



Pergamon

## Synthesis and Cytotoxicity of Dihydroartemisinin Ethers Containing Cyanoarylmethyl Group

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**Abstract**—A new type of ether of dihydroartemisinin containing cyano and aryl groups was prepared and tested for cytotoxicity to A549, P388, L1210 and HT29 cells using the MTT assay. **12k** and **12l** were the most cytotoxic compounds. **13** lacking the peroxy group showed a 1000-fold less potency than **12l**. Similarly, the inactive compound **14** indicated that the position of cyano groups was also important. Flow cytometry data showed that the compounds caused an accumulation of P388 cells in the G<sub>1</sub>-phase of the cell cycle.  
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### Introduction

Traditional Chinese medicine Qinghao (*Artemisia annua* L.) was recorded as a versatile remedy for malaria, dermatitis and other diseases in many Chinese ancient medical books. Based on these clinical experiences, Chinese scientists have developed artemisinin and its derivatives (artemisinin **1**, dihydroartemisinin **2**, artemether **3a** and artesunate **3b**) as a totally new type of antimalarial drugs since 1970s. Up to now, these drugs have been used in the clinic all over the world. Their quick onset, powerful effect and good toleration may be attributed to the 1,2,4-trioxane moieties in their molecules. A number of researchers have been focusing their attention on other components of the plant, artemisinin derivatives/analogues and their bioactivities.<sup>1</sup> More than 20 research papers reporting the cytotoxicity of artemisinin family were recently published.<sup>2–21</sup>

Some natural components of *A. annua* (such as artemisinin, arteannuin-B **4**, artemisinic acid **5**, artemisitene **6**,

flavones and other terpenoids) showed cytotoxic properties at varying concentrations against L 1210, P 388, A 549, HT 29, MCF 7 and KB in vitro.<sup>2,4,9</sup>

Artemisinin and related compounds were tested against Ehrlich Ascites tumour cells, on which artemisinin, artemether, arteether and artesunate exhibited moderate cytotoxicity (IC<sub>50</sub> 12.2–29.8 μM), artemisitene **6** was slightly more active (IC<sub>50</sub> 6.8 μM), and a dimer of dihydroartemisinin **7a** was the most potent (IC<sub>50</sub> 1.4 μM). It was found the nonsymmetric dimer **7a** was more cytotoxic than the symmetric dimer **7b** due to their slight different stereochemistry.<sup>5–7</sup> Other artemisinin dimers, trimers and tetramers and their cytotoxicities were reported recently.<sup>8</sup>

The antitumor effect of artesunate was tested in vitro and in vivo in China.<sup>10–12</sup> It was shown to be cytotoxic for six cell lines (IC<sub>50</sub> 1~100 μg/mL) and displayed antitumor effects on human nasopharyngeal cancer (CNE2, SUNE-1) and human liver cancer (BEL-7402) grafted in nude mice. Recently artesunate has been analyzed for its antitumor activity against 55 cell lines.<sup>13</sup> Leukemia and colon cancer cell lines were the most sensitive lines, and no cross resistance against CEM leukemia sub-lines

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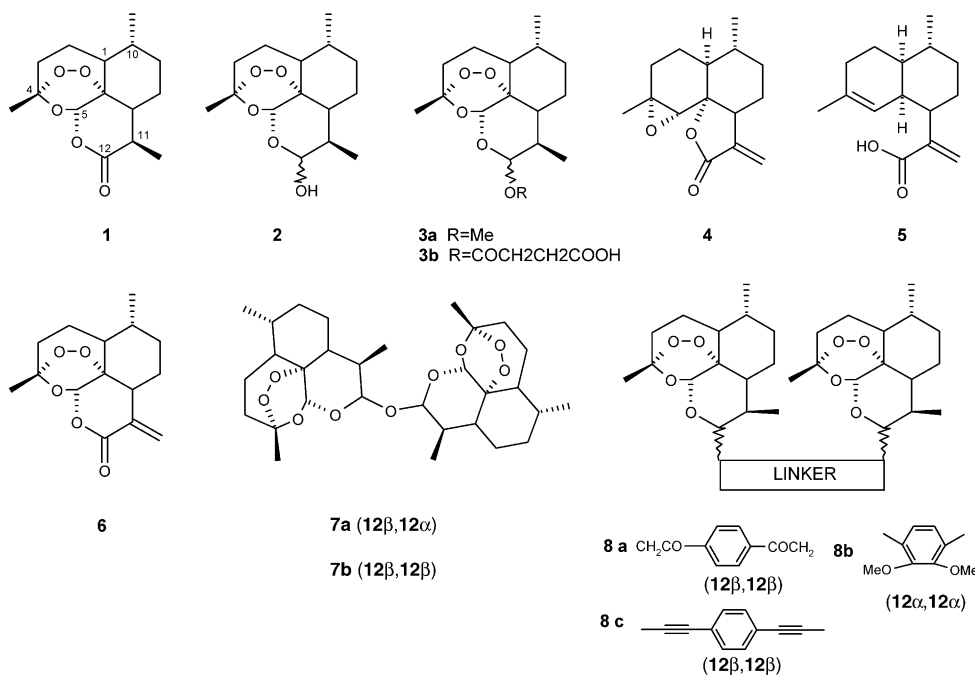


Chart 1.

which are resistant to either doxorubicin, vincristine, methotrexate or hydroxyurea were observed.

Lai's group found that dihydroartemisinin can selectively kill cancer cells in presence of holotransferrin which can increase intracellular iron concentrations, whereas normal breast cells (HTB 125) and lymphocytes were not affected under the same condition. It seems that the mechanisms underlying both antitumor and antimalarial properties are similar.<sup>14–16</sup>

Posner's group found some new artemisinin derivatives and trioxane dimers which had antimalarial, anti-proliferative and antitumor activities. Dimer **8a**, **8b**, **8c** were especially potent and selective at inhibiting growth of some human cancer cell lines, and **8a** was evaluated in vivo assay (Chart 1).<sup>17,18</sup>

In order to search for new artemisinin derivatives with more potent antimalarial and antitumor activity, we synthesized compounds **9**, **10** and investigated their

pharmacological properties. They showed lower anti-malarial activity than artemether but stronger anti-tumor activity in vitro. The most active compound was **10** (R = *p*-COOCH<sub>3</sub>, IC<sub>50</sub> = 1.91, 0.33, 0.02 μM against KB, HCT-8, A 2780 cell lines, respectively).<sup>19,20</sup> Thereafter, we noted that artemisinin derivatives **11** and **12a** were so quite different in their antitumor activity. **12a** with a phenyl group was much more active than **11**. This finding led us to explore the structure–activity relationship of this kind of derivatives. Herein we report synthesis and preliminary biological evaluation of **12** and related compounds (Charts 2 and 3). The brief report has been published in 2001.

