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Preparation of (−)-(*R*)-2-(2,3,4,5,6-pentafluorophenoxy)-2-(phenyl-d_5)acetic acid: an efficient ^{1}H NMR chiral solvating agent for direct enantiomeric purity evaluation of quinoline-containing antimalarial drugs

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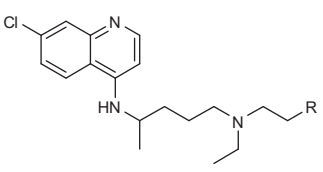
ABSTRACT

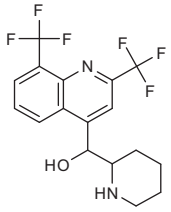
The title compound was prepared as a racemate from (±)-mandelic acid-d_5 in one step. The corresponding (−)-(*R*)-enantiomer (98% ee) was obtained by resolution with (−)-(*R*)-1-phenylethylamine and evaluated as a chiral solvating agent (CSA) for direct ^{1}H NMR enantiomeric excess determination of mefloquine (Lariam®), chloroquine (Chloroquine Bayer®), and hydroxychloroquine (Plaquenil®) enantiomers. The displayed non-equivalence was high for signals in the aromatic region of all three antimalarials. Thus, the mandelic acid derivative described herein may be considered as the first efficient CSA 'invisible' in the aromatic region, useful for direct ^{1}H NMR ee value determination of chiral quinoline-containing antimalarial drugs.

1. Introduction

Malaria is one of the most prevalent and deadly infectious diseases all over the world.[1–3] The last few decades have witnessed the relentless emergence of widespread resistance to old first-line drugs.[1–4] Thus, the need for efficacious antimalarial agents is important. The ideal antimalarial drug should be endowed with efficiency (i.e., fast-action at low single-dosage) and tolerability (absence of severe side-effects, mainly in children and pregnant women).[1] Recent efforts to improve physicians' panoply against malaria have focused on combined therapy and innovative drug development. Unfortunately, partial efficacy,[5] drug resistance, and side-effects[1–4] have seriously flawed these attempts. Several traditional, quinoline-containing antimalarial agents such as chloroquine **1**, hydroxychloroquine **2**, and mefloquine **3** are dispensed as racemates, while evidence indicates that the corresponding isolated enantiomers may have different pharmacodynamic,[6,7,11] toxicological,[8,10,13] and pharmacokinetic properties.[9,10,12,14] Thus, the chiral switch[15] approach (the use of single enantiomers in lieu of the corresponding racemate) might offer a straightforward way to safer and more efficacious drugs.



chloroquine **1** (R = H)
hydroxychloroquine **2** (R = OH)



mefloquine **3** (*R**,*S**)

Given this goal, facile methods to ascertain the enantiomeric excess of the isolated **1**–**3** enantiomers should be available. A plethora of HPLC[7,16,17] and CE[16–20] methods to evaluate the ee values of enantiomerically enriched forms of **1**–**3** have been developed. No reliable ^{1}H NMR spectroscopy methods devoted to the ee determination of these antimalarials have been reported to date. Carroll and Blackwell[21] reported on the use of *tris*[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) to assess the enantiomeric purity of (−)- and (+)-**3**. This chiral lanthanide shift reagent, however, required acetylation of the analytes, caused distortion of the baseline, and did not induce baseline resolution of the acetyl singlets of (−)- and (+)-**3** acetyl derivatives. Aslam and Craig reported[22] that the enantiomeric purity of the diastereomeric

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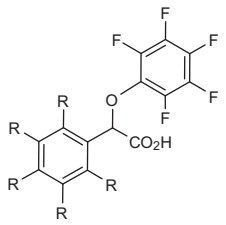
salts of (−)- and (+)-**2** with (+)-(*S*)-binaphthylphosphoric acid can be determined by monitoring the ratio of the two methyl doublets at 1.22 and 1.26 ppm. However, the aliphatic region of the ^{1}H NMR spectrum of (±)-**2**·(+)-(*S*)-binaphthylphosphate reported therein demonstrates that the above doublets were far from being baseline resolved. Recently, a method based on NMR under anisotropic conditions was applied to the enantiodiscrimination of (−)- and (+)-**3**.[23] The polyacrylamide-based gel used as a chiral alignment medium would be applicable for enantiomeric assignment but does not allow ee determination. Over the last decade, we have developed a series of *O*-aryl mandelic acids as chiral solvating agents (CSAs) for the direct ^{1}H NMR ee value determination of several biologically important amines.[24,25] In particular, the *O*-pentafluorophenyl mandelic acid derivative **4** was able to baseline resolve two aromatic signals of a mexiletine analogue presenting no singlets or doublets in a free high field region of its ^{1}H NMR spectrum.[25] Thus, we hypothesized that **4** might form sufficiently stable complexes with **1**–**3** to induce chemical shift non-equivalence on the quinoline ring proton signals. In order to avoid crowding of CSA signals in the aromatic region of the ^{1}H NMR spectrum where splitting of signals should occur, we focused our attention on 2-(2,3,4,5,6-pentafluorophenoxy)-2-(phenyl-d_5)-acetic **5**.



