Organic Process Research & Development

Article

pubs.acs.org/OPRD

Practical Asymmetric Synthesis of (+)-erythro Mefloquine Hydrochloride

William P. Hems,[†] William P. Jackson,[†] Peter Nightingale,[‡] and Rob Bryant*

[†]Creative Chemistry, I-64 Building 1, Brunel Science Park, Kingston Lane, Uxbridge UB8 3PQ, U.K.

[‡]Development Chemicals Limited, UK Operations, 34 The Drive, Orpington, Kent BR6 9AP, U.K.

ABSTRACT: A highly enantioselective and cost efficient process for the synthesis of (+)-erythro mefloquine has been developed. The key step is an enantioselective reduction of pyridyl ketone KI using transfer hydrogenation with formic acid as the hydrogen source. The ratio of formic acid to NEt_3 was found to be very important to achieving a highly efficient process.

Mefloquine is a highly efficacious antimalaria drug that is approved in its racemic form for both treatment (in combination with artesunate) and prophylaxis (as monotherapy) of malaria.[1] The molecule contains two contiguous chiral centres, which means that it can exist in four possible stereoisomers (Figure 1).[2] Larium, the Roche branded formulation, contains *rac*-(±)-erythro mefloquine HCl with undetectable levels of the *rac*-threo stereoisomers. Although *rac*-erythro mefloquine is an attractive antimalaria therapy, its clinical utility has been compromised by CNS side effects. It has been felt on theoretical grounds that these side effects might be mainly a byproduct of the (−)-erythro stereoisomer. In June 2009, Treague Ltd., a small biotech company based in Cambridge, U.K., and Medicine for Malaria Venture (MMV[3]), a specialist malaria funding charity, initiated phase 1 stage clinical development of the single enantiomer (*R*,*S*)-erythro mefloquine HCl for the treatment of malaria.

As part of that program, Development Chemicals Ltd./Creative Chemistry were invited to identify manufacturing options and to develop a process to provide single enantiomer active ingredient for further clinical trials. The perceived benefit of (+)-erythro mefloquine would be the lowering of the CNS side effects and, therefore, better compliance. A higher dose, however, makes the development even more sensitive to cost of goods in that it is not desirable for the single enantiomer to be of greater cost than the racemate. With the fact that the API would be destined for use in combination therapies to be dispensed in predominantly disadvantaged regions of the world, MMV and Treague set a very tough target of half the cost of the current racemate! Therefore, it was extremely important that a cost-effective asymmetric synthesis of (+)-erythro mefloquine was developed. Although the resolution of the rac-erythro mefloquine has been reported, this route was discounted as inevitably the route that produced material of at least twice the cost of the racemate.[4] It was interesting to note, however, that the synthesis of rac mefloquine went via pyridyl ketone KI (Scheme 1).

Roche has reported the Rh(bisphosphine) hydrogenation of pyridyl ketone KI. The product carbinol was typically in the range 82−92% ee in 84−92% yield.[5] After asymmetric reduction of the carbonyl moiety, the pyridyl ring was hydrogenated using a heterogeneous Pt catalyst without isomerisation. More recently, Merck has also published the asymmetric hydrogenation of KI using (*S*)XylBinap-$RuCl_2$-(*S*)Daipen, which gave the chiral alcohol in 88% ee, 92% yield using 1 mol % of catalyst.[6] These two reports provided evidence for the asymmetric reduction approach we favored, but we were worried by the economic issues of using both these expensive Rh and Ru catalysts. Another outstanding catalytic asymmetric reduction technology has been developed in recent years for the enantioselective reduction of ketones. Monosulfonated diamine Ru arene complexes, which utilize hydrogen donors such as 2-propanol or formic acid, have been used to reduce ketones with excellent enantioselectivities.[7] In light of the Merck result, we investigated whether transfer hydrogenation (TH) would yield an efficient enantioselective reduction process.

The pyridyl ketone KI was synthesized using known literature procedures.[8] When standard catalytic asymmetric transfer hydrogenation conditions, using [(*S*,*S*)TsDpen]Ru(*p*-cymene)Cl as the catalyst precursor were applied, the ketone was reduced to the chiral alcohol in full conversion and in 96% ee (Scheme 2). It was extremely gratifying to achieve such high enantioselectivity, and so we continued to investigate the scope of the reaction.

