Crystallization-Induced Diastereoisomer Transformation of Dihydroartemisinic Aldehyde with the Betti Base

Andrea Zanetti,[§] Pauline Chaumont-Olive,[§] Geoffrey Schwertz, Marllon Nascimento de Oliveira, Mario Andrés Gomez Fernandez, Zacharias Amara,* and Janine Cossy*

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ABSTRACT: Artemisinin is an important drug to fight malaria. It is produced either by extraction or via a semisynthetic route involving enzyme engineering. A key intermediate to produce artemisinin by the enzymatic route is dihydroartemisinic aldehyde (**DHAAl**). However, control of the absolute configuration of the stereocenter α to the aldehyde is highly challenging. Herein we report a protocol that allows the diastereomeric enrichment of a mixture of (11R)/(11S)-**DHAAl** to the desired (11R)-**DHAAl** by utilizing a crystallization-induced diastereomer transformation induced by the Betti base. In addition, the Betti base can be quantitatively recovered and reused after the reaction.

KEYWORDS: *artemisinin, dihydroartemisinic aldehyde, CIDT, Betti base, deracemization*

■ INTRODUCTION

Nearly half of the world population is at risk of malaria. In 2017, around 435 000 deaths, mostly located in sub-Saharan African regions, were attributed to this disease.[1] The fight against malaria therefore requires the efficient production of antimalarial drugs at a very low cost. Among these, artemisinin is considered to be one of the most potent drugs on the market, and this natural product is mainly obtained by extraction from *Artemisia annua*. However, the world market price is highly volatile, ranging from US $250 to $1100 per kilogram.[2] To complement the natural production and narrow the market price fluctuation, a semisynthetic process based on isoprenoid fermentation has been developed.[3] This manufacturing route uses bioengineered microorganisms to produce advanced biosynthetic intermediates such as amorphadiene,[4] artemisinic acid,[3] and more recently dihydroartemisinic aldehyde (**DHAAl**)[5] (Scheme 1). The last of these is a key product because it can be obtained directly by fermentation or by means of cost-competitive synthetic chemistry.[6] However, one of the main drawbacks of these strategies is the control of the (11R)-configuration of **DHAAl**, which is relatively unstable and this compound is usually obtained as a mixture of two diastereomers (Scheme 1).[5]

Optical resolution of racemates via the formation of diastereomers using enantiopure auxiliaries and their separation by crystallization is the preferred large-scale purification method to access highly diastereo- and enantioenriched compounds in pharmaceutical companies.[7] One practical way to realize a diastereo- and enantioenrichment is to use a crystallization-induced diastereomer transformation (CIDT), in which an epimerizable compound is converted into a crystalline diastereomer by condensation with a chiral auxiliary.[8] A particularly useful method to realize CIDT relies on the use of the so-called "Betti base", which was first reported in 1900.[9] In 2003, Košmrlj and Weigel demonstrated that racemic 2-ethylhexanal can be transformed to (R)-2-ethylhexanal by CIDT using *trans*-(1R,2R)-1-amino-6-nitroindan-2-ol.[10] Additional examples have recently been reported in the literature,[10−13] and Fülöp et al. showed that treatment of a racemic α-substituted aldehyde with the Betti base leads to the formation of a naphthoxazine ring in which the 1- and 3-substituents are in a trans relationship[14] and that the (S)-Betti base induces the formation of the (1′R,3′S)-naphtoxazine. The epimerization of the stereocenter α to the aldehyde presumably occurs through an imine/enamine equilibrium (Scheme 2).

