Drug Synthesis

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Concise Synthesis and Antimalarial Activity of All Four Mefloquine Stereoisomers Using a Highly Enantioselective Catalytic Borylative Alkene Isomerization**

*Jinyue Ding and Dennis G. Hall**

Dedicated to Professor Pierre Deslongchamps on the occasion of his 75th birthday

Malaria is a mortal disease caused by *Plasmodium* parasites, which are spread to humans by infected mosquitoes. According to the latest estimates,[1] almost half of the world's population—over three billion inhabitants—are in danger of contracting malaria. In 2010, malaria caused about 216 million clinical cases and approximately 655 000 deaths.[1] Currently, a number of effective antimalarial drugs and treatments are available, but drug resistance remains a problem because of the rapid evolution and adaptation of the malaria parasites. Moreover, current antimalarial drugs are still unaffordable for underdeveloped countries where people are most vulnerable. Therefore, novel and economical alternatives are needed.[2]

One of the leading antimalarial drugs, mefloquine, was formulated in the 1970s and was soon developed and marketed under the name Lariam, the Roche branded formulation. Mefloquine remains effective against all human malaria parasites, including the recently identified fifth species, *Plasmodium knowlesi*.[3] Additionally, mefloquine has a longer half-life compared to other antimalarial drugs, and thus allows for less frequent administration making patient compliance less problematic.[4] However, its clinical use as a prophylactic antimalarial drug comes with the risk for severe neurotoxic side effects.[5] As a result, the U.S. military withdrew mefloquine as their primary antimalarial drug in 2009.[5] Regardless, it is still widely prescribed in other countries. Recent reports allege that upon returning from foreign missions, many Canadian soldiers were suffering from adverse side effects from taking mefloquine.[6] Structually, mefloquine is an α-hydroxyalkyl piperidine with two contiguous stereogenic centers, and thus may exist as four

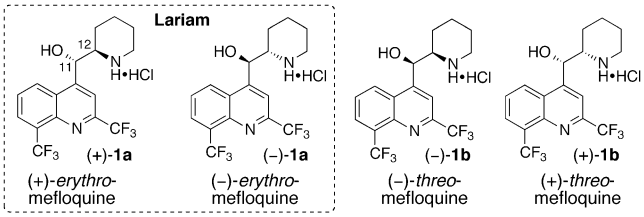

Figure 1. Stereoisomers of mefloquine.

stereoisomers (Figure 1). These stereoisomers have been demonstrated to possess various biological activities.[7,8a] Studies have shown that (+)-*erythro* and *threo* mefloquine ((+)-**1a** and (+)-**1b**) have similar IC_{50} values against *Plasmodium* parasites, and that they are 1.7–2.0 times more active than their respective enantiomers ((−)-**1a** and (−)-**1b**).[8a] On the other hand, (−)-**1a** was found to bind to the adenosine receptor in the central nervous system, which can cause severe psychotropic effects.[8] Furthermore, owing to its higher plasma concentrations, the half-life of (−)-**1a** is 2.5 times longer than that of the (+)-**1a**.[9] Lariam consists of racemic (±)-*erythro* mefloquine (Figure 1), and thus contains both the active and harmful forms of the drug. To the best of our knowledge, use of the *threo* enantiomers **1b** has never been explored for treating malaria, which may be due to a more difficult synthesis. Thus far, they have only been obtained by chiral HPLC separation.[8a] An enantioselective synthesis for all four mefloquine isomers is an unmet need, and its realization could be beneficial in the global fight against malaria parasites.[10] Herein, we describe a concise and scalable synthesis of six mefloquine analogues, including all four stereoisomers, using a carefully optimized Pd-catalyzed asymmetric borylative alkene isomerization in tandem with stereoselective aldehyde allylboration.

