

## AN IMPROVED SYNTHESIS OF LEVOFLOXACIN

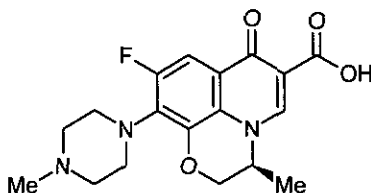
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**Abstract** - The benzoxazinecarboxylic acid (**8**), a precursor of levofloxacin (**1**), was prepared from (*S*)-2-amino-1-propanol (**2**) in 4 steps in good overall yield. The synthesis is characterized by one pot construction of **8** from the useful benzoylacrylates (**7**) which are effectively prepared in three steps. The key intermediates (**7**) were obtained from 2-nitrobenzoyl derivative (**6a**) and 2-fluorobenzoyl derivative (**6b**) through acylation of the acrylates (**5**), respectively.

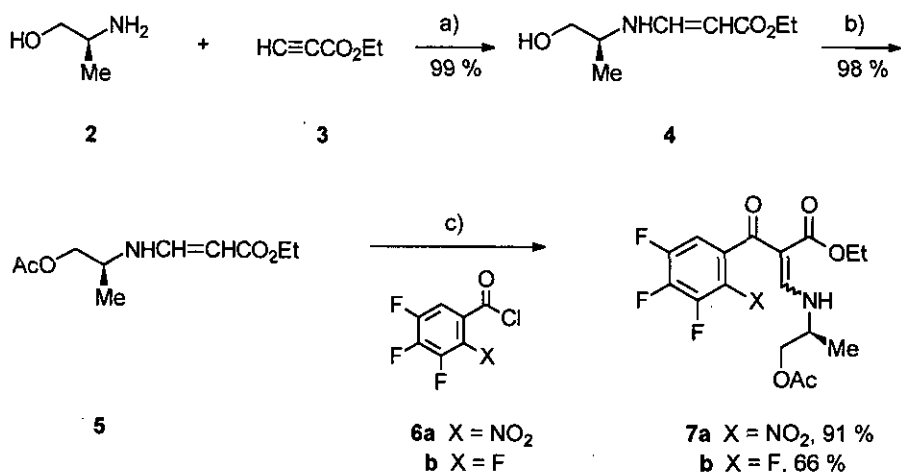
A key intermediate for preparation of levofloxacin (**1**),<sup>1</sup> a potent antibacterial agent on the market, is (–)-9,10-difluoro-2,3-dihydro-3(*S*)-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**8**). Several methods have been reported for the preparation of the compound (**8**)<sup>2</sup> employing the enzymatic resolution of the benzoxazine derivatives,<sup>3</sup> the asymmetric synthesis through the reduction of a cyclic imine with chiral reagents,<sup>4</sup> the resolution of synthetic intermediates,<sup>1(b)</sup> the construction of the chiral pyridobenzoxazine moiety<sup>5</sup> and the asymmetric synthesis from the chiral materials.<sup>6</sup>



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But the published routes adopted for the preparation of levofloxacin (**1**) are rather inefficient, for example, resolving synthetic intermediates by the enzymatic or chemical resolution were wasteful since one isomer

was useless, or the total yields were low due to their long steps. In this paper we wish to report a short and efficient synthesis of **8** including the new chiral benzoylacrylates (**7**) starting from (*S*)-2-amino-1-propanol (**2**).<sup>7</sup> The benzoylacrylate derivatives such as **7** have been used as key intermediates for preparation of the tricyclic quinolones including ofloxacin<sup>8</sup> and levofloxacin.<sup>5</sup> However, it seems like that the reported method for preparation of the benzoylacrylates undesirable owing to its complicated steps.<sup>8,9</sup>