## Results and Discussion

### Chemistry

In the presence of an acidic catalyst, dihydroartemisinin reacted with corresponding cyanohydrin to

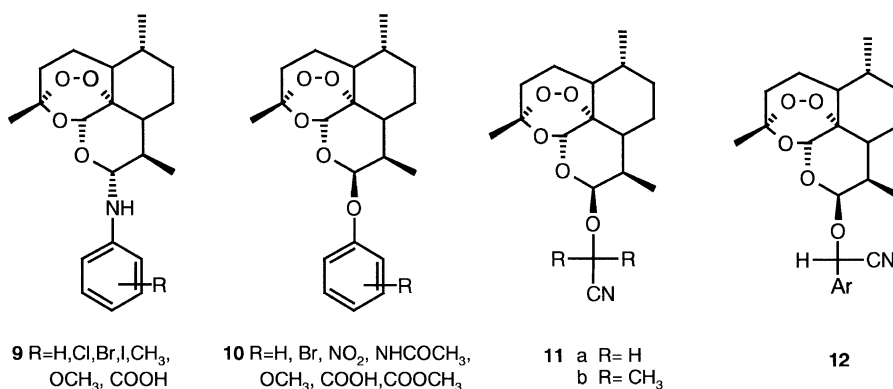


Chart 2.

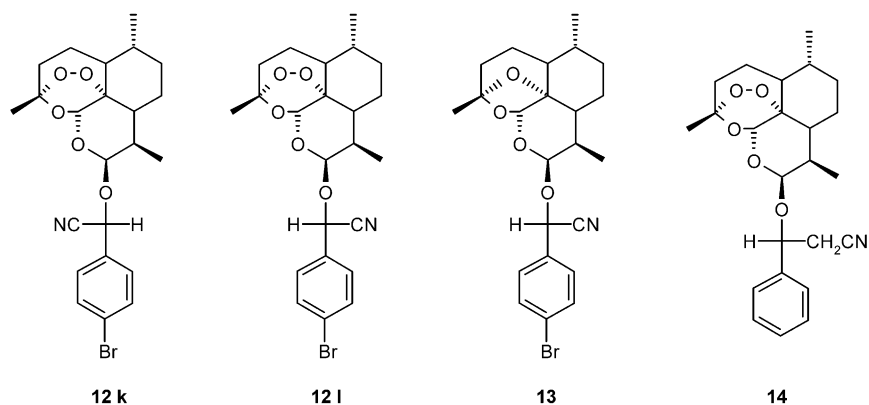


Chart 3.

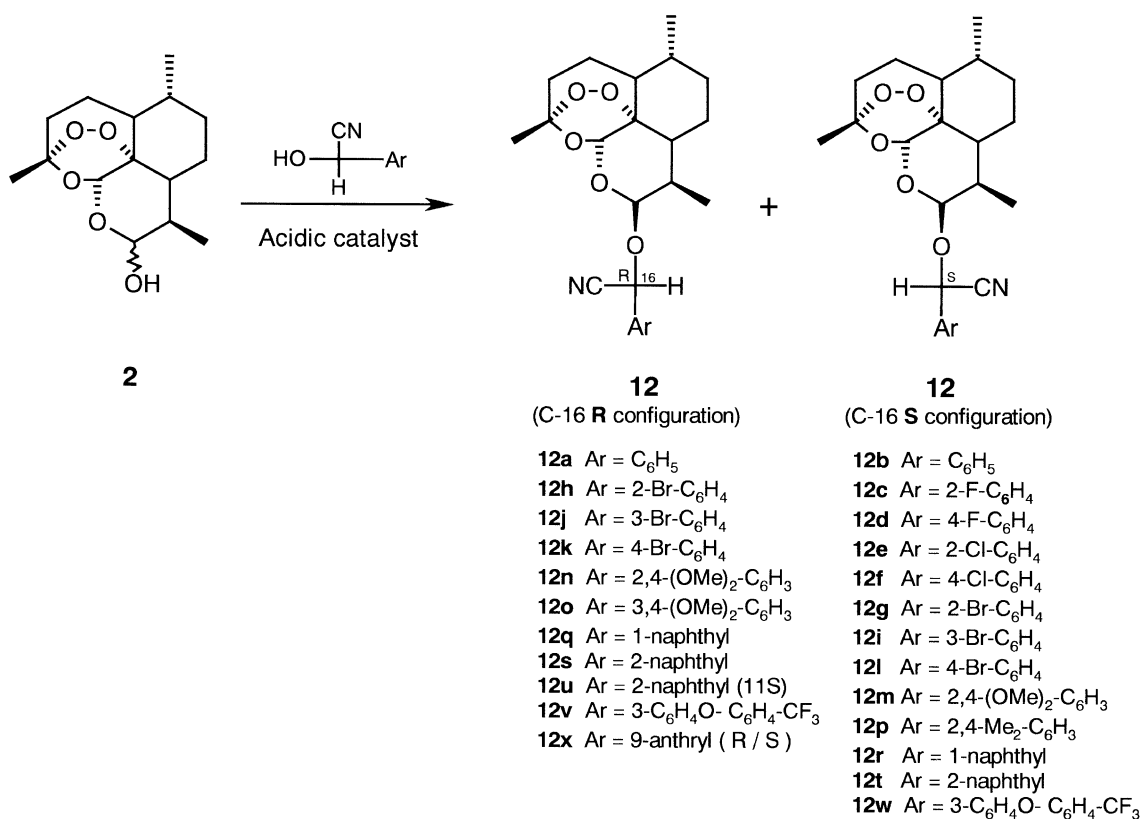
give **12**(16-*R* and 16-*S*) in moderate yield. Generally, the pair of isomers could be separated by careful column chromatography. They are 12- $\beta$  ethers as indicated by the small coupling constants ( $J \sim 3.5$  Hz) between 11-H and 12-H in their  $^1\text{H}$  NMR.<sup>22</sup> The *R* configuration of C-16 of **12k** was established by X-ray diffraction.<sup>21</sup> In the  $^1\text{H}$  NMR spectra of **12k** and **12l**, the values of chemical shifts of C-12 and C-16 were distinguishable (for **12k** 5.22, 5.25; for **12l**, 4.79, 5.46 respectively). Taking these data as a criterion, the stereochemistry of other isomers could be deduced. When dihydroartemisinin reacted with  $\alpha$ -hydroxy-2-naphthyl-acetonitrile, three compound were yielded, normal products **12s**, **12t** and byproduct **12u**, in which the signal due to 11 $\alpha$ -methyl group appeared downfield ( $\delta$