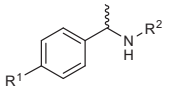
4: R = H
5: R = D

2. Results and discussion

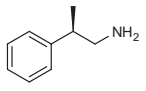
2.1. Synthesis and resolution of *O*-pentafluorophenyl mandelic acid-d_5

Racemic *O*-pentafluorophenyl mandelic acid-d_5 (*RS*)-**5** [2-(2,3,4,5,6-pentafluorophenoxy)-2-(phenyl-d_5)acetic acid] was prepared via the synthetic route shown in Scheme 1. (*RS*)-2-Hydroxy-2-(D_5)phenylacetic acid (*RS*)-**8** was prepared as previously described,[26] by submitting hexadeuterobenzene **6** to Friedel–Crafts acylation with 2,2-dichloroacetyl chloride to give dichloroacetophenone-d_5 **7**. Treatment of **7** with NaOH gave (*RS*)-**8**, which underwent a copper-catalyzed coupling with hexafluorobenzene[25,27] to afford the desired compound (*RS*)-**5**.

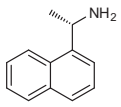
The resolution of *O*-pentafluorophenyl mandelic acid-d_5 (*RS*)-**5** by using (*R*)-1-phenylethylamine [(*R*)-PEA] as the resolving agent was then performed. Thus, a stoichiometric amount of the optically active amine was added to an ethanol solution of (*RS*)-**5** (Scheme 2) and the diastereomeric salt was recrystallized twice from absolute ethanol. In order to liberate the enriched enantiomer of *O*-pentafluorophenyl mandelic acid-d_5, the salt was dissolved in water and, after acidification with 2 M HCl and extraction with EtOAc, white crystals of (−)-**5** (14% yield) were obtained. The partially resolved (+)-*O*-pentafluorophenyl mandelic acid-d_5 was easily recovered from the mother liquors of the first recrystallization step and was then treated with (*S*)-PEA as the resolving agent for further resolution. After two recrystallization steps, (+)-*O*-pentafluorophenyl mandelic acid-d_5 was recovered from (+)-**5**·(*S*)-PEA in 27% yield. The enantiomeric purities of the enantiomers of **5** were tentatively assessed by direct ^{1}H NMR analysis by using a number of homochiral amines (**9**–**21**) as CSAs. By recording the spectra in $CDCl_3$, **9** and **12**–**19** were completely ineffective, while unsatisfactory chemical shift non-equivalences ($\Delta\delta$ <0.02 ppm, Table 1) were observed in the presence of **10** and **11**. With the aim to increase the $\Delta\delta$ value observed using **11** as the CSA, experiments were performed using higher analyte/CSA ratios (entries 1–3, Table 2) but even under these conditions, no suitable non-equivalence was observed. Several deuterated solvents were then used and an encouraging $\Delta\delta$ was finally obtained in toluene-d_8 (entries 4–6). Further increases of the analyte/CSA molar ratio in the latter solvent gave poor improvements (entries 7 and 8). By recording the spectrum at low temperature (−10 °C, entry 9), the highest $\Delta\delta$ value was finally obtained. Unfortunately, under these conditions it was not possible to determine the ee values for (−)-**5** and (+)-**5** since precipitation of the corresponding diastereomeric salts occurred. The best results were obtained when two *N*-benzyl analogues, (+)-(*R*)-*N*-benzyl-α-methylbenzylamine **20** and (+)-bis[(*R*)-1-phenylethyl]amine **21**, were used as CSAs. In fact, the non-equivalences produced on the methine signal in the presence of **20** and **21** were 0.065 and 0.060, respectively, at room temperature. Therefore, **20** was used as the CSA and the ee values of (−)-**5** and (+)-**5** were 98% and 96%, respectively. The CSAs bearing an *N*-benzyl moieties **20**, **21** caused the inversion of the enantiomer CH singlet positions in the corresponding spectra, with the (*S*)-enantiomer signal falling to lower fields than the (*R*)-enantiomer, which was opposite to what was observed in the presence of **11**.