■ RESULTS AND DISCUSSION

In this study, gram-scale quantities of a mixture of (11R)- and (11S)-**DHAAl** with a diastereomeric ratio (dr) of 65:35 were prepared using a non-stereoselective reduction of artemisinic acid followed by oxidation.[15] In order to improve this ratio, a mixture of (11R)- and (11S)-**DHAAl** was treated with the (S)-Betti base, which was identified as the correct enantiomer to access the desired diastereoenriched (11R)-**DHAAl**. Treatment of a 65:35 mixture of **DHAAl** diastereomers with (S)-1-(α-aminobenzyl)-2-naphthol [(S)-**2**] in methanol for 4 h at room temperature (rt) led to the formation of a mixture of naphtho[1,2-e][1,3]oxazines (1′R,3′S,11R)-**3** and (1′R,3′S,11S)-**3** in a ratio of 72:28.[16] When the reaction was performed on a 0.545 mmol scale, the yield of (1′R,3′S,11R)-**3**/(1′R,3′S,11S)-**3** was 63%, and when the reaction was performed on a larger scale (3.694 mmol), the yield of (1′R,3′S,11R)-**3**/(1′R,3′S,11S)-**3** was increased to 83%. The structures of these isomers were established by ^{1}H and ^{13}C NMR analysis, while

Scheme 1. Semisynthetic Approach toward the Synthesis of Dihydroartemisinic Aldehyde (DHAAl)
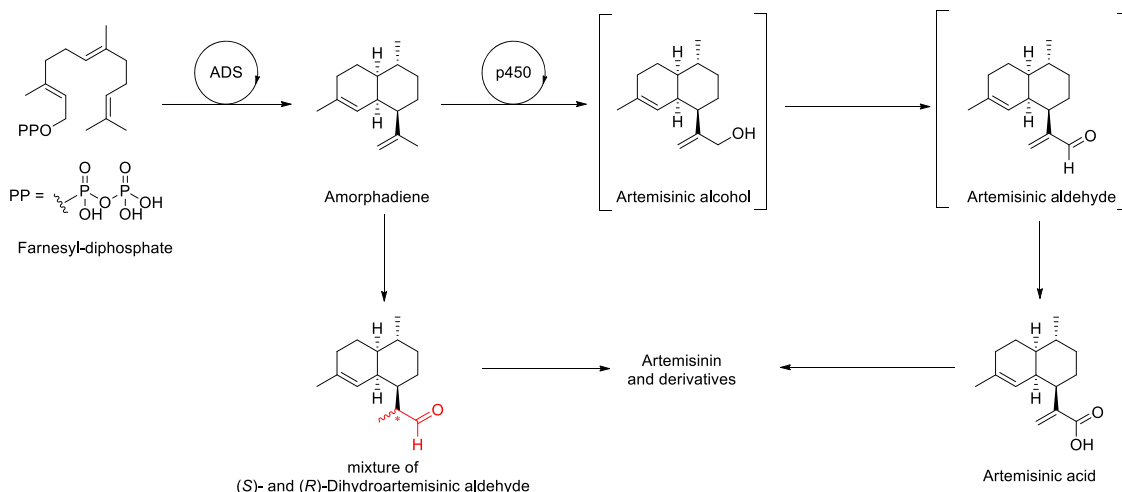
Scheme 2. Formation of One Naphthoxazine Diastereomer by Imine and Enamine Equilibrium
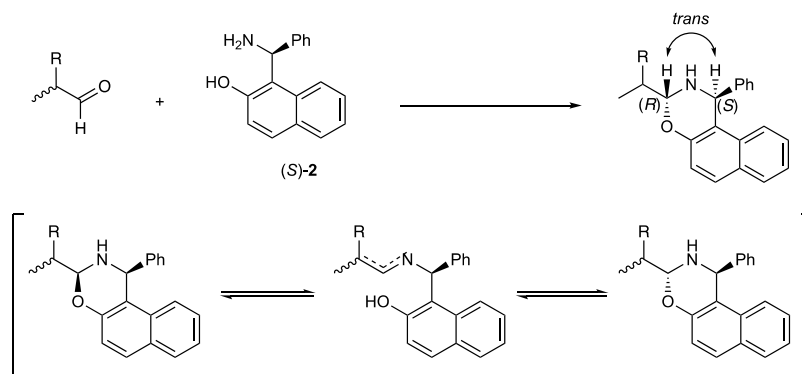
nuclear Overhauser effect (NOE) experiments confirmed that for each isomer, the hydrogen atoms of the 1,3-oxazine ring at C1′ and C3′ are in a trans relationship. The independent preparation of (1′S,3′R,11R)-**3** by reaction of (11R)-**DHAAl** with (S)-**2** confirmed that the major isomer of the 72:28 mixture is the desired (11R)-isomer (Scheme 3).

