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Arbeitsvorschriften und Meßwerte · Procedures and Data

Amino Acid Conjugates and Further New Derivatives of Dihydroartemisinin

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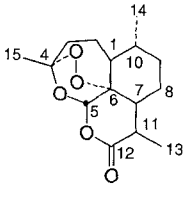
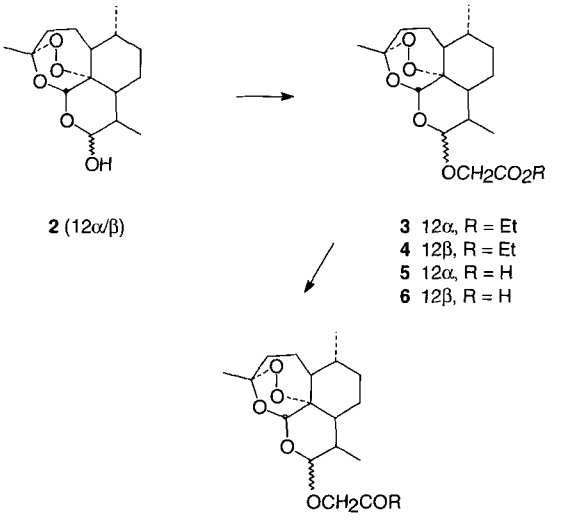
Artemisia annua L. has been used since ancient times in South East Asia for treating fever and malaria. This plant is known in China as qing hao. The effective constituent, named artemisinin or qinghaosu, was isolated by Chinese investigators in 1972. In 1979, its structure was elucidated as **1** by combined spectral, chemical and X–ray analysis [1, 2]. Because of its remarkable antimalaria activity even against multidrug–resistant strains of *Plasmodium falciparum*, artemisinin is currently being developed to a registered antimalaria drug. Furthermore, chemical modifications of artemisinin have resulted in numerous analogues, some of them with improved efficacy and increased solubility [3–7]. However, in spite of these synthetic activities artemisinin derivatives bearing amino acid components have not yet been described. The aim of the present investigation was to synthesize this type of artemisinin-amino acid conjugates for further biological studies.



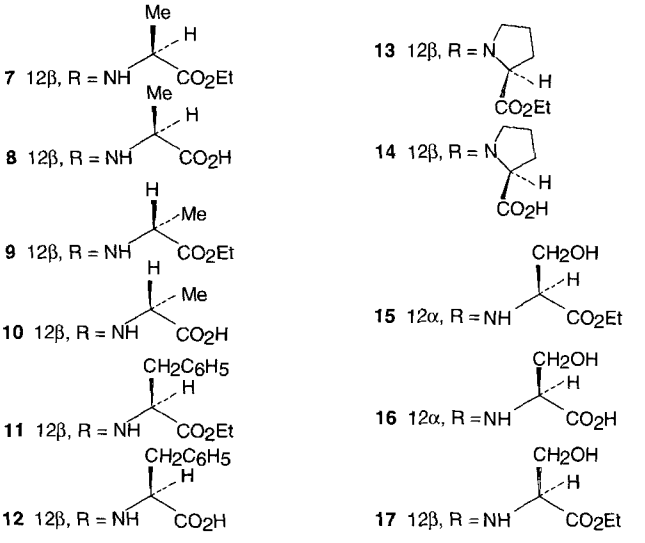
1

Dihydroartemisinin (**2**) was prepared from **1** by reduction with $NaBH_4$ in methanol-*tert*-butanol (10:1) [8]. Compound **2** exists as a mixture of 12α– and 12β–anomers, giving the corresponding acetals **3** and **4** by treatment with ethyl glycolate in the presence of boron trifluoride etherate. Epimer **4** is already described in the literature [9]. The 12α–acetal could be recognized by its ^{1}H NMR coupling constant $J_{11\text{–H},12\text{–H}}$ = 9.3 Hz ($CHCl_3$), whereas the 12β–isomer had $J_{11\text{–H},12\text{–H}}$ = 3.2 Hz (axial/axial and axial/equatorial protons, respectively). Alkaline hydrolysis of **3** and **4** afforded the acids **5** and **6**, respectively. **6** was mentioned in [9] as an unstable compound. **5** and **6** were connected with amino acid ethyl esters by means of dicyclohexylcarbodiimide to give the amides **7**, **9**, **11**, **13**, **15** and **17**. These were hydrolyzed to the amino acid conjugates **8**, **10**, **12**, **14** and **16**.