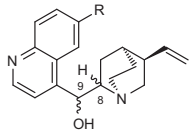
(−)-(*S*)-1-phenylethylamine **9** (R^1 = R^2 = H)
(+)-(*R*)-*N*,α-dimethylbenzylamine **10** (R^1 = H, R^2 = Me)
(+)-(*R*)-α,4-dimethylbenzylamine **11** (R^1 = Me, R^2 = H)



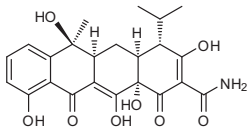
(+)-(*R*)-β-methylphenethylamine **12**



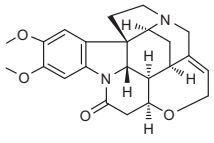
(−)-(*S*)-1-(1-naphthyl)ethylamine **13**



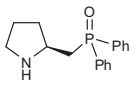
(8*R*,9*S*)-cinchonine **14** (R = H)
(8*S*,9*R*)-cinchonidine **15** (R = H)
(8*R*,9*S*)-quinidine **16** (R = OMe)



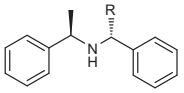
tetracycline **17**



brucine **18**

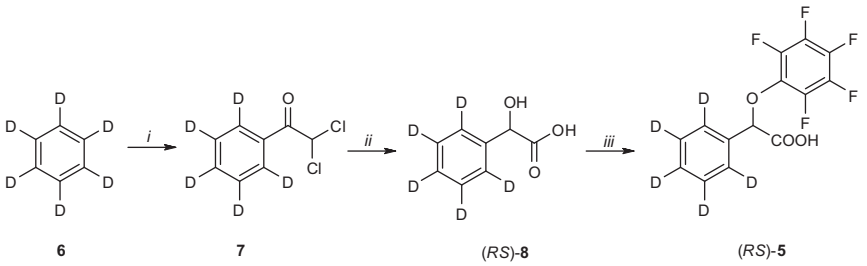


(2*S*)-2-[(diphenylphosphoryl)methyl] pyrrolidine **19**

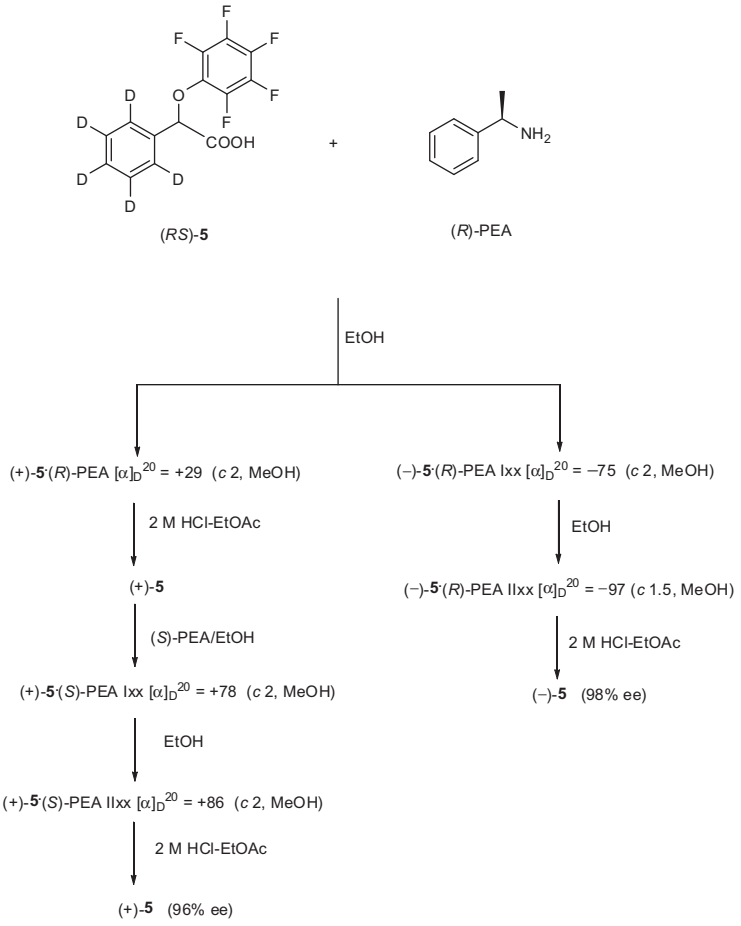


(+)-(*R*)-*N*-benzyl-α–methylbenzylamine **20** (R = H)
(+)-bis[(*R*)-1-phenylethyl]amine **21** (R = Me)

Finally, the absolute configurations of *O*-pentafluorophenyl mandelic acid-d_5 enantiomers were determined on the basis of CD analysis (Fig. 1). The (*R*)-configuration was assigned to the levorotatory isomer of **5** by spectroscopic correlation with (−)-(*R*)-*O*-pentafluorophenyl mandelic acid (−)-(*R*)-**4**, synthesized as previously reported,[25] both their corresponding CD curves showing negative Cotton effects (Fig. 1a).



Scheme 1. Reagents and conditions: (i) 2,2-dichloroacetyl chloride, $AlCl_3$, CH_2Cl_2, microwave irradiation, 70 °C, 8 min; (ii) NaOH, H_2O, microwave irradiation, 110 °C, 11 min; (iii) hexafluorobenzene, Cs_2CO_3, CuI, butyronitrile, 95 °C, 24 h.



Scheme 2. Resolution of (*RS*)-*O*-pentafluorophenyl mandelic acid-d_5 (*RS*)-**5**.