When the 72:28 mixture of (1′R,3′S,11R)-**3** and (1′R,3′S,11S)-**3** was heated in refluxing methanol for an 4 h, no change in the ratio was observed. However, when the same mixture was treated with acetic acid (2.5 mol %) for 3 h in methanol and heated at 65 °C, the (1′R,3′S,11S)-**3** diastereomer was obtained by filtration with a dr of 99:1 in 63% yield. In order to improve the yield of (11R)-**DHAAl**, a screening of solvents, temperatures, and times was performed, and the best conditions were to carry out the reaction at 65 °C in acetonitrile for 92 h in the presence of AcOH (2.5 mol %). Under these conditions, (1′R,3′S,11R)-**3** was isolated in 85% yield with a dr of 95:5 in favor of the (11R)-isomer. Careful monitoring of the crude reaction mixture over time by ^{1}H NMR spectroscopy showed that the diastereomeric excess (de) increased with time in favor of the (11R)-isomer (Scheme 3).

The crucial step was the hydrolysis of dihydronaphthoxazine **3** to isolate pure **DHAAl** and the recovery of the Betti base. Accordingly, treatment of (1′S,3′S,11R)-**3** with Dowex 50WX8-100 (2 g/mmol) in the presence of a 2% TsOH aqueous solution (0.2 mL/mmol) in THF/EtOAc (1:1) at rt for 14 h led to the isolation of the desired (11R)-**DHAAl** epimer in quantitative yield with a dr of 95:5 (Scheme 4). A comparison of the $[\alpha]_D$ of

DHAAl obtained by CIDT with the $[\alpha]_D$ of **DHAAl** prepared by reduction of dihydroartemisinic acid (dr > 99:1) followed by an oxidation step (Py·SO$_3$, Et$_3$N, DMSO)[17] allowed us to attribute the R absolute configuration of the C11 stereogenic center of **DHAAl** obtained by CIDT $[([\alpha]_D^{25} +13, c\ 0.98,$ CHCl$_3$ from a sample obtained by CIDT with a dr of 95:5) versus $([\alpha]_D^{25} +16, c\ 0.98,$ CHCl$_3$ from a sample obtained by reduction and oxidation of pure dihydroartemisinic acid with an 11R/11S ratio of 99:1)]. It is worth mentioning that the Betti base can be easily recovered at the end of the process in quantitative yield[18] and can be recycled in a new CIDT cycle.[19]

■ CONCLUSION

We developed a simple proof-of-concept protocol for the epimerization of the stereogenic center α to the aldehyde of **DHAAl** via a CIDT method utilizing the Betti base, which allowed the isolation of (11R)-**DHAAl** with a dr of 95:5 in a nonoptimized overall yield of 71% (three steps). The chiral auxiliary can be easily recovered and reused in another CIDT cycle.[18,19] This process can potentially offer an alternative to the current route to artemisinin involving hydrogenation, which utilizes an expensive optically active organometallic rhodium catalyst, to control the (11R) stereogenic center.[3] CIDT could be an efficient route for the preparation of artemisinin on scale and open more economically viable alternatives to low-cost artemisinin manufacturing.

