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# An Improved Manufacturing Process for the Antimalaria Drug Coartem. Part I

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**Abstract:**

**Artemisinin and its derivatives, such as artemether, are highly sensitive compounds, which require careful optimized production processes for their manufacture. Due to robustness issues, the manufacturing procedure of the reduction of artemisinin with potassium borohydride to dihydroartemisinin was reinvestigated. The most important factor for obtaining optimal yields is to ensure low levels of contamination of potassium hydroxide in potassium borohydride. Application of a lower reaction temperature, fast addition rate of potassium borohydride, and careful control of the pH during the quench with acid are further important parameters in guaranteeing a robust process. In the redesign of the conversion of dihydroartemisinin to artemether, the yield was increased, and dichloromethane was replaced by the ecologically friendlier methyl acetate. A robust manufacturing process for artemether is now at hand, allowing the production of this important medicine reliably and in good quality and yield.**

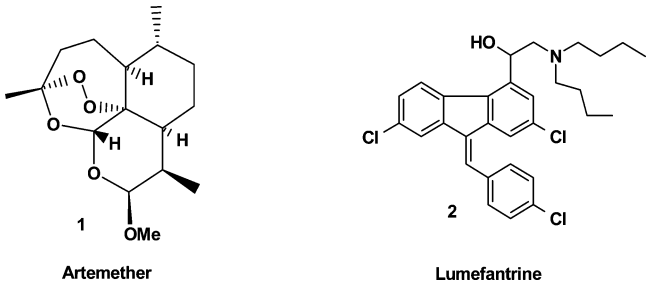


## 1. Introduction

Coartem is a highly effective and well tolerated antimalarial that achieves cure rates of up to 95%, even in areas of multidrug resistance. It is indicated for the treatment of *Falciparum malaria*, the most dangerous form of malaria. Coartem is the only prequalified, fixed-dose combination that combines artemether, **1**, an artemisinin derivative, and lumefantrine, **2**. This fixed-dose combination is of great benefit to patients as it facilitates treatment compliance and supports optimal clinical effectiveness.

Artemisinin, **3**, is a compound derived from the sweet wormwood plant and has been used for centuries in traditional Chinese medicine to treat fever. An artemisinin-based combination therapy is a combination of two or more drugs (one of which is an artemisinin derivative) that have different modes of action and different targets. Studies have shown that using two or more drugs in combination has the potential to delay the development of resistance in areas of low transmission. Artemisinin-based combination therapies in particular have been found to be highly effective treatments for malaria. Their potential to delay resistance in areas of intense transmission is under investigation.

Coartem was co-developed by Novartis in collaboration with Chinese partners, and it is currently registered in 79 countries worldwide. Coartem has been extensively studied in multicenter clinical trials involving more than 3000 patients. Under an agreement with the World Health Organization (WHO), Novartis has supplied Coartem on a nonprofit basis to health authorities in malaria-endemic developing nations since 2001. Production of Coartem, the leading artemisinin-based combination therapy, has increased from 100,000 treatments in 2002 to up to 65 million in 2006.




Artemether Lumefantrine

***Figure 1.*** **The active ingredients for Coartem: artemether 1 and lumefantrine 2.**

In view of the fast-growing demand, the improvement of the manufacturing processes for both active ingredients, the semi-natural product **1** and the fully synthetic tricyclic compound **2** (Figure 1), were urgently needed. In this paper, we present our results from the optimization of the manufacturing process for artemether (**1**). The following paper will deal with the redesign of the manufacturing process for lumefantrine (**2**).

Starting material for the manufacture of **1** is the natural product artemisinin, **3**, which is isolated from *Artemisia annua* by extraction and purified by chromatography on silica gel and crystallization.[1a,b] Artemisinin itself is also a powerful antimalaria agent;[2] however, due to the lactone function, it shows relatively poor stability and has poor solubility properties.[3] It was therefore a breakthrough when it was found that artemisinin, **3**, could be reduced to dihydroartemisinin, **4**, with sodium borohydride[4] without affecting the peroxide linkage. Treatment of **3** with methanol in the presence of hydrochloric acid leads to **1** (Scheme 1).