Table 1
CSAs screened for ^{1}H NMR enantiodiscrimination with (*RS*)-**5**

CSA	Ratio	$\Delta\delta$[a]
9	1:4	0
10	1:1.5	0.009
11	1:1.5	0.017
12	1:1.5	0
13	1:1.5	0
14	1:1.5	0[b]
15	1:1.5	0
16	1:1.5	0
17	1:1.5	0
18	1:1.5	0
19	1:1.5[c]	0

[a] Spectra recorded in $CDCl_3$.
[b] Spectrum recorded in $CDCl_3$/toluene-d_8/MeOH.
[c] 1:2 and 1:0.67 analyte/CSA ratios were also used ($\Delta\delta = 0$).

Table 2
Variation of temperature, solvent, and analyte/CSA ratio to improve the efficiency of **11** as a CSA for ^{1}H NMR enantiodiscrimination with (*RS*)-**5**

Entry	Temp (°C)	Solvent	Ratio	$\Delta\delta$
1	rt	$CDCl_3$	1:2	0.017
2	rt	$CDCl_3$	1:3	0.018
3	rt	$CDCl_3$	1:4	0.019
4	rt	C_5D_5N	1:2	0
5	rt	C_6D_6	1:2	0.036
6	rt	Toluene-d_8	1:2	0.040
7	rt	Toluene-d_8	1:3	0.041
8	rt	Toluene-d_8	1:4	0.042
9	−10	Toluene-d_8	1:4	0.066

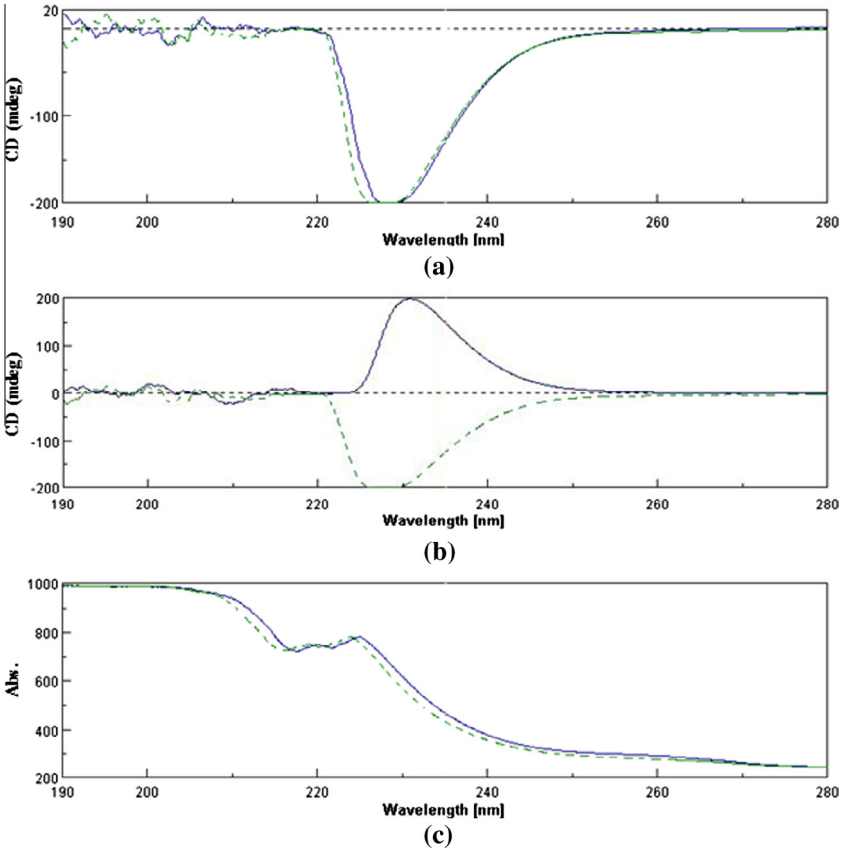
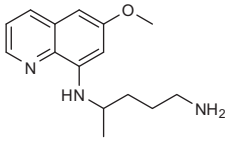


Figure 1. (a) Observed (−)-(*R*)-*O*-pentafluorophenyl mandelic acid [(−)-(*R*)-**4**] and (−)-(*R*)-**5** CD spectra (dashed and solid lines, resp.) in water; (b) observed (−)-(*R*)-**4** and (+)-(*S*)-**5** CD spectra (dashed and solid lines, resp.) in water; (c) observed (−)-(*R*)-**4** and (−)-(*R*)-**5** UV absorption spectra (dashed and solid lines, respectively) in water.