Scheme 3. Synthesis of a 72:28 Mixture of Naphthoxazines 3 and Its Diastereoenrichment[a]

Diasteromeric excess (de) of 3 over time
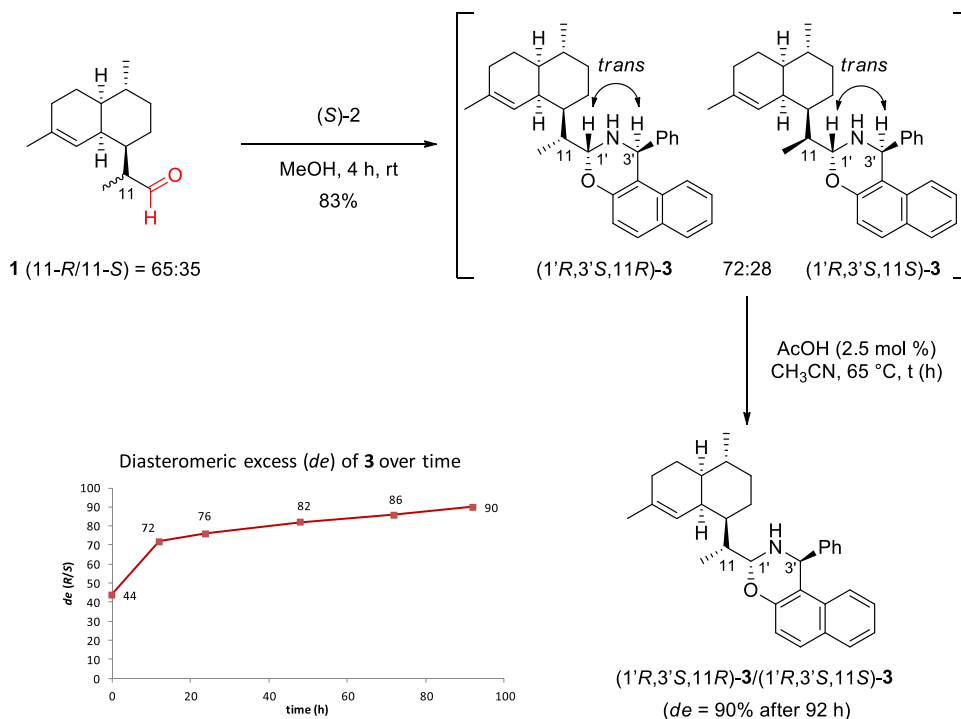
[a]A mixture of naphthoxazines **3** (11R/11S = 72:28) (30 mg, 0.133 mmol, 1 equiv) was suspended in CH₃CN (0.4 mL). AcOH (2 μL from a 10% solution in MeCN, 2.5 mol %) was added, and the suspension was stirred at 65 °C for the indicated times. The white suspension was solubilized in CHCl₃ (1 mL), and the solution was concentrated under reduced pressure. The diastereomeric excess (de) of **3** was measured by ¹H NMR spectroscopy of the crude mixture by integration of the aminal protons.

Scheme 4. Synthesis of Naphthoxazine 3 and Isolation of Diastereoenriched DHAAl Using the Betti Base [(S)-2]
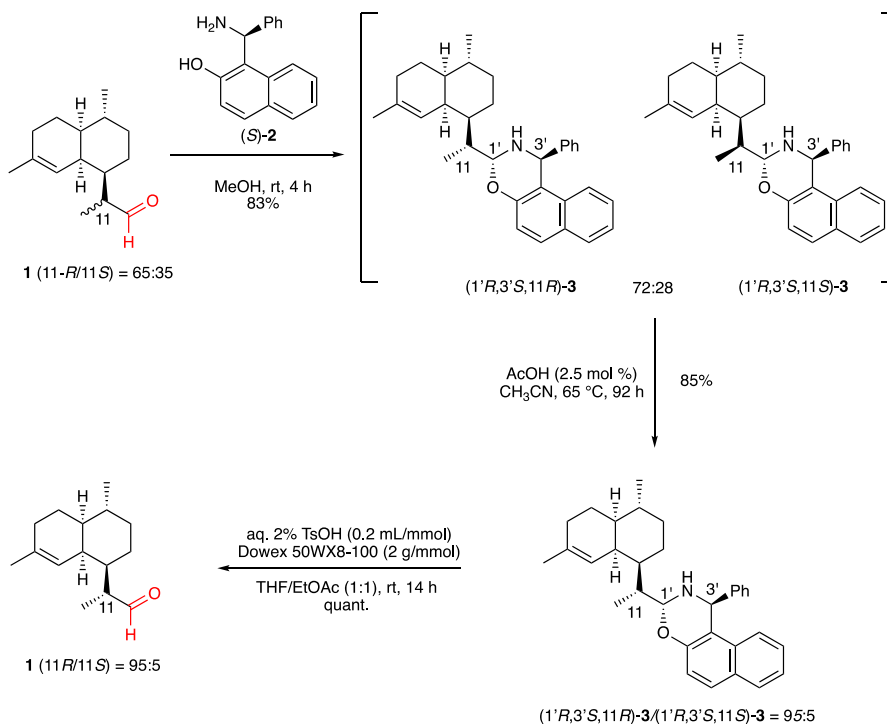
■ EXPERIMENTAL SECTION

