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# Chemo- and Diastereoselective Hydrosilylation of Amorphadiene toward the Synthesis of Artemisinin

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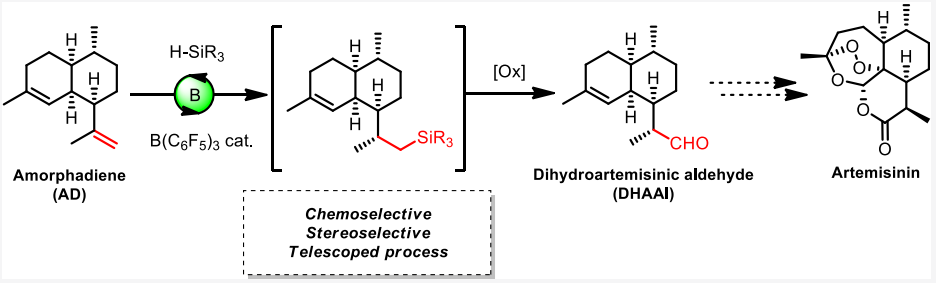


**ABSTRACT:** A formal synthesis of artemisinin starting from amorphadiene is described. This new route relies on the development of a catalytic chemo- and diastereoselective hydrosilylation. The practicability of this method is demonstrated by converting amorphadiene to dihydroartemisinic aldehyde using a one-pot hydrosilylation/oxidation sequence, minimizing the number of purifications and maximizing the productivity through a practical one-pot procedure. In addition, this approach can be coupled with a crystallization-induced diastereoselective transformation (CIDT) to enhance the optical purity of the key target intermediate, dihydroartemisinic aldehyde.

## INTRODUCTION

Artemisinin, a natural product isolated from the sweet wormwood plant *Artemisia annua* L., is a cornerstone in the fight against malaria.[1] Today, the demand for the so-called "artemisinin-based combination therapies" (ACT) is relatively high as the malaria burden remains particularly important with 435 000 deaths registered in 2017.[2] Harvesting *A. annua* plant and extracting the active substance is the major production pathway with ca. 100−120 tons/year. Nevertheless, this approach has been recently supplemented by a semisynthetic route developed by Amyris and Sanofi, which produces approximately 60 tons of artemisinin per year (Scheme 1, eq. 1).[3]

The semisynthetic production of artemisinin involves the formation of artemisinic acid (**AA**) by fermentation from sugars at titers around 25 g/L. This intermediate is then converted into artemisinin by chemical transformations, with an overall yield of around 50% (Scheme 1, eq. 1). Many research efforts have focused either on increasing the production titers of **AA** (fermentation)[4] or improving the efficiency of the chemical transformations,[5] including chemical processing on plant extracts.[6] However, the current production cost of this route remains higher than the extraction from the plant. Therefore, redesigning the current semisynthetic route is required to make it valuable again for large-scale production. Researchers from Amyris have attempted to valorize amorphadiene (**AD**), a byproduct from the fermentation process that can be obtained in very high titers (up to 120 g/L), and convert it into artemisinin (Scheme 1).[7] For example, **AD** was converted into dihydroartemisinic acid (**DHAA**) using a three-step sequence involving a chemoselective hydroboration of the exo-cyclic double bond.[7a] 9-Borabicyclononane (9-BBN) was utilized as the hydroboration reagent and dihydroartemisinic aldehyde (**DHAAl**) was isolated in a moderate diastereoselectivity (dr = 85:15) after two successive oxidations via dihydroartemisinic alcohol. This route is concise, but several purifications by column chromatography were required to isolate the pure products. An alternative route was to convert **AD** into **DHAA** in six steps by masking the internal double bond in the form of an epoxide; subsequently, artemisinin was prepared via **DHAA**.[7b]

Herein, we report our results on the development of a catalytic protecting group-free process toward artemisinin aldehyde starting from **AD** by developing a one-pot chemo- and diastereoselective hydrosilylation/oxidation process