2.2. Application of (−)-(*R*)-*O*-pentafluorophenyl mandelic acid-d_5 as a chiral ^{1}H NMR discriminating agent

The chiral discrimination ability of (−)-(*R*)-*O*-pentafluorophenyl mandelic acid-d_5 (−)-(*R*)-**5** was evaluated toward the clinically relevant antimalarial agents chloroquine **1**, hydroxychloroquine **2**, and mefloquine **3**. When recording the ^{1}H NMR spectra of both **1** and **2** in the presence of 1.5 equiv of (−)-(*R*)-**5** in $CDCl_3$, good enantiodiscrimination was observed for Ar *H*C-5 of both compounds. Baseline separation of the proton doublet signal was obtained for both compounds, with $\Delta\delta$ values of 0.113 and 0.078, respectively (Fig. 2a,b, and Table 3). Compound **2** showed a slightly lower $\Delta\delta$, probably due to the lower basicity and lipophilicity of its tertiary amine group. Higher non-equivalences were obtained for some aromatic protons of mefloquine **3** possibly as a consequence of the higher rigidity of the analyte structure and the participation of the OH group in the transient complex formation and stabilization. As shown in Figure 3a and Table 3 ($CDCl_3$, analyte/CSA molar ratio 1:1.5), enantiodifferentiation with peak baseline resolution was observed for a doublets signal (*H*C-5 or *H*C-7, $\Delta\delta$ 0.27) and for the *H*C-6 triplet ($\Delta\delta$ 0.28). Unfortunately, the upfield doublet and the upfield triplet overlapped with other signals. With the aim of shifting the overlapped signals into a free region of the spectrum, the influence of the analyte/CSA ratio was evaluated. When 2 equiv of CSA were used, no improvement was obtained (Fig. 3b). Conversely, by lowering the mefloquine/CSA molar ratio to 1:0.7, the *H*C-6 triplet shifted downfield, away from the solvent signal ($\Delta\delta$ 0.17, Fig 3d and Table 3). When the spectra were recorded in toluene-d_8 with a mefloquine/CSA molar ratio of 1:1.5, the downfield doublets were almost free from overlapping (*H*C-5 or *H*C-7, $\Delta\delta$ 0.25, Fig. 4a and Table 3). A further increase of CSA resulted in a worsening of the signal separation, with the doublets shifting upfield with a lower $\Delta\delta$ (0.20, Fig. 4b, and Table 3) and partially overlapping the *H*C-3 singlet. Conversely, by reducing the CSA to 1 equiv the enantioseparation was optimal but salt precipitation occurred at room temperature ($\Delta\delta$ 0.20, Fig. 4c, and Table 3). Finally, satisfactory results were obtained when CD_2Cl_2 was added as a co-solvent, with the doublets falling in a free spectrum region with good non-equivalence (0.22, Fig. 4d, and Table 3) and no precipitation occurring. In order to verify the applicability of (−)-(*R*)-**5** as a CSA to ee value determination of quinoline-containing antimalarials characterized by a primary amine group, the $CDCl_3$ spectrum of (±)-primaquine **22** in the presence of 1.5 equiv of (−)-(*R*)-**5** was recorded. Unfortunately, no enantiodiscrimination was observed.



primaquine **22**

Thus, the degree and type of substitution on the most basic nitrogen seems to play a pivotal role in transient complex formation. However, several other structure determinants, such as electron density of the quinoline ring and basicity of its nitrogen atom, as well as the distance between the quinoline and aniline-type nitrogen atoms, might contribute.

3. Conclusions

In conclusion, a simple procedure to obtain *O*-pentafluorophenyl mandelic acid-d_5 enantiomers in highly enriched optically

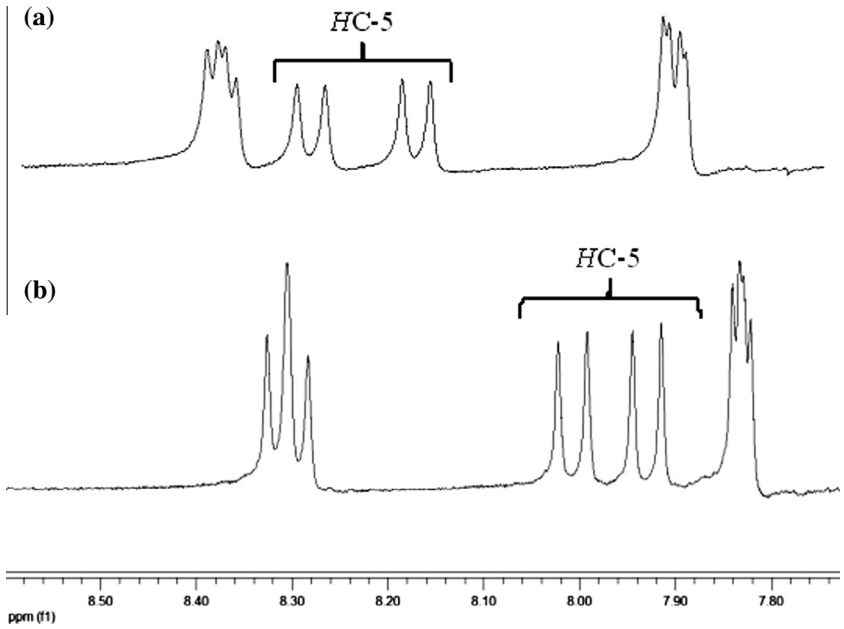


Figure 2. Enantiodiscrimination for *HC*-5 doublets of chloroquine **1** and hydroxychloroquine **2** with (−)-(*R*)-**5** (a and b, respectively), by recording the spectrum in $CDCl_3$ with an analyte/CSA molar ratio of 1:1.5.