The sequence as depicted in Scheme 1 was the basis for the production process with which Novartis started its production of artemether in autumn 2004.

## 2. Manufacture of Dihydroartemisinin, 4

The reduction of artemisinin **3** was performed by adding potassium borohydride[5] in portions to a suspension of **3** and calcium chloride[6] in methanol at 5 °C. After complete

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(1) (a) Tandon, S.; Kahol, A. P.; Jain, D. C.; Bhkuni, R. S.; Kumar, S. *J. Sci. Ind. Res.* **2003**, *62*, 457. (b) Klayman, D. L.; Lin, A. J.; Acton, N.; Scovill, J. P.; Hoch, J. M.; Milhous, W. K.; Theoharides, A. D. *J. Nat. Prod.* **1984**, *47*, 715.

(2) Clinical studies on the treatment of malaria with Qingaosu and its derivatives, *J. Tradit. Chin. Med.* **1982**, *2* (1), 45.

(3) Haynes, R. K.; Vonwiller S. C. *Trans. R. Soc. Trop. Med. Hyg.* **1984**, *88*, Supplement *1*, 23.

(4) Li, Y.; Yu, P.-L.; Chen, Y.-X.; Li, L.-Q.; Gai, Y.-Z.; Wang, D.-S.; Zheng, Y. *Kexue Tonbao* **1979**, *14*, 667.


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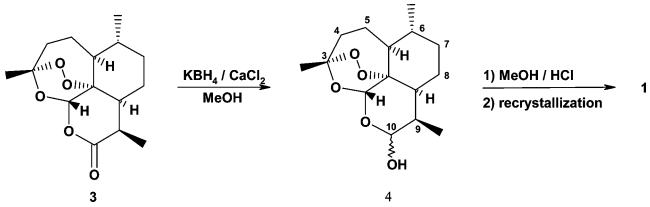
***Scheme 1.*** **Manufacture of artemether 1**




consumption of **3**, the excess of potassium borohydride was destroyed by adding concentrated hydrochloric acid at 0−6 °C until a pH of 0.5−1 was reached. To precipitate the product, water was added, and the pH of the reaction mixture was adjusted to 5−6 by quenching the excess of hydrochloric acid with aqueous potassium hydroxide. Filtration, washing with water, and drying completed the manufacturing process and led to pure dihydroartemisinin in 79% yield. Apart from a somewhat above normal variation in the yield (74−84%), no particular problems were encountered during the early production batches in autumn 2004. However, from batch 20 on, the yield variation became larger, and after a dramatic collapse[7] in batch 35, the campaign was stopped, and a program was initiated to rework the process.

**2.1. Root Cause for Batch Failure.** A batch failure to such an extent as was experienced in batch 35 is a dramatic event in a production plant, particularly with regard to the loss of such a highly valuable starting material. At first, we suspected a severe manipulation error; however, after an in-depth analysis of the batch history, this possibility was ruled out. The speculation of having used contaminated artemisinin as starting material in batch 35 could also be excluded. Consequently, we set up a program to systematically investigate the influence of the various process parameters on the yield by performing a series of scale-down experiments for this reduction process. In parallel, the isolation of the formed by-products in batch 35 was initiated as well (section 2.3).

In view of the acid-sensitive hemiacetal moiety[8a−d] in **4**, studying the influence of the acidic quench conditions on the yield seemed a good starting point for this investigation. Indeed, when the quench was performed at 20 °C (instead of 0−6 °C), the yield loss was 40%. Additionally, if the amount of concentrated hydrochloric acid was increased from 1.5 to 2.3 equiv, a yield loss of 25% was observed. Apparently, the quench conditions are important to obtain an optimal yield, but they could not explain a complete failure.[9] Typical scale-up phenomenon such as the mode of stirring showed only little or no effect at all. Also, no negative effect was noted when iron salts were added to the reaction mixture.[10] The methanol-induced decomposition products of potassium borohydride had no effect either.[11] A minor effect (−5% yield) from humidity was seen when calcium chloride was used which had been exposed to air for 24 h prior to use.

