Asymmetric Reduction of 7,8-Difluoro-3-methyl-2*H*-1,4-benzoxazine. Synthesis of a Key Intermediate of (*S*)-(-)-Ofloxacin (DR-3355)

Shohgo Atarashi*, Hideaki Tsurumi, Toshihiro Fujiwara and Isao Hayakawa

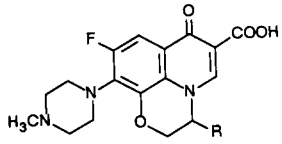
Research Institute, Daiichi Pharmaceutical Co., Ltd.,
1-16-13, Kitakasai, Edogawaku, Tokyo 134, Japan

Received July 18, 1990

An efficient, highly enantioselective synthesis of (*S*)-(-)-7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine, a key intermediate of (*S*)-(-)-ofloxacin, using various chiral sodium triacyloxyborohydrides as reducing agents is reported.

J. Heterocyclic Chem., **28**, 329 (1991).

Ofloxacin (**1**) [OFLX, (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid] has been developed as a highly active new quinolone antibacterial agent against Gram-positive and Gram-negative pathogens [1]. Chemically, it is characterized by a tricyclic structure with a methyl group at the C-3 position of the oxazine ring, thus providing an asymmetric center at this position. We have already reported that two optically active isomers of OFLX, *i.e.*, DR-3355 [(*S*)-(-)-OFLX] **2** and DR-3354 [(*R*)-(+)-OFLX] **3**, were prepared successfully by use of



1 R= —CH_3 (OFLX)
2 R= ◄CH_3 (DR-3355)
3 R= ····CH_3 (DR-3354)

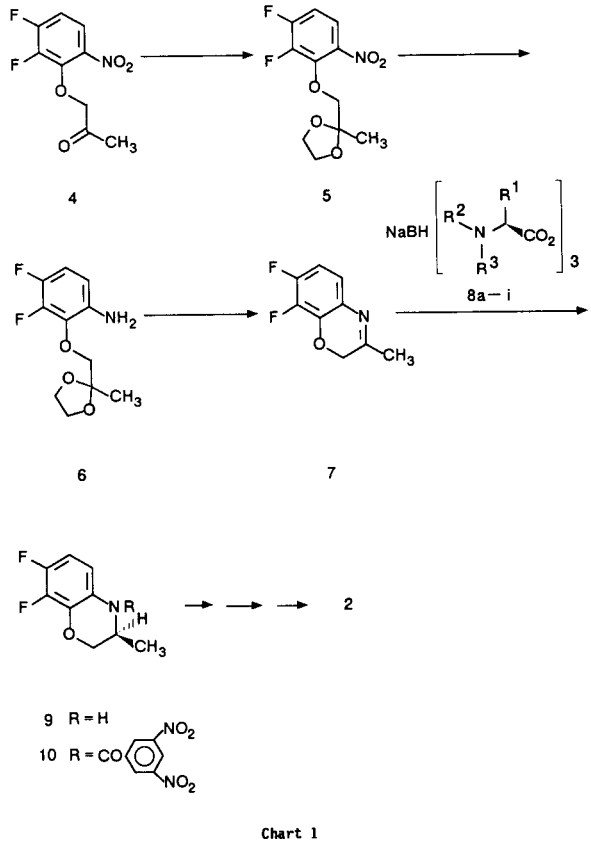
Figure 1

their optically resolved synthetic intermediates, and that **2** was 8 to 128 times more potent than **3** and approximately twice as active as **1** against Gram-positive and Gram-negative bacteria [2,3]. As this method, however, was wasteful since one of the two optical isomers was useless, we have investigated an asymmetric synthesis of **2** through the reduction of a cyclic imine with chiral reagents.

In this paper, we describe a method for the preparation of optically active (*S*)-(-)-7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine (**9**), a key intermediate of **2**, by an asymmetric reduction of 7,8-difluoro-3-methyl-2*H*-1,4-benzoxazine (**7**) derived from the acetonyl compound **4** [4].

