

Supporting information.

Table 1: Yields and Process Stream Analysis for 10- and 40-g Runs

	10 g run	40 g run
Artemisinin (g)	10.17 g	40.00 g
Artemisinin purity	99.6%	99.6%
Corrected artemisinin (g)	10.13 g	39.84 g
Solution yield DHA (g)	10.20 g	40.12 g
Isolated DHA (g)	9.41 g	35.97 g
Isolated DHA purity (%)	>99.9%	>99.9%
Theory (g)	10.20 g	40.12 g
Step Yield (%)	91.8%	89.7%
Loss to streams (g)	0.79 g	4.15 g
Loss to streams (%)	8.2%	10.3%
DHA starting mass (g)	9.41 g	35.9 g
Solution formation of 3 (g)	8.22 g	32.77 g
Solution formation of 4 (g)	0.84 g	3.43 g
Solution formation of 5 (g)	0.35 g	1.15 g
Crude Purity	98.7%	99.4%
Loss to crude streams 3 (g)	0.42 g	2.07 g
Yield loss 3 to crude streams	5.0%	4.9 %
Loss to crude streams 4 (g)	0.77 g	3.43 g
Loss to crude streams 5 (g)	0.27 g	1.21 g
Isolated Purity (%)	>99.9%	>99.9%
Isolated mass (g)	7.47	29.61 g
Theoretical mass (g)	10.70 g	42.10 g
Overall Yield (%)	69.8 %	70.3%
Crystallization loss 3 (g)	0.17 g	0.63 g
Crystallization loss 3 (%)	2.0%	1.5 %
Loss to final streams 4 (g)	0.07 g	0.06 g
4 in streams/ 4 formed	0.84 g/0.84 g	3.49 g/3.43 g
Loss to final streams 5 (g)	0.07 g	0.09 g
5 in streams/ 5 formed	0.34 g/ 0.35 g	1.30 g/1.21 g

HPLC Conditions for analyzing artemisinin starting material, monitoring conversion to **2** and evaluation of purity of **2** (a version of W.H.O. method)

Column: Eclipse XDB-C18, 15cm L X 0.46 cm ID, 5 μ M particles, or equivalent

Mobile phase: 50% acetonitrile/ 50% HPLC grade water

Flow rate: 1.0 mL/min

Run time: 15 minutes

Detection: UV absorbance at 210 nm

Injection: 20 μ L

Sample prep: Weigh 50 mg into 10 mL volumetric flasks as dissolve with mobile phase

Retention times:

Hydrochloric acid: 1.2 minutes

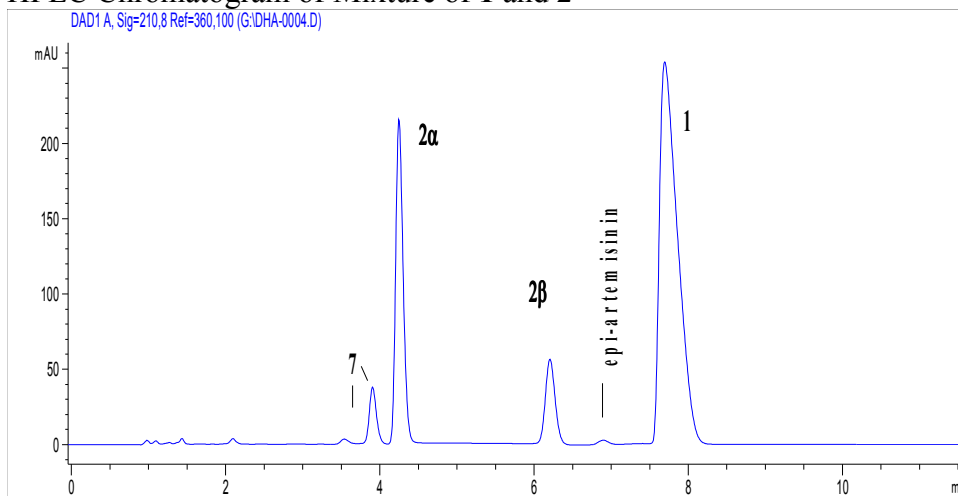
α -dihydroartemisinin (**2 α**): 4.3 minutes

