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Asymmetric metal-free synthesis of fluoroquinolones by organocatalytic hydrogenation

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ABSTRACT

A highly enantioselective organocatalytic transfer hydrogenation enabling the synthesis of both 6-fluoro-2-methyltetrahydroquinoline and 7,8-difluoro-3-methyl-benzoxazine has been developed. These key building blocks can for the first time be synthesized using the same methodology allowing fast and efficient, metal-free access to the antibiotic fluoroquinolones flumequine and levofloxacine.

1. Introduction

The development of new asymmetric methods for the general and efficient synthesis of optically pure, key pharmaceutical building blocks is of ongoing interest. Using readily available starting materials and employing the optimal reaction conditions, the aim is to obtain these valuable products with enhanced selectivity, greater potency or fewer side effects.

Tricyclic fluoroquinolones, including flumequine and levofloxacin, are well known antibacterial agents with broad spectrum activity against Gram-positive and Gram-negative bacteria.[1] Today flumequine is primarily used as a pesticide.[2] Levofloxacin on the other hand is one of the most potent antibacterial agents on the market and the most prescribed quinolone class antibiotic worldwide. The major challenge for the synthesis and straightforward variation of these compounds is the development of the efficient catalytic synthesis of their chiral key building blocks, 6-fluoro-2-methyl-1,2,3,4-tetrahydro-quinoline **3** and 7,8-difluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*]-[1,4]oxazine **4**. Several synthetic methods for the synthesis of these key intermediates have been reported.[3] However, despite these advances, alternative and cost effective procedures are still needed.

Within this context, we report here a practical and straightforward procedure for the asymmetric, metal-free synthesis of two fluoroquinolones, flumequine **1** and levofloxacine **2**. Based on our previous successes in the development of chiral Brønsted acid[4] catalyzed transfer hydrogenations,[5–7] and in continuation of the ongoing research efforts in the synthesis of natural products and biologically active compounds,[8] we decided to examine this organocatalytic process for the asymmetric hydrogenation of quinoline **5** and benzoxazine **6** (Fig. 1).

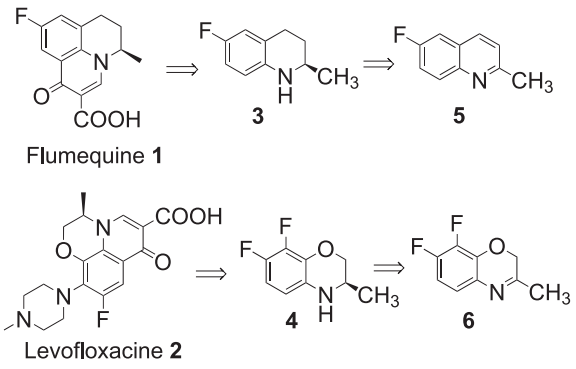

Figure 1.

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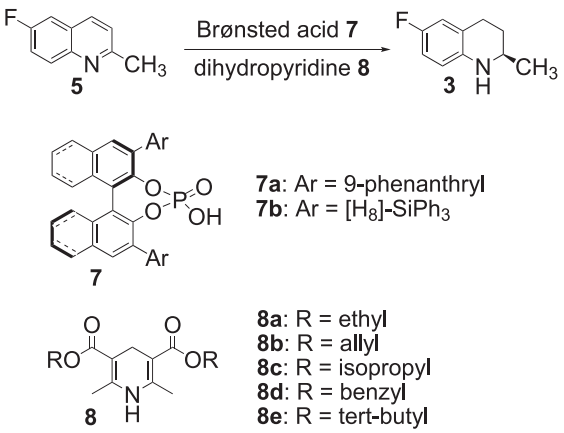
2. Results and discussion