#### Reagents and conditions

a) MeCN, 5 °C, 8 h, and then room temperature, 1 h

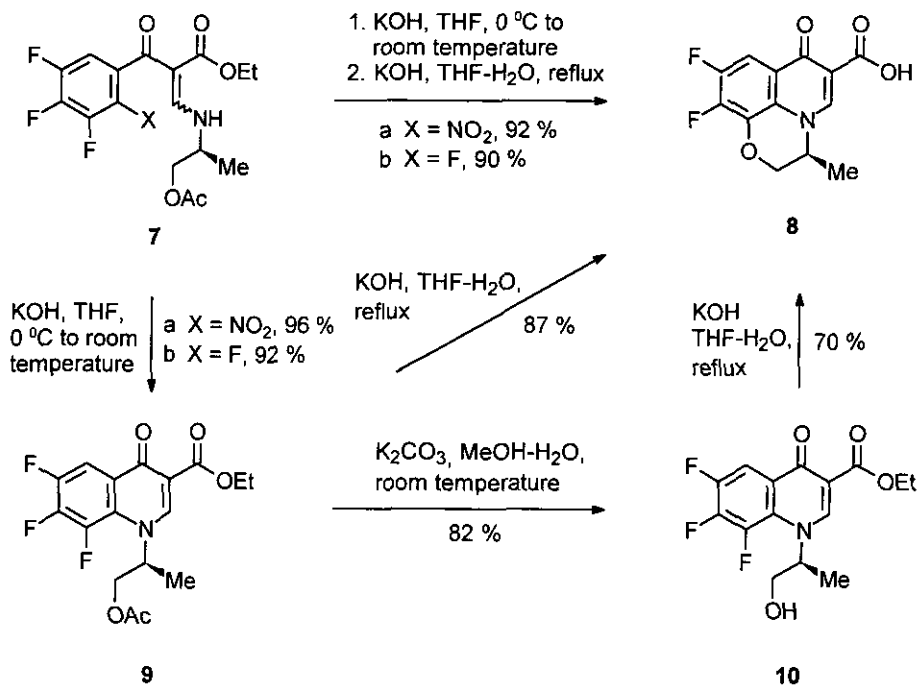
b) AcCl, Et<sub>3</sub>N, cat. DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 min

c) Et<sub>3</sub>N, MeCN, 0 °C, 10 min, and then reflux, 30 min

#### Scheme 1

As shown in Scheme 1, (*S*)-2-amino-1-propanol (**2**) was reacted with 100 M % of ethyl propiolate (**3**) in acetonitrile to give ethyl 3-[(1-hydroxyprop-2(*S*)-yl)amino]acrylate (**4**) in a quantitative yield. The compound (**4**) was an approximately 8:2 mixture of (*Z*)- and (*E*)-geometrical isomers based on the integration of characteristic <sup>1</sup>H nmr signals. The coupling constant between H-2 and H-3 of (*Z*)-isomer of the mixture (**4**) was 8.1 Hz and the chemical shifts of its amino proton occurred around δ 7.7. This downfield chemical shift of its amino proton may result from an intramolecular hydrogen bond between the amino hydrogen and the ester carbonyl group. And the corresponding coupling constant of (*E*)-isomer of the mixture (**4**) was 13.3 Hz and the chemical shift of its amino proton occurred around δ 4.8. Acetylation of **4** with acetyl chloride and base in methylene chloride at 0 °C for 30 minutes afforded ethyl 3-[(1-acetoxyprop-2(*S*)-yl)amino]acrylate (**5**) in 98 % yield which was also an approximately 8:2 mixture

