A practical stereoselective synthesis of (*S*)-(−)-ofloxacin

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Abstract A very efficient and practical procedure for preparation of (*S*)-(−)-ofloxacin has been developed (10 steps, overall yield ≥45%). The key step of this approach is the regioselective nucleophilic substitution of 2-position fluorine atom of 2,3,4-tirfluoronitrobenzene by (*S*)-glycerol acetonide.

Keywords (*S*)-(−)-Ofloxacin, stereoselective synthesis, quinolone antibacterial agent.

(*S*)-(−)-Ofloxacin[1,2] (Levofloxacin) is one of the third generation quinolone antibacterial agents of high potency. Its antibacterial activity is about 8—128 times more active than that of (*R*)-(+)-ofloxacin and twice as active as that of the racemate (ofloxacin). A number of processes[3-7] for preparing this excellent agent have been reported. However, all these processes suffered from low yields, expensive starting materials, or difficulties in scaling up. In order to synthesize new (*S*)-(−)-ofloxacin derivatives we have examined a more convenient route to levofloxacin from readily available starting materials. In this paper we describe a very efficient procedure for preparation of (*S*)-(−)-ofloxacin from 2,3,4-trifluoronitrobenzene and (*S*)-glycerol acetonide.

Results and discussion

The synthetic routes are outlined in Scheme 1. 2,3,4-Trifluoronitrobenzene (**1**) reacted with (*S*)-glycerol acetonide in the presence of K_2CO_3/KOH to produce **2** in almost quantitative yield. Potassium hydroxide or potassium carbonate alone was not equally effective for this regioselectively nucleophilic substitution. Subsequent removal of the acetonide protecting group in **2** with hydrochloric acid in ethanol gave dihydroxy compound **3** in 99% yield. Treatment of **3** with hydrogen bromide in acetic acid (*w*/*w*, 46%) afforded a mixture of acetoxy-bromides **4** (major) and **5** (minor)[8] in 98% yield. The mixture was treated with aqueous sodium hydroxide to give epoxide **6** in 100% yield.

Reductive ring-opening of epoxide **6** under an atmospheric pressure of hydrogen over Pd-C gave cor-

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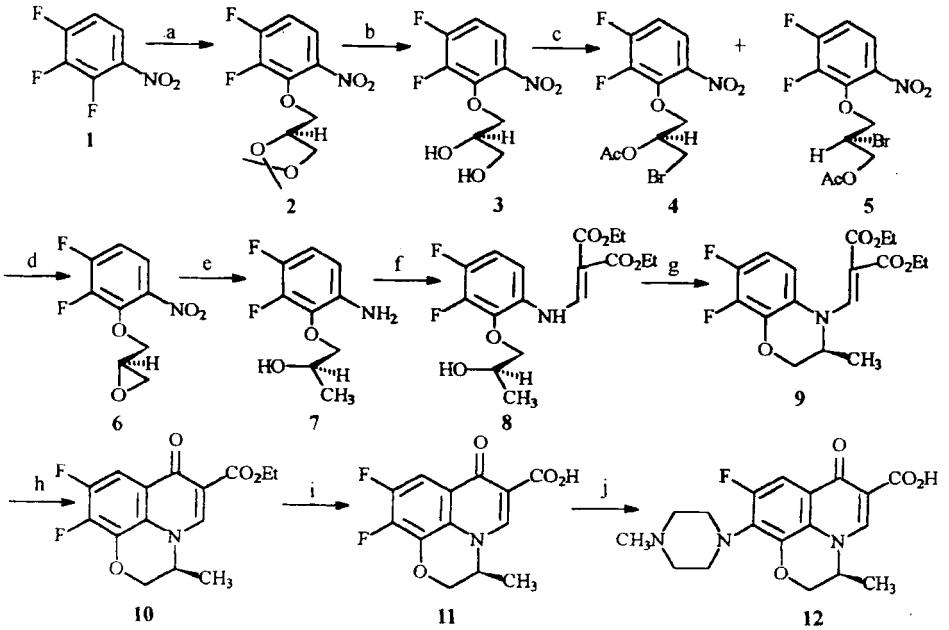
responding secondary alcohol **7** in 90% yield. (*S*)-(−)-Ofloxacin could be prepared from compound **7** by known routes.[5,7] Our modification features more convenient work-up procedures. Heating **7** and diethyl ethoxymethylenemalonate gave **8**. Treatment of **8** with Mitsunobu Reagent[9] in THF yielded **9**, which was cyclized in PPE to give **10**. Hydrolysis of **10** with acetic acid and conc. hydrochloric acid produced a key intermediate **11** in 95% yield. Finally **11** and *N*-methylpiperazine were refluxed in pyridine to give the title compoud (*S*)-(−)-ofloxacin (75%). The spectral data, physical properties and antibacterial activity of (*S*)-(−)-ofloxacin were in agreement with those reported in the literature.[1,2,6]

