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Kinetic resolution of (±)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazines with (*S*)-naproxen

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Abstract

A very effective method for the preparation of the (*S*)-enantiomers of 2,3-dihydro-3-methyl- and 7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazines (**1a** and **2a**) was developed using (*S*)-(+)-naproxen acyl chloride as the chiral agent for kinetic resolution of racemates. This method enables one to obtain the (*S*)-enantiomers of benzoxazines **1a** and **2a** of high enantiomeric purity (99% *ee*) in nearly 50% yield, taking into account that the (*R*)-enantiomers are recycled after their racemisation.

1. Introduction

2,3-Dihydro-3-methyl-4*H*-1,4-benzoxazine derivatives **1** and **2** have attracted considerable interest due to the presence of their skeleton in a number of compounds possessing biological activity.[1] In particular, 7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **1** is one of the key intermediates for the synthesis of ofloxacin **3**, a very potent antibacterial agent. Stereoconfiguration of the asymmetric C-3 carbon in the oxazine ring of ofloxacin is known to be of crucial importance for its pharmacological properties. Indeed, the (*S*)-(−)-isomer of ofloxacin (levofloxacin) **3a** was found be more active against Gram-positive and Gram-negative bacteria and less toxic than the corresponding racemate **3**.[1]

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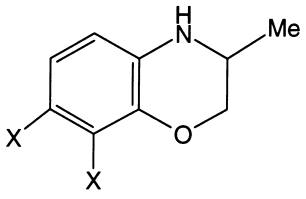

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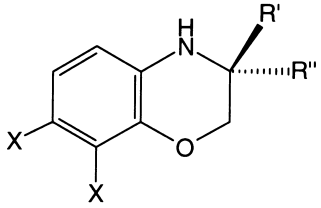
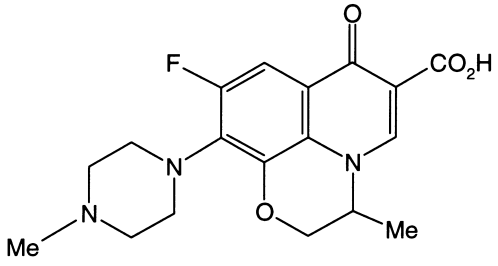
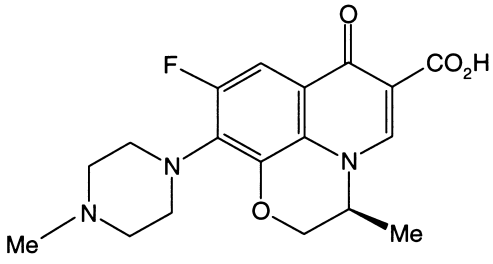


1a, 2a: R' = Me, R'' = H (*S*)
1b, 2b: R' = H, R'' = Me (*R*)



3 (Ofloxacin)



3a (Levofloxacin)

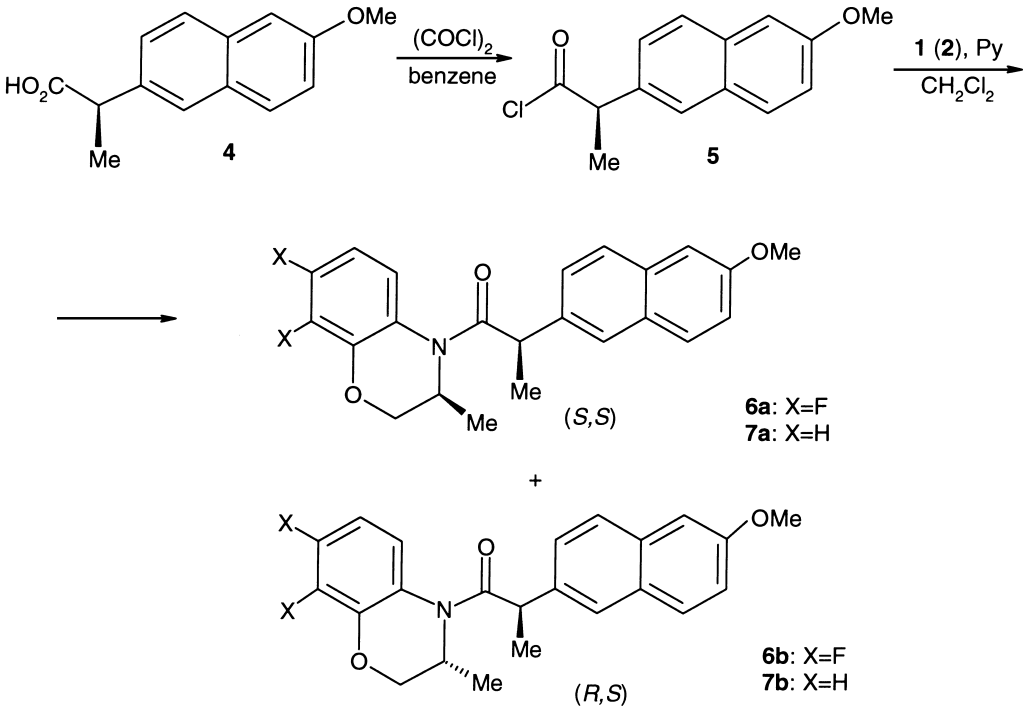
A variety of the reported synthetic procedures leading to (*S*)-(−)-7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **1a**, a key intermediate for the synthesis of **3a**,[1] can be classified into several groups: (i) resolution of diastereoisomeric amides or salts of racemate **1** with chiral acids followed by hydrolysis;[2–4] (ii) asymmetric hydrolysis with enzymes;[3,5] (iii) asymmetric reduction of 7,8-difluoro-3-methyl-2*H*-1,4-benzoxazine;[6] (iv) other synthetic routes including use of chiral auxiliaries such as diols,[7] amino alcohols,[8] and others.[9]

In this paper we wish to describe a new efficient approach to enantiomerically pure benzoxazine derivatives **1a** and **2a** which is based on using the chiral (*S*)-(+)-naproxen, i.e. (*S*)-2-(6-methoxynaphthyl-2)-propionic acid **4**. (*S*)-(+)-Naproxen belongs to the family of non-steroidal anti-inflammatory drugs and is commercially available as a pure (*S*)-(+)-enantiomer. Due to the presence of the 6-methoxynaphthyl fragment compound **4** exhibits a rather characteristic absorption in UV spectra with molar extinction =100 000 at λ=230 nm. This makes (*S*)-(+)-naproxen a very suitable chiral agent for pre-column derivatization of optically active compounds preceding HPLC analysis.[10] It should be noted that (*S*)-(+)-naproxen has not, so far, been used for preparative resolution of racemates.