1.30) as compared with that of the 11 $\beta$ -methyl group in **12s** ( $\delta$  1.04) and in **12t** ( $\delta$  0.96) in their  $^1\text{H}$  NMR spectra (Scheme 1).<sup>23</sup>

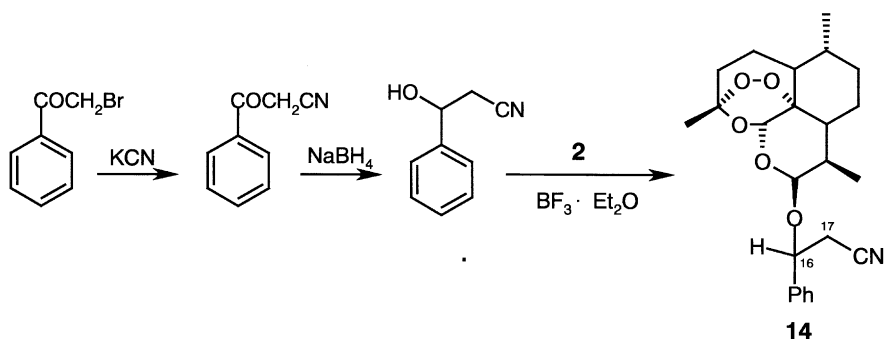
In order to examine the role of peroxy group and cyano group, we synthesized compound **13** and **14**. **13** was derived from **12l** by reduction with zinc powder in acetic acid<sup>21</sup> and **14** was prepared by condensation of dihydroartemisinin and 3-hydroxy-3-phenyl-propionitrile (Scheme 2).

### Biological results

Cytotoxicity and effect on the cell cycle distribution were measured according to the procedures described



Scheme 1.



Scheme 2.

previously.<sup>21</sup> VCR was used as a reference compound with  $IC_{50}$  values of 18 and 2 nM for A549 and P388 cells, respectively. Table 1 showed compound **12** to be cytotoxic against L1210, A549, P388 and HT29 cells. At the concentration of 25–500 nM, they induced a  $G_1$  accumulation in L1210 cells and apoptosis in P388 cells (see Table 1).

### Conclusion

From these data, the following conclusion in terms of structure–activity relationship can be drawn:

1. Compound **12** was more toxic against A549, P388, L1210 cells than HT29 cells.
2. Among the compound **12** series, **12g**, **12h**, **12i**, **12j**, **12k**, and **12l** bearing Br substituent on the phenyl ring were more active than others. **12k** and **12l** were the most active and their  $IC_{50}$  could be comparable to that of VCR, a very potent cytotoxic agent.
3. From Table 1 (**12k** vs **12l**, **12m** vs **12n**, **12s** vs **12t**,

**12v** vs **12w**), it can be seen that the configuration of C-16 had non-significant effect on the cytotoxicity, cell cycle and apoptosis.

4. Compound **12l** was 1000-fold more cytotoxic than **13**. The peroxy group is clearly essential for cytotoxicity.<sup>4,6</sup>
5. Compound **14** was devoid of effect on cell proliferation. This lack of cytotoxicity suggested that the cyanohydrin moiety must be present in the molecule. The activity of compound **12** may be due partly to its degradation products arylcyanohydrin. So far as we know, mandelonitrile glucosides having some similarity with the chemical structure of compound **12** were studied in cancer research and cancer therapy.<sup>24</sup>

### Experimental

Melting points were taken in open capillary on BUCHI-510 melting point apparatus and were uncorrected. The

Table 1. Inhibition of cell proliferation, perturbation of the cell cycle and induction of apoptosis by compounds **12**, **13**

| No.        | $IC_{50}$ (nM) |          |          |        | Cell-cycle effect L1210<br>% $G_1$ (nM) | Cell-cycle apoptosis P388 |             |        |
|------------|----------------|----------|----------|--------|-----------------------------------------|---------------------------|-------------|--------|
|            | L1210          | A549     | P388     | HT29   |                                         | % $G_1$                   | % apoptosis | nM     |
| <b>11</b>  |                | 79,432   | 1855     |        |                                         | 65                        | 7           | 10,000 |
| <b>12a</b> | 113            | 1227     | 238      | 4095   | 69 (400)                                | 67                        | 53          | 500    |
| <b>12b</b> | 34             | 662      | 48       | 2213   |                                         | 61                        | 45          | 100    |
| <b>12c</b> | 38             | 364      | 43       | 447    |                                         | 72                        | 43          | 200    |
| <b>12d</b> | 41             | 306      | 77       | 1471   |                                         | 71                        | 51          | 250    |
| <b>12e</b> | 470            | 10,600   | 290      | 16,200 | 68 (1000)                               |                           |             |        |
| <b>12f</b> | 620            | 8800     | 440      | 7400   | 67 (2500)                               |                           |             |        |
| <b>12g</b> | 27             | 193      | 28       | 9638   |                                         | 70                        | 46          | 100    |
| <b>12h</b> | 150            | 741      | 92       | 809    | 71 (500)                                |                           |             |        |
| <b>12i</b> | 19             | 85       | 20       | 7788   |                                         | 72                        | 58          | 100    |
| <b>12j</b> | 151            | 437      | 108      | 748    | 68 (500)                                |                           |             |        |
| <b>12k</b> | 15             | 47       | 12       | 179    |                                         | 62                        | 49          | 25     |
| <b>12l</b> | 10             | 39       | 11       | 490    |                                         | 63                        | 51          | 25     |
| <b>12m</b> |                |          | 105      |        |                                         | 68                        | 20          | 500    |
| <b>12n</b> |                |          | 152      |        |                                         | 68                        | 16          | 500    |
| <b>12o</b> | 17             | 221      | 13       | 1923   |                                         | 64                        | 49          | 50     |
| <b>12p</b> |                |          | 84       |        |                                         | 71                        | 28          | 500    |
| <b>12s</b> |                |          | 70       |        |                                         | 70                        | 24          | 250    |
| <b>12t</b> |                |          | 76       |        |                                         | 71                        | 26          | 250    |
| <b>12v</b> | 76             | 172      | 61       | 441    | 68 (250)                                | 70                        | ND          | 250    |
| <b>12w</b> | 67             | 140      | 45       | 414    | 67 (250)                                | 69                        | ND          | 250    |
| <b>12x</b> |                |          | 71       |        |                                         | 70                        | 28          | 250    |
| <b>13</b>  |                | 41,990   | 24,200   |        |                                         |                           |             |        |
| <b>14</b>  |                | Inactive | Inactive |        |                                         |                           |             |        |
| Control    |                |          |          |        |                                         | 42                        | 4           |        |

IR spectra were run on a Perkin-Elmer 599B spectrophotometer.  $^1\text{H}$  NMR spectra were determined in  $\text{CDCl}_3$  solution on a NMR Bruker AM-400. Elemental analyses were performed on a CE 1106 elemental analyser and all the results were within 0.4% of the theoretical values.