of (*Z*)- and (*E*)-geometrical isomers (see the Experimental Section). The compound (**5**) and benzoyl chlorides (**6**) in the presence of a base reacted in dioxane according to the method of Grohe<sup>10</sup> to give unknown by-products instead of the benzoylacrylate derivatives (**7**). A number of modifications were made in an attempt to get the desired compounds (**7**). These modifications included changing the solvents (benzene, methylene chloride, tetrahydrofuran, dimethylformamide, acetonitrile), temperature of reaction, and addition order of substrates. Only adding **6** to the solution of freshly prepared compound (**5**) in the presence of triethylamine or pyridine in acetonitrile at 0 °C and then heating it at reflux, we obtained products (**7a**) in 91 % yield from 2-nitro-3,4,5-trifluorobenzoyl chloride (**6a**)<sup>11</sup> and **7b** in 66 % yield from 2,3,4,5-tetrafluorobenzoyl chloride (**6b**), respectively. Interestingly, 2-nitro derivative (**6a**) was more reactive than 2-fluoro derivative (**6b**) in these acylation reactions of the acrylates (**5**). This difference may result from the stronger electron withdrawing effect by 2-nitro substituent of **6a** compared with 2-fluorine atom of **6b**. The nmr spectrum showed that the compounds (**7**) were an approximately 8:2 or 2:8 mixture of (*Z*)- and (*E*)-geometrical isomers (see the Experimental Section). After treatment of the benzoylacrylates (**7**) in tetrahydrofuran with 110 M % of powdered potassium hydroxide at 0 °C to room temperature for 1 hour to form the intermediate (**9**) which was detected by tlc, then a 10 % aqueous solution of potassium hydroxide was added.



Scheme 2

The reaction mixture was refluxed for 2 hours to give a pure solid compound (**8**) in 92 % yield from **7a** and 90 % yield from **7b**, respectively, which gave correct analytical data compared with the reported one.<sup>1(b)</sup> It was of interest to see if the addition of potassium hydroxide in two portions is essential for conversion of **7** to **8** to take place in a high yield since addition of potassium hydroxide in one portion resulted in much lowering the reaction yield. The cyclization of **7a** was carried out by reacting with 110 M % of powdered potassium hydroxide in tetrahydrofuran to give the quinolone derivative (**9**) in 96 % yield, and under same conditions **7b** was also converted to **9** in 92 % yield. The compound (**9**) was hydrolyzed mildly using potassium carbonate to give the compound (**10**) in 82 % yield. When **9** and **10** were reacted in tetrahydrofuran and water in the presence of potassium hydroxide at reflux to yield **8** in 87 % and 70 % yield respectively as shown in Scheme 2. It is very interesting to have the result that the acetyl protected compound (**9**) showed better yield in the cyclization reaction than the unprotected hydroxy compound (**10**).<sup>5(a)</sup> In case of **10**, unidentified side reactions were detected by tlc. Probably, for **9** deprotection and cyclization reactions to form a benzoxazine ring occurred simultaneously to avoid unnecessary side reactions. Thus it is essential to form the intermediate (**9**) at first then cyclize the compound (**9**) to get a higher yield. Our synthetic method have several advantages over the previously reported methods.<sup>5,8,9</sup> First, the important intermediates (**7**) were prepared efficiently from readily available startings in high yields. Second, the intramolecular cyclization reaction has been facilitated by introduction of an acetyl protecting group in **7**. Third, by running the reactions in one pot without isolation of intermediates not only the reaction yield was improved but also the process was suitable for mass production. Thus we could demonstrate in this synthesis that the key intermediates (**7**) were effectively prepared under the easily accessible reaction conditions and its cyclization to form a quinolone ring, deprotection, cyclization to form a benzoxazine ring, and hydrolysis reactions were occurred in one pot.

