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Antimalarial activities of (+)-deoxoartemisitene and its novel C-11, 13 derivatives

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Abstract—(+)-Deoxoartemisitene and its C-11, 13 derivatives were synthesized from artemisinic acid via a short and regiospecific process and several derivatives show 10–20 times more in vitro antimalarial activities against *Plasmodium falciparum* than artemisinin.
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Artemisinin **1**, a sesquiterpene lactone endoperoxide isolated from *Artemisia annua,* and its derivatives have been important as antimalarial drugs with the most effective activity against multi drug resistant forms of *Plasmodium falciparum*.[1] To overcome low solubility, instability in simulated stomach acidic condition, and recently appearing neurotoxicity of artemisinin and its C-12 acetal derivatives such as arteether, artemether, and artelinic acid, we prepared deoxoartemisinin **2**[2] and its C-12 derivatives with non-acetal at C-12.[3] Most efforts have been focused in derivatization at C-12 position of artemisinin. Although some C-13 derivatives of artemisinin were prepared by 1,4-conjugated addition[4] from artemisitene **3** and artemisinic acid **4** and show an effective antimalarial activity, these compounds are still acctal-type at the C-12 position, which are potentially neurotoxic and acid unstable. Deoxoartemisitene **5**, deoxoartemisitone **6** and its C-11, 13 derivatives have non-acetal at C-12, which may overcome acid instability and neurotoxicity. Synthesis of deoxoartemisitene and its derivatives and their structure–antimalarial activity relationship are unknown. In this letter, we report synthesis and the first antimalarial activities of (+)-deoxoartemisitene **5** and its novel C-11 and 13 derivatives including the C-13 ether dimer along with its synthesis (Fig. 1).

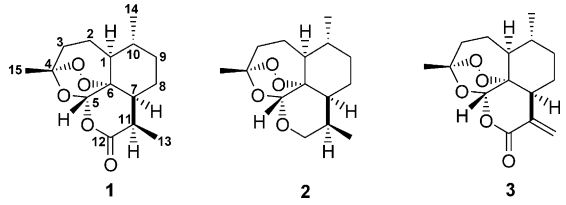

Figure 1.

We utilized photooxidatice cyclization of more abundant artemisinic acid **4**, a useful chiral synthon as a key step to prepare deoxoartemisitene **5**, a versatile starting material for the synthesis of a series of novel C-11, 12 analogues. Thus, reduction of artemisinic acid **4** with DIBAL-H, followed by chiral photooxidative cyclization[2a,5] afforded (+)-deoxoartemisitene **5** in 65% yield. Derivatization at C-13 of deoxoartemisitene could produce a number of novel analogues while maintaining increased stability due to the absence of C–O bond at C-12.[1c] Ozonization of **5** in CH_2Cl_2, −78 °C cleanly gave (+)-deoxoartemisitone **6**[6] in 95% yield. Epoxidation of 5 with *m*-CPBA and $NaHCO_3$ gave 11*S*-(spiroepoxy)-deoxoartemisinin **8** in 81% yield. Compounds **5** and **6** are used as versatile starting material for the preparation of a variety of C-11 derivatives **7**–**14** of deoxoartemisinin by previously known methods.[5] During the derivatization, no destruction of the biologically essential endoperoxide of the deoxoartemisitene was occurred. The right ring opening of the major epoxide, **8** with triethylsilane gave the primary alcohol, **9b** (yield 72%)

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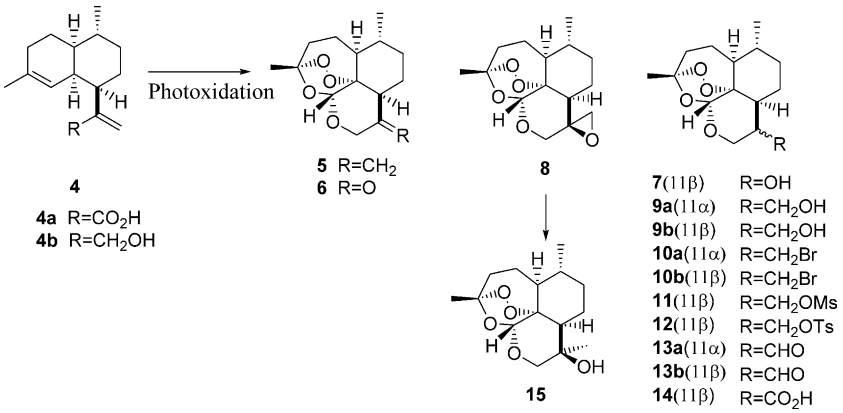
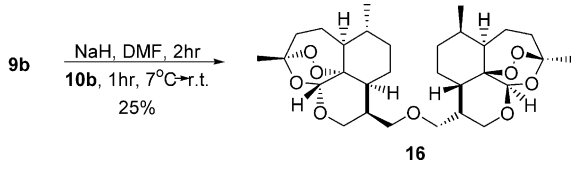


Scheme 1.

and with DIBAL-H gave the tertiary alcohol, **15** (yield 90%) both in the presence of $BF_3{\cdot}Et_2O$, respectively. We suggest the bulkiness of the reducing agents affects the direction of the epoxide ring opening of **8**. The triethylsilane reduction represents a new method for the epoxide opening to afford a primary alcohol. The absolute configuration of 11*R*-hydroxydeoxoartemisinin **15** was unambiguously confirmed by NOSEY technique as shown in Scheme 1. Coupling of **9b** with **10b** in the presence of NaH (DMF, 2 h, 7 °C, then 1 h, rt) afforded the C-13 ether dimer **16**[6] in 45% yield (Scheme 2).

