Total Synthesis Hot Paper

Deutsche Ausgabe: DOI: 10.1002/ange.201507304
Internationale Ausgabe: DOI: 10.1002/anie.201507304

A Concise and Highly Enantioselective Total Synthesis of (+)-*anti*- and (−)-*syn*-Mefloquine Hydrochloride: Definitive Absolute Stereochemical Assignment of the Mefloquines

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Abstract: *A concise asymmetric (> 99:1 e.r.) total synthesis of (+)-anti- and (−)-syn-mefloquine hydrochloride from a common intermediate is described. The key asymmetric transformation is a Sharpless dihydroxylation of an olefin that is accessed in three steps from commercially available materials. The Sharpless-derived diol is converted into either a trans or cis epoxide, and these are subsequently converted into (+)-anti- and (−)-syn-mefloquine, respectively. The synthetic (+)-anti- and (−)-syn-mefloquine samples were derivatized with (S)-(+)-mandelic acid tert-butyldimethylsilyl ether, and a crystal structure of each derivative was obtained. These are the first X-ray structures for mefloquine derivatives that were obtained by coupling to a known chiral, nonracemic compound, and provide definitive confirmation of the absolute stereochemistry of (+)-anti- as well as (−)-syn-mefloquine.*

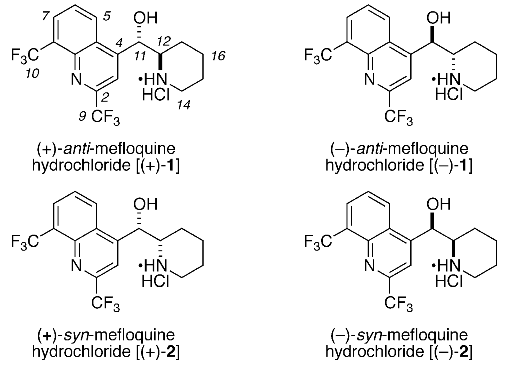

Figure 1. The (+)- and (−)-*anti*-mefloquine hydrochloride and (+)- and (−)-*syn*-mefloquine hydrochloride salts.

Malaria is the deadliest parasitic disease to affect humans. In 2013, an estimated 198 million new cases were reported worldwide, leading to 584 000 deaths.[1] *anti*-Mefloquine hydrochloride[2,3] (**1**; Figure 1) is a highly effective drug that has been used both for malaria treatment and prophylaxis. The drug is manufactured commercially and administered in racemic form, and is marketed under the name Lariam.[4] While effective and widely used, mefloquine hydrochloride suffers from serious side effects.[5,6] It has been reported that the potencies of the two enantiomers of mefloquine hydrochloride appear to be unequal, with the (+)-enantiomer being at least 1.5 times more active than the (−)-enantiomer.[7] Furthermore, although distributed across many different types of tissue, evidence suggests that the (−)-enantiomer has a shorter in vivo half-life owing to higher blood plasma concentrations.[8] This has prompted interest in the enantioselective synthesis of mefloquine to further understand and potentially benefit from its use as a single enantiomer. Herein, we describe a concise asymmetric (> 99:1 e.r.) total synthesis of (+)-*anti*- and (−)-*syn*-mefloquine hydrochloride from a common intermediate. Moreover, we provide definitive confirmation of the absolute stereochemistry of (+)-*anti*-mefloquine as well as the first X-ray crystal structure of (−)-*syn*-mefloquine.