Even though the *threo* enantiomers display promising antimalarial properties,[8a] several research groups focused instead on developing selective syntheses of (+)-*erythro*-mefloquine.[11] The first enantioselective synthesis of (+)-*erythro*-mefloquine was completed in 1993 by Roche et al.[11a] using Rh-catalyzed enantioselective hydrogenation. In 2008, Xie et al.[11b] applied an organocatalytic aldol addition for the asymmetric total synthesis of (+)-*erythro*-mefloquine. Recently, using an asymmetric Darzens reaction[11c] as the key step, another enantioselective total synthesis of (+)-*erythro*-mefloquine was completed by Coltart

[*] J. Ding, Prof. Dr. D. G. Hall
Department of Chemistry, University of Alberta, Gunning-Lemieux Chemistry Centre
4-010 Centennial Centre for Interdisciplinary Science, Edmonton, Alberta, T6G 2G2 (Canada)
E-mail: dennis.hall@ualberta.ca
Homepage: http://www.chem.ualberta.ca/~dhall/

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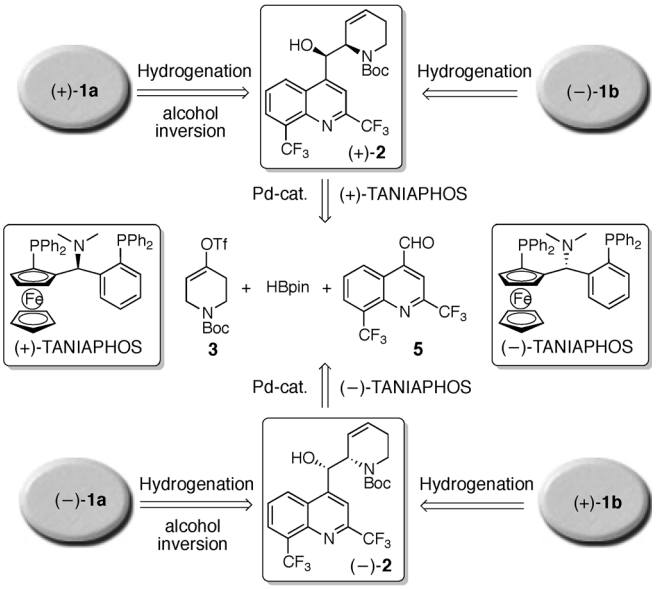
and co-workers.[11d] With respect to the absolute configuration of (+)-*erythro*-mefloquine, all three syntheses conformed with its first assignment, in 1974, to be (11*R*,12*S*),[7a] even though this assignment was reversed in 2002 by Karle and Karle on the basis of X-ray diffraction studies.[12a] This revision was recently validated by Schmidt et al.,[12b] who confirmed the absolute configuration to be (11*S*,12*R*) based on combinational analyses of NMR spectroscopy with optical rotatory dispersion (ORD) and circular dichroism (CD) spectroscopy.

Motivated by these recent developments as well as the lack of a synthetic route to the *threo* mefloquine enantiomers, we designed a new and unified synthetic strategy to access all four stereoisomers. As shown in the retrosynthesis (Scheme 1), (+)-**1a** was prepared from the key dehydro-

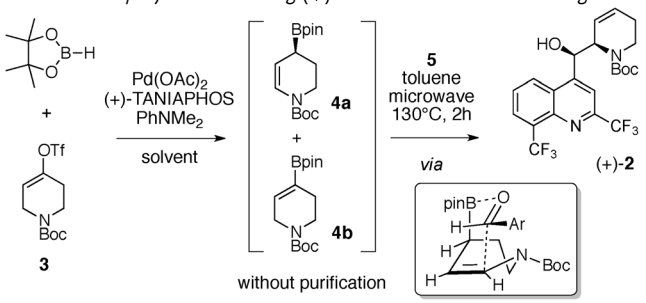


Scheme 1. Unified retrosynthetic scheme for all four mefloquine stereoisomers.