## EXPERIMENTAL

<sup>1</sup>H-Nmr (300 MHz) spectra were recorded on a Varian Gemini 300 spectrometer using TMS as an internal standard. Optical rotations were measured at 589 nm by using a AUTOPOL III Rudolph Research polarimeter. Melting points were determined on a Thomas-Hoover capillary or a Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 16F PC FT-IR and frequencies are given in reciprocal centimeters. Electron-impact mass spectra (EIms) were recorded

in the form of  $m/z$  (intensity relative to base = 100) on a Hewlett Packard GC-MSD (5890 II -5972) system or a Finnigan MAT SSQ 7000 mass spectrometer. High resolution mass spectra (HRms) were determined on a JEOL JMS-DX 303 or a VG70-VSEQ mass spectrometer. All chromatographic isolations were accomplished by flash chromatography using silica gel (Merck 9385, 230~400 mesh). All reactions were monitored by tlc on glass plates coated with a 0.25 mm layer of silica gel (Merck 60-F254). All solvents were dried according to the general procedures and stored under a nitrogen atmosphere.

**(+)-Ethyl 3-[(1-hydroxyprop-2(*S*)-yl)amino]acrylate (4)**

To a stirred solution of (*S*)-2-amino-1-propanol (**2**) (3.76 g, 50 mmol) in MeCN (80 ml) at 5 °C was slowly added ethyl propiolate (4.91 g, 50 mmol) over 1 h. The reaction mixture was stirred at 5 °C for 8 h and further stirred at room temperature for 1 h. After completion of the reaction, the solvent was removed under reduced pressure to give **4** (8.63 g, 99 %) as a colorless oil, which was used directly without further purification. The nmr spectrum showed that **4** was an approximately 8:2 mixture of (*Z*)- and (*E*)-geometrical isomers:  $[\alpha]_D^{25} +75.4^\circ$  ( $c = 2.1$ ,  $\text{CHCl}_3$ );  $^1\text{H}$ -nmr ( $\text{CDCl}_3$ )  $\delta = 1.20$  (d,  $J=6.8$  Hz, 3H,  $\text{NHCHCH}_3$ ), 1.25 and 1.26 (each t,  $J=7.0$  Hz, 3H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 2.36 (br s, 1H, exchangeable with  $\text{D}_2\text{O}$ , OH), 3.26 ~ 3.40 (m, 1H,  $\text{NHCHCH}_3$ ), 3.41 ~ 3.72 (m, 2H,  $\text{HOCH}_2\text{CHCH}_3$ ), 4.10 and 4.12 (each q,  $J=7.0$  Hz, 2H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 4.50 (d,  $J=8.1$  Hz, 1H  $\times$  0.8, (*Z*)-  $\text{NHCH=CHCO}$ ), 4.78 (d,  $J=13.3$  Hz, 1H  $\times$  0.2, (*E*)-  $\text{NHCH=CHCO}$ ), 4.82 ~ 4.88 (m, 1H  $\times$  0.2, exchangeable with  $\text{D}_2\text{O}$ , (*E*)- NH), 6.74 (dd,  $J=13.1$  and 8.1 Hz, 1H  $\times$  0.8, (*Z*)-  $\text{NHCH=CHCO}$ ), 7.50 (dd,  $J=13.3$  and 9.3 Hz, 1H  $\times$  0.2, (*E*)-  $\text{NHCH=CHCO}$ ), 7.65 ~ 7.82 (m, 1H  $\times$  0.8, exchangeable with  $\text{D}_2\text{O}$ , (*Z*)- NH); ir (KBr)  $\nu = 3330, 1730, 1660, 1610 \text{ cm}^{-1}$ ; Elms  $m/z$  (%) = 173 ( $\text{M}^+$ , 14), 142 (48), 128 (14), 96 (100); HRms  $m/z$  calcd for  $\text{C}_8\text{H}_{15}\text{NO}_3$  ( $\text{M}^+$ ): 173.1052; found: 173.1068.