2 (12α/β)

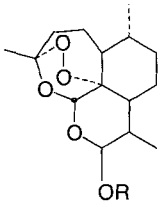
3 12α, R = Et
4 12β, R = Et
5 12α, R = H
6 12β, R = H



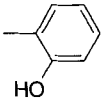
7 12β, R = NH–CH(Me)–CO$_2$Et
8 12β, R = NH–CH(Me)–CO$_2$H
9 12β, R = NH–CH(H)–CO$_2$Et
10 12β, R = NH–CH(H)–CO$_2$H
11 12β, R = NH–CH(CH$_2$C$_6$H$_5$)–CO$_2$Et
12 12β, R = NH–CH(CH$_2$C$_6$H$_5$)–CO$_2$H
13 12β, R = N(H)–CO$_2$Et
14 12β, R = N(H)–CO$_2$H
15 12α, R = NH–CH(CH$_2$OH)–CO$_2$Et
16 12α, R = NH–CH(CH$_2$OH)–CO$_2$H
17 12β, R = NH–CH(CH$_2$OH)–CO$_2$Et

Reaction of dihydroartemisinin (**2**) with catechol, resorcinol or hydroquinone yielded the acetals **18** – **20**, respectively, the 12β-configurations of which were recognized by the coupling constants $J_{11\text{-H},12\text{-H}}$ = 5.4, 5.5 and 5.4 Hz ($CHCl_3$).

The ^1H, ^{13}C NMR [10–12] and electrospray ionization (ESI) mass spectroscopic data of compounds **3** – **20** were in agreement with the given structures. Studies on the antimalaria and further biological activities are under way.



18 R =



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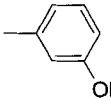
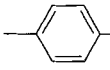


20 R =



We thank the Deutscher Akademischer Austauschdienst and the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie, Bonn, for financial support, Dr. A. Porzel for NMR spectra and Dr. J. Schmidt for mass spectral measurements.

Experimental

The NMR spectra were measured with a NMR VARIAN GEMINI 2000–300 spectrometer at 300 MHz (^1H) and 75.5 MHz (^{13}C), respectively, in $CDCl_3$, the ESI mass spectra with a Finnigan MAT TSQ 7000 instrument (electrospray voltage 4.5 kV).

Ethyl 12-O-(α-Dihydroartemisinin)acetate (**3**)

To a solution of 2.84 g of dihydroartemisinin (**2**) and 5.0 ml of ethyl glycolate in 150 ml CH_2Cl_2–C_6H_6 (1:1) 1.0 ml of boron trifluoride diethyl etherate was added. After 18 hours at 26 °C the mixture was washed with 5% HCl and H_2O, dried over Na_2SO_4, evaporated *in vacuo* and the residue chromatographed over silica gel with $CHCl_3$–EtOAc (100:3). **3** was obtained in 6%, **4** in 30% yield.