Thus far, with all these experiments we had gained knowledge of how to prevent some yield losses, but we had not yet found a deviation which would lead to a complete failure. The situation changed when we ran the reduction in the presence of potassium hydroxide.[12] The effect of a catalytic amount of potassium hydroxide on the degradation rate of dihydroartemisinin, **4**, proved to be dramatic. When the reduction was run in the presence of only 1 mol % of potassium hydroxide (relative to **3**), a large part of **4** was degraded.[13] The isolated yield was below 10%, and the HPLC fingerprints of the by-products in the mother liquor of this laboratory experiment were almost identical with those of failed batch 35. These observations suggest that small amounts of potassium hydroxide have been the main root cause for the complete failure.

**2.2. Optimized Process Conditions for the Manufacture of Dihydroartemisinin, 4.** Having recognized the extreme vulnerability of **4** towards small amounts of strong bases, the further optimization strategy to make the reduction reaction more robust became straightforward. Apparently, the desired conversion **3** → **4** is in competition with the base-induced degradation of **4**. Even with a stringent limitation of potassium hydroxide in potassium borohydride, an element of risk would persist. Some traces of strong bases would certainly not lead to a complete batch failure but would nevertheless have a negative impact on the yield. As a consequence, the reaction time has to be kept short, and the reaction temperature kept as low as possible. In addition, care has to be taken with the conditions of the quench with hydrochloric acid. Consequently, by reducing the addition time of potassium borohydride from around 10 h to below 6 h, adjusting the reaction temperature from 5 to 7 °C to 1−3 °C, and by keeping the pH during the acid quench at 4−6 (instead of 0−1), the whole process became very robust. After reintroduction into production, an increase of the average yield from originally 79% to 89% was observed. In addition, due to the lower reaction temperature, the excess[14] of potassium borohydride could also be reduced. Since a

(5) Compared to sodium borohydride, potassium borohydride is less hygroscopic and therefore easier to handle on large scale.

(6) The reduction is also described with sodium borohydride without addition of calcium chloride: Sing, C.; Tiwari, P. *Ind. J. Chem.* **2002**, *41B*, 2185.

(7) In this batch, the isolated yield dropped from an average yield of 79% to only 2%.

(8) (a) Idowu, O. R.; Maggs, J. L.; Ward, S. A.; Edwards, G. *Tetrahedron* **1990**, *46*, 1871. (b) Yagen, B.; Pu, Y. M.; Yeh, H. J. C.; Ziffer, H. *J. Chem. Soc. Perkin Trans. I* **1994**, 843. (c) Baker, J. K.; Chi, H. T. *Heterocycles*, **1994**, *38*, 1497. (d) Imakura, Y.; Hachiya, K.; Ikemoto, T.; Yamashita, S.; Kihara, M.; Kobayashi, S.; Shingu, T.; Milhous, W. K.; Lee, K. H. *Heterocycles* **1990**, *31*, 1011.

(9) Large deviations in temperature and amount of acid as applied in these laboratory experiments could be ruled out for batch 35.

(10) It is assumed that the iron-catalyzed cleavage of the peroxy function of artemisinin triggers its antiparasitic activity (see for instance Jefford, C. W. *Curr. Med. Chem.* **2001**, *8*, 1803; Wu, Y. *Acc. Chem. Res.* **2002**, *35*, 255). This mechanism of action is in agreement with the cleavage of the peroxy function when artemisinin is treated with $FeCl_2$ in acetonitrile at 25 °C (Jefford, C. W.; Vincente, M. G. H.; Jacquier, Y.; Favarger, F.; Mareda, J.; Millasson-Schmidt, P.; Brunner, G.; Burger, U. *Helv. Chim. Acta* **1996**, *79*, 1475). However, no decomposition was observed after 48 hours upon treating artemisinin with 0.2 mol % $FeCl_2$ in methanol at 5 °C.

(11) To investigate this hypothesis, potassium borohydride was completely decomposed in methanol (leading to a pH around 9). After adding of artemisinin **3** and calcium chloride, the reduction reaction was run under standard conditions. No influence on the yield was noted.