General Information. Reagents were purchased from Aldrich as reagent grade and used without further purification. Dowex 50WX8-100 was also purchased from Aldrich. Reactions were performed in oven-dried glassware under an argon atmosphere. 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) or with silica gel 60 RP-18 F$_{254s}$ (Merck, Macherey-Nagel). Visualization was achieved using an alkaline aqueous solution of potassium permanganate. Evaporation of solvents in vacuo was performed at 25−35 °C under 9− 10 mbar. Reported yields refer to spectroscopically and chromatographically pure compounds that were dried under high vacuum (0.1−0.05 mbar) before analytical characterization. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 400 spectrometer at 400 MHz (^{1}H) or 101 MHz (^{13}C). Chemical shifts (δ) are reported in parts per million upfield using the residual deuterated solvent signals as internal references (CDCl$_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). For ^{1}H NMR spectra, coupling constants (J) are given in hertz, and the resonance multiplicity is described as s (singlet), d (doublet), t (triplet), pent (pentuplet), m (multiplet), or 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 $\tilde{\nu}$ in reciprocal centimeters. High-resolution mass spectrometry (HRMS) and analyses were performed by the Laboratoire de Spectrométrie de Masse at Sorbonne Université, Paris. Melting points were determined using a Büchi melting point apparatus in open capillaries. The enantiomeric ratios were determined by supercritical fluid chromatography (SFC) on a chiral stationary phase using a Minigram Berger SFC-Mettler Toledo apparatus; *i*PrOH was used as the polar eluent. Nomenclature follows the suggestions proposed by the software ChemDraw Professional 16.0.

(1*S*,3*R*)-3-((*R*)-1-((1*R*,4*R*,4a*S*,8a*S*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)ethyl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [(1′*R*,3′*S*,11*R*)-3]. Diastereoenriched dihydroartemisinic aldehyde (11*R*/11*S* = 99:1, 67 mg, 0.304 mmol, 1 equiv) was added to a suspension of (*S*)-Betti base (75 mg, 0.301 mmol, 0.99 equiv) in MeOH (1.3 mL), and the suspension was stirred at 23 °C. After 4 h, the white solid was collected by vacuum filtration, washed with ice-cooled MeOH (2 × 0.4 mL), and dried under reduced pressure to afford the corresponding naphthoxazine as a white solid (79 mg, 58%). Mp: 145−146 °C (MeOH). $[\alpha]_D^{25}$ −24 (*c* 0.92, CHCl$_3$). IR (ATR): $\tilde{\nu}$ = 2907, 1621, 1598, 1514, 1448, 1389, 1233, 967, 918, 809, 743, 699 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.78 (m, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.43 (m, 1H), 7.34−7.20 (m, 7H), 7.12 (d, *J* = 8.9 Hz, 1H), 5.58 (s, 1H), 5.22 (br s, 1H), 4.82 (d, *J* = 3.0 Hz, 1H), 2.50 (m, NH, 1H), 2.46 (br s, 1H), 2.03 (m, 1H), 1.97−1.73 (m, 3H), 1.61 (br s, 3H), 1.54−1.16 (m, 5H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H), 0.76−0.64 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 153.5, 142.9, 135.4, 132.1, 129.4 (2C), 129.2, 128.60, 128.59, 128.0 (2C), 127.2, 126.7, 123.2, 123.0, 120.7, 119.5, 115.0, 83.7, 53.7, 42.8, 42.1, 37.4, 37.2, 35.4, 27.8, 26.8, 26.0, 25.5, 24.0, 19.9, 9.8. HR-ESI-MS: *m/z* calcd for C$_{32}$H$_{37}$NOH$^+$, 452.2948; found, 452.2939 [M + H]$^+$.