Our initial studies focused on the metal-free transfer hydrogenation of 6-fluoro-2-methylquinoline **5** by employing several chiral Brønsted acid catalysts **7** in combination with dihydropyridines **8** as the hydride source. While almost all of the 3,3-aryl-substituted BINOL-phosphoric acids[9] provided the product in good yields, the best results with regard to enantioselectivity were obtained with catalyst **7a**. This is in agreement with our earlier developed Brønsted acid catalyzed reactions, in which **7a** was typically a privileged catalyst. However, here we only obtained a disappointingly low enantiomeric excess of 84% ee (Table 1, entry 1). To further improve the enantioselectivity, we decided to prepare the sterically more demanding triphenylsilyl-substituted Brønsted acid **7b** and apply it in the asymmetric reduction. To our delight we obtained a higher enantioselectivity (Table 1, entry 2). Next we varied the catalyst loading and the ester moiety of dihydropyridine **8**. While the change in catalyst loading had no considerable impact (Table 1, entries 2–4), the variation of the dihydropyridine (Table 1, entries 5–9) resulted in the formation of **3** with better enantiomeric excess (Table 1, entry 8). Thus, with just 1 mol % of Brønsted acid catalyst **7b**, we obtained the desired 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline **3** in good yield and with an enantiomeric excess of 96% ee.

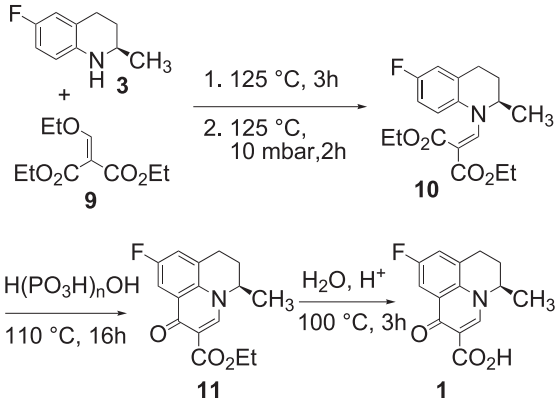
Table 1



Entry[a]	7	mol % 7	HEH 8	Yield[b] [%]	ee[c] [%]
1	**7a**	2	**8e**	77	84
2	**7b**	1	**8a**	81	92
3	**7b**	2	**8a**	79	94
4	**7b**	5	**8a**	83	95
5	**7b**	1	**8b**	79	94
6	**7b**	1	**8c**	82	87
7	**7b**	1	**8d**	81	89
8	**7b**	1	**8e**	79	96
9	**7b**	5	**8e**	76	97

[a] Reactions were performed with quinoline **5** (1.0 equiv), HEH **8** (2.4 equiv), and catalyst **7** in benzene at 60 °C.
[b] Yield of isolated product after column chromatography.
[c] The ee values were determined by chiral HPLC.

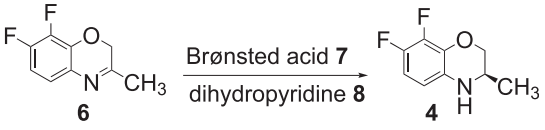
With the enantiomerically enriched key building block **3** in hand we started with the synthesis of flumequine **1** according to a recently reported one pot reaction sequence (Scheme 1).[3h] The alkylation of **3** with diethylethoxymethylene malonate **9** resulted in the formation of **10**, which was directly cyclized to the flumequine ester **11** by employing polyphosphoric acid. The final hydrolysis step afforded the desired product (*R*)-flumequine **1** in 61% overall yield (Scheme 1). Thus, a short and efficient metal-free enantioselective protocol for the synthesis of flumequine has been established in which an asymmetric organocatalytic quinoline reduction represents the key step.



Scheme 1. The synthesis of (*R*)-flumequine.

Following this success we turned our attention to the synthesis of the antibacterial agent levofloxacine **2**. The core of levofloxacine consists of a 3,4-dihydro-2*H*-1,4-benzoxazine **4** and could be obtained by an asymmetric hydrogenation of **6**, which is easily prepared from nitrophenoxy propanone. Thus, our initial experiments concentrated on finding the best catalyst and reaction conditions for the reduction of **6**. Similar to the quinoline reduction, better results were obtained with Brønsted acid **7b** resulting in the product **4** with 89% ee (Table 2, entry 2).