3: *M. p.* 134–137 °C ($CHCl_3$–EtOAc), $[\alpha]_D^{34}$ –60.4° (c = 0.10, $CHCl_3$). – ^1H NMR: δ/ppm = 0.96 (d, J = 6.1 Hz, 13–H_3), 0.99 (d, J = 7.0 Hz, 14–H_3), 1.28 (t, J = 7.1 Hz, 2''–H_3), 1.44 (s, 15–H_3), 4.63 (d, J = 9.3 Hz, 12–H), 5.32 (s, 5–H). – ^{13}C NMR: δ/ppm = 12.5 (C-13), 14.2 (C-2''), 20.3 (C-14), 22.2 (C-8), 24.7 (C-2), 26.0 (C-15), 32.6 (C-11), 34.2 (C-9), 36.3 (C-3), 37.4 (C-10), 45.3 (C-7), 51.6 (C-1), 60.7 (C-1''), 64.2 (C-2'), 80.3 (C-6), 91.3 (C-5), 99.2 (C-12), 104.3 (C-4), 170.4 (C-1'). – ESI-MS: 393 $[M + Na]^+$.

$C_{19}H_{30}O_7$	Calcd.:	C 61.60	H 8.16
(370.44)	Found:	C 61.68	H 7.85.

Ethyl 12-O-(β-Dihydroartemisinin)acetate (**4**)

Oil, [9]: *m. p.* 50–52 °C, $[\alpha]_D^{34}$ +162.2° (c = 0.10, $CHCl_3$). ^1H NMR: δ/ppm = 0.95 (d, J = 6.4 Hz, 13-H_3), 0.99 (d, J = 7.3 Hz, 14-H_3), 1.28 (t, J = 7.2 Hz, 2''–H_3), 1.43 (s, 15-H_3), 4.87 (d, J = 3.2 Hz, 12-H), 5.54 (s, 5-H), with the exception of the magnitudes of two coupling constants identical with the data of [9]. – ^{13}C NMR: δ/ppm = 12.8 (C-13), 14.1 (C-2''), 20.3 (C-14), 24.2 (C-8), 24.6 (C-2), 26.0 (C-15), 30.7 (C-11), 34.6 (C-9), 36.4 (C-3), 37.4 (C-10), 44.3 (C-7), 52.5 (C-1), 60.7 (C-1''), 65.0 (C-2'), 81.1 (C-6), 88.2 (C-5), 102.1 (C-12), 104.1 (C-4), 170.4 (C-1'). – ESI-MS: 393 $[M + Na]^+$, 347 $[M + Na - EtOH]^+$.

12-O-(α-Dihydroartemisinin)acetic Acid (**5**)

3 (370 mg), dissolved in 80 ml of methanol, was hydrolyzed with 1.2 ml of 1N NaOH at 25 °C for 3 hours. 5% HCl was added to pH 4. After dilution with H_2O the mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4 and the solvent evaporated *in vacuo*. Yield 86%, *m. p.* 128–131°C (MeCN–$CHCl_3$), $[\alpha]_D^{21}$ +10.0° (c = 0.32, $CHCl_3$). – ^1H NMR: δ/ppm = 0.95 (d, J = 7.1 Hz, 13-H_3), 0.97 (d, J = 5.6 Hz, 14-H_3), 1.42 (s, 15-H_3), 4.59 (d, J = 9.3 Hz, 12-H), 5.40 (s, 5-H). – ^{13}C NMR: δ/ppm = 12.3 (C-13), 20.1 (C-14), 22.0 (C-8), 24.6 (C-2), 25.7 (C-15), 32.3 (C-11), 34.0 (C-9), 36.0 (C-3), 37.4 (C-10), 45.1 (C-7), 51.2 (C-1), 67.4 (C-2'), 80.1 (C-6), 91.2 (C-5), 101.5 (C-12), 104.8 (C-4), 171.9 (C-1'). – ESI-MS: 341 $[M - H]^-$.

$C_{17}H_{26}O_7$	Calcd.:	C 59.64	H 7.65
(342.39)	Found:	C 59.69	H 7.66.

