Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2657–2662

TETRAHEDRON: *ASYMMETRY*

Synthesis of a key intermediate of levofloxacin via enantioselective hydrogenation catalyzed by iridium(I) complexes

Koji Satoh, Minako Inenaga and Kazuaki Kanai *

Chemical Technology Research Laboratories, Daiichi Pharmaceutical Co. Ltd, 16-13, Kitakasai 1-chome, Edogawa-ku, Tokyo 134-8630, Japan

Received 22 May 1998; accepted 6 July 1998

Abstract

The key intermediate **2** for the antibacterial agent levofloxacin **1** was prepared by utilizing catalytic asymmetric hydrogenation of the cyclic imine **3** with the iridium(I) complex of (2*S*,4*S*)-BPPM in the presence of bismuth(III) iodide.

1. Introduction

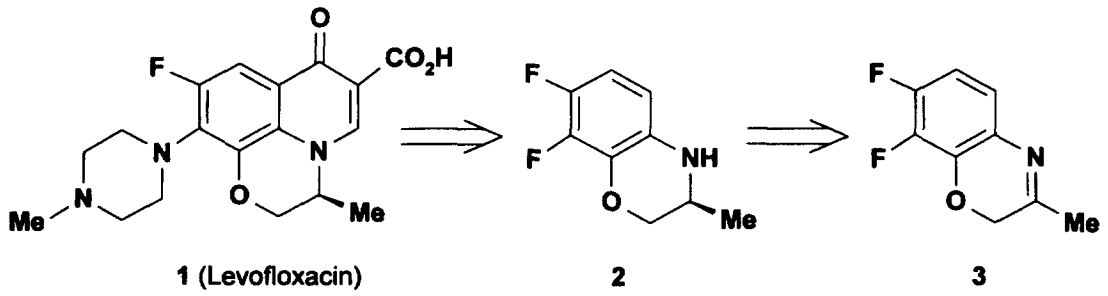
Levofloxacin **1**, a potent antibacterial agent on the market that exhibits potent activity against Gram-positive and Gram-negative bacteria,[1,2] possesses a methyl group at the C-3 position with an (*S*)-configuration of the oxazine ring. Although various synthetic methods to (*S*)-(−)-7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **2**, which is one of the key intermediates for **1**, by resolution,[2] asymmetric hydrolysis with enzyme,[3] asymmetric reduction utilizing a stoichiomeric amount of chiral reducing agents,[4] *N*-alkylation of sulfonanilides with chiral sulfonates[5] and Mitsunobu cyclization using zinc chloride[6] have been reported, an efficient catalytic procedure has not yet been developed.

On the other hand, the catalytic asymmetric hydrogenation of prochiral imines using biphosphine–iridium(I)[7–10] has recently attracted attention as an efficient method for the synthesis of the corresponding chiral amines. However, the enantiomeric excesses obtained have been moderate compared to those of ketones and olefins in the catalytic asymmetric hydrogenation.

We report herein an effective preparation of **2** by enantioselective hydrogenation of 7,8-dihydro-3-methyl-2*H*-1,4-benzoxazine **3** (Scheme 1) utilizing catalytic systems composed of iridium(I)–chiral biphosphine and bismuth(III) iodide.[11]

* Corresponding author.

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00276-6

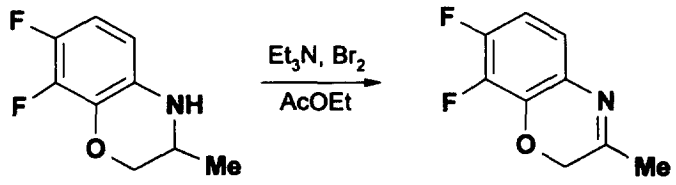


1 (Levofloxacin) 2 3

Scheme 1.

2. Results and discussion

Cyclic imine **3**[4] as a substrate for enantioselective hydrogenation was prepared by *N*-bromination of **4**,[12] followed by elimination in good yield (Scheme 2).



4 3

Scheme 2.

In the first stage, the asymmetric hydrogenation of **3** using iridium(I) complexes prepared in situ from $[Ir(COD)Cl]_2$, optically active biphosphine, and tetrabutylammonium iodide (where COD=1,5-cyclooctadiene) were investigated. The results are summarized in Table 1. The reactivity and enantioselectivity of the hydrogenation of **3** turned out to be dependent on the size of the chelate ring formed by ligands with the iridium metal. Chelating ligands forming five-membered rings such as (2*S*,3*S*)-CHIRAPHOS and (2*R*,3*R*)-NORPHOS gave only low enantioselectivities of 14 and 4% *ee*, and poor chemical yields of 9 and 16% (entries 1 and 2). With the ligand (2*S*,4*S*)-BDPP constituting a six-membered chelate ring, the enantioselectivity of 14% *ee* and chemical yield of 25% were obtained (entry 3). Biphosphines, forming seven-membered chelate rings with iridium, were the most efficient ligands. (4*S*,5*S*)-DIOP, (4*S*,5*S*)-MOD-DIOP and (2*S*,4*S*)-BPPM gave similar enantioselectivities of 48–54% *ee* and good chemical yields of 90–91% (entries 4–6). Interestingly, (2*S*,4*S*)-BCPM gave a low enantioselectivity of 13% *ee* and a modest chemical yield of 57% (entry 7).