Only a few syntheses of **2** and **3** using optically active 2-amino-1-propanols have been previously reported [5,6] in addition to our method [2].

Cyclic imine **7** as a substrate of asymmetric reduction was prepared in a manner similar to that reported by Bartsch *et. al.* [7]. Treatment of **4** with ethyleneglycol and *p*-toluenesulfonic acid in benzene afforded **5** [8], which was further hydrogenated on 5% palladium on charcoal in



9 R=H
10 R=CO

Chart 1

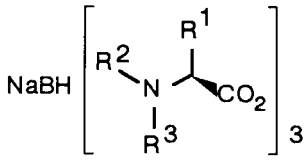
ethanol to give **6** [8]. This aniline was cyclized with concentrated hydrochloric acid and then treated with 28% aqueous ammonia to give **7** [8] in good yield.

Attempts to reduce **7** asymmetrically with a sodium (*S*)-prolinate-borane complex [9] and a lithium borohydride-*N*-benzoylcysteine complex [10] resulted in the formation of racemic 7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine. Enantioselectivity was observed with the reagent prepared from borane and (*S*)-(-)-2-amino-3-methyl-1,1-diphenylbutan-1-ol [11], but the resultant amine had the *R* configuration in excess (51% *e.e.* in tetrahydrofuran and 13% *e.e.* in dichloromethane).

Chiral sodium triacyloxyborohydrides were reported to be excellent reducing agents of cyclic imines [12]. We applied these reagents **8a-i** to the asymmetric reduction of **7**

Table 1

Asymmetric Reduction of 7 with Chiral Reagents 8a-i in Dichloromethane



Compound	R^1	R^2	R^3	Optical yield (%)	Absolute configuration
8a	$-(CH_2)_3-$		CO_2CH_2Ph [a]	78	S
8b	$-(CH_2)_3-$		$CO_2CH_2CHMe_2$	95	S
8c	$-(CH_2)_3-$		$CO_2CH_2CH(Et)^nBu$	70	S
8d	$-(CH_2)_3-$		CO_2Et	56	S
8e	$-(CH_2)_3-$		COEt	56	S
8f	$-(CH_2)_3-$		Ts	racemate	—
8g	CH_2Ph	H	$CO_2CH_2CHMe_2$	22	S
8h	$CHMe_2$	H	$CO_2CH_2CHMe_2$	7	S
8i	Me	H	$CO_2CH_2CHMe_2$	15	S

[a] See reference [12].

and summarize the results in Table 1. Of all the reagents listed in the Table, the newly synthesized **8b** was found to give **9** with a high degree of enantioselectivity (95% *e.e.*). The optical purities of the resulting **9** when using **8a-i** were determined by hplc analysis of **10** by the method described previously [13]. The method of forming a salt between highly optically active **9** and (*R*)-(-)-camphor-10-sulfonic acid, followed by treatment of the salt with aqueous sodium hydroxide has been disclosed by our institute to yield optically pure **9** [14], which can be easily converted to **2** in 5 steps [2].

In summary, we have investigated the asymmetric reduction of **7** with various chiral reducing agents and found that a new sodium (*S*)-hydrotris[1-(2-methylpropyl)1,2-pyrrolidinedicarboxylato-O^2]borate(1-) (**8b**) was very effective for obtaining **9** in excellent optical yield.

EXPERIMENTAL

Melting points were taken on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra were recorded on a Hitachi 270-30 infrared spectrophotometer, the ^{1}H-nmr spectra were recorded on a JEOL FX-90Q spectrometer with tetramethylsilane as the internal standard and the mass spectra were obtained on a JEOL JMS-D300 mass spectrometer.

2-(2,2-Ethylenedioxypropyloxy)-3,4-difluoronitrobenzene (**5**).