Several syntheses of enantiomerically enriched samples of (+)-*anti*-mefloquine hydrochloride have been described, including one instance in which it was obtained by resolution of the racemate.[9] Of the remaining approaches to enantiomerically enriched (+)-*anti*-mefloquine hydrochloride, three employed asymmetric hydrogenation to set the C11 stereogenic center (88–96 % *ee*).[10] This was followed by substrate-controlled catalytic hydrogenation to set the C12 stereogenic center, which gave 85:15 diastereoselectivity in favor of the correct diastereomer.[11] In another approach to enantiomerically enriched (+)-*anti*-mefloquine hydrochloride, an organocatalytic aldol addition was used (71 % *ee*).[12] Further synthetic operations conducted on the aldol product led to an increase in the enantiomeric purity, producing (+)-*anti*-mefloquine hydrochloride in 95 % *ee*. (+)-*anti*-Mefloquine hydrochloride was also prepared in unspecified enantioselectivity starting from (*S*)-(−)-1-*N*-Boc-2-piperidinecarboxylic acid.[13] The groups of Hall[14] and subsequently Leonov[15] independently reported routes to both *syn*- and *anti*-mefloquine hydrochloride in enantiomerically enriched form. In each case, these routes were used to access all four stereoisomers. In Hall's synthesis, a novel enantioselective (99 % *ee*) allyl boration reaction was used as a key step to provide access to a *syn*-vicinal amino alcohol precursor that was used to obtain *syn*-mefloquine hydrochloride.[16] Synthesis of the *anti* isomer required the *syn*-vicinal amino alcohol to be oxidized to a vicinal keto amine, which then underwent diastereoselective (10:1 d.r.) reduction to give an *anti*-vicinal amino alcohol, which was finally converted into *anti*-mefloquine hydrochloride. A key step in Leonov's synthesis was the diastereoselective (12:1 d.r.) addition of trimethylsilyl acetylide to an enantiomerically enriched aldehyde derived from pipecolinic acid. The major diastereomer from this reaction was advanced through a Sonogashira/6π electrocyclization domino reaction to give *anti*-mefloquine hydrochloride as the

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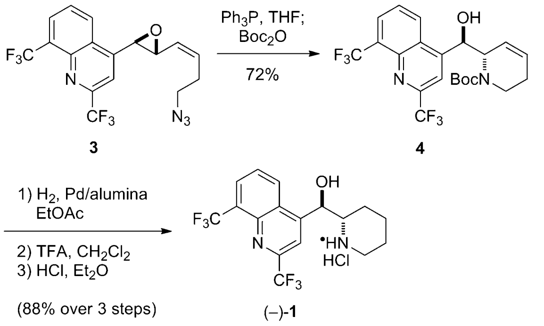
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201507304.

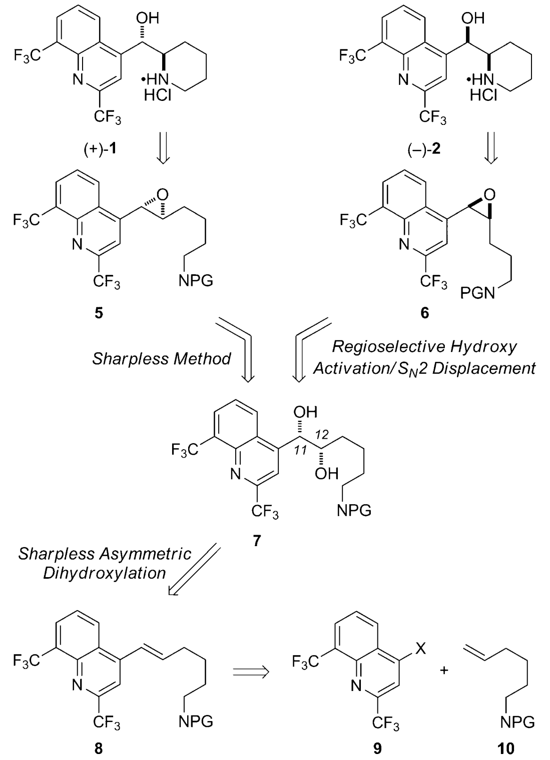
major product and *syn*-mefloquine hydrochloride as the minor product. (The latter was formed as a side product by epimerization during the domino reaction.) The *anti* and *syn* diastereoisomers were separated chromatographically, and the enantiomeric ratio was determined to be either 93:7 or 96:4 depending on the stereoisomer.

We recently reported an asymmetric total synthesis of (−)-*anti*-mefloquine hydrochloride (> 99:1 e.r.).[17] A key step in that synthesis was a cascade azide reduction/epoxide ring-opening reaction beginning with **3** that, following trapping of the 3,4-dehydropiperidine intermediate with Boc_2O, delivered 3,4-dehydro-*N*-Boc-mefloquine (**4**) in a one-pot reaction (Scheme 1). Compound **4** subsequently underwent olefin reduction, acid-mediated removal of the Boc group, and HCl salt formation to give (−)-mefloquine hydrochloride [(−)-**1**] in excellent yield.