(1*S*,3*R*)-3-((*R:S* = 72:28)-1-((1*R*,4*R*,4a*S*,8a*S*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)ethyl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [72:28 (1′*R*,3′*S*,11*R*)-3/(1′*R*,3′*S*,11*S*)-3]. Dihydroartemisinic aldehyde (11*R*/11*S* = 65:35, 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 an 11*R*/11*S* ratio of 72:28 as a white solid (1.317 g, 83%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.78

(m, 1H), [7.74 (d, *J* = 8.8 Hz, major) and 7.69 (m, minor), 1H], 7.34−7.18 (m, 7H), 7.12 (d, *J* = 8.9 Hz, 1H), 5.58 (s, 1H), [5.22 (br s, 0.72H) and 4.91 (br s, 0.28H)], [4.82 (d, *J* = 3.0 Hz, 0.72H) and 4.79 (m, 0.28H)], 2.50 (m, NH, 1H), 2.46 (br s, 1H), 2.04 (m, 1H), 1.97−1.73 (m, 3H), [1.61 (br s, major) and 1.45 (br s, minor), 3H], 1.56−1.16 (m, 5H), 1.02 (d, *J* = 6.9 Hz, 3H), [0.85 (d, *J* = 6.6 Hz, minor) and 0.83 (d, *J* = 6.2 Hz, major), 3H], 0.73−0.64 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ [153.5 (major), 153.2 (minor)], [143.0 (minor), 142.9 (major)], [135.3 (major), 134.7 (minor)], [132.1 (major), 131.99 (minor)], [129.39 (major, 2C), 129.3 (minor, 2C)], [129.2 (major), 129.0 (minor)], [128.7 (minor), 128.60 (major)], [128.59 (major), 128.5 (minor)], [128.3 (minor, 2C), 128.0 (major, 2C)], [127.2 (major), 127.1 (minor)], [126.7 (major), 126.6 (minor)], [123.2 (major), 123.1 (minor)], 123.0, [120.8 (minor), 120.7 (major)], [119.6 (minor), 119.5 (major)], [115.0 (major), 114.9 (minor)], [83.7 (major), 82.8 (minor)], [54.4 (minor), 53.7 (major)], 42.8, [42.14 (major), 42.0 (minor)], [39.0 (minor), 37.2 (major)], [38.4 (minor), 37.4 (major)], [35.9 (minor), 35.4 (major)], [28.0 (minor), 27.8 (major)], [26.8 (major), 26.6 (minor)], [26.4 (minor), 26.0 (major)], [25.8 (minor), 25.5 (major)], [24.00 (major), 23.8 (minor)], [20.0 (minor), 19.9 (major)], [11.3 (minor), 9.8 (major)].