Amazingly, a screen of different solvents and catalysts led to virtually no change in the enantioselectivity of the reaction. It was pleasing to note that the use of TsDACH ligand[9] in place of TsDPEN resulted in equally excellent ee (96%), as this added a cost benefit in terms of lower catalyst cost contribution to the process.[10] The parameter which had the most impact on the reaction was the ratio of formic acid to NEt_3. The results of using different ratios of formic acid/NEt_3 are summarized in Table 1. We found that a narrow window existed in which the reaction proceeded with exceptionally high TOF[11] and enantioselectivity. The reaction appeared fastest when the molar ratio of formic acid to NEt_3 was 1. Increasing the ratio led to a much reduced reaction rate, but maintenance of the enantioselectivity. Lowering the ratio to below 1 resulted in not only a lower rate but also a lowering in ee. The optimized conditions (s/c 1000,[11] formic acid/NEt_3 1:1, DMF, rt, 20 h) were reproduced on 2 × 11 g input of pyridyl ketone KI, and

Received: December 5, 2011
Published: February 21, 2012

dx.doi.org/10.1021/op200354f | *Org. Process Res. Dev.* 2012, 16, 461−463

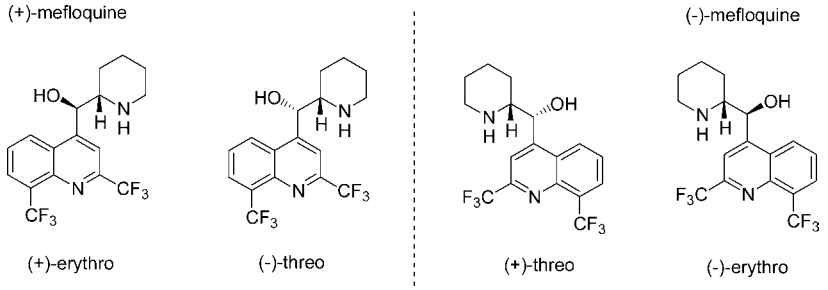
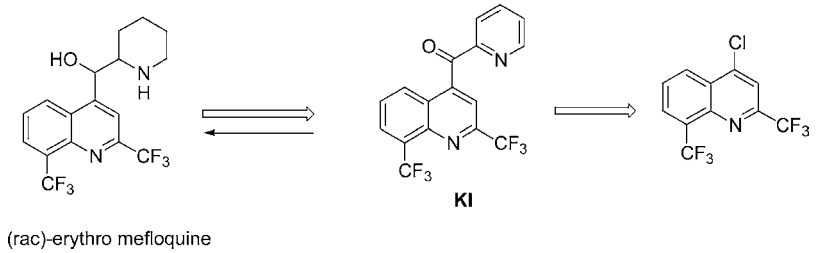
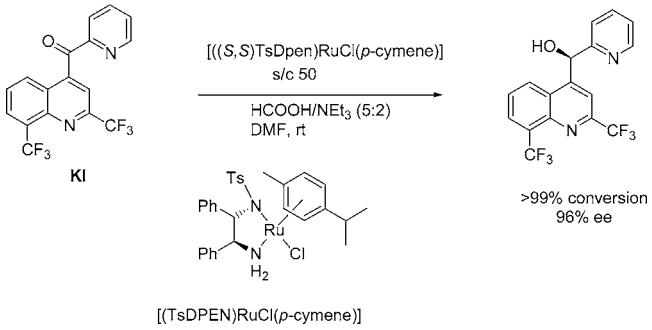


Figure 1. Stereoisomers of mefloquine.

Scheme 1. Retrosynthesis of Racemic Mefloquine



Scheme 2. Preliminary Result for the Catalytic Asymmetric Transfer Hydrogenation of Pyridyl Ketone KI



the rate and selectivity were maintained to give complete conversion in 20 h. The product was simply obtained directly from the reaction mixture by the addition of water in 91% isolated yield and 98% ee.