(12) Potassium hydroxide is a "logical" impurity in potassium borohydride. The latter compound is usually obtained by treating sodium borohydride with ethanolic KOH and subsequent washing with ethanol.

(13) Besides **4**, artemisinin, **3**, is also sensitive towards strong base. However, whereas catalytic amounts of a strong base are sufficient to cause significant degradation in the lactol **4**, molar quantities of base are needed in the case of lacton **3**.

(14) The application of a lower reaction temperature leads to a slower decomposition of potassium borohydride by methanol.

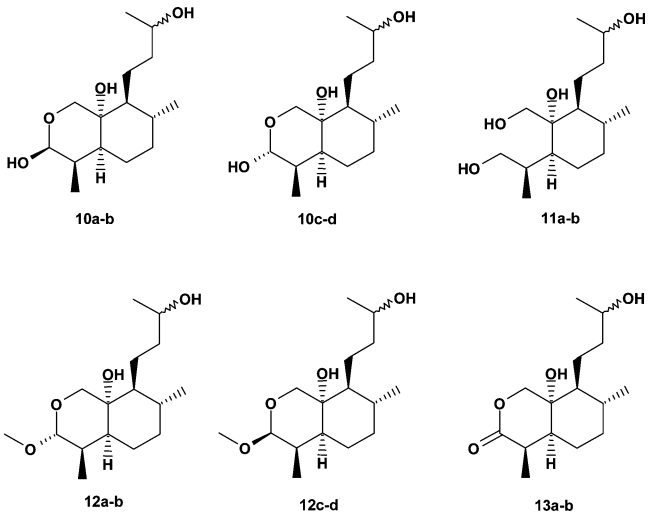



***Figure 2.*** **by-products isolated from the mother liquor of batch 35.**

short reaction time is important and is dependent on the dissolution rate of potassium borohydride in the reaction mixture, the physical properties of this reagent are of importance as well.[15]

In retrospect, both the fluctuating yield in the first series of production batches and the complete failure in batch 35 can now be understood. The most disastrous factor proved to be the contamination of potassium borohydride with small amounts of potassium hydroxide. If such a contamination occurs in combination with a long reaction time, with a reaction temperature at the higher end of the given range and with coarse potassium borohydride particles, all conditions are perfectly set up to lead to the observed failure of batch 35.

**2.3. Isolation of By-products from Batch 35.** By using preparative liquid chromatography followed by preparative peak shaving recycling chromatography, the mayor degradation products (>80%) could be isolated from the mother liquor of batch 35 as six pairs of diastereoisomers and their structures elucidated with $^1$H NMR- and MS-spectroscopy (Figure 2). The absolute configuration at carbon atom 3 (numbering see Scheme 1) could not be derived from the NMR spectra.

The structures of the isolated by-products **10a**−**d** and **11a,b** are in agreement with earlier reports from the literature on the base-catalyzed fragmentation of **4** under reductive conditions.[16] The acetals **12a**−**d** were apparently derived from **10a**−**d** during the acidic workup. The formation of **13a,b** (only in small amounts present in the mother liquor of batch 35) may have started with the base-induced formation of the monocyclic intermediate **14**,[17a−b] followed by the reduction of the various functional groups and subsequent ring-closure reaction (Scheme 2).

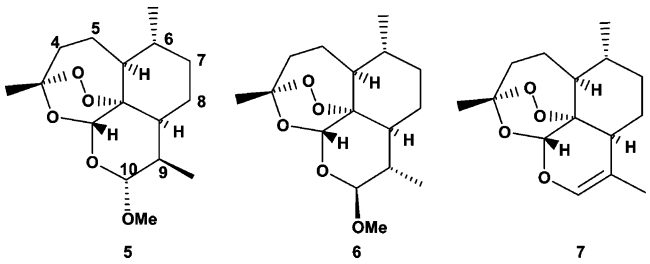
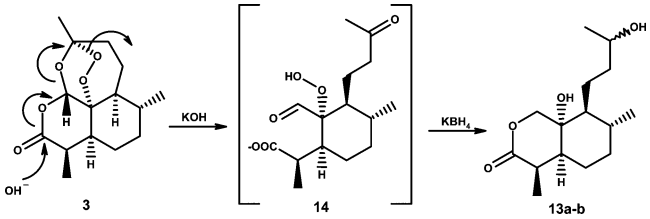