2. Results and discussion

The reaction of the acyl chloride **5** (NAP-Cl), prepared from (*S*)-(+)-naproxen and oxalyl chloride,[11] with racemic benzoxazines **1** or **2** taken in quantities close to stoichiometric has been found to proceed very smoothly under mild conditions and is not accompanied by the formation of any by-products. Indeed, the synthesis can be performed at 20°C in a chloroform (dichloromethane) solution in the presence of amines such as pyridine or triethylamine (Scheme 1). Overall chemical yields of diastereoisomeric amides **6a** and **6b** (**7a** and **7b**) obtained under these conditions proved to be around 55% with (*R*,*S*):(*S*,*S*) diastereoisomeric ratio 1:1 (HPLC).

Due to features in stereo-orientation of the naphthyl substituent in the (*S*,*S*)- and (*R*,*S*)-diastereoisomeric amides, **6a** (**7a**) and **6b** (**7b**), they have different chromatographic behavior, which facilitates their resolution. Preparative resolution of the amides **6a** (**7a**) and **6b** (**7b**) was



Scheme 1.

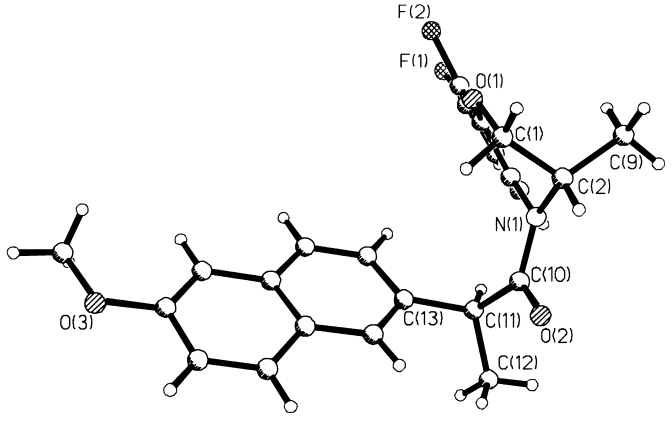


Figure 1. A perspective molecular view of the (*S*,*S*)-amide **6a**

performed by using flash-chromatography on a dry silica gel column (eluent: benzene:ethyl acetate, 95:5), thus giving (*S*,*S*)-amides **6a** (**7a**) in 76% yield with a diastereoisomeric excess of 98% (HPLC).

Assignment of the absolute configuration to (*S*,*S*)-amides **6a** and **7a** became possible on the basis of X-ray crystallographic analysis, as shown in Figs. 1 and 2, respectively. The absolute configuration of amides **6a** and **7a** were established from the known absolute configuration of the starting (*S*)-naproxen.

The ^{1}H and ^{19}F NMR spectral data for benzoxazines **1**,**2** and diastereoisomeric amides **6a**,**b** and **7a**,**b** are presented in Table 1. Although some NMR spectral characteristics of benzoxazine **1**, such as ^{1}H and ^{19}F chemical shifts, have been reported earlier,[6b] additional ^{1}H{^{1}H} and ^{19}F{^{1}H} double resonance experiments had to be performed for measuring long-range coupling constants (Table 1). The feature of the ^{1}H NMR spectra of amides **6a**,**b** and **7a**,**b** measured at ambient temperature is broadening of

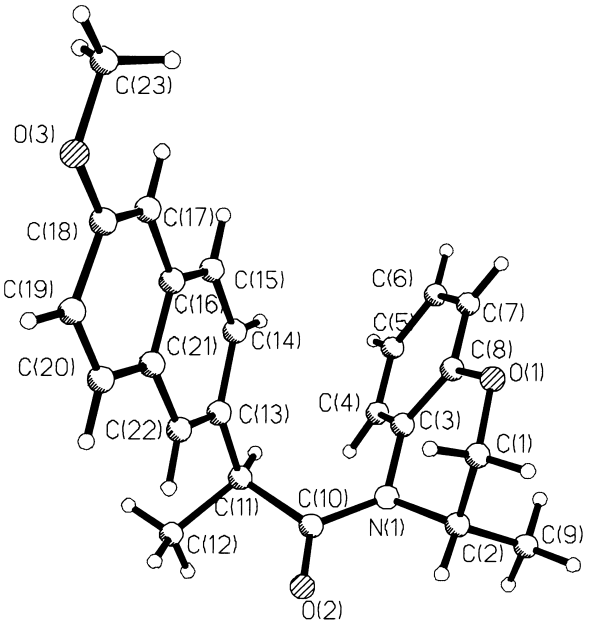


Figure 2. A perspective molecular view of the (*S*,*S*)-amide **7a**

the resonance signals of the oxazine ring protons (see the Experimental section); it was only possible to obtain high-resolution spectra of **6a**,**b** and **7a**,**b** on heating in DMSO-d_6 up to 130 and 160°C, respectively (Table 1).