Table 3
Magnitude of non-equivalences determined in the presence of (−)-(*R*)-**5**

Amine	Affected protons	Analyte/CSA molar ratio	$\Delta\delta$[a]
1	Ar *HC*-5	1:1.5	0.113
2	Ar *HC*-5	1:1.5	0.078
3	Ar *HC*-6	1:1.5	0.28
		1:0.7	0.17
	Ar *HC*-5 or *HC*-7	1:1.5	0.27
		1:1.5	0.25[b]
		1:2	0.20[b]
		1:1	0.20[b]
		1:1	0.22[c]

[a] Spectra were registered in $CDCl_3$, unless otherwise noted.
[b] Solvent: toluene-d_8.
[c] Solvent: toluene-d_8/CD_2Cl_2 = 4:1.

active forms was reported. Unambiguous attributions of (*R*)- and (*S*)-absolute configurations to (−)- and (+)-*O*-pentafluorophenyl mandelic acid-d_5, respectively, have been given. The (*R*)-enantiomer was an efficient CSA for the direct ^{1}H NMR ee determination of mefloquine (Lariam®), chloroquine (Chloroquine Bayer®), and hydroxychloroquine (Plaquenil®), inducing remarkable non-equivalences in the aromatic region of the spectra of these analytes. The signals of the quinoline-containing antimalarials could be used for ee evaluation since they were obscured by those of the CSA, with the latter being devoid of any signal in the aromatic region of its ^{1}H NMR spectrum.

4. Experimental

4.1. General

All chemicals were purchased from Sigma–Aldrich or Lancaster. Solvents were RP grade unless otherwise indicated. Chloroquine **1**, hydroxychloroquine **2**, and mefloquine **3** were recovered by extraction from tablets of Chloroquine Bayer®, Plaquenil®, and Lariam®, respectively. Compound **19** was prepared as previously reported.[28] The reactions under microwave irradiation were carried out at constant temperature in a CEM Discover BenchMate microwave reactor, with continuous stirring. The temperature was measured and controlled by a built-in infrared detector. The structures of the compounds were confirmed by routine spectrometric analyses. Only the spectra for compounds not previously described are given. Melting points were determined on a Gallenkamp melting point apparatus in open glass capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-VX spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively, using $CDCl_3$ as a solvent, unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) relative to the residual non-deuterated solvent resonance: $CDCl_3$, δ 7.26 (^{1}H NMR) and 77.2 (^{13}C NMR). *J* values are given in Hz. Elemental analyses were performed on a Eurovector Euro EA 3000 analyzer. Optical rotations were measured on a Perkin Elmer (Norwalk, CT) Mod 341 spectropolarimeter; concentrations are expressed in g/100 mL, and the cell length was 1 dm, thus $[\alpha]_D^{20}$ values are given in units of 10^{-1} deg cm^2 g^{-1}. TLC analyses were performed on precoated silica gel on aluminum sheets (Kieselgel 60F_{254}, Merck). CD and UV curves were registered on a J-810 model JASCO spectropolarimeter and the concentration of the solution was 10^{-5} M. CD and UV measurements were performed at room temperature and are baseline corrected and smoothed.

4.1.1. (*RS*)-2-Hydroxy-2-(D_5)phenylacetic acid (*RS*)-8

Prepared as reported in the literature.[26] Yield: 82%. Spectrometric and spectroscopic data were in agreement with the literature.[26]

4.1.2. (*RS*)-2-(2,3,4,5,6-Pentafluorophenoxy)-2-(phenyl-d_5)acetic acid (*RS*)-5

A mixture of (*RS*)-mandelic acid-d_5 (*RS*)-**8**, (1.0 g, 6.37 mmol), hexafluorobenzene (2.8 mL, 24.2 mmol), CuI (7%), and Cs_2CO_3 (5.2 g, 16.2 mmol) in butyronitrile (10 mL) was heated to 95 °C under an N_2 atmosphere for 24 h. The solvent was then removed under vacuum; the residue was taken up with water and washed twice with EtOAc. The aqueous phase was acidified with citric acid and extracted three times with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give 1.18 g of the desired product as a brownish solid