Table 2
Evaluation of the hydride source **8**[a]



Entry	Catalyst 7	HEH 8	Yield [%][b]	ee[%][c]
1	**7a**	**8a**	75	66
2	**7b**	**8a**	75	89
3	**7b**	**8b**	78	87
4	**7b**	**8c**	75	80
5	**7b**	**8d**	76	85
6	**7b**	**8e**	74	88

[a] Reactions were performed with benzoxazine **6** (1.0 equiv), HEH **8** (1.2 equiv), and catalyst **7** (5 mol %) in benzene at 60 °C.
[b] Yield of isolated product after column chromatography.
[c] Enantiomeric excess was determined by HPLC.

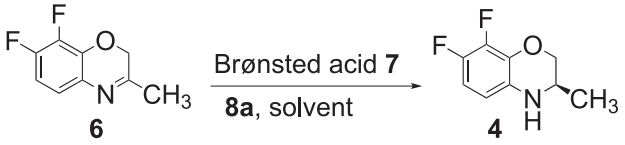
For further reaction optimization we evaluated the different Hantzsch dihydropyridines **8** and solvents as they often have a significant impact on the enantioselectivity.[7] Although, no further improvement was observed if different dihydropyridines **8a–e** (Table 2, entries 2–6) were applied, the use of dichloromethane as the solvent gave the product with an acceptable enantiomeric excess of 93% ee (Table 3, entry 6).

With the key building block **4** in hand we began with our synthesis of (*R*)-levofloxacin in analogy to the protocol described for the synthesis of (*R*)-flumequine (Scheme 2). Thus the one pot condensation with **9** followed by a phosphoric acid catalyzed cyclization resulted in tricyclic ester **12**. The subsequent saponification was followed by a nucleophilic aromatic substitution to give the antibacterial agent levofloxacine **2** in short and efficient reaction sequence.

3. Conclusion

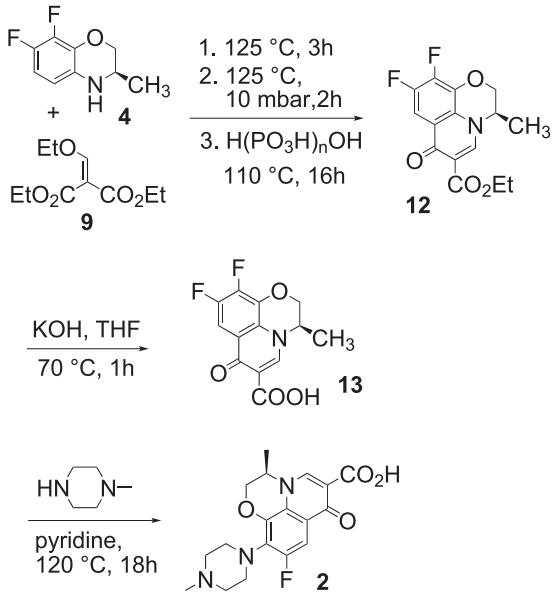
In summary, we describe here the development of an asymmetric organocatalytic transfer hydrogenation as a simple and

Table 3
Optimizing the reaction conditions[a]



Entry	7	mol % 7	Solvent	Yield[c] [%]	ee[d][%]
1	**7a**	5	Benzene	75	66
2	**7b**	5	Benzene	81	90
3	**7b**	2	Benzene	75	89
4	**7b**	1	Benzene	75	89
5[b]	**7b**	1	$CHCl_3$	65	89
6[b]	**7b**	1	CH_2Cl_2	67	93

[a] Reactions were performed with benzoxazine **6** (1.0 equiv), dihydropyridine **8a** (1.2 equiv), and catalyst **7** at 60 °C.
[b] Reaction was performed at ambient temperature.
[c] Yield of isolated product after column chromatography.
[d] The ee values were determined by chiral HPLC.