**General procedure: synthesis of cyano-aryl-methyl 12 $\beta$ -deoxoartemisiny ether (12)**

To a dichloromethane solution of dihydroartemisinin (1.42 g, 5 mmol) and a 1.5 to 2-fold excess of a cyano-hydrin fresh prepared from arylaldehyde at 0 to  $-20^\circ\text{C}$  was added trimethylsilyl trifluoromethanesulfonate or boron trifluoride etherate (0.05–0.1 mL). The resulting mixture was stirred at room temperature for 24 h, and then washed with aqueous sodium bicarbonate and brine. The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give the crude products. Pure 12(16-*R*) and 12(16-*S*) were obtained by column chromatography (silica gel) using petroleum ether–ethyl acetate (100: 3~5 v/v) as eluent.

**(16-*R*) Cyano-phenyl-methyl 12 $\beta$ -deoxoartemisiny ether (12a) and (16-*S*) cyano-phenyl-methyl 12 $\beta$ -deoxoartemisiny ether (12b).** 12a: white crystal, mp  $135\text{--}137^\circ\text{C}$  (from ethyl ether), yield 22%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.44 (5H, m, aromatic-H); 5.68 (1H, s, 5-H); 5.28 (1H, s, 16-H); 5.24 (1H, d,  $J=3.6$  Hz, 12-H); 1.43 (3H, s, 4- $\text{CH}_3$ ); 1.01 (3H, d,  $J=7.3$  Hz, 11- $\text{CH}_3$ ), 0.87 (3H, d,  $J=6.0$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1458, 1375, 1103, 1011, 875, 700. Anal. calcd for  $\text{C}_{23}\text{H}_{29}\text{NO}_5$ : C 69.15, H 7.32, N 3.51; found: C 68.86, H 7.53, N 3.33.

12b: white crystal, mp  $98\text{--}100^\circ\text{C}$  (from ethyl ether), yield 15%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.42 (5H, m, aromatic-H); 5.60 (1H, s, 5-H); 5.50 (1H, s, 16-H); 4.81 (1H, d,  $J=3.5$  Hz, 12-H); 1.44 (3H, s, 4- $\text{CH}_3$ ); 0.95 (3H, d,  $J=6.6$  Hz, 11- $\text{CH}_3$ ), 0.84 (3H, d,  $J=7.5$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1452, 1377, 1192, 1101, 878, 743. Anal. calcd for  $\text{C}_{23}\text{H}_{29}\text{NO}_5$ : C 69.15, H 7.32, N 3.51; found: C 68.85, H 7.42, N 3.18.

**(16-*S*) Cyano-(*o*-fluoro-phenyl)-methyl 12 $\beta$ -deoxoartemisiny ether (12c).** 12c: white crystal, mp  $147\text{--}148^\circ\text{C}$  (from ethyl acetate–petroleum ether), yield 29%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.53 (1H, t,  $J=7.6$  Hz, aromatic-H); 7.38 (1H, m, aromatic-H); 7.19 (1H, t,  $J=7.3$  Hz, aromatic-H); 7.09 (1H, t,  $J=9.5$  Hz, aromatic-H); 5.70 (1H, s, 5-H); 5.61 (1H, s, 16-H); 4.90 (1H, d,  $J=3.5$  Hz, 12-H); 1.38 (3H, s, 4- $\text{CH}_3$ ); 0.85 (3H, d,  $J=6.4$  Hz, 11- $\text{CH}_3$ ); 0.81 (3H, d,  $J=7.5$  Hz, 10- $\text{CH}_3$ ). Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{FNO}_5$ : C 66.17, H 6.76, N 3.36; found: C 66.07, H 6.78, N 3.35.

**(16-*S*) Cyano-(*p*-fluoro-phenyl)-methyl 12 $\beta$ -deoxoartemisiny ether (12d).** 12d: white crystal, mp  $146\text{--}147^\circ\text{C}$  (from ethyl acetate–petroleum ether), yield 24%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.43 (1H, d,  $J=8.6$  Hz, aromatic-H); 7.42 (1H, d,  $J=8.6$  Hz, aromatic-H); 7.09 (1H, t,  $J=8.6$  Hz, aromatic-H); 7.08 (1H, t,  $J=8.5$  Hz, aromatic-H); 5.57 (1H, s, 5-H); 5.47 (1H, s, 16-H); 4.78 (1H, d,  $J=3.5$  Hz, 12-H); 1.41 (3H, s, 4- $\text{CH}_3$ ); 0.88

(3H, d,  $J=6.7$  Hz, 11- $\text{CH}_3$ ); 0.82 (3H, d,  $J=7.5$  Hz, 10- $\text{CH}_3$ ). Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{FNO}_5$ : C 66.17, H 6.76, N 3.36; found: C 66.16, H 6.74, N 3.33.

**(16-*S*) Cyano-(*o*-chloro-phenyl)-methyl 12 $\beta$ -deoxoartemisiny ether (12e).** 12e: white crystal, mp  $118\text{--}120^\circ\text{C}$  (from ethyl acetate–petroleum ether), yield 27%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.63 (1H, m, aromatic-H); 7.42 (1H, m, aromatic-H); 7.36 (2H, m, aromatic-H); 5.76 (1H, s, 5-H); 5.66 (1H, s, 16-H); 5.01 (1H, d,  $J=3.5$  Hz, 12-H); 1.45 (3H, s, 4- $\text{CH}_3$ ); 0.96 (3H, d,  $J=6.4$  Hz, 11- $\text{CH}_3$ ); 0.88 (3H, d,  $J=7.2$  Hz, 10- $\text{CH}_3$ ). Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{ClNO}_5$ : C 63.66, H 6.50, N 3.23; found: C 63.42, H 6.29, N 3.08.

**(16-*S*) Cyano-(*p*-chloro-phenyl)-methyl 12 $\beta$ -deoxoartemisiny ether (12f).** 12f: white crystal, mp  $126\text{--}128^\circ\text{C}$  (from ethyl acetate–petroleum ether), yield 39%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.51 (2H, d,  $J=8.5$  Hz, aromatic-H); 7.24 (2H, d,  $J=8.5$  Hz, aromatic-H); 5.57 (1H, s, 5-H); 5.46 (1H, s, 16-H); 4.78 (1H, d,  $J=3.5$  Hz, 12-H); 1.42 (3H, s, 4- $\text{CH}_3$ ); 0.98 (3H, d,  $J=6.5$  Hz, 11- $\text{CH}_3$ ); 0.81 (3H, d,  $J=7.4$  Hz, 10- $\text{CH}_3$ ). Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{ClNO}_5$ : C 63.66, H 6.50, N 3.23; found: C 63.47, H 6.37, N 3.11.