**(+)-Ethyl 3-[(1-acetoxyp-2(*S*)-yl)amino]acrylate (5)**

To a stirred solution of (*S*)-(+)-**4** (3.46 g, 19.98 mmol),  $\text{Et}_3\text{N}$  (2.33 g, 23.03 mmol), and DMAP (0.24 g, 1.96 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 ml) at 0 °C was added dropwise  $\text{AcCl}$  (1.73 g, 22.04 mmol). The reaction mixture was stirred at the same temperature for 30 min. The resulting precipitate was filtered off, and the filtrate was successively washed with aqueous 0.2-N  $\text{HCl}$  solution (20 ml), saturated aqueous  $\text{NaHCO}_3$  (10 ml), and brine (10 ml). The solvent was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give **5** (4.22 g, 98%) as a pale yellow oil suitable for use without further purification. An analytical colorless oil was prepared by flash chromatography on silica gel using *n*-hexane/ $\text{Et}_2\text{O}$  (2:1)

mixture as an eluent. The nmr spectrum showed that **5** was an approximately 8:2 mixture of (*Z*)- and (*E*)-geometrical isomers:  $[\alpha]_D^{20} +115^\circ$  ( $c = 2.0$ ,  $\text{CHCl}_3$ );  $^1\text{H}$ -nmr ( $\text{CDCl}_3$ )  $\delta = 1.21$  and  $1.25$  (each d,  $J=6.8$  Hz, 3H,  $\text{NHCHCH}_3$ ),  $1.27$  (t,  $J=7.1$  Hz, 3H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ),  $2.08$  (s, 3H,  $\text{CH}_3\text{CO}$ ),  $3.42 \sim 3.67$  (m, 1H,  $\text{NHCHCH}_3$ ),  $3.95 \sim 4.06$  (m, 2H,  $\text{AcOCH}_2\text{CH}$ ),  $4.50$  (d,  $J=8.0$  Hz,  $1\text{H} \times 0.8$ , (*Z*)-  $\text{NHCH}=\text{CHCO}$ ),  $4.80$  (d,  $J=13.4$  Hz,  $1\text{H} \times 0.2$ , (*E*)-  $\text{NHCH}=\text{CHCO}$ ),  $4.85 \sim 4.95$  (br s,  $1\text{H} \times 0.2$ , exchangeable with  $\text{D}_2\text{O}$ , (*E*)- NH),  $6.67$  (dd,  $J=13.0$  and  $8.0$  Hz,  $1\text{H} \times 0.8$ , (*Z*)-  $\text{NHCH}=\text{CHCO}$ ),  $7.44$  (dd,  $J=13.4$  and  $9.2$  Hz,  $1\text{H} \times 0.2$ , (*E*)-  $\text{NHCH}=\text{CHCO}$ ),  $7.70 \sim 7.90$  (br s,  $1\text{H} \times 0.8$ , exchangeable with  $\text{D}_2\text{O}$ , (*Z*)- NH); ir (NaCl)  $\nu = 3330, 1741, 1668, 1616 \text{ cm}^{-1}$ ; EIms  $m/z$  (%) = 215 ( $\text{M}^+$ , 10), 170 (6), 155 (7), 142 (56), 96 (100); HRms  $m/z$  calcd for  $\text{C}_{10}\text{H}_{17}\text{NO}_4$  ( $\text{M}^+$ ): 215.1157; found: 215.1185.