Scheme 1. Prior synthesis of (−)-*anti*-mefloquine hydrochloride [(−)-**1**]. Boc = *tert*-butyloxycarbonyl, TFA = trifluoroacetic acid.

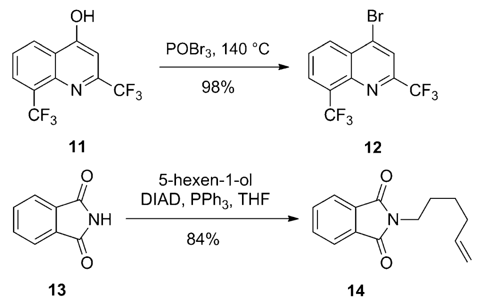
We reasoned that it should be possible to utilize the above cyclization strategy as the basis for a concise synthesis of not only (+)- and (−)-*anti*-mefloquine hydrochloride [(+)-**1** and (−)-**1**, respectively], but also the *syn* diastereoisomers [(+)-**2** and (−)-**2**]. The general idea is retrosynthetically outlined in Scheme 2. Cyclization of *trans* epoxide **5** would lead to (+)-*anti*-mefloquine hydrochloride [(+)-**1**], whereas cyclization of *cis* epoxide **6** would give rise to (−)-*syn*-mefloquine hydrochloride [(−)-**2**]. Access to epoxides **5** and **6** would mark a key divergence point in our strategy, as they would each be obtained from a common diol intermediate (**7**), which would be prepared in enantiomerically enriched form by the asymmetric Sharpless dihydroxylation[18] of olefin **8**. We expected that formation of the *trans* epoxide from **7** would be reasonably straightforward using the Sharpless method.[19] However, the stereospecific formation of the *cis* epoxide would require one of the two hydroxy groups to be regioselectively converted into a leaving group, with the other acting as a nucleophile in an S_N2 reaction. Given the strongly electron-withdrawing nature of the aryl system, we reasoned that the C11 hydroxy group should be considerably more acidic than the one at the C12 position, which should allow selective base-mediated functionalization of the C11 hydroxy group (see below). In turn, the olefin (**8**) required for the dihydroxylation would be generated by a Heck reaction between aryl halide **9** and N-protected 1-aminohexene **10**.



Scheme 2. Proposed synthesis of (+)-**1** and (−)-**2**. PG = protecting group.

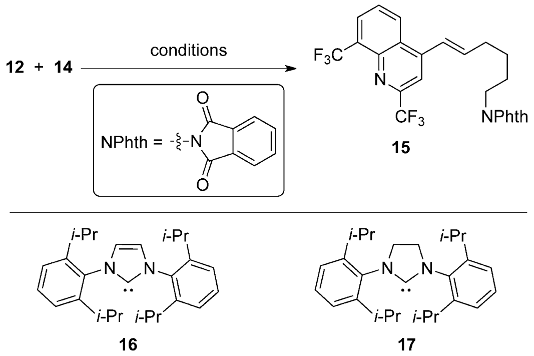
We began our studies by converting commercially available quinolinol **11** into aryl bromide **12** according to a literature procedure (Scheme 3).[20] Compound **14** was prepared from phthalimide and 5-hexen-1-ol. We chose to mask the amine function as a phthalimide rather than an azide as we had done previously (Scheme 1) to avoid the expected complications related to the use of phosphine ligands in the Heck reaction. In the case of the phthalimide-masked amine, we would initiate the cascade deprotection/cyclization sequence (see Scheme 1) by treatment with hydrazine (see below).

With **12** and **14** in hand, we attempted the Heck coupling reaction. As shown in Table 1, of the conditions tried, our best results were obtained using NHC ligand **16**. Purification of **15** from the reaction mixture by column chromatography on silica gel proved extremely difficult. This was also the case for



Scheme 3. Synthesis of the Heck coupling substrates **12** and **14**. DIAD = diisopropyl azodicarboxylate.