**(16-*S*) Cyano-(*o*-bromo-phenyl)-methyl 12 $\beta$ -deoxoartemisiny ether (12g).** 12g: white needle crystal, mp  $128\text{--}129^\circ\text{C}$  (from ethyl acetate–petroleum ether), yield 18%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.65 (1H, d,  $J=7.5$  Hz, aromatic-H); 7.63 (1H, d,  $J=7.8$  Hz, aromatic-H); 7.39 (1H, t,  $J=7.5$  Hz, aromatic-H); 7.25 (1H, t,  $J=7.8$  Hz, aromatic-H); 5.73 (1H, s, 5-H); 5.66 (1H, s, 16-H); 5.04 (1H, d,  $J=3.5$  Hz, 12-H); 1.45 (3H, s, 4- $\text{CH}_3$ ); 0.96 (3H, d,  $J=6.7$  Hz, 11- $\text{CH}_3$ ); 0.89 (3H, d,  $J=7.5$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1571, 1470, 1446, 1377, 1194, 1101, 1032, 982, 931, 878. Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{BrNO}_5$ : C 57.75, H 5.90, N 2.93; found: C 57.89, H 5.92, N 2.99.

**(16-*R*) Cyano-(*o*-bromo-phenyl)-methyl 12 $\beta$ -deoxoartemisiny ether (12h).** 12h: amorphous, yield 20%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.66 (1H, d,  $J=7.8$  Hz, aromatic-H); 7.65 (1H, d,  $J=7.5$  Hz, aromatic-H); 7.41 (1H, d,  $J=8.0$  Hz, aromatic-H); 7.25 (1H, d,  $J=8.0$  Hz, aromatic-H); 5.99 (1H, s, 5-H); 5.43 (1H, s, 16-H); 5.30 (1H, d,  $J=3.7$  Hz, 12-H); 1.43 (3H, s, 4- $\text{CH}_3$ ); 1.01 (3H, d,  $J=5.6$  Hz, 11- $\text{CH}_3$ ); 0.89 (3H, d,  $J=5.8$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1471, 1448, 1375, 1446, 1194, 1101, 1009, 875. Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{BrNO}_5$ : C 57.75, H 5.90, N 2.93; found: C 57.84, H 5.83, N 2.82.

**(16-*S*) Cyano-(*m*-bromo-phenyl)-methyl 12 $\beta$ -deoxoartemisiny ether (12i).** 12i: white crystal, mp  $145\text{--}146^\circ\text{C}$  (from ethyl acetate–petroleum ether), yield 19%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.59 (1H, s, aromatic-H); 7.54 (1H, d,  $J=7.9$  Hz, aromatic-H); 7.38 (1H, d,  $J=7.8$  Hz, aromatic-H); 7.28 (1H, t,  $J=7.8$  Hz, aromatic-H); 5.58 (1H, s, 5-H); 5.47 (1H, s, 16-H); 4.81 (1H, d,  $J=3.5$  Hz, 12-H); 1.44 (3H, s, 4- $\text{CH}_3$ ); 0.96 (3H, d,  $J=6.4$  Hz, 11- $\text{CH}_3$ ); 0.87 (3H, d,  $J=7.2$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1576, 1473, 1433, 1379, 1194, 1101, 1036, 984, 957, 874. Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{BrNO}_5$ : C 57.75, H 5.90, N 2.93; found: C 57.79, H 5.90, N 2.99.

**(16-R) Cyano-(*o*-bromo-phenyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12j).** 12j: amorphous, yield 22%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.61 (1H, s, aromatic-H); 7.55 (1H, d,  $J=7.9$  Hz, aromatic-H); 7.39 (1H, d,  $J=7.8$  Hz, aromatic-H); 7.31 (1H, t,  $J=7.8$  Hz, aromatic-H); 5.64 (1H, s, 5-H); 5.26 (1H, s, 16-H); 5.23 (1H, d,  $J=3.7$  Hz, 12-H); 1.43 (3H, s, 4- $\text{CH}_3$ ); 1.01 (3H, d,  $J=7.5$  Hz, 11- $\text{CH}_3$ ); 0.90 (3H, d,  $J=6.0$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1574, 1475, 1377, 1446, 1194, 1103, 1013, 874. Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{BrNO}_5$ : C 57.75, H 5.90, N 2.93; found: C 57.94, H 5.92, N 2.92.

**(16-R) Cyano-(*p*-bromo-phenyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12k).** 12k: white crystal, mp 128–129 °C (from ethyl acetate–petroleum ether), yield 23%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.57 (2H, d,  $J=8.5$  Hz, aromatic-H); 7.33 (2H, d,  $J=8.5$  Hz, aromatic-H); 5.63 (1H, s, 5-H); 5.25 (1H, s, 16-H); 5.22 (1H, d,  $J=3.7$  Hz, 12-H); 1.43 (3H, s, 4- $\text{CH}_3$ ); 1.00 (3H, d,  $J=7.4$  Hz, 11- $\text{CH}_3$ ); 0.90 (3H, d,  $J=6.1$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1593, 1489, 1375, 1101, 1032, 1011, 955, 876. Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{BrNO}_5$ : C 57.75, H 5.90, N 2.93; found: C 57.80, H 6.07, N 2.85.

**(16-S) Cyano-(*p*-bromo-phenyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12l).** 12l: white needle crystal, mp 144–145 °C (from petroleum ether), yield 25%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.55 (2H, d,  $J=8.3$  Hz, aromatic-H); 7.32 (2H, d,  $J=8.4$  Hz, aromatic-H); 5.58 (1H, s, 5-H); 5.46 (1H, s, 16-H); 4.79 (1H, d,  $J=3.4$  Hz, 12-H); 1.44 (3H, s, 4- $\text{CH}_3$ ); 0.96 (3H, d,  $J=6.3$  Hz, 11- $\text{CH}_3$ ); 0.85 (3H, d,  $J=7.3$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1593, 1487, 1394, 1144, 1103, 1036, 955, 879. Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{BrNO}_5$ : C 57.75, H 5.90, N 2.93; found: C 57.80, H 5.89, N 2.96.