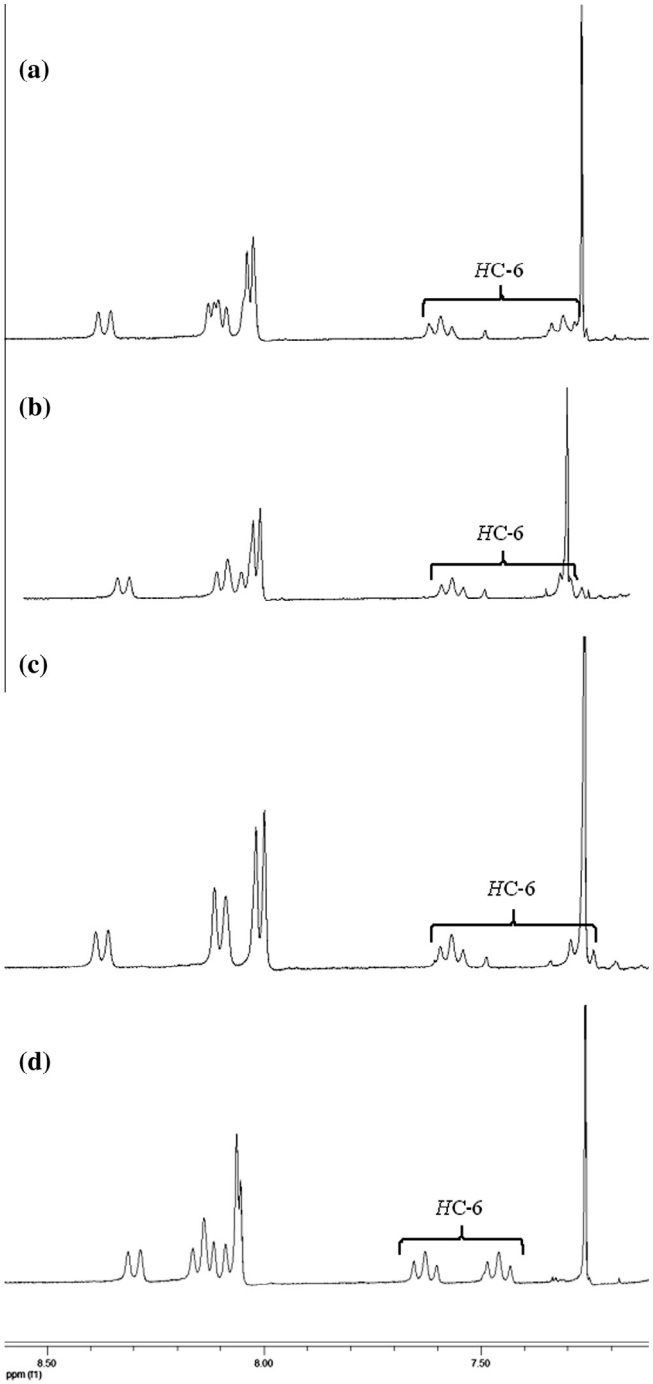


Figure 3. Enantiodiscrimination for aromatic protons of mefloquine **3** in $CDCl_3$ with an analyte/CSA molar ratio of 1:1.5 (a), 1:2 (b), 1:1 (c), 1:0.7 (d).

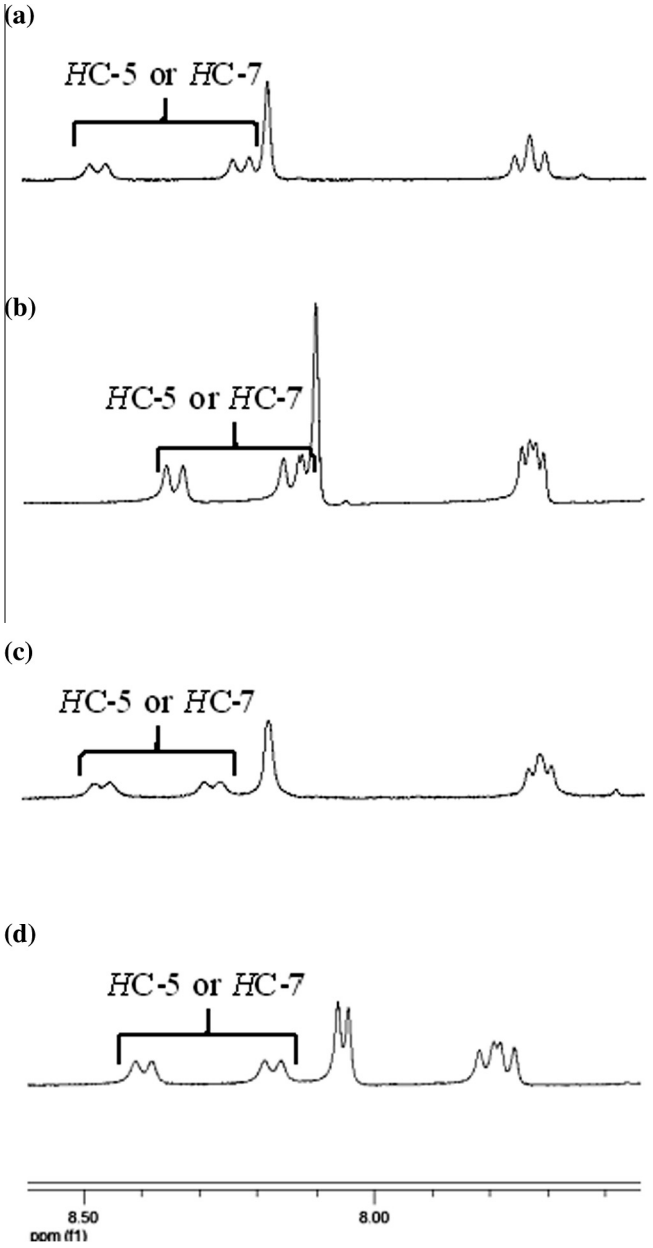


Figure 4. Enantiodiscrimination for aromatic protons of mefloquine **3** in toluene-d_8 with an analyte/CSA molar ratio of 1:1.5 (a), 1:2 (b), 1:1 (c), 1:1 by adding 0.2 mL of CD_2Cl_2 (d).