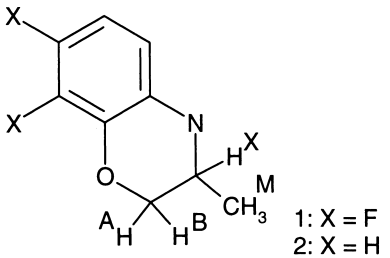
Table 1 shows that diastereoisomeric amides **6a**,**b** and **7a**,**b** can easily be distinguished on the basis of their ^{1}H NMR spectral data, and in this respect the resonance signal of the methyl group of the oxazine moiety is the most indicative one with differences in chemical shifts of 0.42 and 0.32 ppm (Table 1). Also, vicinal coupling constants $^3J_{BX}$ between H^B and H^X protons of the oxazine ring change dramatically (from 7.9–8.0 to 2.9–3.2 Hz), when benzoxazines **1** and **2** are converted into amides **6a**,**b** and **7a**,**b**, thus reflecting serious changes in the geometry of the benzoxazine fragments (Table 1).

To enhance efficiency of this resolution method we studied the possibility of kinetic resolution. We have established that in principle the (*S*,*S*)-amides **6a** and **7a** are formed much faster than the corresponding (*R*,*S*)-diastereoisomers when acyl chloride **5** reacts with racemates **1** or **2**, thus enabling one to obtain a mixture of diastereoisomeric amides enriched with the (*S*,*S*)-diastereoisomer.

In order to find appropriate conditions for a kinetic resolution procedure we carried out the reaction of benzoxazines **1** and **2** with acyl chloride **5** varying: (a) solvent; (b) base; and (c) reaction temperature. Starting concentrations of benzoxazine **1** (**2**), acyl chloride **5**, and amine were 0.1, 0.05 and 0.05 M, respectively. Diastereoisomeric excess (*de*, %) was controlled by HPLC technique at 3, 5 and 24 h from the beginning of the reaction, thus enabling one to determine the conversion extent of the reagents. In all cases analytical data for the (*S*,*S*)-amide *de* in the reaction mixtures taken after 3, 5 and 24 h proved to be the same, thus indicating that the reaction was complete in less than 3 h.

Table 2 shows that the diastereoselectivity for the formation of amides (*S*,*S*)-**6a** and (*S*,*S*)-**7a** with acyl chloride **5** depends on the solvent used. In all solvents examined (*S*)-benzoxazines **1a** and **2a** reacted with (*S*)-naproxen acyl chloride **5** much faster than the corresponding (*R*)-isomers **1b** and **2b**. The best results were obtained in a benzene solution (Table 2, entries 1 and 6). Although it is difficult to correlate the stereoselectivity of the amide formation with a particular solvent parameter, benzene appears to be an appropriate solvent for this process.

Table 1. Spectral ^{1}H and ^{19}F NMR data



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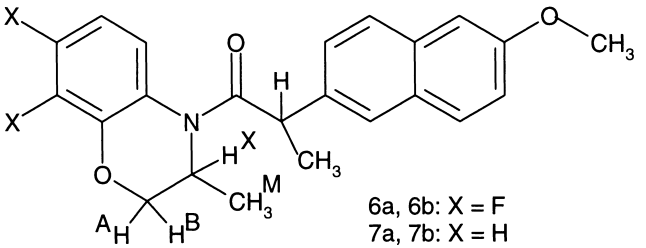


6a, 6b: X = F
7a, 7b: X = H

Compound	T, °C	Chemical shifts, δ (ppm) and coupling constants, *J* (Hz)									
		Benzoxazine fragment						Naproxen fragment			Aryl
		CH_3^M	H^X	H^A	H^B	F^7	F^8	CH_3	OCH_3	CH	
1	35	1.09 d J_{MX} = 6.1	3.40 dqd J_{BX} = 7.9 J_{MX} = 6.1 J_{AX} = 2.7	4.23 ddd J_{AB} = 10.2 J_{AX} = 2.7 $J_{A\text{-}NH}$ = 1.5	3.67 dd J_{AB} = 10.2 J_{BX} = 7.9	9.36 ddd $J_{7\text{-}8}$ = 22.0 $J_{7\text{-}6}$ = 10.4 $J_{7\text{-}5}$ = 5.2	0.37 dddd $J_{7\text{-}8}$ = 22.0 $J_{8\text{-}6}$ = 8.1 $J_{8\text{-}5}$ = 2.0 $J_{8\text{-}NH}$ = 1.4	—	—	—	6.31 ddd (H^5; 9.0, 5.2, 2.0) 6.66 ddd (H^6; 10.4, 9.0, 8.1)
2	35	1.08 d J_{MX} = 6.3	3.37 dqd J_{BX} = 8.0 J_{MX} = 6.3 J_{AX} = 2.8	4.10 dd J_{AB} = 10.3 J_{AX} = 2.8	3.60 dd J_{AB} = 10.3 J_{BX} = 8.0	—	—	—	—	—	6.68-6.41 m
6a	130	0.78 dd J_{MX} = 6.8 J_{BM} = 0.6	4.85 qdq J_{MX} = 6.8 J_{BX} = 3.0 J_{AX} = 1.6	4.21 dd J_{AB} = 11.0 J_{AX} = 1.6	4.01 ddq J_{AB} = 11.0 J_{BX} = 3.0 J_{BM} = 0.6	20.75 ddd $J_{7\text{-}8}$ = 20.2 $J_{7\text{-}6}$ = 10.2 $J_{7\text{-}5}$ = 5.4	1.92 ddd $J_{7\text{-}8}$ = 20.2 $J_{8\text{-}6}$ = 8.0 $J_{8\text{-}5}$ = 2.4	1.51 d *J* = 6.7	3.88 s	4.51 q *J* = 6.7	6.84-7.77 m
6b	130	1.20 dd J_{MX} = 6.8 J_{BM} = 0.5	4.63 qdq J_{MX} = 6.8 J_{BX} = 2.9 J_{AX} = 1.6	4.18 dd J_{AB} = 10.9 J_{AX} = 1.6	3.69 ddq J_{AB} = 10.9 J_{BX} = 2.9 J_{BM} = 0.5	20.88 ddd $J_{7\text{-}8}$ = 20.2 $J_{7\text{-}6}$ = 10.2 $J_{7\text{-}5}$ = 5.4	2.22 ddd $J_{7\text{-}8}$ = 20.2 $J_{8\text{-}6}$ = 8.0 $J_{8\text{-}5}$ = 2.4	1.51 d *J* = 6.7	3.91 s	4.36 q *J* = 6.7	6.80-7.85 m
7a	160	0.86 dd J_{MX} = 6.8 J_{BM} = 0.4	4.82 qdq J_{MX} = 6.8 J_{BX} = 3.2 J_{AX} = 2.0	4.07 dd J_{AB} = 10.9 J_{AX} = 2.0	3.94 ddq J_{AB} = 10.9 J_{BX} = 3.2 J_{BM} = 0.4	—	—	1.51 d *J* = 6.8	3.89 s	4.59 q *J* = 6.8	6.70-7.80 m
7b	160	1.18 dd J_{MX} = 6.7 J_{BM} = 0.6	4.78 qdd J_{MX} = 6.7 J_{BX} = 3.2 J_{AX} = 1.8	4.05 dd J_{AB} = 10.9 J_{AX} = 1.8	3.77 ddq J_{AB} = 10.9 J_{BX} = 3.2 J_{BM} = 0.6	—	—	1.51 d *J* = 6.8	3.91 s	4.39 q *J* = 6.8	6.84-7.83 m