**(16-S) Cyano-(*o*, *p*-dimethoxy-phenyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12m).** 12m: white crystal, mp 149–150 °C (from ethyl acetate–petroleum ether), yield 20%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.40 (1H, d,  $J=8.5$  Hz, aromatic-H); 6.49 (1H, d,  $J=8.4$  Hz, aromatic-H); 6.43 (1H, s, aromatic-H); 5.71 (1H, s, 5-H); 5.63 (1H, s, 16-H); 4.91 (1H, d,  $J=3.5$  Hz, 12-H); 3.81 (3H, s,  $\text{OCH}_3$ ); 3.80 (3H, s,  $\text{OCH}_3$ ); 1.45 (3H, s, 4- $\text{CH}_3$ ); 0.95 (3H, d,  $J=6.4$  Hz, 11- $\text{CH}_3$ ); 0.81 (3H, d,  $J=7.5$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1616, 1585, 1508, 1464, 1265, 1209, 1103, 1099, 987, 955, 937, 874. Anal. calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_7$ : C 65.34, H 7.24, N 3.05; found: C 65.48, H 7.29, N 3.11.

**(16-R) Cyano-(*o*, *p*-dimethoxy-phenyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12n).** 12n: white crystal, mp 149–152 °C (from ethyl acetate–petroleum ether), yield 22%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.46 (1H, d,  $J=8.4$  Hz, aromatic-H); 6.51 (1H, d,  $J=8.4$  Hz, aromatic-H); 6.45 (1H, s, aromatic-H); 5.98 (1H, s, 5-H); 5.40 (1H, s, 16-H); 5.21 (1H, d,  $J=3.4$  Hz, 12-H); 3.83 (3H, s,  $\text{OCH}_3$ ); 3.81 (3H, s,  $\text{OCH}_3$ ); 1.44 (3H, s, 4- $\text{CH}_3$ ); 0.97 (3H, d,  $J=7.4$  Hz, 11- $\text{CH}_3$ ); 0.90 (3H, d,  $J=6.0$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1616, 1589, 1510, 1464, 1284, 1211, 1126, 1097, 1040, 995, 957, 870. Anal. calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_7$ : C 65.34, H 7.24, N 3.05; found: C 65.41, H 7.15, N 3.05.

**(16-R) Cyano-(*m*, *p*-dimethoxy-phenyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12o).** 12o: oil, yield 25%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.02 (1H, d,  $J=8.4$  Hz, aromatic-H); 6.95 (1H, s, aromatic-H); 6.88 (1H, d,  $J=8.1$  Hz, aromatic-H); 5.60 (1H, s, 5-H); 5.26 (1H, s, 16-H); 5.20 (1H, d,  $J=3.6$  Hz, 12-H); 3.83 (3H, s,  $\text{OMe}$ ); 3.81 (3H, s,  $\text{OMe}$ ); 1.43 (3H, s, 4- $\text{CH}_3$ ); 1.00 (3H, d,  $J=7.4$  Hz, 11- $\text{CH}_3$ ); 0.88 (3H, d,  $J=6.2$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1684, 1597, 1518, 1456, 1100, 1040, 950, 875. Anal. calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_7$ : C 65.34, H 7.24, N 3.05; found: C 65.45, H 7.22, N 2.89.

**(16-S) Cyano-(*o*, *p*-dimethyl-phenyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12p).** 12p: oil, yield 64%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.41 (1H, d,  $J=7.7$  Hz, aromatic-H); 7.04 (1H, d,  $J=7.7$  Hz, aromatic-H); 7.03 (1H, s, aromatic-H); 5.77 (1H, s, 5-H); 5.46 (1H, d,  $J=5.4$  Hz, 12-H); 5.38 (1H, s, 16-H); 2.41 (3H, s, Me); 2.31 (3H, s, Me); 1.45 (3H, s, 4- $\text{CH}_3$ ); 1.23 (3H, d,  $J=7.2$  Hz, 11- $\text{CH}_3$ ); 0.91 (3H, d,  $J=6.0$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1616, 1502, 1452, 1377, 1194, 1101, 1010, 956, 875. Anal. calcd for  $\text{C}_{25}\text{H}_{33}\text{NO}_5$ : C 70.23, H 7.78, N 3.28; found: C 70.37, H 7.58, N 3.19.

**(16-R) Cyano-(1'-naphthyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12q) and (16-S) cyano-(1'-naphthyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12r).** 12q: amorphous, yield 24%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 8.17 (1H, d,  $J=8.6$  Hz aromatic-H); 7.92 (1H, t,  $J=7.1$  Hz, aromatic-H); 7.75 (1H, d,  $J=7.0$  Hz, aromatic-H); 7.59 (3H, m, aromatic-H); 7.51 (1H, t,  $J=7.7$  Hz, aromatic-H); 6.26 (1H, s, 5-H); 5.39 (1H, d,  $J=3.7$  Hz, 12-H); 5.30 (1H, s, 16-H); 1.47 (3H, s, 4- $\text{CH}_3$ ); 1.09 (3H, d,  $J=7.3$  Hz, 11- $\text{CH}_3$ ); 0.82 (3H, d,  $J=6.2$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1512, 1450, 1377, 1194, 1101, 1009, 955, 876. Anal. calcd for  $\text{C}_{27}\text{H}_{31}\text{NO}_5$ : C 72.14, H 6.95, N 3.12; found: C 72.47, H 7.33, N 2.99.

12r: amorphous, yield 15%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 8.19 (1H, d,  $J=8.2$  Hz, aromatic-H); 7.92 (1H, t,  $J=6.0$  Hz, aromatic-H); 7.60 (4H, m, aromatic-H); 7.48 (1H, t,  $J=4.1$  Hz, aromatic-H); 6.03 (1H, s, 5-H); 5.70 (1H, s, 16-H); 4.86 (1H, d,  $J=3.6$  Hz, 12-H); 1.48 (3H, s, 4- $\text{CH}_3$ ); 0.99 (3H, d,  $J=6.3$  Hz, 11- $\text{CH}_3$ ); 0.71 (3H, d,  $J=7.4$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1512, 1452, 1373, 1194, 1101, 1011, 986, 876. Anal. calcd for  $\text{C}_{27}\text{H}_{31}\text{NO}_5$ : C 72.14, H 6.95, N 3.12; found: C 72.27, H 6.92, N 3.08.