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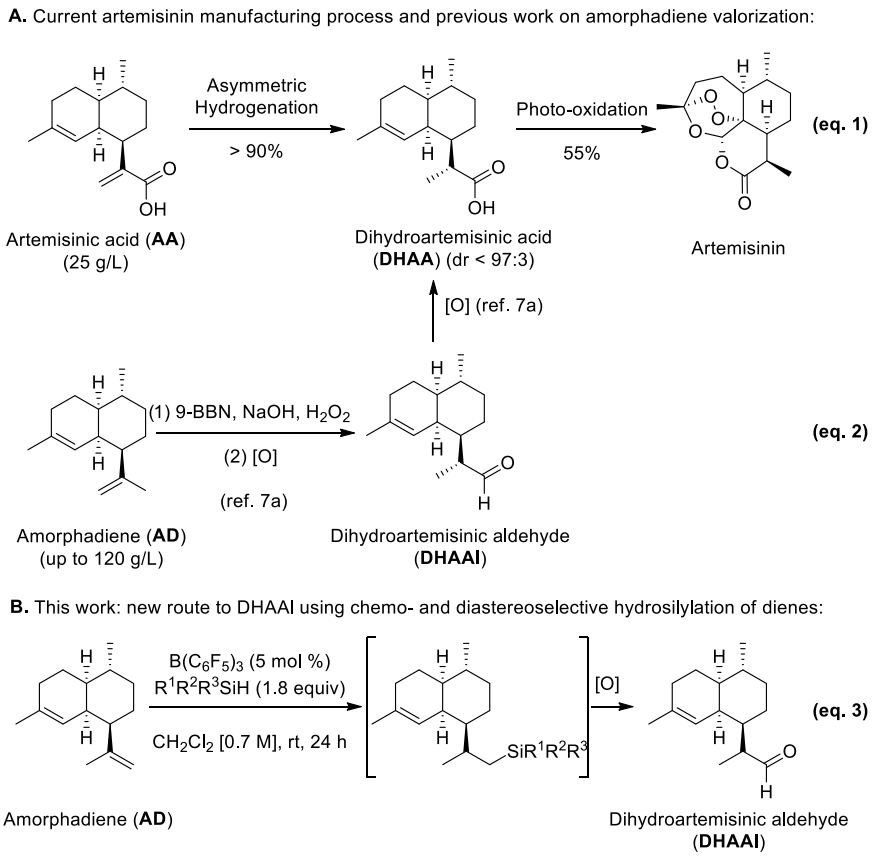
**Scheme 1. Semisynthetic Approaches for the Production of Artemisinin[3] from AA and from the Byproduct AD, and Its Conversion to DHAAl**



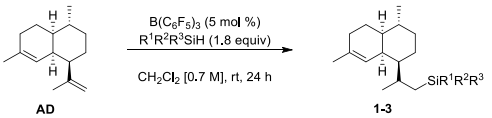

(Scheme 1, eq. 3) requiring only one purification to access dihydroartemisinic alcohol. The latter was transformed to **DHAAl** with a good dr, in favor of the (11*R*)-isomer, by an oxidation step. The dr in the desired (11*R*)-diastereomer could be further improved using our recently reported crystallization-induced diastereoisomer transformation (CIDT) using the Betti base.[8]

## RESULTS AND DISCUSSION

Hydrosilylation is a robust transformation that can be performed using inexpensive reagents in combination with the readily available "off-the-shelf" catalysts. In this regard, the hydrosilylation, catalyzed by tris-pentafluorophenyl borane [$B(C_6F_5)_3$],[9,10] caught our attention. The borane compound, $B(C_6F_5)_3$, has been shown to be a versatile catalyst with high performance in an array of transformations,[9c,d] including the hydrosilylation of aldehydes, ketones, acid chlorides, esters, carboxylic acids,[11] and enamines,[12] reduction of amides, nitriles,[13] sulfides, sulfoxides, and sulfones,[14] hydroarylations,[15] and Conia-ene-type cyclizations.[16] This catalyst was also effective for the hydrosilylation of simple alkenes,[17] and usually an anti-Markovnikov selectivity was obtained. However, the chemoselectivity of the hydrosilylation of substrates bearing two or more nonactivated alkenes has never been investigated. We therefore decided to explore the chemoselectivity of the hydrosilylation of **AD** using $B(C_6F_5)_3$ as the catalyst and then to access **DHAAl** by oxidation of the obtained silane.

For the primary screening, 5 mol % of $B(C_6F_5)_3$ and 1.8 equiv of silane (added in two portions separated by 6 h) were used. Under these conditions, **AD**[18] reacted regio- and chemoselectively with phenyldimethysilane ($PhMe_2SiH$) to give the corresponding hydrosilylated product **1** in good yield (76%). A moderate dr of 69:31 was obtained but with the desired (11*R*)-diastereomer predominating (Table 1, entry 1).[7a] Importantly, no product resulting from the hydrosilylation of the internal double bond was observed. The use of phenylsilane ($PhSiH_3$) led to a full conversion of **AD**, but a