Scheme 1



(a) (*S*)-Glycerol acetonide, $PhCH_3$, KOH/KCO_3, 100%. (b) Ethanol, 3 mol/L HCl, 99%. (c) Hydrogen bromide-acid, 0℃, 98%. (d) 3 mol/L aqueous NaOH, 30℃. (e) H_2, 10% Pd/C, 90%. (f) Diethyl ethoxymethylenemalonate, 145—150℃, 90%. (g) Mitsunobu reagent, THF, 95%. (h) PPE, 145—150℃, 85%. (i) AcOH, conc. HCl, 120℃, 95%. (j) *N*-Methylpiperazine, Py, 130℃, 75%.

Experimental

Melting points were uncorrected and were determined in capillary tubes in a Buchisio apparatus. ^1H NMR spectra were recorded on a Bruker AM-400 spectrometer (chemical shifts in ppm values, *J* in Hz). Mass spectra were recorded on a MAT-95 spectrometer. Elemental analyses were carried out on a Perkin-Elmer 240B micro analyzer. Column chromatography was performed on silica gel (Qingdao Haiyang Chemical Group Co. of China, 200—300 mesh). Optical rotations were measured on a Perkin-Elmer 241

polarimeter.

(*S*)-3,4-*Difluoro*-2-[(2′,3′-*isopropylidenedioxypropyl*)*oxy*]*nitrobenzene* (**2**)

A solution of (*S*)-glycerol acetonide (0.44 g, 3.33 mmol) in toluene (2 mL) was added slowly to a stirred suspension of powdered potassium hydroxides (0.56 g, 10.0 mmol), potassium carbonate (0.45 g, 3.26 mmol) and 2,3,4-trifluoronitrobenzene (0.53 g, 2.99 mmol) in toluene (15 ml) at 0—5℃. The mixture was stirred at r.t. for 1 h, then water (10 mL) was added. The organic layer was separated and the aqueuos solution was extracted once with toluene. The combined organic phase was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford an oily product **2** (0.86 g, 100%). $[\alpha]_D^{24} = -7.36$(*c* 1.0, $CHCl_3$). δ_H($CDCl_3$): 1.35—1.40(s, s, 6H, 2×CH_3), 3.90—3.98(m, 1H, OCH_2), 4.05—4.19(m, 1H, OCH_2), 4.20—4.25(m, 1H, OCH), 4.30—4.47(m, 1H, $ArOCH_2$), 4.45—4.54(m, 1H, $ArOCH_2$), 6.80—7.05(m, 1H, ArH), 7.60—7.70(m, 1H, ArH). *m/z*(%): 274(M^+ − 15, 100), 158(90), 130(10). Anal. $C_{12}H_{13}F_2NO_5$ (289.23). Calcd: C, 49.83; N, 4.84; H, 4.53. Found: C, 50.18; N, 5.07; H, 4.61.