The final step in the sequence was the diastereoselective reduction of the pyridine ring. In the Roche approach, this was carried out using PtO_2 as catalyst. The major disadvantage in this approach, however, is the use of PtO_2, due to its cost and availability. We therefore focused on whether a standard Pt/C catalyst would also achieve the same chemo- and diastereoselectivity. A standard 5% Pt/C catalyst was taken and preactivated under H_2 at 40 °C in MeOH for 1 h, prior to the addition of the chiral alcohol (98% ee) and conc HCl (1.1 equiv) (Scheme 3). The mixture was subsequently stirred under H_2 (2 bar) at rt for 24 h to give full conversion to the desired mefloquine HCl in a 85:15 erythro/threo ratio. Purification of the crude residue by selective crystallization was carried out by literature procedures to give highly pure (+)-erythro mefloquine HCl (>98% ee) in 58% isolated yield.[12] An isolated yield of 58% was slightly lower than had been hoped, although this is 70% of the theoretical yield of the 85:15 mixture obtained from the hydrogenation. Later development of a simplified purification of the racemic salt gave an 80% overall yield, demonstrating the potential for improvement, had the project continued.

In summary, we have developed a highly enantioselective and cost efficient process for the synthesis of (+)-erythro mefloquine. The key step is the enantioselective reduction of pyridyl ketone KI using transfer hydrogenation with formic acid as the hydrogen source. The ratio of formic acid to NEt_3 was found to be very important to achieving a highly efficient process. The improvement from 88% ee to 98% ee is also commercially very significant, and the key improvement was achieved using a substantially different catalyst, which also promotes a faster reaction. An 88% ee product could never be registered for sale as a pharmaceutical product.

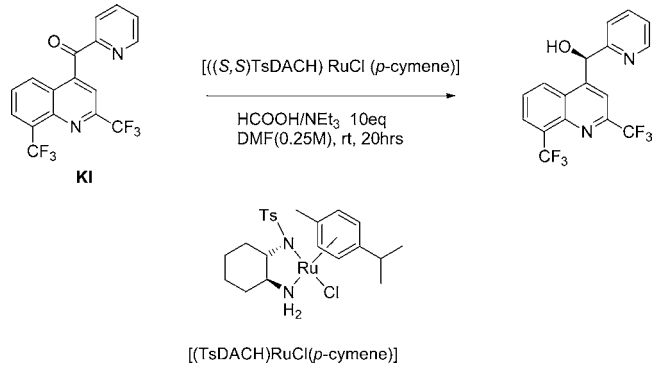
■ EXPERIMENTAL SECTION

Transfer Hydrogenation of KI. Experimental Procedure: In a 500 mL 3-N flask equipped with a thermometer and an N_2 bubbler was added DMF (120 mL). Triethylamine (20.8 mL, 0.15 mol) was then added to the stirred solution. Formic acid (5.6 mL, 0.15 mol) was added dropwise while maintaining the temperature below 30 °C. N_2 was then bubbled through the resulting solution for 5 min before the addition of KI (11 g, 3 0 mmol). The solution was stirred with N_2 bubbling through for a total of 30 min. Then the catalyst (16 mg, 30 μmol) was added to the reaction mixture, and this was stirred at room temperature (24 °C) overnight. The reaction was quenched by the dropwise addition of water whilst cooling the reaction to between 10 and 15 °C. During the addition of water the product precipitated (120 mL of water was added in total). The solid was collected and dried in a vacuum oven to give the chiral alcohol as a colourless solid (10.1 g, 91% yield, 98% ee). HPLC analysis using a Chiralcel OD column (hexane/EtOH: 0.025% Et_2NH, 90:10). mp 133−134 °C (lit.[5] 135−136).

5% Pt/C Reduction of Chiral Alcohol. The 5% Pt/C (3.4 g) catalyst was placed in a glass autoclave with MeOH (100 mL). The mixture was heated to 55 °C under 2 bar hydrogen for 1 h. The flask was cooled, and a solution of chiral alcohol (22.25 g) in MeOH (120 mL) and conc HCl (6.5 mL) was added to the catalyst mixture. The mixture was stirred under hydrogen (2 bar) for 24 h. The hydrogen was released and the catalyst filtered. The amount of MeOH was reduced by