**(16-R) Cyano-(2'-naphthyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12s), (16-S) cyano-(2'-naphthyl)-methyl 12 $\beta$ -deoxoartemisinyll ether (12t) and (16-R) cyano-(2'-naphthyl)-methyl 12 $\beta$ -(11S) deoxoartemisinyll ether (12u).** 12s: amorphous, yield 25%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.97 (1H, s, aromatic-H); 7.90 (3H, m, aromatic-H); 7.54 (3H, m, aromatic-H); 5.84 (1H, s, 5-H); 5.34 (1H, s, 16-H); 5.30 (1H, d,  $J=3.6$  Hz, 12-H); 1.45 (3H, s, 4- $\text{CH}_3$ ); 1.04 (3H, d,  $J=7.3$  Hz, 11- $\text{CH}_3$ ); 0.86 (3H, d,  $J=6.2$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1602, 1510, 1450, 1377, 1194, 1101, 1011, 955, 939, 876, 825. Anal. calcd for  $\text{C}_{27}\text{H}_{31}\text{NO}_5$ : C 72.14, H 6.95, N 3.12; found: C 72.20, H 6.74, N 3.19.

**12t**: amorphous, yield 26%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.91 (1H, s, aromatic-H); 7.86 (3H, m, aromatic-H); 7.54 (3H, m, aromatic-H); 5.67 (1H, s, 5-H); 5.64 (1H, s, 16-H); 4.86 (1H, d,  $J=3.5$  Hz, 12-H); 1.46 (3H, s, 4- $\text{CH}_3$ ); 0.96 (3H, d,  $J=6.3$  Hz, 11- $\text{CH}_3$ ); 0.84 (3H, d,  $J=7.2$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1602, 1510, 1450, 1377, 1280, 1226, 1194, 1101, 1032, 955, 937, 876, 825. Anal. calcd for  $\text{C}_{27}\text{H}_{31}\text{NO}_5$ : C 72.14, H 6.95, N 3.12; found: C 71.96, H 6.90, N 3.28.

**12u**: white crystal, mp 144–146 °C, yield 5%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 8.01 (1H, s, aromatic-H); 7.91–7.84 (3H, m, aromatic-H); 7.58 (1H, d,  $J=8.5$  Hz aromatic-H); 7.52 (2H, m aromatic-H); 5.88 (1H, s, 5-H); 5.50 (1H, d,  $J=4.3$  Hz, 12-H); 5.45 (1H, s, 16-H); 1.47 (3H, s, 4- $\text{CH}_3$ ); 1.30 (3H, d,  $J=6.2$  Hz, 11- $\text{CH}_3$ ); 0.91 (3H, d,  $J=6.1$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1604, 1510, 1458, 1377, 1203, 1126, 1090, 1003, 885. Anal. calcd for  $\text{C}_{27}\text{H}_{31}\text{NO}_5$ : C 72.14, H 6.95, N 3.12; found: C 72.01, H 6.78, N 3.12.

**(16-R) Cyano-[*m*-(3'-trifluorophenoxy)-phenyl]-methyl 12 $\beta$ -deoxoartemisinyl ether (12v) and (16-S) cyano-[*m*-(3'-trifluorophenoxy)-phenyl]-methyl 12 $\beta$ -deoxy-artemisinyl ether (12w).** **12v**: amorphous, yield 23%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.46–7.37 (4H, m, aromatic-H); 7.21 (1H, s, aromatic-H); 7.17 (1H, d,  $J=7.8$  Hz, aromatic-H); 7.08 (1H, s, aromatic-H); 7.05 (1H, d,  $J=8.1$  Hz, aromatic-H); 5.57 (1H, s, 5-H); 5.48 (1H, s, 16-H); 4.82 (1H, d,  $J=3.2$  Hz, 12-H); 1.43 (3H, s, 4- $\text{CH}_3$ ); 0.95 (3H, d,  $J=6.2$  Hz, 11- $\text{CH}_3$ ); 0.80 (3H, d,  $J=7.3$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1589, 1489, 1450, 1329, 1130, 876. Anal. calcd for  $\text{C}_{30}\text{H}_{32}\text{F}_3\text{NO}_6$ : C 64.39, H 5.76, N 2.50; found: C 64.32, H 5.77, N 2.50.

**12w**: amorphous, yield 22%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.47–7.37 (4H, m, aromatic-H); 7.25 (1H, s, aromatic-H); 7.16 (1H, d,  $J=7.9$  Hz, aromatic-H); 7.12 (1H, s, aromatic-H); 7.06 (1H, d,  $J=7.7$  Hz, aromatic-H); 5.67 (1H, s, 5-H); 5.24 (1H, s, 16-H); 5.23 (1H, d,  $J=3.0$  Hz, 12-H); 1.42 (3H, s, 4- $\text{CH}_3$ ); 0.98 (3H, d,  $J=7.3$  Hz, 11- $\text{CH}_3$ ); 0.89 (3H, d,  $J=6.2$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1589, 1489, 1450, 1329, 1130, 876. Anal. calcd for  $\text{C}_{30}\text{H}_{32}\text{F}_3\text{NO}_6$ : C 64.39, H 5.76, N 2.50; found: C 64.54, H 5.81, N 2.38.

**(16-R/S) Cyano-(9-anthryl)-methyl 12 $\beta$ -deoxoartemisinyl ether (12x).** **12x**: white crystal, mp 184–186 °C (from dichloromethane–petroleum ether), yield 15%,  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 8.56 (1H, s, aromatic-H); 8.51 (2H, d,  $J=8.0$  Hz, aromatic-H); 8.04 (2H, d,  $J=8.4$  Hz, aromatic-H); 7.61 (2H, t,  $J=7.2$  Hz, aromatic-H); 7.50 (2H, t,  $J=7.3$  Hz, aromatic-H); 7.14, 7.07 (1H, s, s, 5-H); 5.78, 5.65 (1H, s, s, 16-H); 4.78, 4.63 (1H, d, d,  $J=4.9$  Hz,  $J=3.5$  Hz, 12-H); 1.49 (3H, s, 4- $\text{CH}_3$ ); 0.94 (3H, d,  $J=6.6$  Hz, 11- $\text{CH}_3$ ); 0.46 (3H, d,  $J=7.4$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1626, 1448, 1373, 1192, 1099, 1007, 980, 878. Anal. calcd for  $\text{C}_{31}\text{H}_{33}\text{NO}_5$ : C 74.53, H 6.66, N 2.80; found: C 74.42, H 6.48, N 2.79.

**(16-R) Cyano-(*p*-bromo-phenyl)-methyl 12 $\beta$ -deoxy-deoxy-artemisinyl ether (13).** To a stirring solution of **12l** (100 mg, 0.21 mmole) in 5 mL of glacial acetic acid

at 0 °C was added Zn powder (100 mg). Then the mixture was stirred at room temperature for 2 h. Iced water was added and the mixture was extracted with chloroform. The organic layer was washed with aqueous sodium bicarbonate and brine. The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The crude product was recrystallized to give pure **13** (58 mg, yield 60%).