12-O-(β-Dihydroartemisinin)acetic Acid (**6**)

4 was hydrolyzed, as described for **3**. Yield 89%, oil, $[\alpha]_D^{26}$ +100.4° (c = 0.10, $CHCl_3$). – ^1H NMR: δ/ppm = 0.96 (d, J = 6.3 Hz, 13-H_3), 0.98 (d, J = 7.7 Hz, 14-H_3), 1.43 (s, 15-H_3), 4.89 (d, J = 3.3 Hz, 12-H), 5.51 (s, 5-H). – ^{13}C NMR: δ/ppm = 12.8 (C-13), 20.3 (C-14), 24.2 (C-8), 24.6 (C-2), 26.0 (C-15), 30.6 (C-11), 34.6 (C-9), 36.3 (C-3), 37.4 (C-10), 44.2 (C-7), 52.4 (C-1), 64.6 (C-2'), 81.0 (C-6), 88.2 (C-5), 102.3 (C-12), 104.3 (C-4), 175.0 (C-1'). – ESI-MS: 341 $[M-H]^-$.

$C_{17}H_{26}O_7$	Calcd.:	C 59.64	H 7.65
(342.39)	Found:	C 59.18	H 7.67.

Syntheses of Amino acid Conjugates

1.0 mmol of **5** or **6** and 1.0 mmol of amino acid ethyl ester [13] were dissolved in 100 ml of acetonitrile. After cooling to –5 °C the concentrated solution of 1.0 mmol of dicyclohexylcarbodiimide in acetonitrile was added. After 10 hours at –5 °C and 15 hours at room temperature dicyclohexylurea was removed by filtration, CH_2Cl_2 was added and the solution was washed with 5% HCl, 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4, evaporated *in vacuo* and the residue was chromatographed over silica gel with $CHCl_3$–EtOAc. Hydrolysis was performed, as described for **3**.

N-[12-O-(β-Dihydroartemisinin)acetyl]-(S)-alanin-ethylester (**7**)

Yield 72%, *m. p.* 120–121°C ($CHCl_3$–EtOAc), $[\alpha]_D^{28}$ +112.2° (c = 0.62, $CHCl_3$). – ^1H NMR: δ/ppm = 1.29 (t, J = 7.2 Hz, 2'''–H), 1.44 (d, J = 7.0 Hz, 3''–H), signals of dihydroartemisinin portion analogous to those of **4**. – ^{13}C NMR: δ/ppm =

14.1 (C-2'''), 18.8 (C-3''), 47.6 (C-2''), 61.6 (C-1'''), 67.5 (C-2'), 168.8 (C-1'), 172.7 (C-1''), signals of dihydroartemisinin portion analogous to those of **4**. – ESI-MS: 464 $[M+Na]^+$, 418 $[M+Na-EtOH]^+$.

$C_{22}H_{35}NO_8$	Calcd.:	C 59.85	H 7.99	N 3.17
(441.52)	Found:	C 59.65	H 7.92	N 3.16.

N-[12-O-(β-Dihydroartemisinin)acetyl]-(S)-alanin (**8**)

Yield 87%, amorphous, $[\alpha]_D^{28}$ +119.4° (c = 0.09, $CHCl_3$). – ^1H NMR: δ/ppm = 1.50 (d, J = 7.3 Hz, 3''–H), signals of dihydroartemisinin portion analogous to those of **4**. – ^{13}C NMR: δ/ppm = 18.4 (C-3''), 47.6 (C-2''), 67.4 (C-2'), 169.6 (C-1'), 176.4 (C-1''), signals of dihydroartemisinin portion analogous to those of **4**. – ESI-MS: 436 $[M+Na]^+$.

$C_{20}H_{31}NO_8$	Calcd.:	C 58.10	H 7.56	N 3.39
(413.47)	Found:	C 57.63	H 7.55	N 3.21.