**Table 1. Lewis Acid Catalyzed Hydrosilylation of AD Using Different Silanes**




| entry | $R^1R^2R^3SiH$ | $\tau_c$[a] | 1–3 $R^1R^2R^3Si$ | yield[b] (dr) |
|---|---|---|---|---|
| 1 | $PhMe_2SiH$ | 93% | **1** $PhMe_2Si$ | 80% (69:31) |
| 2 | $PhSiH_3$ | 100% | n.d. | – |
| 3 | $Ph_2SiH_2$ | 100% | **2** $Ph_2SiH$ | 90% (69:31) |
| 4 | $Ph_3SiH$ | 0% | – | – |
| 5 | $Ph_2MeSiH$ | 82–89% | **3** $Ph_2MeSi$ | 81% (78:22) |

[a]Conversions of AD were determined by $^1H$ NMR analysis of the crude mixture using 1,3-dimethoxybenzene as an internal standard. [b]Yields obtained on a 200 mg scale.



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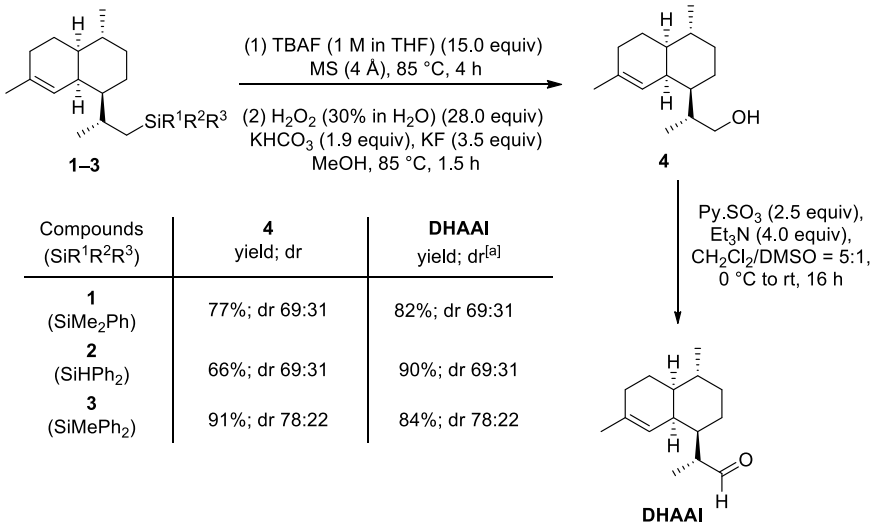
**Scheme 2. Oxidation of Hydrosilylated Derivatives 1−3 to DHAAl**




| Compounds ($SiR^1R^2R^3$) | 4 yield; dr | DHAAl yield; dr[a] |
|---|---|---|
| 1 ($SiMe_2Ph$) | 77%; dr 69:31 | 82%; dr 69:31 |
| 2 ($SiHPh_2$) | 66%; dr 69:31 | 90%; dr 69:31 |
| 3 ($SiMePh_2$) | 91%; dr 78:22 | 84%; dr 78:22 |

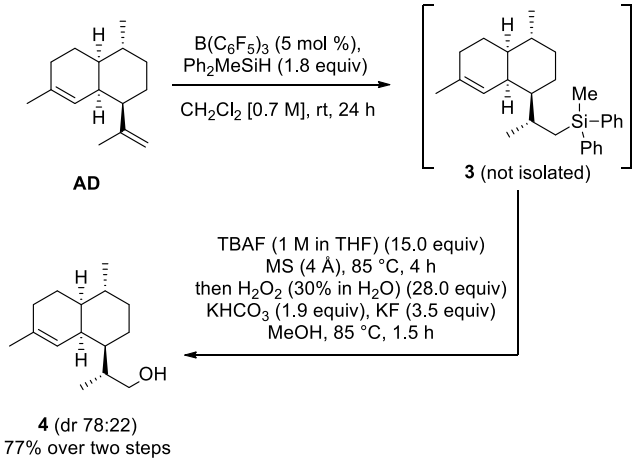
[a]The diastereomers were difficult to separate but were transformed to (11*R*)-**DHAAl** with a dr >95:5.[8]

complex mixture of products was formed (Table 1, entry 2). Good yields of the desired hydrosilylated products **2** and **3** (64−70%) were obtained with $Ph_2SiH_2$ and $Ph_2MeSiH$, respectively (Table 1, entries 3 and 5). The reactions were again chemoselective and, as expected, the diastereoselectivity of the transformation correlates with the bulkiness of the silane partner (dr ranging from 64:36 to 78:22). It is worth mentioning that too bulky silanes, such as triphenylsilane ($Ph_3SiH$) and tris-*iso*propylsilane ($iPr_3SiH$), did not react with **AD** and that $(TMSO)_2MeSiH$ gave high dr (89:11) but low yield in the corresponding hydrosilylated compound due to a competing Piers−Rubinsztajn reaction.[19]