Table 2
Solvent effect on diastereoselectivity of the acylation of benzoxazines **1** and **2** with (*S*)-naproxen acyl chloride **5** leading to amides **6** and **7**[a]

Entry	Amide	Solvent	*S,S*-amide *de*[b](%)
1	**6**	benzene	87
2	**6**	CH_2Cl_2	79
3	**6**	THF	79
4	**6**	1,4-Dioxane—water (8:2)	76
5	**6**	DMF	39
6	**7**	Benzene	81
7	**7**	CH_2Cl_2	72
8	**7**	THF	76
9	**7**	DMF	42

[a]All reactions were carried out with 0.2 mmol of benzoxazine derivative **1**(**2**), and 0.1 mmol of NAP-Cl **5** in 2.0 ml of a solvent at 20 °C for 24 h.

[b]Determined by HPLC analysis with a Silasorb-600 column, eluent: hexane-isopropanol 40:1 for amide **6**, and 80:1 for amide **7**.

It is a common point of view to consider that the amine-catalyzed reactions of acyl chlorides proceed via the formation of acylammonium salts.[12] Also, it is a well-recognized fact that these reactions are extremely rapid and, thus, are difficult to study. Nevertheless, it was of interest to elucidate whether the addition of a tertiary amine affects the diastereoselectivity. We have found that the resultant diastereomeric excess of (*S,S*)-amides **6a** and **7a** is not affected practically by the addition of triethylamine (TEA) or 1,4-dimethylpiperazine; however, it becomes somewhat lower on addition of pyridine (Table 3, entries 3 and 7). This is likely to be related to the greater steric hindrance in acylammonium salts derived from acyl chloride **5** and more bulky tertiary amines, such as TEA, 1,4-dimethylpiperazine, or benzoxazines **1** and **2**, in comparison to that derived from acylation of pyridine.

No marked effect when varying the reaction temperature (−20–+20°C) on diastereoselectivity of the acylation of racemate **2** with acyl chloride **5** in CH_2Cl_2 without addition of any tertiary amine was found.

The different rates for interaction of (*R*)- and (*S*)-enantiomers of benzoxazines **1** and **2** with acyl chloride **5** is evidently associated with steric hindrances arising when the NH-group of benzoxazine is attacked by the CO-group of acyl chloride **5**, or the difference in energies of the transition states is influenced by steric interactions of these parts of the molecules. However, because of considerable conformational mobility of both interacting molecules, it is difficult to judge which fragments of the reacting molecules contribute substantially to such interactions.

It should be noted that fluoro substituents in the 7,8-positions of benzoxazine **1** do not have a substantial effect on the stereoselectivity of the reaction with acyl chloride **5** (cf. entries 1 and 6, 2 and 7, 3 and 8 in Table 2).

Summarizing the data presented above we can state that the optimal conditions for kinetic resolution of racemic benzoxazines **1** and **2** by acyl chloride **5** are the following: (i) molar ratio of reagents 1.0: 0.5, respectively; and (ii) realization of the process in benzene solution at room temperature for 3–5 h without any tertiary amine. After a standard work-up procedure (washing the reaction mixture consecutively with

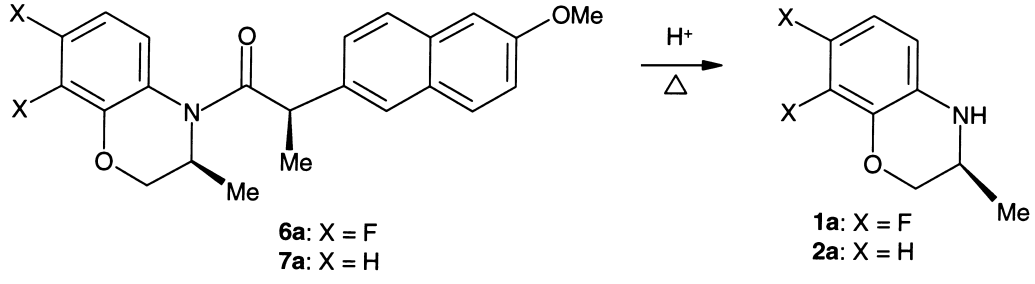
Table 3
Effect of tertiary amine on the diastereoselectivity of the acylation of benzoxazines **1** and **2** with (*S*)-naproxen acyl chloride **5** leading to amides **6** and **7** in a benzene solution at 20°C[a]

Entry	Amide	Additive	*S,S*-amide *de*[b](%)
1	**6**	---	87
2	**6**	Triethylamine	89
3	**6**	Pyridine	78
4	**6**	1,4-Dimethylpiperazine	90
5	**7**	---	81
6	**7**	Triethylamine	81
7	**7**	Pyridine	76

[a]All reactions were carried out with 0.2 mmol of benzoxazine derivative **1**(**2**), 0.1 mmol of NAP-Cl **5** and 0.1 mmol of appropriate tertiary amine in 2.0 ml of benzene at 20 °C for 24 h.

