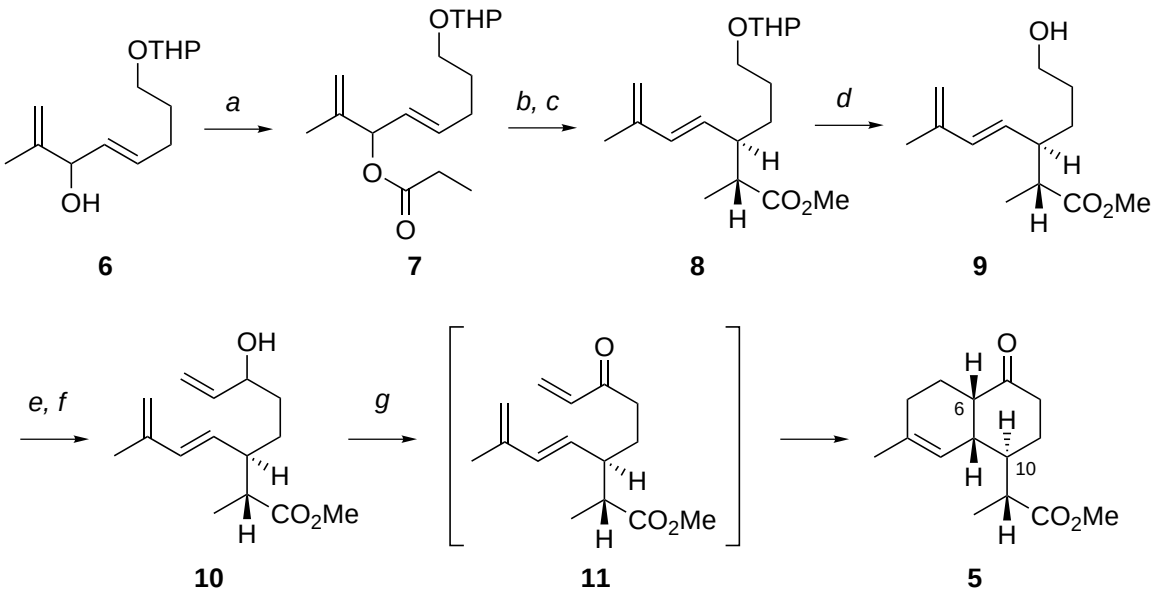
artemisinic acid (**4**)

† Dedicated to Professor Sho Ito on the occasion of his 77th Birthday.

planned that the analogue (**2**) might be synthesized from the corresponding octalone by utilizing Roth's method. In this communication, we report the synthesis and antimalarial evaluation of a new class of artemisinin analogue.[5]

Octalone (**5**) was synthesized as shown in Scheme 1, by an alternative method to that reported by Parker.[6] Thus, the known bis-allylic alcohol (**6**)[6] was acylated with propionyl chloride to give ester (**7**) in 86% yield. Treatment of **7** with LDA in the presence of TMSCl at low temperature promoted regio- and stereoselective Ireland-Claisen rearrangement.[7] After its esterification with CH_2N_2, diene (**8**) having (*l*, *E*) configuration was preferentially obtained in 72% yield (2 steps). The excellent regio- and stereoselectivity could be explained by the formation of *Z*-enolate from **7** which is in agreement with Parker's previous results. THP group of **8** was deprotected in MeOH containing a catalytic amount of *p*-toluenesulfonic acid to provide alcohol (**9**) in 94% yield. Oxidation of **9** with PDC, followed by the addition of vinylmagnesium bromide, afforded triene (**10**) in 65% yield for 2 steps. The construction of *cis*-octalone (**5**) was accomplished by Dess–Martin oxidation of **10**, followed by the subsequent spontaneous Diels–Alder reaction of the corresponding intermediate (**11**). Compound (**5**) was obtained in 78% yield as a sole diastereomer, whose configuration was confirmed by the NOESY spectrum. The diastereoselectivity was very high as expected from the previous results.[7,8]

