ORGANIC LETTERS

2011
Vol. 13, No. 12
3118–3121

Asymmetric Total Synthesis of the Antimalarial Drug (+)-Mefloquine Hydrochloride via Chiral *N*-Amino Cyclic Carbamate Hydrazones

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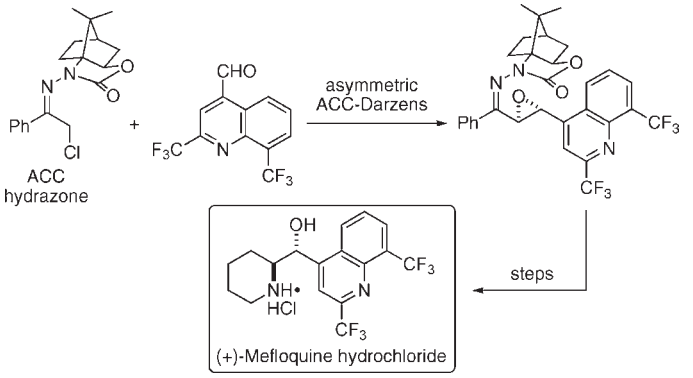
Received April 18, 2011

ABSTRACT



Mefloquine hydrochloride is an important antimalarial drug. It is currently manufactured and administered in racemic form; however there are indications regarding the biological activity of the two enantiomers that suggest the superiority of the (+)-form. The asymmetric total synthesis of the (+)-enantiomer of mefloquine hydrochloride is described. The key asymmetric transformation utilized is a novel asymmetric Darzens reaction of a chiral α-chloro-*N*-amino cyclic carbamate hydrazone derived from an *N*-amino cyclic carbamate (ACC) chiral auxiliary.

Malaria causes more mortality than any other parasitic disease.[1] There are greater than 500 million new cases each year, worldwide. In the US alone there are approximately 1500 malaria cases per year, with essentially all being imported from endemic areas. *Plasmodium falciparum* is responsible for the most severe cases of malaria, and an estimated 1.5 to 2.7 million malaria-related deaths each year result from this organism.[1] The majority of these deaths occur in African children less than five years of age, in pregnant women, and in nonimmune adults traveling to endemic areas. Most malaria deaths occur despite treatment with our best drugs.

Mefloquine is a highly effective antimalarial drug that has been used for both malaria treatment and prophylaxis. The drug is manufactured commercially and administered in racemic form.[2] However, the potency of the two enantiomers of mefloquine (Figure 1) against malaria appear to be unequal, with the (+)-enantiomer [(+)-**1**] indicated as being at least 1.5 times more active than the (−)-enantiomer [(−)-**1**].[3] Additionally, although distributed across many different types of tissue, evidence suggests that the (−)-enantiomer has a shorter half-life *in vivo* due to higher blood plasma concentrations.[4]

While highly effective and widely used as an antimalarial, mefloquine causes serious side effects.[5,6] These include nausea, diarrhea, dizziness, weakness, priuritus, mouth

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10.1021/ol2010193
Published on Web 05/26/2011

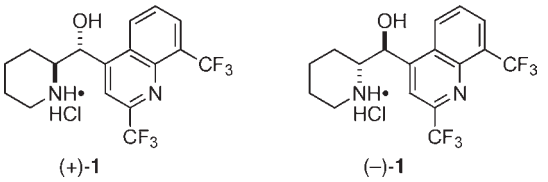


Figure 1. Mefloquine hydrochloride.