A solution of compound **4** [4] (4.6 g, 20 mmoles), ethylene glycol (1.5 g, 24 mmoles) and *p*-toluenesulfonic acid (catalytic amount) in dry benzene (60 ml) was refluxed for 18 hours while removing water using a Dean-Stark adapter. After cooling, the mixture was washed with saturated sodium bicarbonate solution

and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a residue which was chromatographed on a silica gel (80 g) (eluted with chloroform) to afford **5** (5 g, 91%) as a pale yellow oil; ^{1}H-nmr (deuteriochloroform): δ 1.50 (s, 3H, CH_3), 4.0 (s, 4H, CH_2CH_2), 4.16 (AB-q, 2H, J = 10.5 Hz, CH_2), 7.0 (ddd, 1H, J = 10.5, 9, 8 Hz), 7.66 (ddd, 1H, J = 9, 5.5, 3 Hz).

2-(2,2-Ethylenedioxypropyloxy)-3,4-difluoroaniline (**6**).

A mixture of **5** (1.6 g, 5.8 mmoles) and 5% palladium on charcoal (50% wet, 2g) in absolute ethanol (70 ml) was shaken under hydrogen atmosphere at room temperature for 4 hours. After removing the catalyst by filtration, the filtrate was evaporated under reduced pressure to give **6** (1.3 g, 92%) as a colorless oil; ^{1}H-nmr (deuteriochloroform): δ 1.50 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 4.04 (s, 4H, CH_2CH_2), 3.8-4.2 (brm, 2H, NH_2), 6.36 (ddd, 1H, J = 9.5, 5.5, 3 Hz), 6.70 (ddd, 1H, J = 11, 9.5, 9 Hz).

7,8-Difluoro-3-methyl-2*H*-1,4-benzoxazine (**7**).

Compound **6** (1.8 g, 7.3 mmoles) was added to 35% hydrochloric acid (9 ml) and stirred for 1 minute at 80°. The mixture was cooled in an ice bath and this solution was added dropwise to ice cooled 28% aqueous ammonia (14.5 ml). The aqueous solution was extracted three times with dichloromethane, and the extract was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give **7** (1.3 g, 97%) as colorless crystals, mp 51-53°; ir (potassium bromide): 3000, 1660, 1520, 1480, 1070 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.16 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.28 (ddd, 1H, J = 9, 5, 3 Hz), 6.5-6.8 (m, 1H); ms: (m/e) 183 (M^+).

Anal. Calcd. for $C_9H_7F_2NO$: C, 59.02; H, 3.85; N, 7.65. Found: C, 58.91; H, 3.89; N, 7.49.

Sodium (*S*)-Hydrotris[1-(2-methylpropyl)1,2-pyrrolidinedicarboxylato-*O*^{2}]borate (1-) (**8b**).

A solution of isobutyl chloroformate (12.6 ml) in acetone (150 ml) was added dropwise to a mixture of *L*-proline (11.5 g, 0.1 mole) and sodium bicarbonate (30.2 g, 0.36 mole) in water (150 ml). It was stirred at room temperature for 6 hours. After removal of acetone, the aqueous solution was washed with ethyl acetate and acidified to *p*H 2.5 with concentrated hydrochloric acid below 20°. The separated oil was taken up in ethyl acetate, which was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed to give (*S*)-*N*-isobutyloxycarbonylproline (19.6 g, 91%) as a colorless viscous oil; ir (neat): 2968, 1760 (shoulder), 1710, 1680, 1438, 1390, 1368, 1184, 1126, 1092, 998, 772 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.92 (brd, 6H, J = 7 Hz), 1.7-2.4 (m, 5H), 3.4-3.8 (m, 2H), 3.8-4.1 (m, 2H), 4.2-4.6 (m, 1H), 10.2 (brs, 1H). A solution of (*S*)-*N*-isobutyloxycarbonylproline (19.6 g, 91.2 mmoles) obtained above in anhydrous tetrahydrofuran (40 ml) was added to a stirred suspension of sodium borohydride (1.16 g, 30.5 mmoles) in anhydrous tetrahydrofuran (50 ml) over a period of 40 minutes at 0 ~ 5°. After vigorous hydrogen evolution ceased, the mixture was stirred at room temperature for 5 hours. Removal of the solvent gave **8b** (18.1 g, 99%) as a colorless solid foam; ir (potassium bromide): 2968, 2884, 2472, 1712, 1432, 1388, 1366, 1256, 1124, 1090, 1036, 994, 772 cm^{-1}.