(57%): ^{1}H NMR ($CDCl_3$): δ 5.79 (s, 1H); ^{13}C NMR (irradiated at 282.32 MHz for ^{19}F-decoupling): δ 82.4 (d, $J_{^1H-^{13}C}$ = 151.9 Hz, 1C), 127.5 (t, $J_{^2H-^{13}C}$ = 24.4 Hz, 2C), 128.8 (t, $J_{^2H-^{13}C}$ = 24.7 Hz, 2C), 129.9 (t, $J_{^2H-^{13}C}$ = 24.6 Hz, 1C), 131.3 (1C), 133.3 (1C), 136.4 (2C), 140.2 (2C), 143.4 (1C), 173.9 (1C); GC–MS (70 eV) (methyl ester) *m*/*z* (%) 278 (M^+−59, 17), 126 (100).

4.2. Resolution of (*RS*)-2-(2,3,4,5,6-pentafluorophenoxy)-2-(phenyl-d_5)acetic acid (*RS*)-5

To a solution of racemic *O*-pentafluorophenyl mandelic acid-d_5 (14.2 g, 0.044 mol) in 50 mL of ethanol, (*R*)-PEA (5.66 mL, 0.044 mol) was added and a crude solid formed (Scheme 2). The mixture was heated to 70 °C to dissolve the solid and then slowly cooled to room temperature. The obtained crystalline salt was collected by filtration and washed with cold ethanol (30 mL) to give (−)-**5**·(*R*)-PEA diastereomeric salt {3.5 g, mp: 178–180 °C; $[\alpha]_D^{20}$ = −75 (*c* 2, MeOH)}. This diastereomeric salt was recrystallized from ethanol (35 mL) to afford 1.4 g of (−)-**5**·(*R*)-PEA as white crystals {mp: 184–185 °C; $[\alpha]_D^{20}$ = −97 (*c* 1.5, MeOH)}. This salt was dissolved in H_2O and the resulting solution was acidified with 2 M HCl. The liberated acid was extracted by ethyl acetate and the combined organic phases were dried over Na_2SO_4 and removed under reduced pressure. (−)-*O*-Pentafluorophenyl mandelic acid-d_5 (−)-**5** was obtained as a beige solid {1.02 g, 14% yield based on (−)-*O*-pentafluorophenyl mandelic acid-d_5 in the starting racemic mixture; mp: 86–88 °C; $[\alpha]_D^{20}$ = −151 (*c* 2, $CHCl_3$), $[\alpha]_D^{20}$ = −135 (*c* 1, MeOH); 98%

ee, ^{1}H NMR. Anal. Calcd for ($C_{14}H_2D_5F_5O_3$): C, 52.02; H, 0.62; D, 3.12. Found: C, 52.21; H + D, 2.84}.

The partially resolved (+)-*O*-pentafluorophenyl mandelic acid-d_5 was easily recovered from the mother liquor (+)-**5**·(*R*)-PEA {mp: 118–119 °C; $[\alpha]_D^{20}$ = +29 (*c* 2, MeOH)} and used for further resolution. Thus, 8.55 g of (+)-**5** were treated with (*S*)-PEA as the resolving agent. After the first recrystallization from ethanol (30 mL), 5.0 g of diastereomeric salt was obtained {mp: 177–178 °C; $[\alpha]_D^{20}$ = +78 (*c* 2, MeOH)}. This salt was recrystallized from ethanol (24 mL) to give 2.66 g of (+)-**5**·(*S*)-PEA {mp: 176–177 °C; $[\alpha]_D^{20}$ = +86 (*c* 2, MeOH)}. Finally, applying the above extraction procedure to the so-obtained salt, (+)-*O*-pentafluorophenyl mandelic acid-d_5 [(+)-**5**]was obtained as a beige solid {1.93 g, 27% yield based on (+)-*O*-pentafluorophenyl mandelic acid-d_5 in the starting racemic mixture, mp: 87–88 °C; $[\alpha]_D^{20}$ = +119 (*c* 2, $CHCl_3$); 96% ee, ^{1}H NMR. Anal. Calcd for ($C_{14}H_2D_5F_5O_3$): C, 52.02; H, 0.62; D, 3.12. Found: C, 52.06; H + D, 2.60}.

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