(1*S*,3*R*)-3-((*R*)-1-((1*R*,4*R*,4a*S*,8a*S*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)ethyl)-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine [95:5 (1′*R*,3′*S*,11*R*)-3/(1′*R*,3′*S*,11*S*)-3]. A mixture of naphthoxazines (11*R*/11*S* = 72:28, 150 mg, 0.332 mmol, 1 equiv) was suspended in CH$_3$CN (2 mL). AcOH (10% in CH$_3$CN, 9 μL, 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) and brine (2 mL), dried over Na$_2$SO$_4$, 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 an 11*R*/11*S* ratio of 95:5 as a white solid (85%, 127 mg). Mp: 149−153 °C (MeOH). $[\alpha]_D^{25}$ −19 (*c* 0.68, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.78−7.74 (m, 2H), 7.45−7.19 (m, 8H), 7.12 (d, *J* = 8.9 Hz, 1H), 5.58 (s, 1H), [5.22 (br s, 0.95H) and 4.91 (br s, 0.05H)], [4.82 (d, *J* = 3.0 Hz, 0.95H) and 4.79 (d, *J* = 3.0 Hz, 0.05H)], 2.50 (m, NH, 1H), 2.46 (br s, 1H), 2.08−1.73 (m, 4H), 1.61 (br s, 3H), 1.56−1.18 (m, 5H), 1.02 (d, *J* = 6.9 Hz, 3H), [0.85 (d, *J* = 6.6 Hz, minor) and 0.83 (d, *J* = 6.2 Hz, major), 3H], 0.75−0.64 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 153.5, 142.9, 135.4, 132.1, 129.4 (2C), 129.2, 128.60, 128.59, 128.0 (2C), 127.2, 126.7, 123.2, 123.0, 120.7, 119.5, 115.0, 83.7, 53.7, 42.8, 42.1, 37.4, 37.2, 35.4, 27.8, 26.8, 26.0, 25.5, 24.0, 19.9, 9.8.

(*R*)-2-((1*R*,4*R*,4a*S*,8a*S*)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl)propanal [95:5 (11*R*)-1/(11*S*)-1]. The naphthoxazines (11*R*/11*S* = 95:5, 127 mg, 0.281 mmol) were dissolved in a 1:1 THF/EtOAc solution (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$_2$O (1.12 mL × 3, 6 mL/g of resin). The organic layer was cooled with a water/ice bath and washed with a saturated aqueous solution of Na$_2$CO$_3$ (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 silica gel (85:15 hexanes/EtOAc) to afford dihydroartemisinic aldehyde as a colorless oil (62 mg, quantitative yield). R_f = 0.78 (SiO_2; 9:1 petroleum ether/EtOAc). $[\alpha]_D^{25}$ +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, $CDCl_3$): δ [9.63 (d, J = 4.0 Hz, 0.05H) and 9.57 (d, J = 4.0 Hz, 0.95H)], [5.27 (br s, 0.05H) and 5.13 (br s, 0.95H)], 2.48 (br s, 1H), 2.36 (m, 1H), 2.00−1.76 (m, 3H), 1.64 (br s, 3H), 1.62−1.22 (m, 6H), 1.12 (ddd_{app}, J_{AB} = 3.3, 13.0, 25.0 Hz, 1H), 1.06 (d, J = 7.0 Hz, 3H), 0.95 (ddd_{app}, J_{AB} = 3.2, 12.1, 26.0 Hz, 1H), 0.87 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.2, 136.2, 119.7, 48.6, 42.0, 41.6, 36.7, 35.4, 27.8, 27.5, 26.7, 25.9, 24.0, 19.8, 11.9. t_R: 2.84 and 3.07 min (93:7) (SFC, OD-H column, 100 bar, 4 mL/min, isocratic gradient 99:1 CO_2/iPrOH). HR-ESI-MS: m/z calcd for $C_{15}H_{24}OH^+$, 221.1900; found, 221.1899 $[M + H]^+$.