(*S*)-3,4-*Difluoro*-2-[(1′,2′-*dihydroxypropyl*)*oxy*]*nitrobenzene* (**3**)

A solutian of **2** (2.60 g, 8.99 mmol) in ethanol (10 mL) was added 3 mol/L hydrochloric acid (7 mL). The mixture was stirred at 60℃ for 1 h and then evaporated. The residue was extracted with chloroform (3×20 mL). The combined organic solution was dried over anhydrous sodium sulfate, filtered and evaporated to give **3** (2.22 g, 99%. $[\alpha]_D^{20} = 13.34$(*c* 1.4, $CHCl_3$). δ_H($CDCl_3$): 3.68—3.88 (m, 2H, $HOCH_2$), 4.05—4.15(m, 1H, HOCH), 4.28-4.47(m, 2H, $ArOCH_2$), 6.80—7.08(m, 1H, ArH), 7.69—7.78(m, 1H, ArH). Anal. $C_9H_9F_2NO_5$ (249.17). Calcd: C, 43.38; N, 5.62; H, 3.64. Found: C, 43.74; N, 5.65; H, 3.55.

(*S*)-3,4-*Difluoro*-2-(1′-*bromo*-2′-*acetoxypropyloxy*)*nitrobenzene and* (*R*)-3,4-*difluoro*-2-(1′-*acetoxy*-2′-*bromopropyloxy*) *nitrobenzene* (**4** *and* **5**)

Hydrogen bromide-acetic acid (43%, *w/w*, 4.68 g, 23.6 mmol) was added to **3** (1.91 g, 7.67 mmol) with ice-bath during about 5 min, after stirring at r.t. for 45 min, water (10 mL) was added, and the mixture was neutralized with 5 mol/L aqueous sodiumn hydroxide. The neutral solution was extracted with ether (3×20 mL). The combined ether solution was dried and evaporated to give **4** and **5** (2.66 g, 98%) as an oily mixture. $[\alpha]_D^{16} = 30.5$(*c* 2.5, $CHCl_3$). δ_H($CDCl_3$): 2.12(s, 3H, CH_3CO), 3.55—3.75(m, 2H, $BrCH_2$), 4.48—4.52(m, 2H, $ArOCH_2$), 5.24—5.32 (m, 1H, ACOCH), 7.00—7.08(m, 1H, ArH), 7.65—7.72(m, 1H, ArH). *m/z*(%): 354(M^+, 10), 356 (M^+ +2, 10), 313(10), 181(100), 179(100). Anal. $C_{11}H_{10}BrF_2NO_5$ (354.10). Calcd: C, 37.31; N, 3.95; H, 2.84. Found: C, 37.38; N, 4.21; H, 2.84.

(*R*)-3,4-*Difluoro*-2-[(1′,2′-*epoxyethenylpropyl*)*oxy*]*nitrobenzene* (**6**)

Aqueous sodium hydroxide (3 mol/L, 10 mL) was added to a mixture of **4** and **5** (1.60 g, 4.51 mmol). The mixture was stirred at 30℃ for half an hour and then extracted with ether (3 × 20 mL), the combined ether solutions were washed with water (10 mL), dried, filtered and evaporated to give oily **6** (1.04 g, 100%.). $[\alpha]_D^{20} = -11.93$ (*c* 2.4, $CDCl_3$). δ_H($CDCl_3$): 2.65—2.90(m, 2H, OCH_2), 3.38—3.42(m, 1H, OCH), 4.15—4.48(m, 2H, $ArOCH_2$), 7.69—7.05 (m, 1H, ArH), 7.75—7.80(m, 1H, ArH). *m/z*(%): 231(M^+), 188(18), 175(68), 145(100), 130(50), 100(99). Anal. $C_9H_7F_2NO_4$ (231.15). Calcd: C, 46.76; N, 6.06; H, 3.05. Found: C, 46.79; N, 6.10; H, 3.17.