The isolated hydrosilylated derivatives **1**−**3** were successfully converted to alcohol **4** and further oxidized to **DHAAl** in good to high yields (Scheme 2). When compounds **1**−**3** were subjected to the Tamao−Kumada oxidation conditions (TBAF then $H_2O_2/KHCO_3/KF$ at 85 °C), the desired alcohol **4** was isolated in yields ranging from 66 to 91% (Scheme 2). After a sulfur trioxide−pyridinium oxidation ($Py.SO_3$, $Et_3N$, $CH_2Cl_2$/DMSO),[7] **DHAAl** was isolated in good to excellent yields (82−90%) (Scheme 2). Control experiments enabled to ensure that no epimerization of **DHAAl** occurred under the reaction conditions used for the final oxidation step.[20]

To improve the scalability of the method, a one-pot process was evaluated to access dihydroartemisinic alcohol **4** from **AD**. When the reaction was carried out in a one-pot process in $CH_2Cl_2$, alcohol **4** was isolated in only 7% yield along with the hydrosilylated intermediate **3**, which was recovered in 68% yield. As $CH_2Cl_2$ is reactive under basic conditions, we decided to carry out a solvent exchange. Prior to the oxidation of **3** to **4** ($H_2O_2/KHCO_3/KF$, MeOH), $CH_2Cl_2$ was evaporated and replaced by THF containing TBAF (1 M). Accordingly, 85% of **AD** was transformed to **4**, and this latter was isolated in excellent yield of 77% over two steps without isolating the hydrosilylated intermediate **3** (Scheme 3). Even if the dr of the obtained **DHAAl** is moderate to good, a CIDT applied to the mixture of diastereomers, using the Betti base,[8] led to (11*R*)-**DHAAl** with an excellent dr (95:5). Using the hydrosilylation/CIDT sequence, (11*R*)-**DHAAl** can be obtained from **AD** with an overall yield of 57.8%.

**Scheme 3. Direct Transformation of AD to Alcohol 4**




## CONCLUSIONS

The development of a chemoselective method for the oxidation of amorphadiene (**AD**) to dihydroartemisinic aldehyde (**DHAAl**), a key precursor of the antimalarial artemisinin, was achieved using a hydrosilylation step catalyzed by $B(C_6F_5)_3$. This catalyst proved to be particularly effective for the regioselective hydrosilylation of **AD** as 5 mol % was required to obtain the different hydrosilylated intermediates in high yields (up to 90%) and good diastereoselectivities (up to 89:11). We showed that **AD** can be directly transformed to alcohol **4** in 77% yield in a one-pot hydrosilylation/oxidation sequence without the need of isolating the hydrosilylated product and without the erosion of the diastereoselectivity. In addition, the dr of **DHAAl** can be increased to 95:5 using a CIDT. This strategy was validated to access **DHAAl** that could be further transformed to produce dihydroartemisinic acid and artemisinin, as reported previously.[7]

## EXPERIMENTAL SECTION

**General Information.** Reagents (Aldrich and TCI) were purchased as a reagent grade and used without further purification. Reactions in the absence of air and moisture were performed in an oven-dried glassware under an argon atmosphere. Flash column



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chromatography was performed using $SiO_2$ (60 Å, 230−400 mesh, particle size 0.040−0.063 mm, Merck). The solvent compositions are reported individually in parentheses. Analytical thin-layer chromatography (TLC) was performed on aluminum sheets coated with silica gel 60 F254 (Merck, Macherey-Nagel). Visualization was achieved using a potassium permanganate ($KMnO_4$) solution. Reported yields refer to spectroscopically and chromatographically pure compounds that were dried under a high vacuum (0.1−0.05 mbar) before analytical characterization. $^1H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV 400 spectrometer at 400 MHz ($^1H$) and 101 MHz ($^{13}C$). Chemical shifts $\delta$ are reported in ppm using the residual deuterated solvent signals as an internal reference ($CDCl_3$: $\delta H$ = 7.26 ppm, $\delta C$ = 77.16 ppm). For $^1H$ NMR, coupling constants $J$ are given in Hz and the resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet), and br (broad). All spectra were recorded at 298 K. Infrared (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer and are reported as wavenumbers $\nu$ ($cm^{-1}$). High-resolution mass spectrometry (HRMS) was obtained on a LTQ Orbitrap-XL-ETD, Thermo Scientific in the ESI mode. Gas chromatography coupled with mass spectrometry (GC/MS) analysis was performed on a Shimadzu GCMS-QP2010S using an electronic impact (EI) spectrometer. Melting points were determined using a Büchi melting point apparatus in open capillaries.