Scheme 2. The synthesis of (*R*)-levofloxacin.

straightforward method to access both valuable key intermediates 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline and 7,8-difluoro-3-methyldihydrobenzoxazine. These reactions proceed with excellent stereoinduction and can be performed with low catalyst loadings under mild reaction conditions. The resulting chiral building blocks were subsequently used in the metal-free synthesis of the valuable drugs (*R*)-flumequine and (*R*)-levofloxacine.

4. Experimental

4.1. 6-Fluor-2-methyl-1,2,3,4-tetrahydroquinoline 3

Quinoline **5** (0.70 mmol), catalyst **7b** (1 mol %), and dihydropyridine **8e** (1.7 mmol) were suspended in benzene (10 mL) in a screw-capped vial. The resulting mixture was allowed to stir at 60 °C for 14 h. The solvent was removed under reduced pressure and purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane) afforded the product **3** as colorless solid (0.55 mmol, 79%). Mp: 39–42 °C (lit.[3h] mp: 40–43 °C); $[\alpha]_D^{20}$ +58.8 (*c* 1.0, ethanol) (lit.[3h] $[\alpha]_D^{20}$ +70.2 (*c* 1.0, ethanol)); ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.79–6.65 (m, 2H), 6.49–6.37 (m, 1H), 3.58–3.29 (m, 2H), 2.97–2.65 (m, 2H), 2.08–1.85 (m, 1H), 1.71–1.46 (m, 1H), 1.24 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 115.5, 115.2, 114.8, 114.6, 113.3, 112.9, 47.3, 29.8, 26.6, 22.4; IR (KBr, cm^{-1}) 3396, 2960, 2924, 2850, 1502, 1259, 1234, 1144, 1095, 1022, 810; MS-ESI *m*/*z*: 165.7 $[M]^+$; HPLC condition: OD-H column, *n*-hexane/2-propanol 98/2, flow rate 0.6 mL/min, major enantiomer t_R=11.38 min, minor enantiomer t_R=15.32 min.

4.2. (*R*)-Flumequine 1

To 6-fluoro-1,2,3,4-tetrahydro-2-methylchinoline **3** (0.55 mmol) was added diethylethoxymethylene malonate (0.67 mmol). The resulting mixture was stirred at 125 °C for 3 h and subsequently at reduced pressure (10 mbar) for 1 h. The mixture was allowed to cool down to room temperature and polyphosphoric acid (1.4 mmol) was added. The mixture was heated to 110 °C for 14 h. Water (0.3 ml) was added and the resulting mixture was stirred at 100 °C for 3 h. Then the mixture was cooled down to 0 °C, the precipitate was filtered off and recrystallized from DMF. The product was isolated as white powder (0.47 mmol, 77%). Mp: 249–252 °C (lit.[3h] mp: 247–250 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 14.81 (s, 1H), 8.67 (s, 1H), 7.99–7.88 (m, 1H), 7.36–7.27 (m, 1H), 4.63–4.48 (m, 1H), 3.28–2.95 (m, 2H), 2.34–2.08 (m, 2H), 1.48 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 167.0, 161.8, 146.2, 130.2, 128.3, 121.9, 121.5, 110.1, 109.7, 108.2, 58.1, 26.1, 22.1, 20.5; IR (KBr, cm^{-1}) 3054, 2991, 1722, 1620, 1566, 1468, 1194, 1065, 885, 810; MS-ESI *m*/*z*: 262.0 $[M+H]^+$.