[b]Determined by HPLC analysis with a Silasorb-600 column, eluent: hexane-isopropanol 40:1 for amide **6**, and 80:1 for amide **7**.

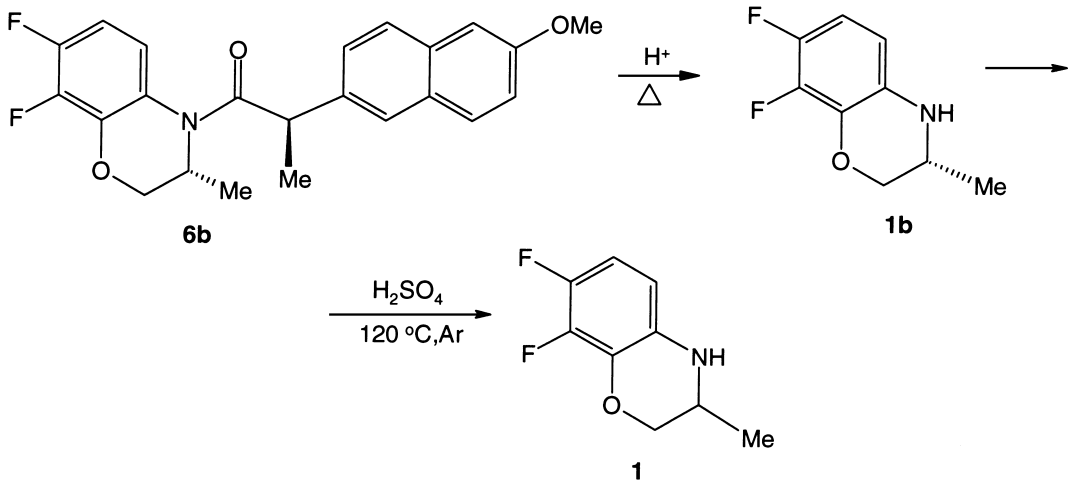
1N HCl and water, consequently, drying with $MgSO_4$, and evaporating to dryness) followed by washing the residue with hexane, the reaction product can be isolated as the pure (*S,S*)-diastereoisomeric amide **6a** (or **7a**) with overall chemical yield of 30–35% and diastereomeric excess of 99%. (*S,S*)-Amides **6a** and **7a** were hydrolyzed on heating under reflux in a mixture of concentrated hydrochloric (or sulfuric) and acetic acids (Scheme 2). (*S*)-(−)-7,8-Difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **1a** and (*S*)-(+)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **2a** were isolated by column chromatography in 60% yield and high enantiomeric purity (99% *ee*).



Scheme 2.

Yields of the target (*S*)-enantiomers **1a** and **2a** can be enhanced by racemisation of the corresponding (*R*)-enantiomers and then recycling as racemates. The best results were obtained when (*R*)-(+)-isomer **1b** was heated at 120°C with 0.5 mol of H_2SO_4 for 8–10 h in an atmosphere of inert gas (e.g. argon) under racemisation conditions similar to those reported for (*R*)-(+)-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline.[13] Combined racemisation of both unreacted (*R*)-(+)-isomer and the one isolated after hydrolysis of (*R,S*)-amide **6b** makes it possible to recycle the racemic benzoxazine **1** (Scheme 3), thus enabling one to reach the overall yield of the target (*S*)-(−)-benzoxazine **1a** of up to 48–50%.

^1H and ^{19}F chemical shifts of benzoxazine **1** have been reported.[6b] We have made the full analysis of ^1H and ^{19}F NMR spectra of compound **1** and determined all coupling constants. Long-range coupling



Scheme 3.

constants to NH–proton were observed in ^{1}H and ^{19}F NMR spectra of pure **1** in dry DMSO-d_6 solution: $^{4}J_{NH-H_A}$=1.4 Hz, $^{5}J_{NH-F^8}$ =1.5 Hz. The splitting of the H_A and F^8 resonance disappeared under irradiation of the NH-proton in homo- $^{1}H\{^{1}H\}$ and heteronuclear $^{19}F\{^{1}H\}$ double resonance experiments. The same was observed when acetic acid-d_4 was added to the studied solution.

3. Conclusion

Effective methods for the preparation of (*S*)-enantiomers of benzoxazines **1** and **2** using commercially available (*S*)-(+)-naproxen as a chiral resolving agent have been developed. The reaction conditions providing the highest diastereomeric excess of the (*S,S*)-amides in the kinetic resolution of racemic benzoxazines **1** and **2** by acyl chloride of (*S*)-(+)-naproxen **5** were found. The procedure allows one to obtain (*S*)-enantiomers of benzoxazines **1** and **2** of high enantiomeric purity (99% *ee*) in overall chemical yield of about 50% after recycling (*R*)-enantiomers through their racemisation.