**General Procedure for the Lewis Acid Catalyzed Hydrosilylation of AD on 1 mmol Scale.** To a solution of $B(C_6F_5)_3$ (25 mg, 0.049 mmol, 0.05 equiv) in $CH_2Cl_2$ (2.0 mL) was added **AD** (200 mg, 0.97 mmol, 1.0 equiv), which led to a yellow solution. The silane (1.16 mmol, 1.2 equiv) was added dropwise to the solution, resulting in a gas evolution and formation of a colorless solution. After 6 h at rt, an additional amount of silane (0.58 mmol, 0.6 equiv) was added and the mixture was stirred at rt for 18 h and passed through a pad of $SiO_2$ eluting with $CH_2Cl_2$ (50 mL); then, the solvent was evaporated. The crude was purified by flash column chromatography on silica gel to isolate the products.

**Characterization of Derivatives 1−3.** *Mixture of (11R)- and (11S)-Dihydroartemisinic Dimethylphenylsilane (**1**).* The crude was purified by flash column chromatography on silica gel (hexane) to give **1** (264 mg, 80%, dr = 69:31) as a colorless oil. rf = 0.59 (hexane); IR (ATR): $\nu$ = 2906, 2868, 1517, 1448, 1427, 1376, 1247, 1209, 1187, 1156, 1111, 1086, 991, 970, 929 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.28−0.34 (4 s, 6H), 0.50 (m, 1H), 0.76−0.91 (m, 8H), 0.96 (m, 1H), 1.07−1.19 (m, 2H), 1.40 (m, 1H), 1.49−1.69 (m, 3H), [1.59 (s, 1H), 1.62 (s, 2H)], 1.73−1.99 (m, 4H), [2.51 (br s, 0.7H), 2.58 (br s, 0.3H)], [5.08 (br s, 0.3H), 5.16 (br s, 0.7H)], 7.32−7.38 (m, 3H), 7.46−7.61 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta$ = [−1.9, −1.6 (1C)], [−1.7, −1.3 (1C)], [19.97, 19.99 (1C)], [20.5, 21.3 (1C)], [21.1, 22.2 (1C)], [23.96, 24.02 (1C)], [26.02, 26.05 (1C)], [26.3, 26.8 (1C)], [26.8, 26.9 (1C)], [27.8, 27.9 (1C)], [30.6, 30.7 (1C)], [36.10, 36.13 (1C)], [38.0, 38.1 (1C)], [42.26, 42.28 (1C)], [49.6, 49.9 (1C)], [121.2, 121.3 (1C)], 127.8 (2C), 128.8 (1C), [133.67, 133.73 (2C)], [134.75, 134.82 (1C)], [140.5, 140.6 (1C)] ppm; HRMS (ESI-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{23}H_{36}SiNa^+$ 363.2478; found 363.2503; GC/MS: $m/z$ (%): 263 (6, $[M - C_6H_5]^+$), 262 (28), 221 (4, $[M - C_9H_{11}]^+$), 220 (20), 163 (1, $[M - C_{11}H_{17}Si]^+$), 162 (10), 135 (100), 121 (10), 107 (7), 105 (6).

*Mixture of (11R)- and (11S)-Dihydroartemisinic Diphenylsilane (**2**).* The crude was purified by flash column chromatography on silica gel (hexane) to give **2** (338 mg, 90%, dr = 69:31) as a colorless oil. rf = 0.41 (hexane); IR (ATR): $\nu$ = 2906, 2868, 1447, 1428, 1377, 1304, 1264, 1207, 1186, 1156, 1114, 991, 956 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = [0.84 (d, $J$ = 6.7 Hz, 1H), 0.85 (d, $J$ = 6.7 Hz, 2H)], 0.80−0.94 (m, 3H), [0.99 (d, $J$ = 6.7 Hz, 2H), 1.02 (d, $J$ = 6.7 Hz, 1H)], 1.06 (m, 1H), 1.15 (m, 1H), 1.40 (m, 1H), [1.58 (s, 1H), 1.60 (s, 2H)], 1.47−1.97 (m, 8H), [2.53 (br s, 0.7H), 2.63 (br s, 0.3H)], 4.97 (m, 1H), [5.05 (br s, 0.3H), 5.13 (br s, 0.7H)], 7.28−7.47 (m, 6H), 7.48−7.84 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta$ = [17.7, 18.9 (1C)], [19.95, 19.98 (1C)], [20.1, 20.8 (1C)], [23.9, 24.0 (1C)], [26.00, 26.02 (1C)], [26.4, 26.7 (1C)], [26.8, 26.9 (1C)], [27.8, 27.9 (1C)], [30.6, 31.1 (1C)], [35.97, 36.03 (1C)], [37.9, 38.1 (1C)], [42.15, 42.23 (1C)], [49.3, 49.6 (1C)], [121.05, 121.13 (1C)], [128.02, 128.06, 128.09, 128.11 (4C)], [129.50, 129.56, 129.61, (2C)], [134.90, 134.92 (1C)], 135.2 (2C), [135.3, 135.4 (2C)], [135.7, 135.8 (2C)] ppm; HRMS (ESI-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{27}H_{36}SiNa^+$ 411.2478; found 411.2115.