Scheme 1



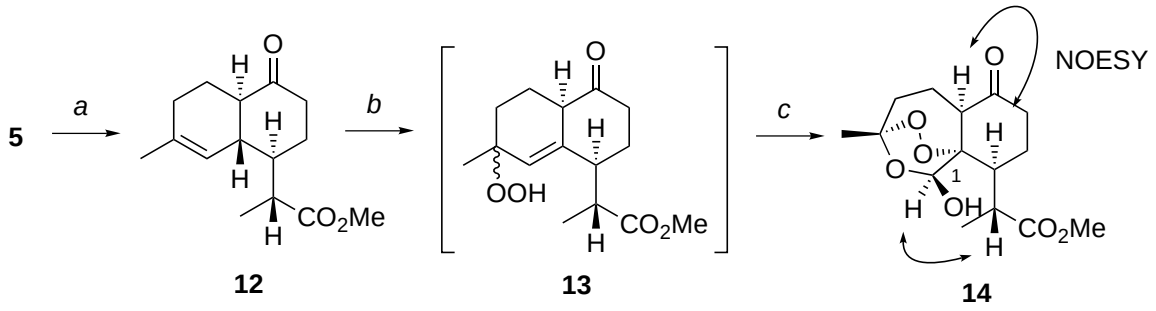
(*a*) C_2H_5COCl, pyridine, rt; (*b*) LDA, –78 °C; TMSCl, to rt; (*c*) CH_2N_2, rt; (*d*) TsOH, H_2O, rt; (*e*) PDC, molecular sieves 4Å, rt; (*f*) CH_2=CHMgBr, –78 °C; (*g*) Dess-Martin reagent, rt

Although the oxidation of **5** was investigated under several conditions analogous to Roth's method,[4a] no 1,2,4-trioxane was obtained. We suspected that the lack of reactivity was due to the relative *trans*-configuration between C(6) and C(10) of **5**, whereas Roth's **4** has *cis* stereochemistry. That is, 1,2,4-trioxane would be obtained from *trans*-octalone (**12**).

Treatment of **5** with sodium hydride in THF led to a mixture of ketones (**5**) and (**12**) in a ratio of approximately 55 : 45. Exposure of the epimerized ketone mixture under Roth's conditions gave *endo*-

peroxy compound (**14**) in 5% yield based on **5**. Namely, **12** was irradiated with 100W tungsten lump in acetone containing catalytic amount of methylene blue under O_2 current to produce tertiary hydroperoxide (**13**) *in situ*. Treatment of crude **13** with a catalytic amount of trifluoroacetic acid and atmospheric oxygen afforded **14**.[9] The ^{1}H NMR spectrum exhibited characteristic singlet (5.80 ppm), which corresponds to acetal hydrogen attached to C(1). The IR spectrum indicated the existence of hydroxyl function (3500–3200 cm^{-1}) and peroxy ether (1160 cm^{-1}). The structure of **14** was firmly determined by the 2D NMR technique. Due to the intramolecular hydrogen bonding, β-hydroxyl group would be thermodynamically favorable. Consequently, the lactonization could not occur although artemisinin analogues generally undergo lactonization.

Scheme 2



(*a*) NaH, rt; (b) O_2, methylene blue, *h*ν, 0 °C; (c) CF_3CO_2H, O_2, rt

Antimalarial effectiveness of 1,2,4-trioxane (**14**) and synthetic intermediate (**12**) against *P. falciparum* was investigated *in vitro* (Table 1).[10] Compound (**14**) possesses a remarkable antimalarial activity, IC_{50} = 3.9 x 10^{-8} (M), comparable to natural artemisinin (**1**). Notably, the selective toxicity is quite high (>1,000). On the contrary, **12** having no trioxane structure showed much weaker activity than **14**.

Table 1 *In Vitro* Antimalarial Activities and Cytotoxicities

compound	IC_{50} (M) *P. falciparum*[a]	IC_{50} (M) FM3A cell[b]	selective toxicity[c]
(±)-**14**	3.9 x 10^{-8}	2.4 x 10^{-5} [d]	>1,000
(±)-**12**	5.8 x 10^{-5} [e]	—	—
(+)-artemisinin (**1**)	7.9 x 10^{-9}	1.0 x 10^{-5}	1,300

[a] Chloroquine sensitive strain (FCR-3). [b] Mouse mammary tumor FM3A cells representing a model of host. [c] Selective toxicity = IC_{50} value for FM3A / IC_{50} for *P.falciparum*. [d] IC_{22} value (78% Growth of FM3A cells was observed.) [e] IC_{22} value (78% Growth of *P. falciparum* was observed.)

In summary, a new class of artemisinin analogue having a keto carbonyl group at the C(6) position was synthesized and evaluated for the antimalarial activity. Its promising activity suggests a possibility of a lead compound for antimalarial agent. Further modification of analogue and the optimization of its synthetic strategy are now in progress.

ACKNOWLEDGEMENT

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