***Figure 3.*** **Potential by-products in the conversion 4 → 1.**

***Scheme 2.*** **Proposed pathway for the formation of the diastereomers 13a,b**




## 3. Manufacture of Artemether 1

**3.1. Conversion of Dihydroartemisinin to Artemether in Dichloromethane.** For the conversion of **4** to **1**, the applied procedure was improved. The reaction in dichloromethane is performed in the presence of an excess of methanol and concentrated hydrochloric acid at 28−32 °C. After cooling to 12−15 °C, neutralizing with aqueous sodium bicarbonate, and phase separation, most of the solvent is distilled off, and crude **1** is precipitated[18] by adding large amounts of water. Filtration, washing with methanol/water, and drying at 40 °C leads to crude **1** in 77% yield. The final purification is accomplished by dissolving crude **1** in methanol at 40−44 °C, precipitating with water at 40 °C, and cooling to 5−10 °C. With this procedure, the overall yield from **3** to **1** is 74%.

**3.2. Improved Process Conditions for the Conversion of Dihydroartemisinin to Artemether**. In parallel to the rework of the reduction step, we also wanted to improve the ketalization **4** → **1**. In particular we wanted to replace dichloromethane by an ecologically more acceptable solvent and to improve the yield by making the process more selective, in particular by suppressing the formation of the main by-product, 10α-epimer **5**. Two other by-products, 9α-epimer **6**[19] and anhydroartemisinin **7**[20] (Figure 3), were formed only in small amounts; however, their depletion by crystallization (in particular in the case of compound **6**) was more difficult.[21]

As shown in Table 1, the best result was achieved when the reaction was run in methyl acetate. In this solvent, the ratio of **1**/**5** could be increased from 85:15 up to 89:11. However, somewhat more of the undesired 9α-isomer **6** was

(15) For details on the analytical specifications of potassium borohydride, see Experimental Section.
(16) Sy, L. K.; Hui, S.-M.; Cheung, K. K.; Brown, G. D. *Tetrahedron* **1997**, *53*, 7493.
(17) (a) Zeng, M. Y.; Li, L. N.; Chen, S. F.; Li, G. Y.; Liang, X. T.; Chen, M.; Clardy, J. *Tetrahedron* **1983**, *39*, 2941. (b) Shang, X.; He, C.; Zheng, Q.; Yang, J.; Liang, X. *Heterocycles* **1989**, *28*, 421.
(18) In our plant, some of the first production batches failed to meet specifications due to insufficient depletion of 10α-epimer **5** and 9α-epimer **6**. To reach the required quality, a recrystallization procedure had to be developed. Furthermore, the precipitation and washing procedures had to be optimized (for details, see Experimental Section).
(19) Pu, Y. M.; Ziffer, H. *Heterocycles* **1994**, *39*, 649.
(20) Haynes, R. K.; Chan, H.-W.; Cheung, M.-K.; Chung, S. T.; Lam, W.-L.; Tsang, H.-W.; Voerste, A.; Williams, I. D. *Eur. J. Org. Chem.* **2003**, *11*, 2098.
(21) Precipitation of artemether crude from methanol/water 55:45 mol/mol % leads to >95% depletion of **5**, 90% of **7**, but only 40% of **6**.