4. Experimental

4.1. General procedures

Solvents were purified according to standard procedures. Routine monitoring of reactions was carried out using Silufol UV 254 (Kavalier) TLC aluminium plated silica gel. Melting points were determined on a Boetius melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured in a solution of DMSO-d_6 on a Bruker WM-250 (250 MHz) and ^{19}F NMR spectra were measured on a Tesla BS-587 A (75.3 MHz) spectrometers. All signals are expressed in ppm (δ) with tetramethylsilane as an internal standard for ^{1}H and hexafluorobenzene for ^{19}F. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Column chromatography was performed on silica gel Silpearl (Kavalier). The *de* values of amides **6** and **7** were measured by HPLC on a Milichrom chromatograph [Silasorb-600 column; mobile phase hexane:*i*-PrOH=40:1 (A) and 80:1 (B); flow rate 0.1 ml/min; UV detection 230 nm; retention time for amide **6**: t_{RS} 3.4 min, t_{SS} 5.0 min (A); amide **7**: t_{RS} 4.0 min, t_{SS} 5.2 min (B)]. Microanalyses were

carried out on a CHNS-O model EA-1102 elemental analyzer and were in good agreement with the calculated values.

4.2. N-[(2S)-2-(6-Methoxynaphthyl-2)propionyl]-(3RS)-7,8-difluoro-2,3-dihydro-3-methyl-4H-1,4-benzoxazine **6a**–**6b**

A solution of (*S*)-naproxen acyl chloride **5** (0.96 g, 3.86 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise to a stirred solution of racemate **1** (0.65 g, 3.51 mmol) in CH_2Cl_2 (1.5 ml) at 0°C (ice-cooling). The mixture was stirred at room temperature for 20 h, then washed consequently with 1N HCl, water, 5% $NaHCO_3$, water and dried ($MgSO_4$). The solution was evaporated in vacuo to dryness to give a yellow oily residue which was treated with hexane yielding amide **6a**–**6b** as a yellow oil (0.77 g, 55%). The diastereoisomeric mixture of (*R,S*)- and (*S,S*)-amides was subjected to flash chromatography on a dry column with silica gel for TLC (Silpearl), eluent: benzene:ethyl acetate 50:1–5:1 to give **6b** (0.18 g, 97% *de*) as colorless crystals, mp 128–129°C. $[\alpha]_D^{20}$ +67.7 (*c* 1.36, $CHCl_3$). Anal. calcd for $C_{23}H_{21}F_2NO_3$: C, 69.54; H, 5.33; N, 3.52; F, 9.56. Found: C, 69.64; H, 5.34; N, 3.40; F, 9.71. ^{1}H NMR: δ 1.16 (3H, d, CH_3-benzoxazine, *J*=6.0 Hz), 1.46 (3H, d, CH_3-naproxen, *J*=6.8 Hz), 3.45 (1H, d, C^2H_B, *J*=10.3 Hz), 3.86 (3H, s, O-CH_3), 4.15 (1H, d, C^2H_A, *J*=10.3 Hz), 4.36 (1H, q, CH-naproxen, *J*=6.8 Hz), 4.63 (1H, m, C^3H-benzoxazine), 6.80–7.85 (8H, arom). ^{19}F NMR: δ 2.0 (F^8, dd, J_{F-F}=21 Hz, J_{F-H^6}=7.4 Hz), 20.4 (F^7, m); and **6a** (0.30 g, 99.0% *de*) as colorless crystals, mp 113–114°C. Anal. calcd for $C_{23}H_{21}F_2NO_3$: C, 69.51; H, 5.33; N, 3.52; F, 9.56. Found: C, 69.54; H, 5.25; N, 3.51; F, 9.54.

4.3. N-[(2S)-2-(6-Methoxynaphthyl-2)propionyl]-(3S)-7,8-difluoro-2,3-dihydro-3-methyl-4H-1,4-benzoxazine **6a**

To a stirred solution of racemate **1** (3.95 g, 21.3 mmol) in benzene (30 ml) a solution of (*S*)-naproxen acyl chloride **5** (2.66 g, 10.7 mmol) in benzene (30 ml) was added dropwise at 5–10°C (ice-cooling). The mixture was stirred at room temperature for 3–5 h. Then 30 ml of 1N HCl was added to the reaction mixture. The organic layer was separated, washed and dried ($MgSO_4$). The solution was treated with activated carbon followed by the evaporation of the solvent. The yellow oily residue was stirred with 50 ml of hexane under ice-cooling. The treatment with hexane was repeated twice to obtain (*S,S*)-amide **6a** (2.55 g, 60.3%) as colorless crystals (99.2% *de*), mp 113–114°C. $[\alpha]_D^{20}$ +66.5 (*c* 1.4, $CHCl_3$). Anal. calcd for $C_{23}H_{21}F_2NO_3$: C, 69.54; H, 5.33; N, 3.52; F, 9.56. Found: C, 69.70; H, 5.33; N, 3.53; F, 9.54. ^{1}H NMR: δ 0.51 (3H, d, CH_3-benzoxazine, *J*=6.3 Hz), 1.43 (3H, d, CH_3-naproxen, *J*=6.8 Hz), 3.85 (3H, s, O-CH_3), 4.08 (1H, m, C^2H_B), 4.25 (1H, d, C^2H_A, *J*=10.3 Hz), 4.55 (1H, q, CH-naproxen, *J*=6.8 Hz), 4.80 (1H, m, CH-benzoxazine), 6.84–7.77 (8H, arom). ^{19}F NMR: δ 1.8 (F^8, dd, J_{F-F}=21 Hz, J_{F-H^6}=7.4 Hz), 20.6 (F^7, m).