4.3. 7,8-Difluoro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazine 4

Benzoxazine **6** (1.1 mmol), catalyst **7b** (1 mol %), and Hantzsch dihydropyridine **8a** (1.3 mmol) were suspended in dichloromethane in a screw-capped vial. The resulting mixture was allowed to stir at room temperature for 48 h. The solvent was removed under reduced pressure and purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane) afforded the (0.78 mmol, 65%) pure product as yellowish oil. $[\alpha]_D^{20}$ +2.2 (*c* 1.0, $CHCl_3$) (lit.[3d] $[\alpha]_D^{20}$ +9.5 (*c* 1.86, $CHCl_3$)); ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.55–6.41 (m, 1H), 6.23–6.13 (m, 1H), 4.21 (dd, *J* 10.4, 2.8 Hz, 1H), 3.77–3.66 (m, 1H), 3.51–3.35 (m, 1H), 1.13 (d, *J* 6.4 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 108.5, 108.4, 108.4, 108.3, 107.9, 107.6, 70.9, 44.8, 17.4; IR (neat, cm^{-1}) 3390, 2974, 2929, 2879, 1504, 1464, 1348, 1329, 1317, 1227, 1167, 1045, 931, 791, 677 cm^{-1}; MS-ESI *m*/*z*: 185.7 $[M]^+$; HPLC condition: OD-H column, *n*-hexane/2-propanol 90/10, flow rate 0.6 mL/min, major enantiomer t_R=12.39 min, minor enantiomer t_R=14.40 min.

4.4. Ethyl-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido-[1,2,3-*de*]-1,4-benzoxazin-carboxylate 12

To 5,6-difluoro-2-methyl-3,4-dihydrobenzoxazine **4** (0.73 mmol) was added diethylethoxymethylene malonate **9** (0.87 mmol). The resulting mixture was stirred at 125 °C for 3 h and additional 1 h at reduced pressure (10 mbar). After cooling down to room temperature polyphosphoric acid (1.94 mmol) was added and heated to 110 °C for 20 h. Then water (3.5 mL) was added and the resulting mixture was stirred at room temperature for 16 h. The precipitate was recrystallized from ethanol. The product was obtained as a yellowish solid (0.39 mmol, 54%). Mp: 254–255 (lit.[3b] mp: 259–260 °C); ^{1}H NMR (250 MHz, $CDCl_3$/MeOD): δ 8.28 (s, 1H), 7.55–7.43 (m, 1H), 4.02–4.34 (m, 4H), 3.07–3.02 (m, 1H), 1.30 (d, *J* 6.8 Hz, 3H), 1.10 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$/MeOD): δ 167.8, 153.9, 149.3, 146.4, 143.1, 138.1, 138.0, 126.7, 112.8, 107.9, 71.7, 63.8, 57.9, 20.3, 16.5; IR (KBr, cm^{-1}) 3028, 2989, 1722, 1601, 1485, 1354, 1315, 1300, 1254, 1174, 1093, 1070, 800 cm^{-1}; MS-ESI *m*/*z*: 309.9 $[M]^+$.

4.5. Synthesis of (*R*)-Levofloxacine 2

To ethylcarboxylate **12** (0.37 mmol) in dried THF (18 mL) was added 10% KOH solution (3 mL). The mixture was heated to 70 °C for 1.5 h. The THF was removed under reduced pressure. The residue was acidified to pH 5 with acetic acid. The precipitate was filtered and washed with water and diethylether. The resulting carboxylic acid was dissolved in dried pyridine (0.5 mL). To the solution was added dropwise *N*-methylpiperazine (0.36 mL). The mixture was heated to 125 °C for 16 h. The solvent was removed under reduced pressure and the crude product was recrystallized from methanol to afford the product (0.19 mmol, 53%) as yellow solid; ^{1}H NMR (250 MHz, $CDCl_3$/MeOD): δ 8.50 (s, 1H), 7.52 (d, *J* 11.8 Hz, 1H), 4.53–4.39 (m, 1H), 4.32 (dd, *J* 11.8, 2.3 Hz, 1H), 3.56–2.56 (m, 10H), 2.71 (s, 3H), 1.38 (d, *J* 6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$/MeOD): δ 179.9, 170.7, 160.7, 156.7, 148.5, 143.5, 133.5, 127.5, 124.5, 109.9, 107.4, 105.0, 71.2, 58.5, 56.9, 45.9, 43.1, 20.5; IR (KBr, cm^{-1}) 3450, 2951, 2686, 1711, 1622, 1527, 1292, 1055, 980, 804 cm^{-1}; MS-ESI *m*/*z*: 361.9 $[M]^+$.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.091.

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