N-[12-O-(β-Dihydroartemisinin)acetyl]-(R)-alanin-ethylester (**9**)

Yield 62%, *m. p.* 118–122 °C ($CHCl_3$–EtOAc), $[\alpha]_D^{26}$ +103.3° (c = 0.40, $CHCl_3$). – ^1H NMR: δ/ppm = 1.29 (t, J = 7.2 Hz, 2'''-H), 1.44 (d, J = 7.2 Hz, 3''-H), signals of dihydroartemisinin portion analogous to those of **4**. – ^{13}C NMR: δ/ppm = 14.1 (C-2'''), 18.7 (C-3''), 47.6 (C-2''), 61.6 (C-1'''), 67.7 (C-2'), 168.9 (C-1'), 172.7 (C-1''), signals of dihydroartemisinin portion analogous to those of **4**. – ESI-MS: 464 $[M+Na]^+$, 418 $[M+Na-EtOH]^+$.

$C_{22}H_{35}NO_8$	Calcd.:	C 59.85	H 7.99	N 3.17
(441.52)	Found:	C 59.78	H 7.94	N 3.27.

N-[12-O-(β-Dihydroartemisinin)acetyl]-(R)-alanin (**10**)

Yield 51%, amorphous, not completely pure. – ^1H NMR: δ/ppm = 1.50 (t, J = 7.1 Hz, 3''–H), signals of dihydroartemisinin portion analogous to those of **4**. – ^{13}C NMR: δ/ppm = 18.2 (C-3''), 47.6 (C-2''), 67.6 (C-2'), 169.8 (C-1'), 175.3 (C-1''), signals of dihydroartemisinin portion analogous to those of **4**. – ESI-MS: 412 $[M-H]^-$, 366 $[M-HCO_2H]^-$.

$C_{20}H_{31}NO_8$	Calcd.:	C 58.10	H 7.56	N 3.39
(413.47)	Found:	C 58.18	H 7.53	N 3.27.

N-[12-O-(β-Dihydroartemisinin)acetyl]-(S)-phenylalanin-ethylester (**11**)

Yield 70%, *m. p.* 106–108 °C ($CHCl_3$–EtOAc), $[\alpha]_D^{23}$ +123.6° (c = 0.31, $CHCl_3$). – ^1H NMR: δ/ppm = 1.26 (t, J = 7.1 Hz, 2'''-H), 7.07 (dd, J = 7.6 and 1.8 Hz, 5''-H, 9''-H), 7.25 (m, 6''-H, 7''-H, 8''-H), signals of dihydroartemisinin portion analogous to those of **4**. – ^{13}C NMR: δ/ppm = 14.1 (C-2'''), 37.8 (C-3''), 52.4 (C-2''), 61.5 (C-1'''), 67.3 (C-2'), 127.1 (C-7''), 128.5, 129.4 (C-5'', C-6'', C-8'', C-9''), 135.6 (C-4''), 168.8 (C-1'), 171.0 (C-1''), signals of dihydroartemisinin portion analogous to those of **4**. – ESI-MS: 540 $[M+Na]^+$, 494 $[M+Na-EtOH]^+$.

$C_{28}H_{39}NO_8$	Calcd.:	C 64.97	H 7.59	N 2.71
(517.62)	Found:	C 65.22	H 7.78	N 2.71.

N-[12-O-(β-Dihydroartemisinin)acetyl]-(S)-phenylalanin (**12**)

Yield 79%, amorphous, $[\alpha]_D^{25}$ + 96.0° (c = 0.10, $CHCl_3$). – ^1H NMR: δ/ppm = 7.14 (dd, J = 7.4 and 1.8 Hz, 5''-H, 9''-H), 7.28 (m, 6''-H, 7''-H, 8''-H), signals of dihydroartemisinin portion analogous to those of **4**. – ^{13}C NMR: δ/ppm = 37.3 (C-3''), 52.3 (C-2''), 67.2 (C-2'), 127.4 (C-7''), 128.7, 129.3 (C-5'', C-6'', C-8'', C-9''), 135.3 (C-4''),169.6 (C-1'), 174.6 (C-1''), signals of dihydroartemisinin portion analogous to those of **4**. – ESI-MS: 512 $[M+Na]^+$.