Table 1: Ligand screen for the Heck coupling of **12** and **14**.[a]



Entry	Ligand	Yield [%]
1	P(*t*Bu)$_3$	–
2	XPhos	48
3	**16**	68
4	**17**	65

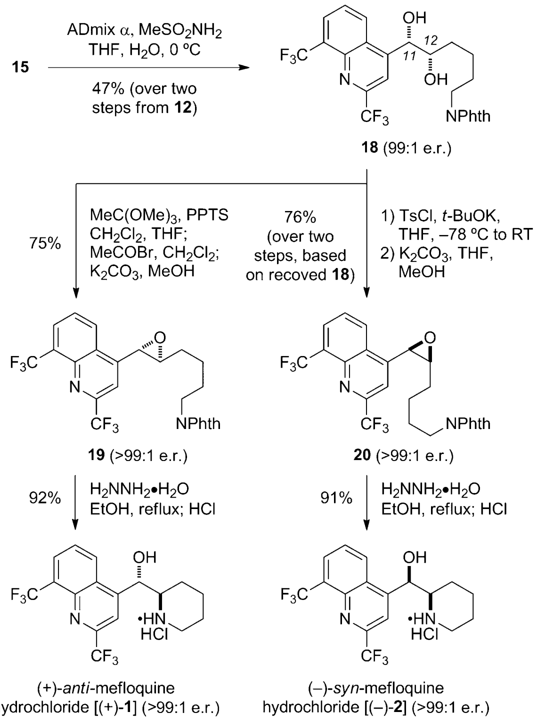
[a] Reaction conditions: Pd(OAc)$_2$ (5 mol%), ligand (10 mol%), Et$_3$N, DMF, 110 °C. XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

entries 2 and 4 of Table 1. Therefore, the yields given in Table 1 correspond to material of approximately 95 % purity.

At this point, we tried the Sharpless asymmetric dihydroxylation on the semi-purified material, suspecting that the diol product might be easier to purify than the olefin. Therefore, **15** (approximately 95 % pure, as judged by ^{1}H NMR analysis, obtained by the reaction shown in entry 3 of Table 1) was subjected to the dihydroxylation conditions[18] (**15**→**18**, Scheme 4). Gratifyingly, this produced the pure diol in 47 % over two steps based on **12**, following column chromatography on silica gel. The enantiomeric purity of **18** was established by converting it into the corresponding acetonide[21,22] and comparing it with a racemic acetonide[23] sample by HPLC analysis on a chiral stationary phase.[24] The e.r. of the acetonide was found to be 96:4, which we assume to be a reasonable indication of the enantiomeric purity of diol **18**. The enantiomeric purity of **18** was readily increased to 99:1 by a single and efficient (92 % yield) recrystallization.

With access to the diol secured, we converted it into *trans* epoxide **19** in very good yield by the Sharpless one-pot procedure (**18**→**19**).[19] To ensure that there was no loss of stereochemical integrity during epoxide formation, it was compared to a corresponding racemic sample[25] by HPLC analysis on a chiral stationary phase.[24] The e.r. of epoxide **19** was thus found to be > 99:1. Compound **19** was next treated with hydrazine followed by acidification with HCl, which, as anticipated, provided (+)-*anti*-mefloquine hydrochloride [(+)-**1**] in excellent yield. The optical rotation of the HCl salt was found to be $[\alpha]_D^{20} = +26.0$ ($c = 0.45$, MeOH), which matches quite well with the reported value of $[\alpha]_D^{20} = +29.8$ ($c = 0.45$, MeOH).[14] The enantiomeric purity of our synthetic material was established in the same manner as we described previously,[17] and was found to be > 99:1 e.r.

We next turned our attention to preparing *syn*-mefloquine [(−)-**2**]. As indicated above, we needed to convert diol **18** into *cis* epoxide **20** or its enantiomer. We planned to do this by taking advantage of the predicted enhanced acidity of the C11 hydroxy group—which would allow it to be regioselectively activated—and having it undergo S_N2 displacement by the C12 hydroxy group. After considerable experimentation, we found that this was most effectively achieved by treatment of **18** with 0.8 equiv of *t*BuOK and 1.0 equiv of *p*-TsCl to give the C11 tosylate. This was then converted into epoxide **20** in 76 % yield over two steps (based on recovered **18**) by treatment with K$_2$CO$_3$. The enantiomeric purity of **20** was determined by comparison to the corresponding racemate[26] by HPLC analysis on a chiral stationary phase, and found to be > 99:1 e.r.[24]



Scheme 4. Synthesis of (+)-**1** and (−)-**2**. PPTS = pyridinium *para*-toluenesulfonate, Ts = *para*-toluenesulfonyl.