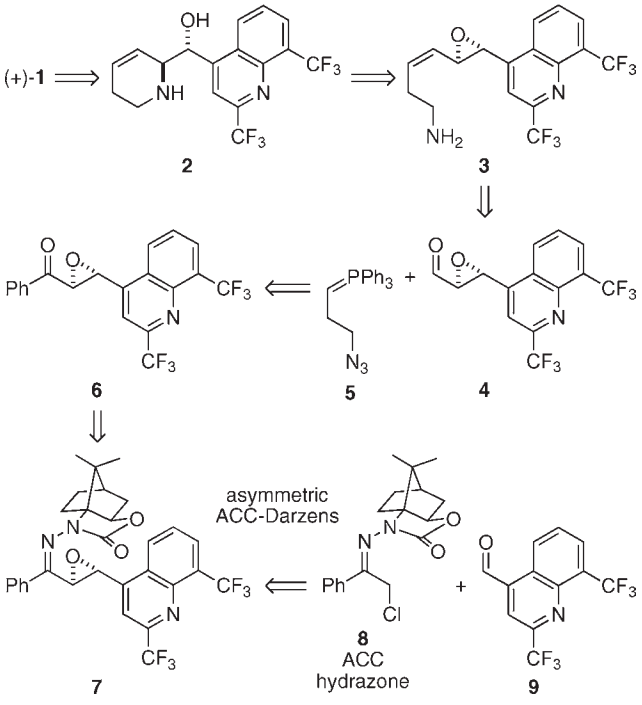
ulcers, severe depression, anxiety, paranoia, aggression, nightmares, insomnia, and other central nervous system problems.[7] The more mild central nervous system events have been reported to occur in up to a quarter of all patients taking mefloquine while the severe events occur in 1/6000 to 1/13 000.[4] To date, there has been no definitive biochemical basis for the neurotoxicity of this drug. Research has suggested that mefloquine may interfere with calcium homeostasis in the endoplasmic reticulum within neuron cells.[8] This type of disruption leads to problems in protein synthesis and folding in eukaryotic cells. There has also been some research suggesting a link between the more severe psychotropic side effects and the (−)-enantiomer, which, unlike the (+)-enantiomer, may be able to bind specifically to adenosine receptors in neuron cells.[9]

The side effects severely restrict the usefulness of mefloquine, nearly eliminating use of this otherwise effective drug. Clearly, it is important to understand the toxicities of this drug and how to avoid them so that it can be used more safely. To initiate our studies along these lines, we required access to significant quantities of each of the enantiomers of mefloquine in pure form for cell-based and animal studies, a goal most reasonably achieved via asymmetric total synthesis. Herein, we describe the asymmetric total synthesis of (+)-mefloquine hydrochloride utilizing, as a key step, a novel asymmetric Darzens reaction of a chiral α-chloro-*N*-amino cyclic carbamate hydrazone (**8**) derived from an *N*-amino cyclic carbamate (ACC) chiral auxiliary[10] (**18**).

(+)-Mefloquine has been prepared previously via resolution of the racemate.[11] It has also been obtained via asymmetric total synthesis. In one instance asymmetric hydrogenation was utilized for asymmetric induction (92% ee),[12] while in another approach an organocatalytic aldol addition was used (71% ee).[13] In each instance, further synthetic operations conducted on the products of these asymmetric transformations are reported to have led to an increase in the enantiomeric purity of the (+)-mefloquine produced (99% ee and 95% ee, respectively).

Our plan for the asymmetric synthesis of (+)-mefloquine is shown in Scheme 1. Compound (+)-**1** would be obtained via hydrogenation of olefin **2**. To establish the 1,2-*anti*-amino alcohol function of **2**, we would take advantage of the stereospecific, regioselective opening of *trans*-epoxide **3**. Regiocontrol would be expected on the basis of both the

Scheme 1. Synthetic Plan



stereoelectronic factors favoring formation of the 6- over the 7-membered ring, as well as the electronic factors favoring ring opening at the more electron-rich allylic carbon of the epoxide. The benzylic carbon in this case would be made relatively electron deficient by the (bis)trifluoromethyl quinoline system. Access to compound **3** would be gained from α,β-epoxy aldehyde **4** by Wittig olefination with ylide **5**, followed by azide reduction. In turn, **4** would be prepared by regioselective Baeyer–Villiger oxidation of α,β-epoxy ketone **6**, followed by oxidation state adjustment of the resulting phenylester. In order to prepare key intermediate **6** in single enantiomer form, we would make use of the asymmetric Darzens reaction of ACC hydrazone **8** and aldehyde **9** to prepare **7**, the hydrolysis of which would provide **6**.