*Mixture of (11R)- and (11S)-Dihydroartemisinic Diphenylmethylsilane (**3**).* The crude was purified by flash column chromatography on silica gel (hexane) to give **3** (319 mg, 81%, dr = 78:22) as a colorless oil. rf = 0.38 (hexane); IR (ATR): $\nu$ = 2906, 2862, 1487, 1448, 1427, 1376, 1304, 1250, 1187, 1157, 1109, 991 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = [0.63 (s, 1.9H), 0.64 (s, 1.1H)], 0.83 (d, $J$ = 6.8 Hz, 3H), 0.86 (d, $J$ = 6.8 Hz, 3H), 0.78−0.94 (m, 5H), 1.00 (m, 1H), 1.15 (m, 1H), 1.40 (m, 1H), [1.58 (s, 1.1H), 1.61 (s, 1.9H)], 1.45−1.97 (m, 8H), [2.50 (br s, 0.8H), 2.63 (br s, 0.2H)], [5.06 (br s, 0.2H), 5.12 (br s, 0.8H)], 7.30−7.45 (m, 6H), 7.46−7.65 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta$ = [−3.3, −2.9 (1C)], 20.0 (1C), [19.4, 20.6 (1C)], [20.5, 21.3 (1C)], [23.95, 24.02 (1C)], 26.0 (1C), [26.2, 26.8 (1C)], [26.8, 26.9 (1C)], [27.8, 27.9 (1C)], [30.4, 30.7 (1C)], 36.1 (1C), [38.0, 38.1 (1C)], 42.3 (1C), [49.7, 50.0 (1C)], [121.1, 121.3 (1C)], [127.9−128.1 (4C)], [129.0−129.7 (2C)], [134.76, 134.84 (1C)], [134.6−135.0 (4C)], [137.9, 138.2 (1C)], [138.6, 138.8 (1C)] ppm; HRMS (ESI-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{28}H_{38}SiNa^+$ 425.2635; found 425.2634.

**Oxidation of 1 to Dihydroartemisinic Alcohol 4.** A solution of **1** (150 mg, 0.44 mmol, 1.0 equiv) in TBAF (1 M in THF) (6.6 mL, 6.60 mmol, 15.0 equiv) was added to activated molecular sieves (4 Å) (1.6 g) in a 20 mL flask. The flask was sealed and heated at 85 °C. After 4 h, the solution was cooled to rt, treated with KF (90 mg, 1.54 mmol, 3.5 equiv), $KHCO_3$ (84 mg, 0.84 mmol, 1.9 equiv), MeOH (3.7 mL), and $H_2O_2$ (30% in $H_2O$) (1.6 mL, 11.2 mmol, 28.0 equiv), stirred at 85 °C for 1.5 h, cooled to rt, diluted with EtOAc (10 mL) and $H_2O$ (10 mL), and filtered. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography on silica gel (PE/EtOAc 95:05) gave **4** (75 mg, 77%, dr = 69:31) as a white solid. The two diastereomers were not separated.

*− Major Isomer: (11R)-Dihydroartemisinic Alcohol **4**.* rf = 0.22 (petroleum ether/EtOAc = 95:05); IR (ATR): $\nu$ = 3335, 3328, 2920, 2865, 1467, 1451, 1432, 1370, 1025, 991, 955 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.86 (d, $J$ = 6.4 Hz, 3H), 0.88−1.08 (m, 2H), 1.00 (d, $J$ = 6.8 Hz, 3H), 1.14−1.30 (m, 2H), 1.41 (m, 1H), 1.53 (m, 1H), 1.61 (s, 3H), 1.57−1.69 (m, 3H), 1.72−2.08 (m, 3H), 2.47 (br s, 1H), 3.52 (m, 1H), 3.75 (dd, $J$ = 10.6, 3.3 Hz, 1H), 5.21 (br s, 1H) ppm, the OH signal was too weak to be observed; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta$ = 15.1 (1C), 20.0 (1C), 24.0 (1C), 26.0 (1C), 26.5 (1C), 26.8 (1C), 27.8 (1C), 35.8 (1C), 36.8 (1C), 37.7 (1C), 42.2 (1C), 42.8 (1C), 67.0 (1C), 120.8 (1C), 135.3 (1C) ppm; HRMS (ESI-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{15}H_{26}ONa^+$ 245.1876; found 245.1875; GC/MS: $m/z$ (%): 222 (11, $[M]^+$), 191 (14, $[M - CH_3O]$), 163 (100, $[M - C_3H_7O]^+$), 149 (10), 135 (15), 121 (25), 107 (36), 105 (14).