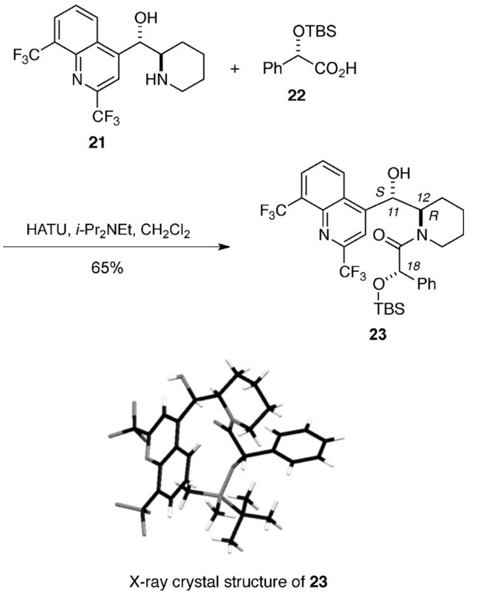
With *cis* epoxide **20** in hand, we were pleased to find that in an analogous manner to the synthesis of (+)-**1** described above, it could be smoothly converted into the *syn* diastereomer (−)-**2** by treatment with hydrazine followed by HCl. The optical rotation of (−)-**2** was measured as $[\alpha]_D^{20} = -41.4$ ($c = 0.91$, MeOH), which is in reasonable agreement with the reported value of $[\alpha]_D^{20} = -49.9$ ($c = 0.91$, MeOH).[14] The enantiomeric purity of our synthetic material was determined in a similar manner to that described above,[17] and found to be > 99:1 e.r.

We next set out to confirm the absolute stereochemistry of our synthetic material. Over the years, there has been controversy regarding the absolute configuration of *anti*-mefloquine. Originally, on the basis of circular dichroism (CD) experiments, (+)-*anti*- and (−)-*anti*-mefloquine were assigned the structures opposite to those shown in Figure 1 by Carroll and Blackwell.[9a] Subsequently, using X-ray diffraction studies on *anti*-mefloquine hydrochloride, Karle and Karle argued that the correct structures of (+)-*anti*- and (−)-

anti-mefloquine were those shown in Figure 1 [(+)-**1** and (−)-**1**, respectively].[7] Arguments against this revised assignment were then made by Xie and co-workers[12] based upon a Mosher analysis[27] carried out as part of their total synthesis of (−)-*anti*-mefloquine hydrochloride, which supported the original Carroll–Blackwell assignment (i.e., the opposite of what is shown in Figure 1). Recently, another argument regarding the absolute configuration of (+)- and (−)-*anti*-mefloquine was put forth in a study by Reinscheid, Griesinger, and co-workers.[2] This analysis was based upon residual dipolar coupling (RDC) enhanced NMR spectroscopy in combination with optical rotatory dispersion (ORD) and CD spectroscopy. The result of this study recognized the absolute configuration given by Karle and Karle[7] to be correct [i.e., (+)-**1** and (−)-**1**, Figure 1]. Support for this assignment based on a synthetic study was subsequently provided by Hall and Ding.[14]