***Table 1.*** **Reaction conditions and product distribution for the conversion 4 → 1[a]**

| solvent | temp (°C) | HCl (equiv) | **1** (%) | **5** (%) | **6** (%) | **7** (%) | **1/5** |
|---|---|---|---|---|---|---|---|
| methyl acetate | 23 | 0.09 | 84.3 | 10.6 | 0.8 | 0.2 | 89:11 |
| | 30 | 0.18 | 82.6 | 11.5 | 2.5 | 0.2 | 88:12 |
| acetone | 30 | 0.18 | 79.0 | 16.6 | 3.7 | 0.5 | 83:17 |
| dichloromethane | 30 | 0.18 | 76.9 | 13.6 | 0.5 | 0.3 | 85:15 |
| dimethoxyethane | 30 | 0.18 | 76.5 | 19.7 | 3.3 | 0.3 | 80:20 |
| methanol | 30 | 0.18 | 76.4 | 20.4 | < 0.1 | 0.3 | 79:21 |
| toluene | 30 | 0.18 | 75.7 | 19.4 | 4.4 | 0.3 | 80:20 |
| acetonitrile | 30 | 0.18 | 54.1 | 37.2 | 4.8 | 1.2 | 59:41 |
| tetrahydrofuran[b] | 30 | 0.18 | 43.0 | 6.1 | 0.5 | 0.6 | 88:12 |

[a] Product distribution in the reaction mixture determined by HPLC; relative response factors for **1**/**5**/**6**/**7** 1.0:1.0:1.0:16.7. [b] Approximately 50% conversion after 6 h.

also formed. Reduction of the temperature and of the amount of acid reduces the formation of **6**. Its depletion was assured by precipitation of artemether in a mixture of methyl acetate, methanol, and water, and the final purification by crystallization from methanol and water. With these new process conditions, the overall yield from **3** to **1** could be improved from 74% to 77%.

## 4. Summary

The manufacturing procedure of the reduction of artemisinin with potassium borohydride to dihydroartemisinin was thoroughly reworked. The most important factor for obtaining optimal yields was to ensure low levels of contamination of potassium hydroxide in potassium borohydride. Application of a low reaction temperature, fast addition rate of potassium borohydride, and careful control of the pH during the quench with hydrochloric acid were further parameters for guaranteeing a robust and optimal process. In the conversion of dihydroartemisinin to artemether, yield and quality were improved by an optimized manufacturing procedure, including optional recrystallization. Furthermore, dichloromethane could be replaced by methyl acetate. With this solvent switch, a procedure is now at hand, which is not only ecologically more friendly but also results in an increased $\beta$:$\alpha$ ratio, giving rise to a somewhat better overall yield.[22]

## 5. Experimental Section

**5.1. Starting Materials and Reagents.** Artemisinin was purchased from several sources in China and Vietnam; 100 mg gave a clear solution in 10 mL of acetonitrile/water (7/3, v/v). Potassium borohydride was purchased from Finnish Chemicals or Rohm & Haas and was used only within the following specifications: appearance: fine, free-flowing powder (no agglomerated, caked material); particle size: median value approximately 50 $\mu$m, particles above 100 $\mu$m less than 5% (laser diffraction); titration in sodium carbonate solution with 0.1 M HCl: max 0.05 (basic contents) or max 0.35 (acidic contents) mL/g $KBH_4$. Iodometric redox titration: min 98%. Calcium chloride water-free (purity ≥98%) was purchased from Koma as granules.

**5.2. Manufacture of Dihydroartemisinin (4), New Process Conditions**. In a 2500-L glass-lined reactor a suspension containing **3** (117 kg, 415 mol), water-free, granulated calcium chloride (15.6 kg, 141 mol), and methanol (1290 L) was chilled to 0−4 °C with stirring. Potassium borohydride (27 kg, 502 mol) was added in 3-kg portions. Due to the evolution of hydrogen, the first portions were added with great care.[23] In our equipment, the following parameters for the next addition of potassium borohydride gave good results: internal temperature 0−4 °C, time between portions: 10 min, gas flow: <9 $m^3$/h, internal pressure: max 1250 mbar. The progress of the reaction was monitored by TLC. The reaction mixture was quenched when the content of artemisinin was <2%. With hydroxide-free borohydride the addition and reaction were complete within 3−6 h. The quench was performed by adding hydrochloric acid 32% w/w (40 L) at −2 to +8 °C within 30 min, leading to a pH of 4−6. Deionized water (1000 L) was added at 0−15 °C, raising the pH to 7−8. For efficient use of the equipment train, the mixture was transferred to a 4000-L glass-lined reactor, internal temperature was set to +2 to 15 °C, and deionized water (1200 L) was added. The product was collected on a centrifuge and washed with deionized water (10 × 240 L), dried in a shelf dryer for 9 h at 50 °C to give 105 kg (89%) of dihydroartemisinin **4** as a white, crystalline powder with a purity of 98% (HPLC).