4.4. Isolation of (R)-(+)-7,8-difluoro-2,3-dihydro-3-methyl-4H-1,4-benzoxazine **1b** and its racemisation

The aqueous acid layer after washing the previous reaction mixture was alkalized by 10N NaOH up to pH 8 under ice-cooling, extracted by CH_2Cl_2, washed with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo gave 1.35 g of a yellow oil. Combined hexane filtrates after amide (*S,S*)-**6a** isolation were evaporated to dryness in vacuo. The residue was subjected to acid hydrolysis in a mixture of 20 ml acetic acid and 20 ml hydrochloric acid under reflux for 9 h. The reaction mixture was evaporated to dryness in vacuo followed by addition of water and ice-cooling. The precipitate was filtered off and washed with water. The combined filtrates were alkalized by 10N NaOH up to pH 8 under ice-cooling,

extracted by CH_2Cl_2, washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave **1b** (1.02 g) as a yellow oil (72% *ee* by HPLC after derivatization with acyl chloride **5**). The overall yield was 2.37 g (60%). Anal. calcd for $C_9H_9F_2NO$: C, 58.38; H, 4.90; N, 7.57; F, 20.52. Found: C, 58.67; H, 4.80; N, 7.35; F, 20.38.

Compound **1b** (0.60 g, 3.24 mmol, 72% *ee*) and concentrated sulfuric acid (0.09 ml, 1.62 mmol) were placed into a tube, and the reaction mixture was heated under an argon atmosphere at 120°C for 9 h. Then 20 ml of water was added and the reaction mixture was alkalized by 10N NaOH up to pH 8 under ice-cooling, extracted by CH_2Cl_2, washed with brine and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave 0.50 g of a yellow oil. The latter was purified by flash chromatography on a dry silica gel column with hexane:chloroform (75:25–5:95) as an eluent. TLC (benzene) monitoring. Evaporation of the solvents in vacuo gave 0.38 g (63.3%) of racemate **1** as a yellow oil which was crystallized out while storing to give white or slightly colored crystals, mp 41–43°C. $[\alpha]_D^{20}=0$. Anal. calcd for $C_9H_9F_2NO$: C, 58.38; H, 4.90; N, 7.57; F, 20.52. Found: C, 58.93; H, 4.83; N, 7.29; F, 20.45. ^{1}H NMR: δ 1.09 (3H, d, CH_3, *J*=6.1 Hz), 3.40 (1H, m, C^3H), 3.67 (1H, dd, C^2H_B, *J*=10.2, 7.9 Hz), 4.23 (1H, ddd, C^2H_A, *J*=10.2, 2.7, 1.5 Hz), 5.9 (1H, br s, NH), 6.31 (1H, ddd, C^5H, *J*=9.0, 5.2, 2.0 Hz), 6.66 (1H, ddd, C^6H, *J*=10.4, 9.0, 8.1 Hz). ^{19}F NMR: δ 0.37 (F^8, dddd, *J*=22.0, 8.1, 2.0, 1.4 Hz), 9.36 (F^7, ddd, *J*=22.0, 10.4, 5.2 Hz).

4.5. (S)-(−)-7,8-Difluoro-2,3-dihydro-3-methyl-4H-1,4-benzoxazine ***1a***

(*S*,*S*)-Amide **6a** (1.3 g, 3.27 mmol) was refluxed in the mixture of 20 ml of acetic acid and 20 ml of hydrochloric acid for 9 h. The reaction mixture was evaporated to dryness in vacuo. Water was then added and the reaction mixture was cooled in an ice bath. The precipitate was filtered off and washed with water. The combined filtrates were alkalized by 10N NaOH up to pH 8 under ice-cooling, extracted by CH_2Cl_2, washed with brine and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave benzoxazine **1a** (0.60 g, 99%, 99.2% *ee* by HPLC after derivatization with acyl chloride **5**) as a yellow oil. The overall yield was 48.5%, taking into account the recycling racemate **1**. $[\alpha]_D^{20}$ −8.9 (*c* 3.5, $CHCl_3$) [Lit.[2] −9.6 (*c* 2.17, $CHCl_3$)]. Anal. calcd for $C_9H_9F_2NO$: C, 58.38; H, 4.90; N, 7.57; F, 20.52. Found: C, 58.45; H, 4.90; N, 7.57; F, 20.52. ^{1}H NMR and ^{19}F NMR see *rac*-**1**.

4.6. N-[(2S)-2-(6-Methoxynaphthyl-2)propionyl]-(3S)-2,3-dihydro-3-methyl-4H-1,4-benzoxazine ***7a–7b***

In a way similar to that described for amide **6**, starting from racemate **2** (0.50 g, 3.35 mmol) and (*S*)-naproxen acyl chloride **5** (0.92 g, 3.69 mmol) in CH_2Cl_2, amide **7a–7b** was obtained in 71% yield as a yellow oil. The diastereoisomeric mixture of (*R*,*S*)- and (*S*,*S*)-amides was subjected to flash chromatography on a dry column with silica gel for TLC (Silpearl), eluent: benzene:ethyl acetate to give **7b** (95% *de*) as a yellow oil. Anal. calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.50; H, 6.34; N, 3.57. ^{1}H NMR: δ 1.13 (3H, d, CH_3-benzoxazine, *J*=6.7 Hz), 1.51 (3H, d, CH_3-naproxen, *J*=6.8 Hz), 3.77 (1H, ddq, C^2H_B, *J*=10.9, 3.2, 0.6 Hz), 3.86 (3H, s, O-CH_3), 4.05 (1H, dd, C^2H_A, *J*=10.9, 1.8 Hz), 4.36 (1H, q, CH-naproxen, *J*=6.8 Hz), 4.63 (1H, m, C^3H-benzoxazine), 6.84–7.83 (8H, arom); and **7a** (98.0% *de*) as colorless crystals, mp 78–80°C. Anal. calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.48; H, 6.47; N, 3.65.