intermediate (+)-**2** through hydrogenation and alcohol inversion. Without the alcohol inversion, its diastereomer (−)-**1b** was afforded directly. The synthesis of optically pure (+)-**2** was achieved by optimizing a Pd-catalyzed asymmetric borylative isomerization/aldehyde allylboration process previously examined in a preliminary manner by our group.[13] Both triflate **3**[13] and aldehyde **5**[11b,c] can be synthesized in gram scale from cheap starting materials in only two steps. Using this same approach, the two other mefloquine stereoisomers (−)-**1a** and (+)-**1b** could be accessed from (−)-**2**, using (−)-TANIAPHOS[15] as the chiral ligand (Scheme 1).

We first attempted the Pd-catalyzed asymmetric borylation/isomerization/allylboration using (+)-TANIAPHOS[14] as the chiral ligand. The previously developed conditions[13] exclusively afforded the diastereomer (+)-**2** in moderate yield and enantioselectivity (Table 1, entry 1). The relative *threo* stereochemistry of (+)-**2** can be rationalized by the usual chair-like six-membered transition structure of carbonyl allylboration reactions.[13] Moreover, when this step was run

Table 1: Optimization of the key Pd-catalyzed asymmetric borylation/isomerization/allylboration using (+)-TANIAPHOS as the chiral ligand.[a]

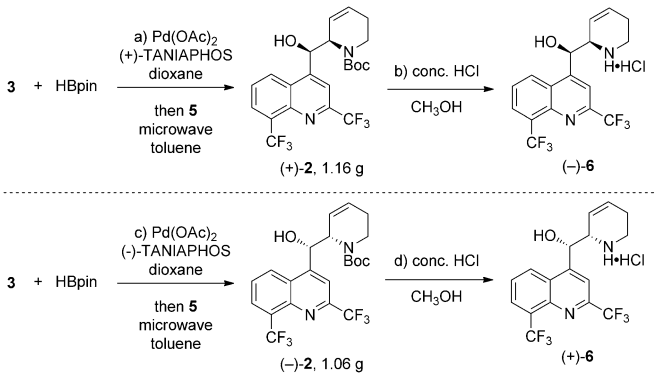


Entry	Catalyst loading $Pd(OAc)_2$/L [mol%]	Solvent	T [°C]	t [h]	**4a**:**4b**[b]	(+)-**2**[c]
1	5:10	dioxane	25	4 h	3:1	56%, 83% *ee*
2[d]	5:10	dioxane	25	4 h	1:1	–
3	5:10	THF	25	4 h	2:1	–[e]
4	5:10	toluene	25	4 h	1.3:1	–[e]
5	5:10	CH_2Cl_2	25	4 h	2:1	38%, 85% *ee*
6	5:10	dioxane	0	24 h	–	–[e]
7	5:10	dioxane	50	1 h	1:1.5	–
8[f]	5:10	dioxane	25	4 h	4:1	58%, 99% *ee*
9[f]	1:2	dioxane	25	4 h	2:1	42%, 91% *ee*
10[f]	3:6	dioxane	25	12 h	4:1	63%, 99% *ee*
11[d,f]	3:6	dioxane	25	12 h	3:1	59%, 99% *ee*

[a] Reaction conditions: **3** (1.33 g, 4.00 mmol), $Pd(OAc)_2$ (26.8 mg, 0.20 mmol), (+)-TANIAPHOS (165.2 mg, 0.40 mmol), HBpin (640 μL, 4.40 mmol), $PhNMe_2$ (592 μL, 4.40 mmol) in dioxane (96 mL), RT, 12 h; after a quick filtration and solvent evaporation, toluene was added (15 mL), **5** (1.76 g, 6.0 mmol), in a Biotage microwave reactor, 130°C, 2 h. [b] Ratio determined by ^{1}H NMR spectroscopy. [c] Yield over two steps; *ee* determined by chiral HPLC. [d] Reaction on a gram scale. [e] Low conversion. [f] Using ≥99.9% $Pd(OAc)_2$; commercial dry dioxane was deoxygenated under dry nitrogen for three hours before use.