$C_{26}H_{35}NO_8 \cdot H_2O$	Calcd.:	C 61.52	H 7.35	N 2.76
(507.58)	Found:	C 61.83	H 7.21	N 2.81.

N-[12-O-(β-Dihydroartemisinin)acetyl]-(S)-prolin-ethylester (**13**)

Yield 34%, *m. p.* 131.5–133 °C ($CHCl_3$–EtOAc), $[\alpha]_D^{26}$ + 71.0° (c = 0.50, $CHCl_3$). – ^1H NMR: δ/ppm = 1.26 (t, J = 7.2 Hz, 2'''-H), signals of dihydroartemisinin portion analogous to those of **4**. – ^{13}C NMR: δ/ppm = 14.1 (C-2'''), 24.7, 28.8 (C-3'', C-4''), 45.7 (C-5''), 58.8 (C-2''), 61.1 (C-1'''), 66.0 (C-2'), 167.8 (C-1''), 172.0 (C-1'), signals of dihydroartemisinin portion analogous to those of **4**. – ESI-MS: 490 $[M+Na]^+$, 444 $[M+Na-EtOH]^+$.

$C_{24}H_{37}NO_8$	Calcd.:	C 61.65	H 7.98	N 3.00
(467.56)	Found:	C 62.30	H 8.10	N 3.03.

N-[12-O-(β-Dihydroartemisinin)acetyl]-(S)-prolin (**14**)

Yield 71%, amorphous, $[\alpha]_D^{27}$ + 66.0° (c = 0.10, $CHCl_3$). – ^1H NMR: Signals of dihydroartemisinin portion analogous to those of **4**. – ^{13}C NMR: δ/ppm = 24.8, 27.2 (C-3'', C-4''), 46.5 (C-5''), 60.0 (C-2''), 65.8 (C-2'), 171.1 (C-1''), 172.3 (C-1'), signals of dihydroartemisinin portion analogous to those of **4**. – ESI-MS: 462 $[M+Na]^+$.

$C_{22}H_{33}NO_8$	Calcd.:	C 60.12	H 7.57	N 3.19
(439.51)	Found:	C 60.97	H 8.37	N 2.75.

N-[12-O-(α-Dihydroartemisinin)acetyl]-(S)-serin-ethylester (**15**)

Yield 79%, amorphous, $[\alpha]_D^{28}$ + 31.1° (c = 0.57, $CHCl_3$). – ^1H NMR: δ/ppm = 1.30 (t, J = 7.2 Hz, 2'''-H), signals of dihydroartemisinin portion analogous to those of **3**. – ^{13}C NMR: δ/ppm = 14.1 (C-2'''), 54.5 (C-2''), 61.8 (C-1'''), 63.4 (C-3''), 69.4 (C-2'), 169.9 (C-1''), 170.0 (C-1'), signals of dihydroartemisinin portion analogous to those of **3**. – ESI-MS: 480 $[M+Na]^+$, 434 $[M+Na-EtOH]^+$.

$C_{22}H_{35}NO_9$	Calcd.:	C 57.75	H 7.71	N 3.06
(457.52)	Found:	C 57.69	H 7.47	N 3.06.

N-[12-O-(α-Dihydroartemisinin)acetyl]-(S)-serin (**16**)

Yield 72%, amorphous, $[\alpha]_D^{30}$ + 14.5° (c = 0.29, $CHCl_3$). – ^1H NMR: signals of dihydroartemisinin portion analogous to those of **3**. – ^{13}C NMR: δ/ppm = 54.2 (C-2''), 62.5 (C-3''), 68.8 (C-2'), 171.1 (C-1'), 172.3 (C-1''), signals of dihydroartemisinin portion analogous to those of **3**. – ESI-MS: 452 $[M+Na]^+$.