4.7. N-*[(2*S*)-2-(6-Methoxynaphthyl-2)propionyl]-(3*S*)-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine* ***7a***

In a way similar to that described for amide (*S,S*)-**6**, starting from racemate **2 (**1.18 g, 7.91 mmol) and (*S*)-naproxen acyl chloride **5** (0.98 g, 3.95 mmol) in benzene, (*S,S*)-amide **7a** was obtained in 56% yield as colorless crystals (99.0% *de*), mp 79–81°C. $[\alpha]_D^{20}$ +26.6 (*c* 1.1, $CHCl_3$). Anal. calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.43; H, 6.51; N, 3.66. ^{1}H NMR: δ 0.54 (3H, d, CH_3-benzoxazine, *J*=6.4 Hz), 1.44 (3H, d, CH_3-naproxen, *J*=6.7 Hz), 3.84 (3H, s, O-CH_3), 3.94 (1H, m, C^2H_B), 4.08 (1H, d, C^2H_A, *J*=10.7 Hz), 4.57 (1H, q, CH-naproxen, *J*=6.7 Hz), 4.75 (1H, m, CH-benzoxazine), 6.70–7.80 (10H, arom).

*4.8. (*S*)-(+)-2,3-Dihydro-3-methyl-4*H*-1,4-benzoxazine* ***2a***

In a way similar to that described for benzoxazine derivative **1a**, starting from amide (*S,S*)-**7** (1.3 g, 3.27 mmol), benzoxazine **2a** was obtained in 100% yield (99.2% *de* after derivatization with acid chloride **5**) as a yellow oil. $[\alpha]_D^{20}$ +19.8 (*c* 1.0, $CHCl_3$). Anal. calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.48; H, 7.42; N, 9.21. ^{1}H NMR: δ 1.08 (3H, d, CH_3, *J*=6.3 Hz), 3.37 (1H, dqd, C^3H, *J*=8.0, 6.3, 2.8 Hz), 3.60 (1H, dd, C^2H_B, *J*=10.3, 8.0 Hz), 4.10 (1H, dd, C^2H_A, *J*=10.3, 2.8 Hz), 5.7 (1H, br s, NH), 6.41–6.68 (4H, arom).

*4.9. (*R*)-(−)-2,3-Dihydro-3-methyl-4*H*-1,4-benzoxazine* ***2b***

In a way similar to that described for isolation of compound **1b** from the reaction mixture, benzoxazine **2b** was obtained in 42.4% yield (in account for racemate **2**) as a yellow oil (91% *ee* by HPLC after derivatization with acyl chloride **5**). $[\alpha]_D^{20}$ −18.0 (*c* 1.84, $CHCl_3$). Anal. calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.08; H, 7.39; N, 9.57. ^{1}H NMR, see **2b**.

4.10. Kinetic resolution. General procedure

To a solution of compounds **1** (37.0 mg, 0.2 mmol) or **2** (29.4 mg, 0.2 mmol), and an appropriate amine (0.1 mmol) (or without any amine) in an appropriate solvent (1 ml), was added a solution of compound **5** (24.9 mg, 0.1 mmol) in the same solvent (1 ml). The reaction mixture was then stirred for the appropriate time and temperature, and filtered through silica gel. A measure of 0.2 ml of the filtrate was diluted with 0.5 ml CH_2Cl_2. Then 0.02 ml of the obtained solution was diluted with 0.5 ml of an appropriate mobile phase and analyzed by HPLC.

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References

1. (a) Bouzard, D. In *Antibiotics and Antiviral Compounds*; Krohn, K.; Rirst, H. A.; Maag, H., Eds.; VCH: Weinheim, 1993. (b) *Quinolone Antibacterial Agents*; Hoope, D. C.; Wolfson, J. S., Eds.; ASM: Washington, 1993.

2. Atarashi, S.; Yokohama, S.; Yamazaki, K.; Sakano, K.; Imamura, M.; Hayakawa, *J. Chem. Pharm. Bull. Jpn* **1987**, *35*, 1896–1902.
3. Hayakawa, J.; Atarashi, S.; Yokohama, S.; Imamura, M.; Sakano, K.; Higashihashi, N.; Ohshima, M. *EP 206,283* (1986) (*Chem. Abstr*. **1987**, *106*, 119895t).
4. (a) Fujiwara, T.; Yokota, T. *JP 01,175,975* (1989) (*Chem. Abstr*. **1990**, *112*, 35875x). (b) Fujiwara, T.; Tsurumi, H.; Sato, Y. T. *EP 304,684* (1989) (*Chem. Abstr*. **1989**, *111*, 134170z).
5. Miyadera, A.; Imura, A. *Tetrahedron: Asymmetry* **1999**, *10*, 119–123.
6. (a) Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, J. *J. Heterocycl. Chem*. **1991**, *28*, 329–331. (b) Satoh, K.; Inenaga, M.; Kanai, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2657–2662.
7. Van Zoest, W. J.; Marx, A. F.; Koger, H. S.; Booy, Y. *EP 368,410* (1990) (*Chem. Abstr*. **1990**, *113*, 172032e).
8. (a) Schriewer, M.; Grohe, K.; Zeiler, M. J.; Metzger, K. G. *DE 3,543,513* (1987) (*Chem. Abstr*. **1987**, *107*, 154342c). (b) Mitscher, L. A.; Sharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A. G. *J. Med. Chem*. **1987**, *30*, 2283–2286.
9. Xie, L. J. *Chin. Chem. Lett*. **1995**, *6*, 857–860.
10. Buschges, R.; Linde, H.; Mutschler, E.; Spahn-Langguth, H. *J. Chromat. A* **1996**, *725*, 323–334.
11. Wang, C. P.; Howell, S. R.; Scatina, J.; Sisenwine, S. F. *Chirality* **1992**, *4*, 84–90.
12. (a) Kivinen, A. In *The Chemistry of Acid Halides*; Patai, S., Ed.; Interscience: New York, 1972; Chapter 6. (b) Hubbard, P.; Brittain, W. J. *J. Org. Chem*. **1998**, *63*, 677–683.
13. Hashimoto, K.; Okaichi, Y.; Nomi, D.; Miyamoto, H.; Bando, M.; Kido; Fujimura, T.; Furuta, T.; Minamikawa, J. *Chem. Pharm. Bull. Jpn.* **1996**, *44*, 642–645.