on a gram scale, poor selectivity of **4a**/**4b** was observed (entry 2). Thus, to become effective and practical, this key transformation required significant optimization. Alternative solvents (entries 3–5) and different temperatures (entries 6,7) were attempted, which however gave either low selectivities for the borylative isomerization product **4a** or low conversions. Upon further optimization, we found that the enantioselectivity could be enhanced reproducibly by using a higher grade of $Pd(OAc)_2$ and by deoxygenation of the solvent dioxane (entry 8). To make the key step more economical, a lower catalytic loading was attempted, which resulted in lower conversion and enantioselectivity (entry 9). Further adjustment of catalytic loading identified the use of 3 mol% of $Pd(OAc)_2$/6 mol% ligand as being the optimal stoichiometry (entry 10). To our satisfaction, these optimal conditions worked efficiently on a gram scale (entry 11).

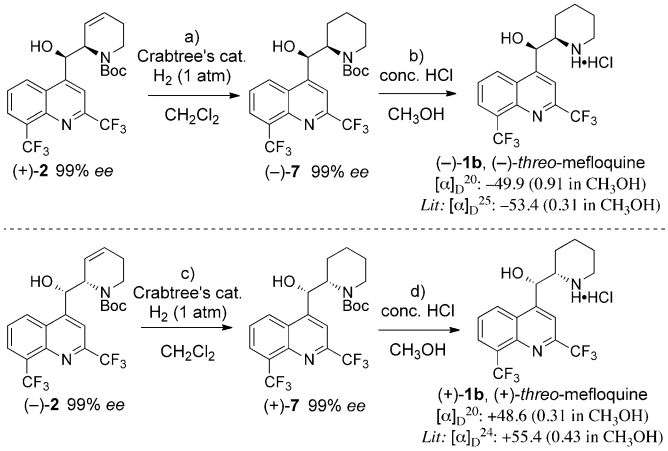
Conducting the key step on a gram scale (Scheme 2), the unsaturated piperidine derivative (+)-**2** was accessed as a single enantiomer with a good overall yield without purification of the borylation/isomerization intermediate **4a**, which was subjected to the thermal allylboration with aldehyde **5** after a quick filtration and solvent change. It is crucial to the high enantioselectivity of this sequence, and remarkable that allylic boronate **4a** preserves its stereochem-



Scheme 2. Synthesis of dehydro-mefloquine analogues (+)-**6** and (−)-**6**. a) $Pd(OAc)_2$, (+)-TANIAPHOS, DMA, dioxane, RT, 12 h; then **5**, toluene, microwave, 130 °C, 2 h, 61% overall yield, 99% *ee*; b) conc. HCl, CH_3OH, RT, 1 h, 82%; c) $Pd(OAc)_2$, (−)-TANIAPHOS, DMA, dioxane, RT, 12 h; then **5**, toluene, microwave, 130 °C, 2 h, 56% overall yield, 99% *ee*; d) conc. HCl, CH_3OH, RT, 1 h, 78%. DMA = *N*,*N*-dimethylaniline; HBpin = pinacolborane.

ical integrity at a temperature of 130 °C.[15] The other key intermediate (−)-**2** was also obtained with high efficiency using (−)-TANIAPHOS as the chiral ligand. With both key intermediates (+)-**2** and (−)-**2** in hand, the optically pure dehydro-mefloquine analogues (−)-**6** and (+)-**6** were respectively obtained as hydrochloride salts, in good yields, following an *N*-Boc deprotection/protonation with methanolic HCl.[11b,d]