Anal. Calcd. for $C_{30}H_{49}N_3O_{12}BNa\cdot H_2O$: C, 51.81; H, 7.39; N, 6.04. Found: C, 51.46; H, 7.34; N, 6.12.

Compounds **8c-i** were obtained in the same manner as described above and they were oily products except **8f** (mp 83-95°).

(*S*)-(-)-7,8-Difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine (**9**).

The general procedure for **9** was described with the chiral agent **8b**.

To a cooled (-40°) solution of **8b** (15.5 g, 22.9 mmoles) in dry dichloromethane (30 ml) was added a solution of **7** (1.4 g, 7.65 mmoles) in dry dichloromethane (15 ml) under nitrogen atmosphere. The reaction mixture was stirred at -40 ~ -5° for 40 minutes, washed with 5% citric acid solution, saturated sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. Removal of the solvent gave **9** (1.3 g, 92%) as a pale yellow oil, whose ^{1}H-nmr spectrum and tlc behavior were identical with those of the racemate [4].

REFERENCES AND NOTES

[1] K. Sato, Y. Matsuura, M. Inoue, T. Une, Y. Osada, H. Ogawa and S. Mitsuhashi, *Antimicrob. Agents Chemother.*, **22**, 548 (1982).

[2] S. Atarashi, S. Yokohama, K. Yamazaki, K. Sakano, M. Imamura and I. Hayakawa, *Chem. Pharm. Bull.*, **35**, 1896 (1987).

[3] I. Hayakawa, S. Atarashi, S. Yokohama, M. Imamura, K. Sakano and M. Furukawa, *Antimicrob. Agents Chemother.*, **29**, 163 (1986).

[4] I. Hayakawa, T. Hiramitsu and Y. Tanaka, *Chem. Pharm. Bull.*, **32**, 4907 (1984).

[5] M. Schriewer, K. Grohe, H. J. Zeiler and K. G. Metzger, German Offen. DE 3,543,513 (1987); *Chem. Abstr.*, **107**, 154342c (1987).

[6] L. A. Mitscher, P. N. Sharma, D. T. W. Chu, L. L. Shen and A. G. Pernet, *J. Med. Chem.*, **30**, 2283 (1987).

[7] H. Bartsch, W. Kropp and M. Pailer, *Monatsh. Chem.*, **110**, 197 (1979).

[8] I. Hayakawa and S. Atarashi, European Patent Application EP 273,399 (1988); *Chem. Abstr.*, **109**, 211064f (1988).

[9] N. Umino, T. Iwakuma and N. Itoh, *Chem. Pharm. Bull.*, **27**, 1479 (1979).

[10] K. Soai, T. Yamanoi and H. Oyamada, *Chem. Letters*, 251 (1984).

[11] S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda and K. Ito, *J. Chem. Soc., Perkin Trans. I*, 2039 (1985).

[12] K. Yamada, M. Takeda and T. Iwakuma, *ibid.*, 265 (1983).

[13] K. Sakano, S. Yokohama, I. Hayakawa, S. Atarashi and S. Kadoya, *Agric. Biol. Chem.*, **51**, 1265 (1987).

[14] T. Fujiwara, H. Tsurumi and Y. Sato, European Patent Application EP 304,684 (1989); *Chem. Abstr.*, **111**, 134170z (1989).