**(+)-Ethyl 2-(2-nitro-3,4,5-trifluorobenzoyl)-3-[(1-acetoxyp-2(*S*)-yl)amino]acrylate (**7a**)**

To a stirred solution of (*S*)-(+)-**5** (1.08 g, 5 mmol),  $\text{Et}_3\text{N}$  (0.56 g, 5.53 mmol) in MeCN (40 ml) at  $0^\circ\text{C}$  was added dropwise 2-nitro-3,4,5-trifluorobenzoyl chloride (**6a**)<sup>7</sup> (1.26 g, 5.26 mmol). The reaction mixture was stirred at the same temperature for 10 min, and then was heated at reflux for 30 min. After cooling to room temperature, the resulting precipitate was filtered off and the reaction mixture was concentrated under reduced pressure to leave a yellow solid. The residue was diluted with  $\text{CH}_2\text{Cl}_2$  (40 ml) and the solution was successively washed with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (5 ml), saturated aqueous  $\text{NaHCO}_3$  solution (5 ml), and brine (5 ml). The solvent was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to leave a dark yellow oil, which was purified by flash chromatography on silica gel using benzene/ $\text{Et}_2\text{O}$  (12:1) mixture as an eluent to give **7a** (1.9 g, 91 %) as a pale yellow oil. The nmr spectrum showed that **7a** was an approximately 8:2 or 2:8 mixture of (*Z*)- and (*E*)-geometrical isomers:  $[\alpha]_D^{25} +65.9^\circ$  ( $c = 0.27$ ,  $\text{CHCl}_3$ );  $^1\text{H}$ -nmr ( $\text{CDCl}_3$ )  $\delta = 0.93$  (t,  $J=7.1$  Hz,  $3\text{H} \times 0.2$ ,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ),  $1.12$  (t,  $J=7.1$  Hz,  $3\text{H} \times 0.8$ ,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ),  $1.40$  and  $1.43$  (each d,  $J=6.8$  Hz, 3H,  $\text{NHCHCH}_3$ ),  $2.13$  (s, 3H,  $\text{CH}_3\text{CO}$ ),  $3.78 \sim 3.86$  (m, 1H,  $\text{NHCHCH}_3$ ),  $3.94 \sim 4.25$  (m, 2H,  $\text{AcOCH}_2\text{CH}$ ),  $4.03$  (q,  $J=7.1$  Hz, 2H,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ),  $6.91 \sim 7.02$  (m, 1H, aromatic H),  $8.17$  (d,  $J=14.0$  Hz,  $1\text{H} \times 0.8$ , vinyl H),  $8.26$  (d,  $J=14.8$  Hz,  $1\text{H} \times 0.2$ , vinyl H),  $9.54 \sim 9.69$  and  $10.69 \sim 10.91$  (each br, 1H, NH); ir (KBr)  $\nu = 1740, 1700, 1640, 1550 \text{ cm}^{-1}$ ; EIms  $m/z$  (%) = 418 ( $\text{M}^+$ , 6), 371 (11), 327 (6), 299 (100), 271 (2), 225 (29), 199 (24), 101 (74); HRms  $m/z$  calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_7\text{F}_3$  ( $\text{M}^+$ ): 418.0988; found: 418.0962.

**(+)-Ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-[(1-acetoxyp-2(*S*)-yl)amino]acrylate (**7b**)**

To a stirred solution of (*S*)-(+)-**5** (1.08 g, 5 mmol),  $\text{Et}_3\text{N}$  (0.56 g, 5.53 mmol) in  $\text{CH}_3\text{CN}$  (40 ml) at  $0^\circ\text{C}$  was added dropwise 2,3,4,5-tetrafluorobenzoyl chloride (**6b**) (1.12 g, 5.27 mmol). The reaction mixture