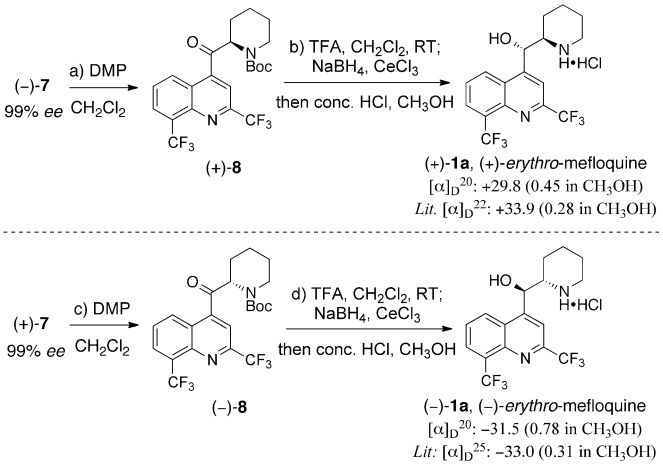
To prepare the *threo*-mefloquine enantiomers, hydrogenation of (+)-**2** was first performed. Using Crabtree's catalyst,[16] hydrogenation of the β-hydroxy alkene of (+)-**2** afforded the desired saturated product (−)-**7** in excellent yield without any apparent enantiomeric erosion (Scheme 3). The resulting optically pure (−)-**7** was then deprotected to provide (−)-**1b** in excellent yield. (+)-**1b** was also obtained efficiently using the same sequence of reactions. To the best of our knowledge, this is the first isolation of the two *threo*-



Scheme 3. Synthesis of *threo*-mefloquine enantiomers (−)-**1b** and (+)-**1b**. a) $[CODIr(PCy_3)(Py)]PF_6$, H_2 (1 atm), CH_2Cl_2, RT, 48 h, 97%, 99% *ee*; b) conc. HCl, CH_3OH, RT, 1 h, 93%; c) $[CODIr(PCy_3)(Py)]PF_6$, H_2 (1 atm), CH_2Cl_2, RT, 48 h, 94%, 99% *ee*; d) conc. HCl, CH_3OH, RT, 1 h, 95%.

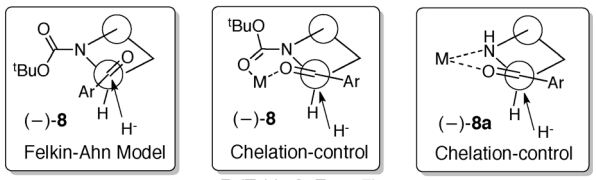
mefloquine enantiomers by way of a stereoselective total synthesis.

To synthesize the *erythro*-mefloquine enantiomers (+)-**1a** and (−)-**1a**, the stereochemistry of the secondary carbinol derivatives (−)-**7** and (+)-**7** needed to be inverted.[17] To this end, we applied an oxidation/reduction sequence[18] for the alcohol inversion. Thus, oxidation of the alcohols (−)-**7** and (+)-**7** with Dess–Martin periodinane[19] led to the ketones (+)-**8** and (−)-**8** in excellent yields (Scheme 4). A selection of



Scheme 4. Synthesis of *erythro*-mefloquine enantiomers (+)-**1b** and (−)-**1b**. a) DMP, CH_2Cl_2, RT, 3 h, 97%; b) TFA, CH_2Cl_2, RT, 1 h; at −78 °C $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in EtOH, 3 h; then conc. HCl, CH_3OH, RT, 1 h, 85%; c) DMP, CH_2Cl_2, RT, 3 h, 94%; b) TFA, CH_2Cl_2, RT, 1 h; at −78 °C $CeCl_3 \cdot 7H_2O$ and $NaBH_4$ in EtOH, 3 h; then conc. HCl, CH_3OH, RT, 1 h, 83%. DMP = Dess–Martin periodinane, TFA = trifluoroacetic acid.

results for the optimization of reduction conditions of the α-amino ketone (−)-**8** is shown in Table 2.[20] Most reducing agents showed poor diastereoselectivities, in which the desired inverted alcohol (−)-**9** was obtained as the minor diastereomer (Table 2, entries 1–6). A Felkin–Anh model (Figure 2 A) was proposed to rationalize this outcome. How-