**5.3. Isolation and Identification of By-products of Batch 35.** *5.3.1. Isolation of By-products **12a−d**.* Five milliliters of mother liquor of batch 35 were filtered and injected onto a Waters LC/MS system equipped with a Micromass ZQ 2000 mass detector and a Waters Symmetry semipreparative column (5 $\mu$m, 19 mm × 50 mm). Using acetonitrile/water = 4/6 (V/V) as the mobile phase at room temperature and a flow rate of 20 mL/min, 10.5 mg of by-products **12a,b** (retention times: 11.5−11.75 min) and 23.5 mg by-products **12c,d** (retention times: 12.5−13.26 min) could be separated within one single run. The mass detector in its atmospheric pressure ionization mode (AP+) turned out to be superior in comparison to electrospray ionization (ES+). The structures of all four isomers were confirmed with $^1$H NMR- and MS-spectroscopy. Seventy-seven milligrams of the first eluting peak at 8.69 min turned out to be a complex mixture of eight isomers which were separated separately by preparative peak shaving recycling chromatography.

*5.3.2. Isolation of By products **10a−d**, **11a,b** and **13a,b**.* Evaporation residue (77 mg) of the first eluting peak (from the previous separation) was dissolved in 5 mL of acetonitrile, filtered, and injected onto a Kromasil C8 column (10 $\mu$m, 2.0 cm × 20 cm) while using the same LC/MS system in its AP+ mode as mentioned above. Again acetonitrile/water = 4/6 (v/v) was used as mobile phase at room temperature with a flow rate of 20 mL/min. By-product **10a**, eluting first, was removed directly, and the area of incomplete separation was recycled. During the second run, by-product **10b** was removed at the front of the elution profile, and

(22) The feasibility of the conversion **4** → **1** in methyl acetate has been demonstrated on a kilogram scale. Since artemether will in future be produced externally, this process was not implemented at Chemical Production Novartis.

(23) With hydroxide-free borohydride, the reaction and gas evolution were vigorous from the beginning.

during the third run by-products **10c,d** from the front and by-product **13a** from the end of the elution profile. The remaining by-products, **11a**, **11b**, and **13b**, were baseline separated during the final recycling. The structures of all by-products were confirmed with $^1$H NMR- and MS spectroscopy. As mentioned in section 2.3, it is at present not possible to distinguish the stereochemistry at carbon 3 (even for the isolated isomers); the NMR data are therefore not disclosed. Complete structure elucidation will only be possible after applying further structure elucidation technologies.