The analytical data correspond to the data reported in the literature.[18]

**Oxidation of 4 to DHAAl.** A solution of **4** (125 mg, 0.56 mmol, 1.0 equiv, dr = 78:22) in $CH_2Cl_2$/DMSO 5:1 (3.0 mL) was treated with $Et_3N$ (0.31 mL, 2.25 mmol, 4.0 equiv), cooled with an ice bath, and treated with $SO_3$·Py (225 mg (3 × 75 mg), 1.41 mmol, 2.5 equiv, one portion every 10 min). The solution was stirred at rt for 16 h, poured into a 10% citric acid solution (3.2 mL), and stirred for 10 min; then, the two layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with a 10% citric acid solution (3.2 mL), then with a sat. $NaHCO_3$ aqueous solution (3.2 mL), and then brine (3.2 mL), dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography on silica gel (hexane/EtOAc = 95:05) gave **DHAAl** (104 mg, 84%, dr 78:22) as a colorless oil.


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J. Org. Chem. 2020, 85, 9607−9613

N.B.: Enantio-enriched **DHAAl** (dr > 98:02) was obtained from pure **4** (dr > 98:02) and used as reference for characterization. Pure **DHAAl**: $[\alpha]_D^{25}$ + 16.0 (*c* 1.56, $CHCl_3$).

– *Major Diastereomer.* rf = 0.59 (hexane/EtOAc 95:05); IR (ATR): $\nu$ = 2910, 2868, 2699, 1724, 1448, 1374, 1265, 1235, 1220, 1184, 1151, 1109, 1067, 1015, 991, 957, 939, 921 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.87 (d, *J* = 6.5 Hz, 3H), 0.95 (td, *J* = 12.9, 3.3 Hz, 1H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.12 (td, *J* = 12.7, 3.2 Hz, 1H), 1.27 (m, 1H), 1.40 (m, 1H), 1.64 (d, *J* = 1.1 Hz, 3H), 1.62–1.68 (m, 3H), 1.73–2.01 (m, 3H), 2.36 (dtt, *J* = 10.9, 7.0, 3.5 Hz, 1H), 2.48 (br s, 1H), 5.13 (br s, 1H), 9.58 (d, *J* = 4.0 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta$ = 11.9 (1C), 19.8 (1C), 24.0 (1C), 25.9 (1C), 26.7 (1C), 27.5 (1C), 27.8 (1C), 35.4 (1C), 36.7 (1 C), 41.6 (1C), 42.0 (1C), 48.6 (1C), 119.7 (1C), 136.2 (1C), 206.2 (1C) ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{25}O^+$ 221.1900; found 221.1901.

**Direct Transformation of AD to Alcohol 4.** To a solution of $B(C_6F_5)_3$ (15 mg, 0.029 mmol, 0.05 equiv) in $CH_2Cl_2$ (0.85 mL) was added **AD** (120 mg, 0.587 mmol, 1.0 equiv), which led to a yellow solution. The mixture was treated dropwise with $Ph_2MeSiH$ (0.14 mL, 0.704 mmol, 1.2 equiv), which led to gas evolution, and a colorless solution was obtained. The mixture was stirred at rt for 6 h, treated with $Ph_2MeSiH$ (70 $\mu$L, 0.352 mmol, 0.6 equiv), and stirred at rt for 18 h. The mixture was passed through a pad of $SiO_2$ eluting with $CH_2Cl_2$ (50 mL) and evaporated. The yellow oil was dissolved in TBAF (1 M in THF) (8.5 mL, 8.5 mmol, 15.0 equiv), treated with activated molecular sieves (4 Å) (2.2 g), stirred at 85 °C for 4 h, cooled to rt, treated with KF (118 mg, 2.03 mmol, 3.5 equiv), $KHCO_3$ (113 mg, 1.12 mmol, 1.9 equiv), MeOH (4.7 mL), and $H_2O_2$ (30% in $H_2O$) (2.0 mL, 16.43 mmol, 28.0 equiv). After 1.5 h at 85 °C, the mixture was cooled to rt, diluted with EtOAc (15 mL) and $H_2O$ (15 mL), and filtered. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. Flash column chromatography ($SiO_2$, PE/EtOAc 95:05 → 90:20) gave **4** (101 mg, 77%, dr 78:22) as a white solid (see above for the characterization of **4**). Unreacted **AD** (18 mg) was recovered.