(*R*)-3,4-*Difluoro*-2-[(2′-hydroxypropyl)oxy]*aniline* (**7**)

To a solution of **6** (1.00 g, 4.33 mmol) in absolute ethanol (30 mL) was added 10% Pd/C (0.2 g) and the mixture was hydrogenated under 1 atm H_2 at r.t. with stirring. After the required amount of H_2 had been absorbed, the reaction mixture was filtered and the filtrate was concentrated to give **7** (0.79 g, 90%). The product of **7** was used directly in next step. mp 50—51℃ (Lit.[7] mp 51.5℃). δ_H($CDCl_3$): 1.20(d, J = 7 Hz, 3H, CH_3), 3.15(br, s, 1H, HO), 3.80—3.85(m, 1H, MeCH), 3.88—4.15(m , 2H, $ArOCH_2$), 6.38—6.42 (m, 1H, ArH), 6.67—6.75(m, 1H, ArH).

(*S*)-2,3-*Difluoro*-6-(2′,2′-*diethoxycarbonylethenyl*)*amino*-1-[(2′-*hydroxypropyl*)-*oxy*]*benzene* (**8**)

7 (0.76 g, 3.74 mmol) and diethyl ethoxymethylenemalonate (0.82 g, 3.79 mmol) were heated at 145—150℃ for 1.5 h and then the mixture was further heated at the same temperature under reduced pressure for 30 min. The mixture was cooled and the solid was recrystallized from petroleum ether-ethyl acetate (4:1, *v/v*) to give **8** (1.25 g, 90%) as a white solid. mp 88—89℃ (Lit.[5] mp 88—90℃). δ_H($CDCl_3$): 1.22—1.38(m, 9H, 3 × CH_3), 3.50(br, 1H, NH), 4.15—4.32(m, 7H, 2 × OCH_2Me, MeCH, $ArOCH_2$), 6.84—6.94(m, 2H, ArH_2), 8.48(d, J = 14 Hz, 1H, CH = C,). *m/z* (%): 373(M^+), 328(10), 286(40), 227(44), 184(80), 171(100), 115(75).

(*S*)-*Diethyl* (7,8-*difluoro*-3-*methyl*-3,4-*dihydro*-2*H*-[1.4]-*benzoxazine*-4-*yl*)*methylenemalonate* (**9**)

Diethyl azodicarboxylate (0.67 g, 3.87 mmol) and triphenylphosphine (1.01 g, 3.87 mmol) were dissolved in anhydrous THF (20 mL) and stirred at 0℃ for 20 min. A solution of **8** (0.79 g, 2.12 mmol) in anhydrous THF (2 mL) was slowly added to the mixture. The mixture was stirred at r.t. over night. The solvent was removed under reduced pressure and the residue was purified through silica gel column chromatography using petroleum ether/ethyl acetate (3:1, *v/v*) as the eluting solvent to yield an oliy **9** (0.71g, 95%). δ_H($CDCl_3$): 1.20—1.24(m, 9H, 3 × CH_3), 3.90—4.40(m, 7H, 2 × OCH_2Me, MeCH, $ArOCH_2$), 6.71—6.78(m, 2H, ArH_2), 7.76(s, 1H, CH = C).

(S)-Ethyl-9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1.2.3-dl][1.4]benzoxazine-6-carboxylate (**10**)

The mixture of **9** (1.33 g, 3.75 mmol) and PPE (5 g) was heated at 140—145℃ for 1.5 h. After being cooled the reaction mixture was poured into ice-water and extracted with chloroform (3 × 30 mL). The combined organic layers were washed with 5% sodium carbonate solution and water. The organic solution was dried over anhydrous sodium sulfate and filtered, evaporated to dryness. The solid was washed to pale white with ethanol and gave **10** (0.98 g, 85 %). The product of **10** was used directly in next step. mp 254—255℃ (Lit.,[6] 254—255℃).