β -dihydroartemisinin (**2 β**): 6.2 minutes

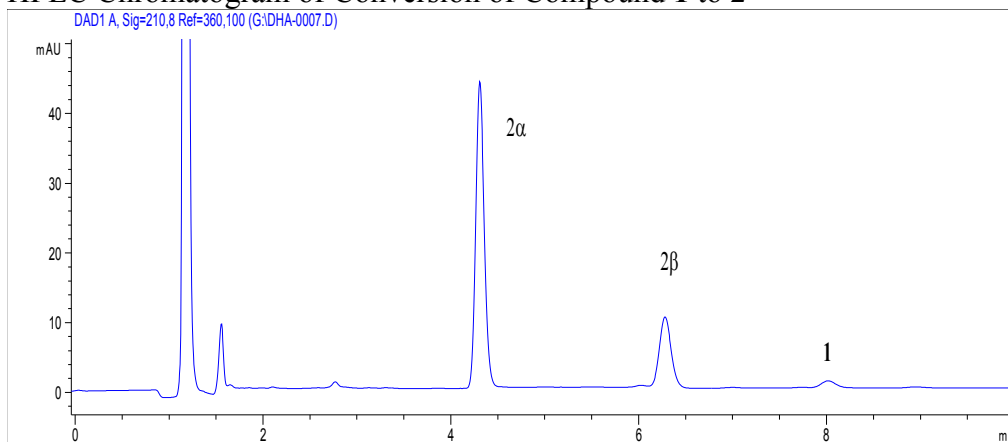
9-epi-Artemisinin: 6.8 minutes

Artemisinin (**1**): 7.6 minutes

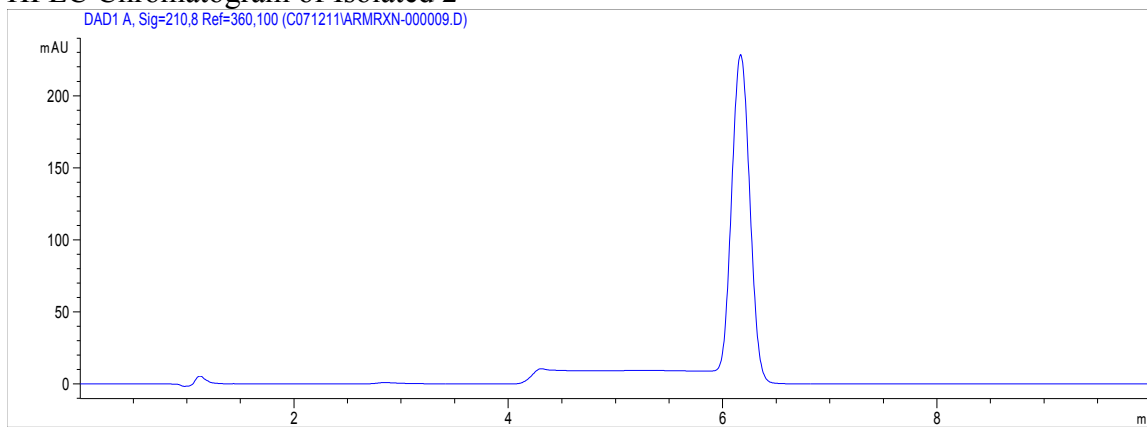
HPLC Chromatogram of Mixture of **1 and **2****



HPLC Chromatogram of Conversion of Compound **1 to **2****



HPLC Chromatogram of Isolated **2**



Formation of **7** occurs in solution as well as during drying. Depending on sample diluent, erroneously low purity assays in HPLC may result. Sample diluents described in the draft WHO monograph for dihydroartemisinin¹ do not take this into account. In methanol—as prescribed for purity assessment—**7** forms at a rate of 0.6% per hour. This decomposition is sufficiently rapid to cause isolated pure **2** to fail its purity specification if not analyzed within 1 hour after dilution. Degradation is much faster (>12%/hour) in the acetonitrile/water diluent prescribed for assay. We find that dilution in neat acetonitrile greatly retards formation of **7**.

Conditions for monitoring conversion of **2** to **3** and evaluation of purity of **3** (a version of W.H.O. method)

Column: Eclipse XDB-C18, 15cm L X 0.46 cm ID, 5 μ M particles, or equivalent

Mobile phase: 62% acetonitrile/ 38% HPLC grade water

Flow rate: 1.0 mL/min

Run time: 15 minutes

Detection: UV absorbance at 210 nm

Injection: 20 μ L

Retention times

Trimethylorthoformate: 1.6 minutes

α -dihydroartemisinin (**2 α**): 2.8 minutes

β -dihydroartemisinin (**2 β**): 3.7 minutes

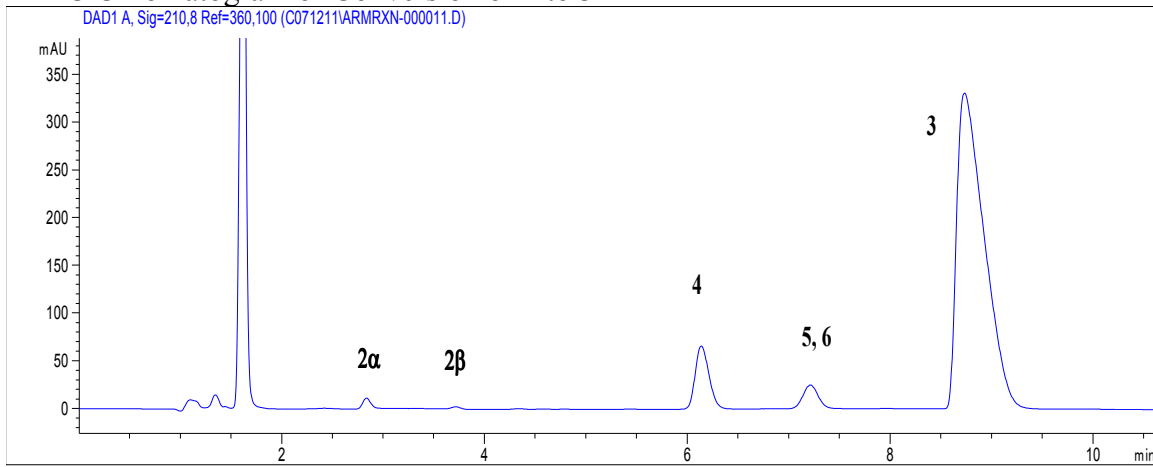
α -artemether (**4**): 6.1 minutes

5, 6 (putative) 7.2 minutes

β -artemether (**3**): 8.7 minutes

¹ QAS/11.437 World Health Organization

HPLC Chromatogram of Conversion of 2 to 3



Overlay of Chromatograms of crude (red) and pure (blue) **3**. The crude material contains impurities **4** and **5** present at 0.3% and 0.4%, respectively. These impurities are not detected in the recrystallized product.