**5.4. Manufacture of Artemether Crude in Dichloromethane. 4** (160 kg, 562 mol) was loaded into a 2500-L glass-lined reactor. Dichloromethane (2000 L) was added, and the suspension was stirred at a moderate speed. Methanol (150 L) and concentrated hydrochloric acid (9 L) were added. The now almost clear solution was heated to 28−32 °C (applying a target jacket temperature of 45 °C), and the solution was stirred at 28−32 °C for 3 h. Reaction progress was monitored by TLC (requirement: ≥2% of **4**). The reaction mixture was cooled to 11−15 °C, and a solution of sodium bicarbonate (10 kg) in water (240 L) was added. The organic phase was transferred to a 4000-L stainless steel reactor, and the aqueous phase was extracted with dichloromethane (2 × 160 L). The combined organic phases were concentrated to ∼400 L under reduced pressure at 18−23 °C. Methanol (550 L) was added. The mixture was transferred to a 1600-L stainless steel reactor, and the reactor and pipes were flushed with dichloromethane (50 L). The mixture was once more concentrated to ∼400 L under reduced pressure at 20−30 °C. This procedure was repeated by addition of 600 L of methanol and subsequent distillation to ∼400 L volume. After addition of methanol (500 L) at 20 °C, the solution was clear-filtered, and the reactor and pipes were flushed with methanol (160 L) into the precipitation reactor (4000-L stainless steel). The solution was heated to 29 °C using a target jacket temperature of 45 °C. Artemether crude was precipitated by the addition of water (620 L).[24] To reach the required quality of pure artemether, water was added at a constant rate within ca. 2 h via a lance especially designed for this purpose. Nitrogen pressure was applied to spray the water onto the surface of the methanol solution, which was kept at 27−30 °C throughout the addition of water. Initially, the set point in our procedure was 520 L of water. Using less than 620 L of water for precipitation gave the same quality; using over 640 L resulted in the precipitation of by-products. During process optimization, 620 L proved to be the optimal amount of water to obtain the highest yields.[25] After addition of water, the suspension was stirred for 15 min, cooled to 2 °C, and stirred for 1 h at 2 °C. After filtration on a centrifuge, the filter cake was washed with a 1:1 (v/v) mixture of methanol and water (320 L), and with water (2 × 160 L). Typical impurity levels of water-wet product: **5** < 0.1% and **7** = 0.2%. The average yield using this optimized manufacturing procedure was 77.1%. If the wet product did not comply with respect to the content of the critical by-products **5**, **6**, and **7**, an optional recrystallization procedure was applied: The wet filter cake was dissolved in methanol (1100 L) and precipitated by adding water (550 L) at 27−30 °C via a spray-ring device followed by the same cooling, filtration, and washing procedure as described above. Drying was performed under reduced pressure in a 1600-L stainless steel double cone dryer for 4 h at 40 °C by applying a stream of nitrogen of 3000 L/h.

**5.5. Preparation of Artemether Crude in Methyl Acetate.** Into a 1-L reactor equipped with a propeller stirrer, a pH probe, and a distillation apparatus was placed a suspension of dihydroartemisinin (50.0 g, 0.176 mol) in methyl acetate (625 mL) which was then treated at 20 °C with methanol (56.0 g, 1.75 mol) and aqueous hydrochloric acid (2.1 g, 0.021 mol). The suspension was stirred for 4.5 h at 23 °C. The conversion of dihydroartemisinin was monitored by TLC. The solution was cooled to 14 °C, and a solution of sodium hydrogen carbonate (6 g) in water (75 mL) was added. The mixture was stirred for 10 min, and phase separation was performed at pH 6−8. The organic phase (∼750 mL) was concentrated (250−200 mbar) to a volume of ∼160 mL. The residue was diluted with methanol (185 mL) and concentrated in vacuo (200−100 mbar) to a volume of ∼160 mL. The suspension was heated to 29 °C and diluted with methyl acetate (31 mL) and methanol (94 mL). The resulting solution was filtered. The reactor and the filter were washed with methanol (50 mL). The solution was treated at 29 °C with water (140 mL) over 2 h. The resulting suspension was cooled in 2 h to 2 °C and stirred at this temperature for at least 1 h. The product was filtered and washed with cold methanol/water 1:1 (100 mL) and with cold water (2 × 50 mL). Drying (∼10 mbar/ 40 °C) afforded artemether crude (42.0 g, 80%) as sand-like, colorless crystals.

**5.6. Crystallization of Artemether Crude.** Artemether crude (150 kg) was dissolved in methanol (650 kg) at 40−44 °C. After clear filtration and rinsing with methanol (190 L), water (175 kg) was added at 40 °C in 30 min, and the solution was seeded in three portions with a total of 3 kg of artemether pure. Again at 40 °C, water was added (710 kg) in ca. 3 h. The suspension was cooled within 2−3 h to 5−10 °C. Filtration was performed on a centrifuge, and the product was washed in three portions with a precooled 1:1 methanol/water mixture. After drying, 144 kg (96%) of pure artemether **1** was obtained.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(24) Since four out of the first six batches failed to meet the specifications due to high levels of by-products (up to 2.3% of **5** and up to 0.67% of **7**), amount and addition mode of water had to be optimized.

(25) In this optimization work we found also that seeding is not necessary.