**13**: white crystal, mp 122–122.5 °C (from ethyl acetate–petroleum ether),  $^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.54 (2H, d,  $J=8.5$  Hz, aromatic-H); 7.31 (2H, d,  $J=8.5$  Hz, aromatic-H); 5.47 (1H, s, 5-H); 5.34 (1H, s, 16-H); 4.78 (1H, d,  $J=4.1$  Hz, 12-H); 1.47 (3H, s, 4- $\text{CH}_3$ ); 0.91 (3H, d,  $J=7.3$  Hz, 11- $\text{CH}_3$ ); 0.88 (3H, d,  $J=6.4$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1593, 1487, 1394, 1211, 1103, 930, 868. Anal. calcd for  $\text{C}_{23}\text{H}_{28}\text{BrNO}_4$ : C 59.74, H 6.10, N 3.03; found: C 59.85, H 5.78, N 3.31.

**(Cyanomethyl)-benzyl 12 $\beta$ -deoxoartemisinyl ether (14).** Dihydroartemisinin (200 mg, 0.7 mmol) reacted with 3-hydroxy-3-phenyl-propionitrile using boron trifluoride etherate as a catalyst, according to the general procedure. The product was a mixture of 16R and 16S isomers (amorphous, 84 mg, yield 29%).

$^1\text{H}$  NMR (400 MHz,  $\delta$ , ppm,  $\text{CDCl}_3$ ): 7.38 (5H, m, aromatic-H); 5.74, 5.63 (1H, s, s, 5-H); 5.19, 5.17 (1H, m, 16-H); 4.79, 4.65 (1H, d, d,  $J=3.7$  Hz, 12-H); 2.68 (2H, m, 17-H); 1.39 (3H, s, 4- $\text{CH}_3$ ); 0.94 (3H, d,  $J=6.2$  Hz, 11- $\text{CH}_3$ ); 0.87 (3H, d,  $J=7.3$  Hz, 10- $\text{CH}_3$ ). IR (KBr,  $\text{cm}^{-1}$ ): 1456, 1375, 1194, 1101, 1013, 981, 875. Anal. calcd for  $\text{C}_{24}\text{H}_{31}\text{NO}_5$ : C 69.71, H 7.56, N 3.39; found: C 69.52H 7.56 N 2.99.

## References and Notes

- Li, Y. *Med. Trop.* **1998**, *58*, 9.
- Jung, M.; ElSohly, H. N.; McChesney, J. D. *Planta Med.* **1990**, *56*, 624.
- Sun, W. S.; Han, J. X.; Yang, W. Y.; Deng, D. A.; Yue, X. F. *Acta Pharmacol. Sin.* **1992**, *13*, 541.
- Zheng, G. Q. *Planta Med.* **1994**, *60*, 54.
- Woerdenbag, H. J.; Moskai, T. A.; Pras, N.; Malingre, T. M.; El-Feraly, F. S.; Kampinga, H. H.; Konings, A. W. T. *J. Nat. Prod.* **1993**, *56*, 849.
- Beekman, A. C.; Barentsen, A. R. W.; Woerdenbag, H. J.; Uden, W. V.; Pras, N.; Konings, A. W. T.; El-Feraly, F. S.; Galal, A. M.; Wikström, H. *J. Nat. Prod.* **1997**, *60*, 325.
- Beekman, A. C.; Wierenga, P. K.; Woerdenbag, H. J.; Uden, W. V.; Pras, N.; Konings, A. W. T.; El-Feraly, F. S.; Galal, A. M.; Wikström, H. *Planta Med.* **1998**, *64*, 615.
- Ekthawatchai, S.; Kamchonwongpaisan, S.; Kongsaree, P.; Tarnchompoo, B.; Thebtaranonth, Y.; Yuthavong, Y. *J. Med. Chem.* **2001**, *44*, 4688.
- Jung, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1091.
- Yang, X. P.; Pan, Q. C.; Liang, Y. G.; Zhang, Y. L. *Cancer* **1997**, *16*, 186 (in Chinese).
- Zhang, X.; Yang, X. P.; Pan, Q. C. *Chin. Tradit. Herb. Drugs* **1998**, *29*, 467.
- Zhang, J. X.; Wang, S. X.; Zhang, F. G.; Zhang, Y. H.; Liu, A. H. *Chin. Tradit. Herb. Drugs* **2001**, *32*, 345.
- Efferth, T.; Dunstan, H.; Sauerbrey, A.; Miyachi, H.; Chitambar, C. R. *Int. J. Oncol.* **2001**, *18*, 767.

14. Lai, H.; Singh, N. P. *Cancer Lett.* **1995**, *91*, 41.
15. Moore, J. C.; Lai, H.; Li, J. R.; Ren, R. L.; McDougall, J. A.; Singh, N. P.; Chou, C. K. *Cancer Lett.* **1995**, *98*, 83.
16. Singh, N. P.; Lai, H. *Life Sci.* **2001**, *70*, 49.
17. Posner, G. H.; Ploypradith, P.; Hapangama, W.; Wang, D.; Cumming, J. N.; Kensler, T. W.; Klinedinst, D.; Shapiro, T. A.; Zheng, Q. Y.; Murray, C. K.; Pilkington, L. G.; Jayasinghe, L. R.; Bray, J. F.; Daughenbaugh, R. *Bioorg. Med. Chem.* **1997**, *5*, 1257.
18. Posner, G. H.; Ploypradith, P.; Parker, M. H.; O'Dowd, H.; Woo, S. H.; Northrop, J.; Krasavin, M.; Dolan, P.; Kensler, T. W.; Xie, S. J.; Shapiro, T. A. *J. Med. Chem.* **1999**, *42*, 4275.
19. Yang, Y. H.; Li, Y.; Yang, J. D.; Wu, B. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1791.
20. Liang, J.; Li, Y. *Chin. J. Med. Chem.* **1996**, *6*, 22.
21. Li, Y.; Shan, F.; Wu, J. M.; Wu, G. S.; Ding, J.; Xiao, D.; Yang, W. Y.; Atassi, G.; Leonce, S.; Caignard, D. H.; Renard, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 5.
22. Li, Y.; Yu, P. L.; Chen, Y. X.; Li, L. Q.; Gai, Y. Z.; Wang, D. S.; Zhang, Y. P. *Acta Pharma. Sin.*; **1981**, *16*, 429.
23. Wang, D. Y.; Wu, Y. K.; Wu, Y. L.; Li, Y.; Shan, F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1827.
24. Reitnauer, P. G. *Arzneim.-Forsch.* **1972**, *22*, 1347.