dx.doi.org/10.1021/op200354f | Org. Process Res. Dev. 2012, 16, 461−463

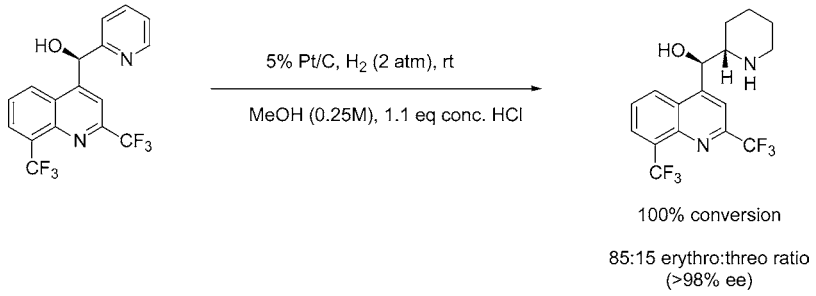
Table 1. Effect of the Ratio of Formic Acid to Triethylamine on the Catalytic Asymmetric Transfer Hydrogenation of Pyridyl Ketone KI



entry	$HCOOH/NEt_3$ ratio[a]	s/c[b]	conv 2 h[c]	%ee 2 h	conv 20 h	%ee 20 h
1	10:1	500	5		8	
2	5:2	500	56	96	>98	96
3	1:1	500	98	96	>99	96
4	1:1[d]	1000	57	97	99	96
5	0.75:1	1000	29	92	99	92

[a]Reaction conditions carried out in a 100 mL 3-N flask with a N_2 bubbler. HCOOH is added dropwise to NEt_3 in DMF prior to addition of substrate and catalyst. [b]Substrate to catalyst ratio. [c]% conversion and ee measured by HPLC analysis. [d]5 equiv of $HCOOH/NEt_3$ was used in this reaction.

Scheme 3. Diastereoselective 5% Pt/C Reduction of Chiral Alcohol



approximately half by rotary evaporation. Water (300 mL) was added to the MeOH solution, resulting in precipitation of a fine white solid. The mixture was heated to 80 °C slowly and kept at that temperature for 30 min. The mixture was cooled to 5 °C and kept at that temp for 2 h. The resulting mixture was then filtered and the white solid dried in a vacuum oven. The dried solid was recrystallised again from MeOH/water[12] to give pure (+)-mefloquine HCl (14.4 g, 58% yield, >99% ee). HPLC analysis of free base using a Chiralpak AD column (hexane/EtOH: 0.025% Et_2NH, 98:2). mp 170−171 °C (lit.[5] 170.5−171.0).

AUTHOR INFORMATION

Corresponding Author

*E-mail: rob@developmentchemicals.co.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Robert Tansley of Treague Ltd for awarding the contract to Development Chemicals Ltd and Dr. Timothy Wells of MMV for funding the project.

REFERENCES

(1) Ohnmaat, J.; Patel, A. R.; Lutz, R. E. *J. Med. Chem.* **1971**, *14*, 926−928.
(2) Carroll, F. I.; Blackwell, T. *J. Med. Chem.* **1974**, *17*, 210.
(3) www.mmv.org.
(4) Baxter, A. D.; Harris, M. J.; Brown, S. (Arakis Ltd). Resolution of Mefloquine with O,O-Di-*p*-Aroyltartaric acid. International Patent Publication WO/2004/050625 A1, 2004.
(5) Broger, E. A.; Hofheinz, W.; Meili, A. (Hoffmann-La Roche). Asymmetric Synthesis Process. US Patent 5,514,805, 1996.
(6) Chen, C.; Reamer, R. A.; Chilenski, J. R.; McWilliams, C. J. *Org. Lett.* **2003**, *5*, 5039.
(7) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.
(8) Adam, S. *Tetrahedron* **1991**, *47*, 7609.
(9) TsDACH: *N*-(*p*-toluenesulfonyl)-1,2-diaminocyclohexane.
(10) Aldrich Chemical price comparison: (*S,S*)TsDACH 1 g £66.70; (*S,S*)TsDPEN 1 g £136.
(11) s/c, substrate to catalyst molar ratio; TOF, catalyst turnover frequency.
(12) Bomches, H.; Hardegger, B. (Hoffmann-La Roche). Purification of Mefloquine Hydrochloride, US Patent 4,507,482, 1985.