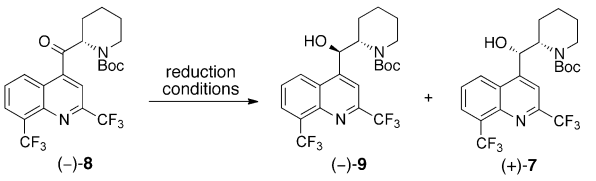


A (Table 2, Entries 1-6) **B** (Table 2, Entry 7) **C** (Table 2, Entry 9)

Figure 2. Diastereoselective reduction models for ketone (−)-**8**.

ever, the chelation-control model (Figure 2 B) would be expected to provide the opposite, desired diastereoselectivity. Accordingly, chelation-controlled conditions[21] were attempted, only to give disappointing selectivities (entries 7,8). Presumably, chelation between the ketone carbonyl and the Boc carbonyl requires formation of a thermodynamically unfavored seven-membered complex. We surmised that 1,2-chelation between the ketone oxygen and

Table 2: Optimization of reduction of ketone (−)-**8**.



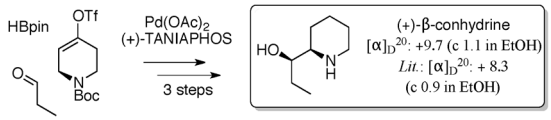
Entry	Reducing reagent	Reaction conditions	(−)-**9**:(+)-**7**[a]	Conversion [%][b]
1	$NaBH_4$	−78 °C, EtOH	1:3	99
2	$LiBH_4$	−78 °C, THF	1:3	75
3	Red-Al	0 °C, EtOH	–	0
4	$LiH(OtBu)_3$	−78 °C, Et_2O	1:2	80
5	L-selectride	−78 °C, THF	1:1	65
6	$LiEt_4BH$	−78 °C, THF	1:5	80
7	$NaBH_4$, $CeCl_3$	−78 °C, EtOH	2.5:1	99
8	$ZnBH_4$	−78 °C, THF	1:3	80
9[c]	$NaBH_4$, $CeCl_3$	−78 °C, EtOH	10:1	99[d]

[a] Ratio determined by ^{1}H NMR spectroscopy. [b] Conversion determined by ^{1}H NMR spectroscopy. [c] Reduction after Boc deprotection of (−)-**8**. [d] Enantiomeric excess of (−)-**9** could not be determined by chiral HPLC, however that of the recovered (+)-**7** was determined to be 99% *ee*. L-selectride = lithium tri-*sec*-butylborohydride.

the nitrogen atom would be more efficient (Figure 2C). In the event, the chelation-controlled reduction of the free piperidine was executed under Luche conditions to afford (−)-**9** in excellent yield and high diastereoselectivity (entry 9).

The optimized reduction conditions (entry 9, Table 2) were applied to the diastereoselective reduction of both (+)-**8** and (−)-**8**. Further optimization showed that the Boc deprotection/ketone reduction/HCl protonation sequence could be achieved in one-pot, thus affording *erythro*-mefloquine enantiomers directly without any purification. Thus, ketone (+)-**8** was treated with trifluoroacetic acid (TFA, 3 equiv) to remove the Boc group, followed by slow addition of a solution of $CeCl_3$ (6 equiv) and $NaBH_4$ (6 equiv) in EtOH at −78 °C (Scheme 4). After aqueous work-up, the desired α-amino alcohol was obtained as the main diastereomer, which was directly protonated without any further purification to provide (+)-**1a** in good yield. The other enantiomer (−)-**1a** was also obtained with high efficiency using the same sequence (Scheme 4).