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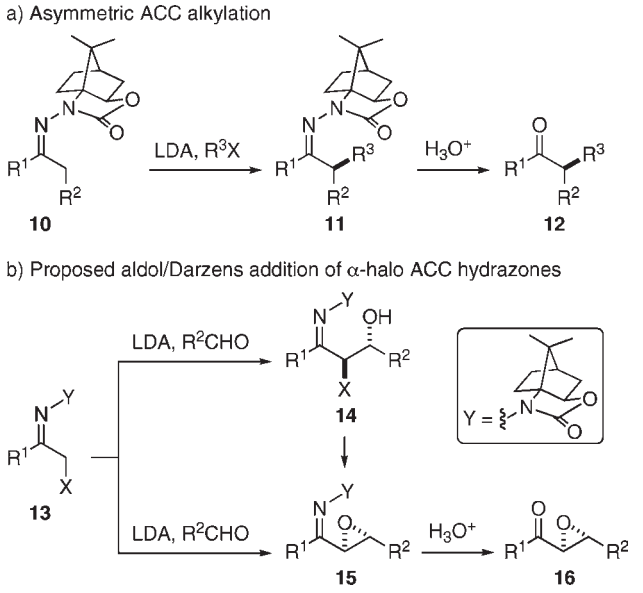
A short time ago, we described a new method for the asymmetric α-alkylation of ketones using chiral *N*-amino cyclic carbamate (ACC) auxiliaries (Scheme 2a). Given the practical simplicity of this method, along with the high levels of asymmetric induction produced, we initiated a study of the use of ACC auxiliaries in the context of the aldol addition and related transformations. One such reaction of interest to us in the present context was the asymmetric addition of α-halo ACC hydrazones to aldehydes (Scheme 2b). Providing the addition step was *anti*-selective,[14] this could provide a convenient means of accessing *trans*-α,*β*-epoxy ketones (**16**), either directly from Darzens[15] intermediate **15** or via the corresponding

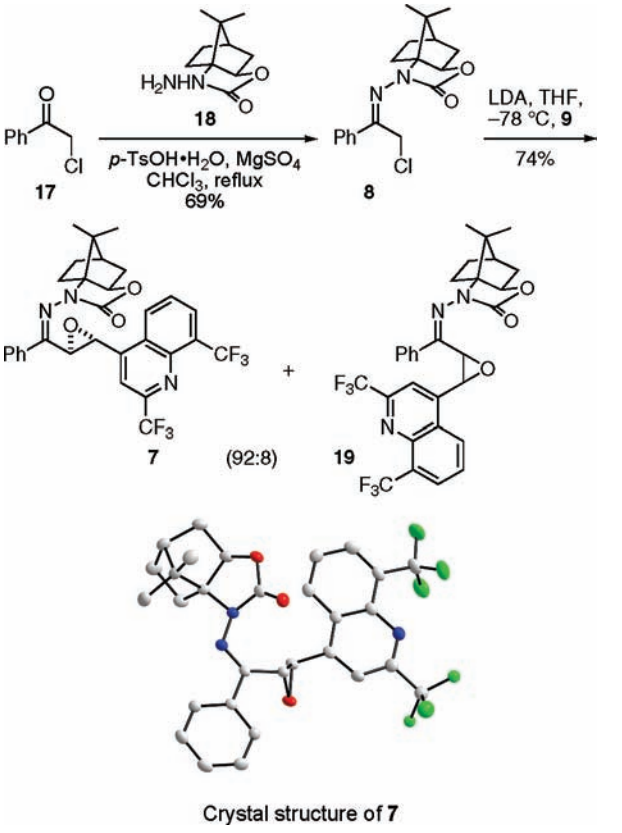
Scheme 2. Asymmetric ACC Transformations



α-halo-*β*-hydroxy hydrazones (**14**). Application of this method in the context of aldehyde **9** could then provide access to key intermediate **6** for the synthesis of (+)-mefloquine.