Synthesis of (R)-2-[(1R,4R,4aS,8aS)-4,7-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-1-yl]propanal (DHAAl) from Dihydroartemisinic Alcohol. Dihydroartemisinic alcohol (dr > 98:2, 99 mg, 0.450 mmol, 1 equiv), obtained by $LiAlH_4$ reduction of dihydroartemisinic acid, was dissolved in CH_2Cl_2 (2 mL) and DMSO (0.5 mL). The mixture was cooled to −10 °C with an ice/NaCl bath and slowly treated with Et_3N (0.25 mL, 1.80 mmol, 4 equiv). $Py·SO_3$ (179 mg, 1.124 mmol, 2.5 equiv) was added in three portions over 20 min. The mixture was allowed to warm to 23 °C and stirred for 16 h. GC/MS analysis showed full conversion of dihydroartemisinic alcohol to **DHAAl**. The mixture was treated with citric acid (aq, 10%, 2 mL) and stirred for 10 min. The layers were then separated, and the organic layer was washed with citric acid (aq, 10%, 2 mL), a saturated aqueous solution of $NaHCO_3$ (2 mL), and brine (4 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The yellow residue was filtered on silica gel (85:15 hexanes/EtOAc) to afford **DHAAl** as a colorless oil (81 mg, 82%). It is worth mentioning that when the reaction was performed on 300 mg of dihydroartemisinic alcohol, **DHAAl** was obtained in 97% yield. R_f = 0.78 (SiO_2; 9:1 petroleum ether/EtOAc). $[\alpha]_D^{25}$ +16 (c 0.98, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 9.57 (d, J = 4.0 Hz, 1H), 5.13 (br s, 1H), 2.48 (br s, 1H), 2.36 (m, 1H), 2.00−1.76 (m, 3H), 1.64 (br s, 3H), 1.66−1.22 (m, 6H), 1.12 (ddd_{app}, J_{AB} = 3.2, 12.6, 25.1 Hz, 1H), 1.06 (d, J = 7.0 Hz, 3H), 0.95 (ddd_{app}, J_{AB} = 3.2, 12.2, 26.1 Hz, 1H), 0.87 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.2, 136.2, 119.7, 48.6, 42.0, 41.6, 36.7, 35.4, 27.8, 27.5, 26.7, 25.9, 24.0, 19.8, 11.9. t_R: 2.84 min (SFC, OD-H column, 100 bar, 4 mL/min, isocratic gradient 99:1 CO_2/iPrOH).

Recovery of the Betti Base. The solid residue, Dowex/Betti base (562 mg), was suspended in THF (1.23 mL), and then MeOH (0.15 mL) was added, followed by the addition of a 28% NH_4OH aqueous solution (0.31 mL). The mixture was stirred for 45 min at rt. After filtration, the filtrate was washed with THF (3 × 1 mL), and the solvents were evaporated under reduced pressure. The Betti base was recovered in quantitative yield as a white solid (70 mg, 0.281 mmol). Mp: 130−131 °C (lit.[1] 133−134 °C). $[\alpha]_D^{25}$ +93.0 (c 0.42, $CHCl_3$) [lit.[20] +94.1 (c 1.0, $CHCl_3$)].

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.9b00481.

Stability of **DHAAl** and naphthoxazines under basic and acidic conditions, ^1H and ^{13}C NMR spectra, and SFC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Reduction was carried out by following the procedure reported by Jung et al. See: Jung, M.; Li, X.; Bustos, D. A.; Elsohly, H. N.; McChesney, J. D.; Milhous, W. K. Synthesis and antimalarial activity of (+)-deoxoartemsinin. *J. Med. Chem.* **1990**, *33*, 1516−1518. This afforded a 65:35 diastereomeric mixture of the alcohol, which was then oxidized according to the procedure reported in ref 4.

(16) The (1′*R*,3′*S*,11*R*)-**3**/(1′*R*,3′*S*,11*S*)-**3** ratio was established from ¹H NMR spectra of the filtered mixture recorded in C₆D₆ (see the Experimental Section).

(17) The $[\alpha]_D^{25}$ of **DHAAl** is not reported in the literature.

(18) The recovery of the Betti base varied between 75% (use of Et₃N) and 99% (use of a 28% aqueous solution of NH₄OH).

(19) When **DHAAl** in a diastereomeric ratio of 65:35 was treated with the recovered Betti base (under otherwise identical conditions), a (1′*R*,3′*S*,11*R*)-**3**/(1′*R*,3′*S*,11*S*)-**3** mixture was obtained in a ratio and yield similar to the ones obtained during the first run.

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