To determine the absolute configuration of all mefloquine stereoisomers, we conducted a total synthesis of (+)-β-conhydrine (Scheme 5) using the same synthetic strategy.[22] In contrast to the conflicting stereochemical assignment of mefloquine, the absolute stereochemistry of (+)-β-conhydrine has been well established.[23] The total synthesis of optically pure (+)-β-conhydrine was achieved in only three steps with 52% overall yield using a similar borylative isomerization/aldehyde allylboration reaction of **3**, with



Scheme 5. Total synthesis of (+)-β-conhydrine.[22]

(+)-TANIAPHOS as the chiral source. The observed optical rotation value $[\alpha]_D^{20} = +9.7$ ($c = 1.1$ in EtOH)) matches the reported value for (+)-β-conhydrine ($[\alpha]_D^{20} = +8.0$ ($c = 0.85$ in EtOH)).[23a] Accordingly, the known absolute stereochemistry for (+)-β-conhydrine provides strong evidence for the absolute stereochemical assignment of all the mefloquine stereoisomers reported herein. Hence, this work constitutes the first chemical proof of absolute stereochemistry of (+)-mefloquine and thus confirms the (11*S*,12*R*) assignment claimed in the Karle[12a]/Schmidt[12b] revision.

With all four optically pure mefloquine stereoisomers and two dehydro-mefloquine analogues in hand, their antimalarial activity against *Plasmodium falciparum* NF54 were evaluated. As shown in Table 3, all samples showed great

Table 3: Antimalaria activity of mefloquine stereoisomers/analogues.

Samples	EC_{50} [nM][a] Tested against: *Plasmodium falciparum* NF54	IC_{50} [nM][b] Tested against: Sierra Leone and the Indochina *Plasmodium falciparum* clones
(−)-**6**	23.5	N/A
(+)-**6**	9.2	N/A
(+)-**1b**	7.6	13.0 ± 6.5
(−)-**1b**	82.7	22.5 ± 8.6
(−)-**1a**	12.9	42.3 ± 7.2
(+)-**1a**	14.5	23.4 ± 3.8
Chloroquine[a]	19.6	N/A
Artesunate[a]	5.9	N/A

[a] Data from Medicines for Malaria Venture (MMV). See Supporting Information for details. [b] Previous data reported by Karle et al.[8a]

potency against the malaria parasite, except for (−)-**1b** ($EC_{50} = 82.7$ nM). The EC_{50} values of (+)-**1b**, (+)-**1a**, (−)-**1a** match quite well with IC_{50} values previously reported by Karle et al.[8a] on samples purified by chiral HPLC. Notably, the most potent stereoisomer in both assays is (+)-**1b**, not the commercial *erythro* isomers, and it matches closely the potency of artesunate. To our satisfaction, the two novel *threo*-dehydromefloquine enantiomers (−)-**6** and (+)-**6**, which were prepared with great efficiency in only two steps from known substrates (Scheme 2), are also very potent and thus have potential to be developed as alternative antimalarial drugs.

In summary, we have optimized a highly enantioselective catalytic borylative alkene isomerization strategy for the stereoselective synthesis of the antimalarial drug mefloquine. All four mefloquine stereoisomers and analogues were accessed in two to four steps in gram scale from known substrates with high optical purities. The absolute configuration of these compounds was validated for the first time using a chemical approach. It was confirmed that the configurational assignments in the recent revisions are correct.[12] The *threo* enantiomers and the two novel dehydro-mefloquine enantiomers displayed potent antimalarial activities against *Plasmodium falciparum* NF54, which confers potential to these analogues as alternative antimalarial drugs. With an outstanding level of enantioselectivity now achievable in gram scale, this work demonstrates that the

borylative alkene isomerization/aldehyde allylboration process can be applied with high efficiency to the preparation of various drugs and natural products containing a piperidine core.

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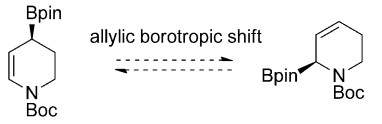

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