We began our study by testing the validity of the proposed aldol/Darzens addition of α-halo ACC hydrazones (Scheme 3). To do so, hydrazone **8** was prepared from 2-chloroacetophenone (**17**) and ACC auxiliary **18** and was then treated with LDA at −78 °C, followed by aldehyde **9**. Interestingly, no α-chloro-*β*-hydroxy hydrazone products (cf. **14**) were observed. Instead, two diastereomeric Darzens products were formed in a 92:8 ratio. Based on ^{1}H NMR analysis, the minor product appeared to contain a *cis*-configured epoxide, whereas the major product appeared to be a *trans*-epoxide. The diastereomers were easily separable using silica gel chromatography. An X-ray crystal structure of the major product was obtained (Scheme 3), establishing it as *trans*-diastereomer **7**. We subsequently found that the conversion of **8** to **7** could be carried out on a multigram scale without compromising the outcome of the reaction.

Scheme 3. Asymmetric ACC Darzens Reaction



Having established an effective route to compound **7**, we embarked on the remainder of our synthesis, which began with the removal of the chiral auxiliary (Scheme 4). This was achieved using our previously reported[10a] conditions (*p*-TsOH•H_2O in acetone), giving **6** and the corresponding acetone hydrazone (**20**), with quantitative conversion. Unfortunately, attempted separation of **6** and **20** via silica gel chromatography or crystallization proved extremely difficult. This problem was easily solved by conducting the auxiliary cleavage reaction in 3-pentanone instead of acetone, which gave readily separable hydrazone **21** as the byproduct. Next, we needed to effect the regioselective Baeyer−Villiger oxidation of **6** to phenyl ester **22**. In studies on chalcone-derived epoxides, it has been shown that the migratory aptitude of the phenyl substituent is greater than that of the epoxide function and that the corresponding phenyl esters could be obtained in high yield.[16] This proved to be the case for α,*β*-epoxy ketone **6** as well, which gave the desired phenyl ester (**22**) after

(14) Other studies conducted by us on the aldol addition using, for example, the 3-pentanone-derived ACC hydrazone (**13**, R^1 = Et; X = Me) showed the reaction to be highly *anti*-selective for the diastereomer corresponding to **14** (R^1 = Et; X = Me). Unpublished results.

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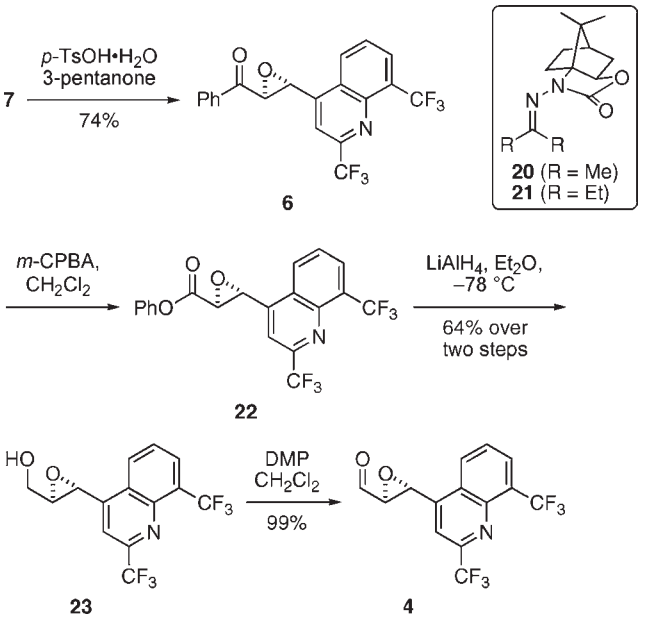
refluxing in the presence of *m*-CPBA. Treatment of the crude material with lithium aluminum hydride gave 2, 3-epoxy alcohol **23** in very good yield over the two steps. Oxidation of **23** by Dess–Martin periodinane then gave aldehyde **4**, cleanly.