The antimalarial activity (IC_{50} values) of deoxoartemisitene and its related derivatives was determined in vitro against the chloroquine-sensitive 3D7 strain[7] and the chloroquine-resistant K1 strain[8] of *P. falciparum* by Desjardins measurement[9,10] and presented in Table 1. Standard drugs were artemisinin and chloroquine disphosphate. Deoxoartemisitene **5**, deoxoartemisitone **6** and most C-11, 13 derivatives exhibit less antimalarial activity than artemisinin while **10b** show a comparable antimalarial activity to that of artemisinin. It is noteworthy that electron withdrawing group at C-13 induces a dramatic decrease of the antimalarial activity as seen in compounds **13a**,**b**, and **14**. However, **9b** and **10a** show 10–20 times more in vitro antimalarial activities than artemisinin, respectively and comparable activity to that of artesunate and arteether. The stereochemistry of hydroxymethyl group at C-11 of compound **9** should be in β-configuration to maintain high activity. C-13 ether dimer **16** of deoxoartemisinin is inactive in sharp contrast to several C-12 acetal-type dimers.[11] This structure–activity relationship (SAR) may play an useful role for antimalarial drug design.



Scheme 2.

Table 1. In vitro antimalarial activities [IC_{50}(ng/mL)] against two clones of *Plasmodium falciparum*

Compd	3D7[a]	K1[b]	Compd	3D7[a]	K1[b]
5	20	20	**13a**	2020	460
6	20	6	**13b**	120	3010
8	30	10	**14**	1090	650
9a	60	50	**15**	70	50
9b	<0.1	0.6	**16**	40	20
10a	0.2	<0.1	Artemisinin, **1**	10	2
10b	10	3	Artesunate	0.2	0.6
11	90	60	Arteether	<0.1	<0.1
12	300	50	Chloroquine	8	220

[a] Chloroquine-sensitive clone.
[b] Chloroquine-resistant clone.

In summary, non acetal-type C-13 derivatives of deoxoartemisinin, **9b** and **10a** are advocating much interest as new antimalarial drug candidates and the in vivo antimalarial test results of **9b** with its increased water-solubility (3.1 mg/mL) and **10a** will be reported in due course.

Acknowledgements

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6. Selected spectroscopic data for compound **5**: mp 95 °C δ_H ($CDCl_3$, 250 MHz) 5.34 (1H, s), 4.98 (1H,s), 4.90 (1H, s), 4.41 (1H, d, $J=13$ Hz, 12-CH), 4.28 (1H, d, $J=13$ Hz, 12-CH), 2.39–2.21 (2H, m), 1.41 (3H, s), 0.98 (3H, d, $J=6.1$ Hz); IR (KBr, cm^{-1}) 3026, 2933, 2881, 1788, 1736, 1466, 1387, 1229, 1117, 1021, 768; Mass (EI) m/z 266 (M^+); $[\alpha]_D^{25}=+10.3°$ (c 0.123, $CHCl_3$). For **9b**: mp 136 °C δ_H ($CDCl_3$, 250 MHz,) 5.20 (1H, s), 4.00 (1H, dd, $J=3.8$, 11.6 Hz, 12-CH), 3.53 (1H, t, $J=11.6$ Hz, 12-CH), 3.47 (2H, m, 13-CH_2), 2.71 (1H, m), 2.50 (1H, bs), 2.36 (1H, ddd, $J=3.9$, 3.3, 3.9 Hz), 1.40 (3H, s), 0.95 (3H, d, $J=5.90$ Hz); LC-Mass (ESI) m/z 284 (M^+); $[\alpha]_D^{25}=+103.2°$ (c 0.12, $CHCl_3$). For **10a**: δ_H ($CDCl_3$, 250 MHz,) 5.14 (1H, s), 4.12 (1H, d, $J=12.3$ Hz, 12-CH), 4.00 (1H, d, $J=9.7$ Hz, 12-CH), 3.67–3.59 (2H, q, $J=5.4$ Hz, 13-CH_2), 1.52–1.44 (1H, m), 1.40 (3H, s), 0.95 (3H, d, $J=5.8$ Hz); IR (neat, cm^{-1}) 3407, 2933, 2874, 1604, 1453, 1380, 1104, 1051; 1025; LC-Mass (ESI) m/z 349 (M^+); $[\alpha]_D^{25}=+15.3°$ (c 0.21, $CHCl_3$). For 15: δ_H ($CDCl_3$, 250 MHz), 5.22 (1H, s), 3.72 (1H, d, $J=11.6$ Hz, 12-CH), 3.64 (1H, d, $J=11.6$ Hz, 12-CH), 2.38–2.25 (1H, m), 1.57 (3H, s), 1.40 (3H, s), 0.95 (3H, d, $J=5.95$ Hz); $[\alpha]_D^{25}=+107.1°$ (c 0.154, $CHCl_3$). For **16**: mp 120–122 °C. δ_H ($CDCl_3$, 250 MHz), 5.21 (2H, s), 4.01–3.81 (6H, m), 3.56 (2H, t, $J=11.6$ Hz), 2.91–2.79 (2H, m), 2.43–2.31 (4H, m), 1.42 (6H, s), 0.97 (6H, d, $J=5.95$ Hz); IR (KBr, cm^{-1}) 3407, 2927, 2854, 1742, 1459, 1380, 1235, 1104, 755; LC-Mass (ESI) m/z 550 (M^+); $[\alpha]_D^{25}=+65.7°$ (c 0.14, $CHCl_3$).
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