was stirred at the same temperature for 10 min, and then was heated at reflux for 30 min. Following the work up described for the preparation of **7a** from **5**, the compound (**7b**) (1.30 g, 66 %) was obtained as a pale yellow solid. A white analytical sample was prepared by recrystallization from EtOH. The nmr spectrum showed that **7b** was also an approximately 8:2 or 2:8 mixture of (*Z*)- and (*E*)-geometrical isomers:  $[\alpha]_D^{25} +56.8^\circ$  ( $c = 0.701$ ,  $\text{CHCl}_3$ );  $^1\text{H}$ -nmr ( $\text{CDCl}_3$ )  $\delta = 0.98$  (t,  $J=7.1$  Hz,  $3\text{H} \times 0.2$ ,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 1.11 (t,  $J=7.1$  Hz,  $3\text{H} \times 0.8$ ,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 1.42 and 1.39 (each d,  $J=6.8$  Hz,  $3\text{H}$ ,  $\text{NHCHCH}_3$ ), 2.13 (s,  $3\text{H}$ ,  $\text{CH}_3\text{CO}$ ), 3.74 ~ 3.88 (m,  $1\text{H}$ ,  $\text{NHCHCH}_3$ ), 4.04 and 4.08 (each q,  $J=7.1$  Hz,  $2\text{H}$ ,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 4.04 ~ 4.24 (m,  $2\text{H}$ ,  $\text{AcOCH}_2\text{CH}$ ), 6.96 ~ 7.04 (m,  $1\text{H} \times 0.8$ , aromatic H), 7.07 ~ 7.16 (m,  $1\text{H} \times 0.2$ , aromatic H) 8.13 and 8.16 (each d,  $J=14.3$ ,  $13.9$  Hz,  $1\text{H}$ ,  $=\text{CHNH}$ ), 9.39 ~ 9.54 and 10.74 ~ 10.95 (each br,  $1\text{H}$ , NH); ir (KBr)  $\nu = 1750$ ,  $1701$ ,  $1644$ ,  $1528$   $\text{cm}^{-1}$ ; EIms  $m/z$  (%) = 391 ( $\text{M}^+$ , 8), 331 (12), 318 (30), 272 (85), 243 (28), 193 (24); HRms  $m/z$  calcd for  $\text{C}_{17}\text{H}_{17}\text{NO}_5\text{F}_4$  ( $\text{M}^+$ ): 391.1043; found: 391.1042. Anal. Calcd for  $\text{C}_{17}\text{H}_{17}\text{NO}_5\text{F}_4$ : C, 52.16; H, 4.38; N, 3.58. Found: C, 52.28; H, 4.56; N, 4.49.

**(-)-9,10-Difluoro-2,3-dihydro-3(*S*)-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**8**)**

**From 7a.** To a stirred solution of (*S*)-(+)-**7a** (0.16 g, 0.39 mmol) in THF (5 ml) at  $0^\circ\text{C}$  was added a powdered KOH (0.028 g, 0.43 mmol) and the reaction mixture was stirred at  $0^\circ\text{C}$  to room temperature for 1 h (until tlc showed the absence of (*S*)-(+)-**7a** in the reaction mixture). To this solution, a 10 % aqueous solution of KOH (2 ml) was added and then the reaction mixture was heated at reflux for 2 h. The reaction mixture was concentrated under reduced pressure to leave a residue, which was taken up in water (3 ml) and acidified to pH 3-4 by the addition of aqueous 1-N HCl solution in an ice bath. The white precipitate was filtered and successively washed with water, EtOH, and  $\text{Et}_2\text{O}$  to give **8** (0.099 g, 92 %) as a colorless pure solid:  $\text{Mp} > 300^\circ\text{C}$  (DMF);  $[\alpha]_D^{25} -66.0^\circ$  ( $c = 0.95$ , DMSO) [lit., <sup>1(b)</sup>  $[\alpha]_D^{23} -65.6^\circ$  ( $c = 0.95$ , DMSO),  $\text{mp} > 300^\circ\text{C}$ ].

**From 7b.** Acid (**8**) was prepared in 90 % yield from **7b** by following the procedure described above. The product was identical in all respects with an authentic sample.

**From 9.** To a stirred solution of (*S*)-(-)-**9** (0.37 g, 1 mmol) in THF (20 ml) at room temperature was added a 10 % aqueous solution of KOH (3.6 ml), and the reaction mixture was heated at reflux for 2 h. Following the work up described for the preparation of **8** from **7a**, the compound (**8**) (0.24 g, 87 %) was obtained as a colorless pure solid. The product was identical in all respects with an authentic sample.

**From 10.** Acid (**8**) was prepared in 70 % yield from **10** by the procedure described for the conversion of **9**

to **8**. This result was the same as reported in reference 5(a) and the product was identical in all respects with an authentic sample.