(S)-9,10-Difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1.2.3-dl][1.4]benzoxazine-6-carboxylic acid (**11**)

A mixture of **10** (0.73 g, 2.36 mmol) in acetic acid (8.7 mL) and conc. hydrochloric acid (2.3 mL) was heated at reflux temperature for 3 h. After cooling to room temperature the white needle crystals were collected by filtration and washed successively with water, ethanol and diethyl ether to give **11** (0.63 g, 95%). mp > 300℃ (Lit.[1,2] mp > 300℃). $[\alpha]_D^{18} = -64.7$(*c* 1.0, DMSO). Lit.[1,2] $[\alpha]_D^{18} = -64.9$(*c* 1.0, DMSO). $\delta_H(CF_3CO_2D)$: 1.85 (d, J = 7 Hz, 3H, CH_3,), 4.68—4.80(m, 2H, OCH_2Ar), 5.18—5.25(m, 1H, CHMe), 8.10—8.35(dd, J = 8, 8 Hz, 1H, ArH), 9.40 (s, 1H, CH = C). *m/z*(%): 281(M^+), 237(100), 222(90), 196(18), 149(15).

(S)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methy-1-piperazinyl)-7-oxo-7H-pyrido-[1.2.3-dl][1.4]benzoxazine-6-carboxylic acid (**12**). *(S)-(−)-Ofloxacin*

N-Methylpiperazine (0.25 g, 2.5 mmol) and **11** (0.28 g, 0.99 mmol) were dissolved in pyridine (10 mL), the mixture was refluxed with stirring over night. After cooling the pyridine was evaperated under reduced pressure and the residue was recrystallized from ethanol to afford **12** (0.27 g, 75%). mp 238—240℃. [Lit.[6] mp 240—245℃]. $[\alpha]_D^{20} = -76.9$(*c* 0.2, 0.05 mol/L NaOH) [Lit.[6] $[\alpha]_D^{20} = -77.8$(*c* 0.2, 0.05 mol/L NaOH)]. $\delta_H(CF_3CO_2D)$: 2.10(d, J = 6 Hz, 3H, CH_3), 3.45(s, 3H, NCH_3), 3.70—4.15(m, 8H, 2 × NCH_2CH_2N), 4.58—5.00(m, 2H, OCH_2Ar), 5.31—5.39(m, 1H, CHMe), 8.28(d, J = 11 Hz, 1H, ArH,), 9.50(s, 1H, CH = C). *m/z*(%): 361(M^+). Anal. $C_{18}H_{20}FN_3O_4$ (361.55). Calcd: F, 5.25. Found: F, 5.14.

References

1. Hayakawa, I.; Atarashi, S.; Yokohama, S.; Imamuka, M.; Sakano, K.-I.; Furukawa, M., *Antimicrob. Agents Chemother.*, **29**, 163(1986).
2. Atarashi, S.; Yokohama, S.; Yamazaki, K.-I.; Sakano, K.-I.; Imamura, M.; Hayakawa, I., *Chem. Pharm. Bull.*, **35**, 1896(1987).
3. Mitscher, L.A.; Sharma, P.N.; Chu, D.T.W.; Shen, L.L.; Pernet, A.G., *J. Med. Chem.*, **30**, 2283

(1987).

4. Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, I., *J. Heterocyclic Chem.*, **28**, 329(1991).
5. Fujiwara, T.; Ebata, T., *EP* 322815(1989) [*Chem. Abstr.*, **112**, 35434c (1990)].
6. Zoest, W. J.; Marx, A.F.; Koger, H.S., *EP* 368410 (1990)[*Chem. Abstr.*, **113**, 172032e (1989)].
7. Kany, S.B.; Ahn, E.J.; Kim, Y., *Tertrahedron Lett.*, **37**, 9317(1996).
8. Golding, B. T.; Hall, D. R.; Sakrikar, S., *J. Chem. Soc. Perkin Trans. I.*, 1214(1973).
9. Mitsunobu, O., *Synthesis*, 1(1982).

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