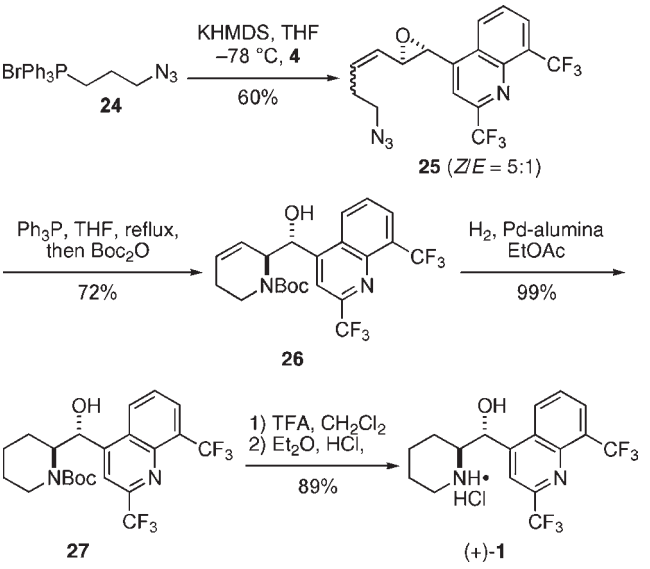
Scheme 4. Synthesis of Aldehyde **4**



With aldehyde **4** in hand, we undertook the final stages of the synthesis of (+)-mefloquine (Scheme 5). Thus, compound **4** was allowed to react with the ylide obtained from **24** upon deprotonation with KHMDS,[17] which gave olefins **25** as a 5:1 (*Z*/*E*) mixture. This set the stage for a cascading azide reduction–epoxide opening sequence, which was effected by treatment with Ph_3P in wet THF. In order to facilitate purification, the resulting amino alcohol was not isolated but was instead converted directly to the *N*-Boc protected compound **26** by addition of Boc_2O to the reaction mixture. Olefin hydrogenation was then carried out to give **27**. Finally, the Boc protecting group was removed, and the resulting TFA salt was converted to (+)-mefloquine hydrochloride [(+)-**1**].

The enantiomeric purity of our synthetic material was established as follows. A racemic sample of **27** was prepared from commercially available (±)-mefloquine. This was then analyzed by chiral HPLC to establish conditions that gave baseline resolution of the enantiomers. The synthetic **27** we had prepared was then analyzed under the same conditions and found to exist as a single enantiomer.

Scheme 5. Synthesis of (+)-Mefloquine Hydrochloride



In conclusion, we have developed an effective asymmetric total synthesis of (+)-mefloquine hydrochloride. Establishment of the stereochemistry is achieved early in the synthesis via a novel ACC-mediated Darzens reaction.

Acknowledgment. We thank Dr. Wayne Beyer (Duke University), Dr. Timothy Haystead (Duke University), Dr. Brandy Salmon (Duke University), and Dr. Brice Weinberg (Duke University) for their assistance in the development of this project. S.J.S. is grateful for support from the Pharmacological Sciences Training Program – Duke University. We thank Nicholas J. Amato, Stacey D. Gates, and Dr. Kristin Kirschbaum (University of Toledo) for X-ray crystal structure determination. This work was supported by Duke University's CTSA Grant 1 UL1 RR024128-01 from NCRR/NIH, and NCBC (2008-IDG-1010).

Supporting Information Available. Experimental procedures and analytical data for all new compounds, as well as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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