$C_{20}H_{31}NO_9$	Calcd.:	C 55.93	H 7.28	N 3.26
(429.47)	Found:	C 56.48	H 7.50	N 2.59.

N-[12-O-(β-Dihydroartemisinin)acetyl]-(S)-serin-ethylester (**17**)

Yield 75%, *m. p.* 152–155 °C ($CHCl_3$–MeOH), $[\alpha]_D^{27}$ + 81.2°

(c = 0.10, $CHCl_3$). – ^1H NMR: δ/ppm = 1.31 (t, J = 7.0 Hz, 2'''-H), signals of dihydroartemisinin portion analogous to those of **4**. – ^{13}C NMR: δ/ppm = 14.1 (C-2'''), 54.8 (C-2''), 62.0 (C-1'''), 63.6 (C-3''), 67.9 (C-2'), 170.0 (C-1''), 170.1 (C-1'), signals of dihydroartemisinin portion analogous to those of **4**. – ESI-MS: 480 $[M+Na]^+$, 434 $[M+Na-EtOH]^+$.

$C_{22}H_{35}NO_9$	Calcd.:	C 57.75	H 7.71	N 3.06
(457.52)	Found:	C 57.43	H 7.64	N 3.03.

Syntheses of the Acetals 18–20

O-(o-Hydroxyphenyl)-β-dihydroartemisinin (**18**)

The acetals **18–20** were synthesized analogously to **3**. **18**: Yield 22%, oil, not completely pure. – ^1H NMR: Signals of dihydroartemisinin portion analogous as those of **4**. – ^{13}C NMR: δ/ppm =102.9 (C-12), 115.6, 117.1, 120.6, 123.4 (C-3' to C-6'), 145.1, 146.5 (C-1', C-2'), C-1 to C-11 and C-13 to C-15 analogous to those of **4**. – ESI-MS: 399 $[M+Na]^+$.

$C_{21}H_{28}O_6$	Calcd.:	C 67.00	H 7.50	
(376.45)	Found:	C 67.23	H 8.23.	

O-(m-Hydroxyphenyl)-β-dihydroartemisinin (**19**)

Yield 43%, *m. p.* 165–166 °C (CH_2Cl_2–*n*-hexane–EtOAc), [14]: 142–144 °C, $[\alpha]_D^{22}$ +130.4° (c = 0.34, $CHCl_3$). – ^1H NMR: Signals of dihydroartemisinin portion analogous as those of **4**.– ^{13}C NMR: δ/ppm = 100.5 (C–12), 104.3, 109.1, 109.3, 130.1 (C-2', C-4' to C-6'), 156.8, 158.7 (C-1', C-3'), C-1 to C-11 and C-13 to C-15 analogous to those of **4**. – ESI-MS: 399 $[M+Na]^+$.

$C_{21}H_{28}O_6$	Calcd.:	C 67.00	H 7.50	
(376.45)	Found:	C 66.98	H 7.62.	

O-(p-Hydroxyphenyl)-β-dihydroartemisinin (**20**)

Yield 35%, *m. p.* 170–172°C (CH_2Cl_2–EtOAc), $[\alpha]_D^{21}$ +199.5° (c = 0.12, $CHCl_3$). – ^1H NMR: δ/ppm = 6.72 (d, J = 8.8 Hz, H-2' and H-6' or H-3' and H-5'), 6.94 (d, J = 9.1 Hz, H-2' and H-6' or H-3' and H-5'), signals of dihydroartemisinin portion analogous as those of **4**. – ^{13}C NMR: δ/ppm = 101.7 (C-12), 116.0, 118.5 (C-2', C-3', C-5', C-6'), 150.9, 151.5 (C-1', C-4'), C-1 to C-11 and C-13 to C-15 analogous to those of **4**. – ESI-MS: 399 $[M+Na]^+$.

$C_{21}H_{28}O_6$	Calcd.:	C 67.00	H 7.50	
(376.45)	Found:	C 66.89	H 7.69.	

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