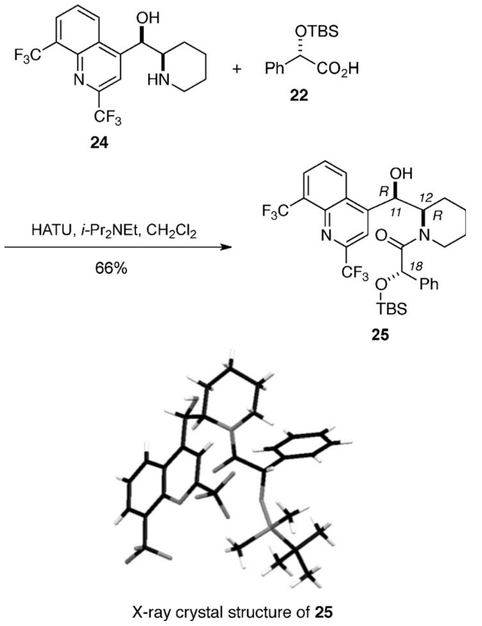
Notwithstanding the importance of the above studies to determine the absolute configuration of (+)- and (−)-*anti*-mefloquine hydrochloride, we were surprised to find that no studies had been reported on the derivatization of the mefloquine enantiomers with a known chiral, nonracemic compound, followed by X-ray crystallographic analysis of the derivative. Consequently, we set out to do this.

Thus, compound **21** was prepared according to Scheme 4, but without the final HCl salt formation step that was used to prepare (+)-**1**. It was then coupled with (*S*)-(+)-mandelic acid *tert*-butyldimethylsilyl ether (**22**)[28] under non-epimerizing conditions to give **23** (Scheme 5). By reference to the known *S* configuration of the mandelic acid derived stereogenic center, X-ray crystallography determined the absolute stereochemistry of the C11 and C12 positions of **23** to be *S* and *R*, respectively. This analysis confirmed the absolute stereochemistry of (+)-*anti*-mefloquine to be that shown in Figure 1 [(+)-**1**], thus verifying the assignment by Karle and Karle.[7]



Scheme 5. Synthesis and X-ray crystal structure of **23**. HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, TBS = *tert*-butyldimethylsilyl.

We next carried out the same type of absolute configuration analysis on compound **24**, which was again prepared according to Scheme 4, but without the final HCl salt formation step. Coupling of **24** with (*S*)-**22** gave **25** (Scheme 6). Again, using the known *S* configuration of the mandelic acid derived stereogenic center as a reference, X-ray crystallographic analysis established the absolute stereochemistry of the C11 and C12 positions of **25** to be *R* and *R*, respectively. Again, this is the first X-ray structure reported for a *syn*-mefloquine derivative obtained by coupling to a known chiral, nonracemic compound. On this basis, we were able to unambiguously establish the absolute stereochemistry of (−)-*syn*-mefloquine hydrochloride to be that shown in Figure 1 [(−)-**2**].



Scheme 6. Synthesis and X-ray crystal structure of **25**.

In conclusion, we have developed a concise and highly enantioselective (> 99:1 e.r.) approach to both (+)-*anti*- and (−)-*syn*-mefloquine hydrochloride [(+)-**1** and (−)-**2**, respectively]. A key step in the synthesis of each compound is the enantioselective conversion of olefin **15** into diol **18**, which is then converted into either a *trans* or *syn* epoxide and ultimately into (+)-*anti*-mefloquine hydrochloride [(+)-**1**] or (−)-*syn*-mefloquine hydrochloride [(−)-**2**], respectively. As a result of X-ray crystallographic and optical rotation studies on our synthetic material, the absolute stereochemistry of (+)-*anti*-mefloquine hydrochloride has been definitively confirmed as that reported by Karle and Karle[7] [(+)-**1**, Figure 1]. Furthermore, a similar analysis has unambiguously established the absolute stereochemistry of (−)-*syn*-mefloquine hydrochloride [(−)-**2**, Figure 1].

Acknowledgements

We are grateful to James Korp of the University of Houston for determining the X-ray crystal structures of **23** and **25**. We thank Professor K. C. Nicolaou (Rice University) for generously allowing us use of his laboratory for polarimetry measurements. We also thank the University of Houston and the NSF for financial support (NSF 1300652).

Keywords: asymmetric synthesis · malaria · mefloquine · Sharpless dihydroxylation · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14070–14074
Angew. Chem. **2015**, *127*, 14276–14280

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[22] Generated using 2,2-dimethoxypropane. See the Supporting Information for details.

[23] Generated from **15** using OsO_4 and NMO and then 2,2-dimethoxypropane. See the Supporting Information for details.

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Received: August 5, 2015