*(11R)/(11S)-Dihydroartemisinic Aldehyde = 95:5 (DHAAl) by CIDT.* A mixture of (11*R*/11*S*)-dihydroartemisinic aldehyde (814 mg, 3.694 mmol, 1 equiv) was added to a suspension of (*S*)-Betti base (875 mg, 3.509 mmol, 0.95 equiv) in MeOH (16 mL), and the suspension was stirred at 23 °C for 4 h. The white solid was collected by vacuum filtration, washed with ice-cooled MeOH (2 × 2 mL), and dried under reduced pressure to afford the corresponding naphthoxazines in a 11*R*/11*S* ratio of 72:28 as a white solid (1.317 g, 83%).

A mixture of naphthoxazines (11*R*/*11S* = 72:28, 150 mg, 0.664 mmol, 1 equiv) was suspended in $CH_3CN$ (2 mL). AcOH 10% in $CH_3CN$ (9 $\mu$L, 2.5 mol %) was added and the suspension was stirred at 65 °C for 92 h. The white suspension was solubilized in $CHCl_3$ (5 mL), washed with a saturated aqueous solution of $NaHCO_3$ (2 mL), brine (2 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford a white solid. The solid was suspended in methanol (1 mL), filtered, and washed with ice-cooled methanol (0.5 mL). The residue was dried under reduced pressure to afford the naphthoxazines in a 11*R*/11*S* ratio of 95:5 as a white solid (85%, 127 mg).

The naphthoxazines (11*R*/11*S* = 95:5, 127 mg, 0.281 mmol) were dissolved in a solution of THF/EtOAc (1:1, 1.12 mL). The solution was treated with Dowex 50WX8-100 (0.562 g, 2 g/mmol) and a 2% TsOH aqueous solution (0.056 mL, 0.2 mL/mmol). The suspension was stirred at 23 °C. After 14 h, the suspension was filtered under vacuum and the brown residue was washed with $Et_2O$ (1.12 × 3, 4 mL/g of resin). The organic layer was cooled with a water-ice bath and washed with a saturated aqueous solution of $Na_2CO_3$ (2 × 3 mL). The organic layer was washed with water (2 × 3 mL) and brine (2 × 3 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was filtered on a silica gel (hexanes/EtOAc = 85:15) to afford dihydroartemisinic aldehyde **DHAAl** as a colorless oil (62 mg, quantitative yield, dr = 95:5).

rf = 0.78 (petroleum ether/EtOAc = 9:1); $[\alpha]_D^{25}$ + 13 (*c* 0.98, $CHCl_3$); IR (ATR): $\tilde{\nu}$ = 2912, 2868, 1706, 1449, 1377, 1289, 1264, 1165, 1110, 1078, 1032, 990 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 0.87 (d, *J* = 6.5 Hz, 3H), 0.95 ($ddd_{app}$, $J_{AB}$ = 3.2, 12.1, 26.0 Hz, 1H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.12 ($ddd_{app}$, $J_{AB}$ = 3.3, 13.0, 25.0 Hz, 1H), 1.22–1.62 (m, 6H), 1.64 (br s, 3H), 1.76–2.00 (m, 3H), 2.36 (m, 1H), 2.48 (br s, 1H), [5.13 (br s, 0.95H) and 5.27 (br s, 0.05H)], [9.57 (d, *J* = 4.0 Hz, 0.95H) and 9.63 (d, *J* = 4.0 Hz, 0.05H)] ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) $\delta$ = 11.9, 19.8, 24.0, 25.9, 26.7, 27.5, 27.8, 35.4, 36.7, 41.6, 42.0, 48.6, 119.7, 136.2, 206.2 ppm; $R_T$ = 2.84 min and 3.07 min (93:07) (SFC, OD-H column, 100 bar, 4 mL/min, isocratic gradient $CO_2$/*i*PrOH 99:1); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{24}OH^+$ 221.1900, found: 221.1899.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00617.

Characterization data, and spectra copies of $^1H$ and $^{13}C$ NMR (PDF)

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### Notes

The authors declare no competing financial interest.

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