**(-)-Ethyl 1,4-Dihydro-1-[1(*S*)-(acetoxymethyl)ethyl]-4-oxo-6,7,8-trifluoroquinoline-3-carboxylate (**9**)**

**From 7a.** To a stirred solution of (*S*)-(+)-**7a** (0.17 g, 0.41 mmol) in THF (5 ml) at 0 °C was added a powdered KOH (0.03 g, 0.45 mmol) and the reaction mixture was stirred at the same temperature for 1 h. and then stirred at room temperature for 1 h. The insoluble material was filtered off, and the filtrate was successively washed with aqueous 0.2-N HCl solution (2 ml), saturated aqueous NaHCO<sub>3</sub> (2 ml), and brine (4 ml). The solvent was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give **9** (0.14 g, 96 %) as a yellow solid suitable for use without further purification. A colorless analytical sample was prepared by recrystallization from a mixture of EtOH and CH<sub>2</sub>Cl<sub>2</sub>: Mp 125.5 ~ 126 °C; [ $\alpha$ ]<sub>D</sub><sup>29</sup> -20.9° (*c* = 0.667, CHCl<sub>3</sub>); <sup>1</sup>H-nmr (CDCl<sub>3</sub>)  $\delta$  = 1.42 (t, *J*=7.1 Hz, 3H, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.70 (d, *J*=6.8 Hz, 3H, NCHCH<sub>3</sub>), 2.01 (s, 3H, CH<sub>3</sub>CO), 4.41 (q, *J*=7.1 Hz, 2H, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 4.29 ~ 4.53 (m, 2H, AcOCH<sub>2</sub>CH), 5.32 ~ 5.47 (m, 1H, NCHCH<sub>3</sub>), 8.19 (m, 1H, aromatic H), 8.63 (s, 1H, vinyl H); ir (KBr)  $\nu$  = 3437, 1736, 1699, 1618, 1485 cm<sup>-1</sup>; Elms *m/z* (%) = 371 (M<sup>+</sup>, 26), 327 (8), 299 (100), 225 (18), 101 (44); HRms *m/z* calcd for C<sub>17</sub>H<sub>16</sub>NO<sub>5</sub>F<sub>3</sub> (M<sup>+</sup>): 371.0981; found: 371.0985; Anal. Calcd for C<sub>17</sub>H<sub>16</sub>NO<sub>5</sub>F<sub>3</sub>: C, 54.99; H, 4.34; N, 3.77. Found: C, 55.10; H, 4.55; N, 3.87.

**From 7b.** The compound (**9**) was prepared in 92 % yield from **7b** by using the procedure described for the conversion of **7a** to **9**. The product was identical in all respects with an authentic sample.

**(-)-Ethyl 1,4-Dihydro-1-[1(*S*)-(hydroxymethyl)ethyl]-4-oxo-6,7,8-trifluoroquinoline-3-carboxylate (**10**)**

To a stirred solution of (*S*)-(-)-**9** (0.33 g, 0.89 mmol) in a mixture of MeOH (8 ml) and water (4 ml) was added K<sub>2</sub>CO<sub>3</sub> (0.07 g, 0.51 mmol) at room temperature and the reaction mixture was stirred for 30 min. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure to leave a residue, which was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The reaction mixture was successively washed with aqueous 0.2-N HCl solution (4 ml), saturated aqueous NaHCO<sub>3</sub> (4 ml), and brine (5 ml). The solvent was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give a pale yellow solid, which was recrystallized from a mixture of CH<sub>2</sub>Cl<sub>2</sub> and Et<sub>2</sub>O to afford **10** (0.24 g, 82 %): Mp 163 ~ 163.5 °C; [ $\alpha$ ]<sub>D</sub><sup>24</sup> -28.6° (*c* = 0.217, CHCl<sub>3</sub>) [lit., <sup>5(a)</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> -28° (*c* = 0.2, CHCl<sub>3</sub>), mp 170 ~ 175 °C].

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