It is known that the asymmetric hydrogenation of imines utilizing the catalytic system composed of a neutral metal [e.g. iridium(I) or rhodium(I)–chiral biphosphine] gave higher enantioselectivities by addition of an iodide to the system.[7,13] Hence, various metal iodides were screened using neutral iridium(I) complexes of (4*S*,5*S*)-DIOP. The results are summarized in Table 2. In the presence of magnesium(II) iodide and zinc(II) iodide as additives instead of tetrabutylammonium iodide, the enantioselectivities increased but the reactivities decreased (entries 7 and 14). The additive bismuth(III) iodide afforded the highest enantioselectivity, up to 72% *ee* (entry 16). The reactivity was unchanged compared with that utilizing tetrabutylammonium iodide as an additive. Bismuth(III) iodide was more effective than bismuth(III) bromide or bismuth(III) chloride. These additives decreased both reactivities and enantioselectivities (77%, 66% *ee* and 75%, 61% *ee*, respectively).

Further investigations of enantioselective hydrogenation of **3** were carried out using catalytic systems

Table 1
Iridium(I)–chiral biphosphines catalyzed asymmetric hydrogenation of cyclic imine **3**[a]

Entry	Ligand	Yield (%)	*ee*[b] (%)
1	(2*S*,3*S*)-CHIRAPHOS[c]	9	14
2	(2*R*,3*R*)-NORPHOS[d]	16	4
3	(2*S*,4*S*)-BDPP[e]	25	14
4	(4*S*, 5*S*) -DIOP[f]	90	54
5	(4*S*, 5*S*)-MOD-DIOP[g]	91	53
6	(2*S*,4*S*)-BPPM[h]	90	48
7	(2*S*,4*S*)-BCPM[i]	57	13

[a] All hydrogenation reactions were carried out with 1.26 mmol of substrate **3**, 6.28×10^{-3} mmol of $[Ir(COD)Cl]_2$, 1.38×10^{-2} mmol of ligand, and 2.51×10^{-2} mmol of tetrabutylammonium iodide in 5.0 ml of solvent (benzene / MeOH = 1:1) at 25 °C for 20hrs under initial hydrogen pressure of 40 bar. [b] Determined by HPLC analysis with a chiral column of Chiralcel OD (Daicel) employing hexane/isopropyl alcohol (9:1) as the eluent. The absolute configuration (*S*) was determined by comparison of its retention time on HPLC (Chiralcel OD) with an authentic specimen **2** prepared by a reported procedure.[2] [c] (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane. [d] (2*R*,3*R*)-2,3-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene. [e] (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane. [f] (4*S*,5*S*)-4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolane. [g] (4*S*,5*S*)-4,5-bis[[bis(4'-methoxy-3',5'-dimethylphenyl)phosphino]methyl]-2,2-dimethyl-1,3-dioxolane. [h] (2*S*,4*S*)-*N*-(*t*-butoxy-carbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine. [i] (2*S*,4*S*)-*N*-(*t*-butoxycarbonyl)-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine.

Table 2
Influence of various metal iodides on the reactivity and enantioselectivity[a]

Entry	Additive	Yield (%)	*ee* (%)
1	---	80	49
2	Bu_4N-I	90	54
3	NaI	88	46
4	KI	87	44
5	RbI	94	54
6	CsI	55	8
7	MgI_2	73	62
8	CaI_2	94	57
9	MnI_2	54	55
10	FeI_2	56	32
11	CoI_2	58	54
12	NiI_2	85	54
13	CuI	29	28
14	ZnI_2	82	62
15	SnI_2	45	56
16	BiI_3	91	72
17	SmI_2	88	18

[a] All hydrogenation reactions were carried out with 1.26 mmol of substrate **3**, 6.28×10^{-3} mmol of $[Ir(COD)Cl]_2$, 1.38×10^{-2} mmol of (4*S*,5*S*)-DIOP, and 2.51×10^{-2} mmol of additive in 5.0 ml of solvent (benzene / MeOH = 1:1) at 25 °C for 3hrs under initial hydrogen pressure of 40 bar.

Table 3
Effect of solvents on the reactivity and enantioselectivity[a]

Entry	Solvent	Yield (%)	*ee* (%)
1	benzene-MeOH	91	72
2	MeOH	91	70
3	EtOH	94	46
4	benzene	90	37
5	THF	88	51
6	CH_2Cl_2	91	37

[a] All hydrogenation reactions were carried out with 1.26 mmol of substrate **3**, 6.28×10^{-3} mmol of $[Ir(COD)Cl]_2$, 1.38×10^{-2} mmol of (4S,5S)-DIOP, and 2.51×10^{-2} mmol of BiI_3 in 5.0 ml of solvent at 25 °C for 3hrs under initial hydrogen pressure of 40 bar.

composed of iridium(I)–(4*S*,5*S*)-DIOP and bismuth(III) iodide to optimize parameters. The reactivity and the *ee* remained constant over a wide range of pressure (5–100 bar). There was some effect of solvents on this reaction with respect to the *ee* (Table 3). It was clear that the *ee*s were higher in benzene–methanol and methanol than in other solvents (entries 1 and 2, respectively). Furthermore, lower temperatures had a beneficial effect on the enantioselectivity (Fig. 1). Thus, at 0°C, **3** was obtained in 95% chemical yield and 80% enantiomeric excess.

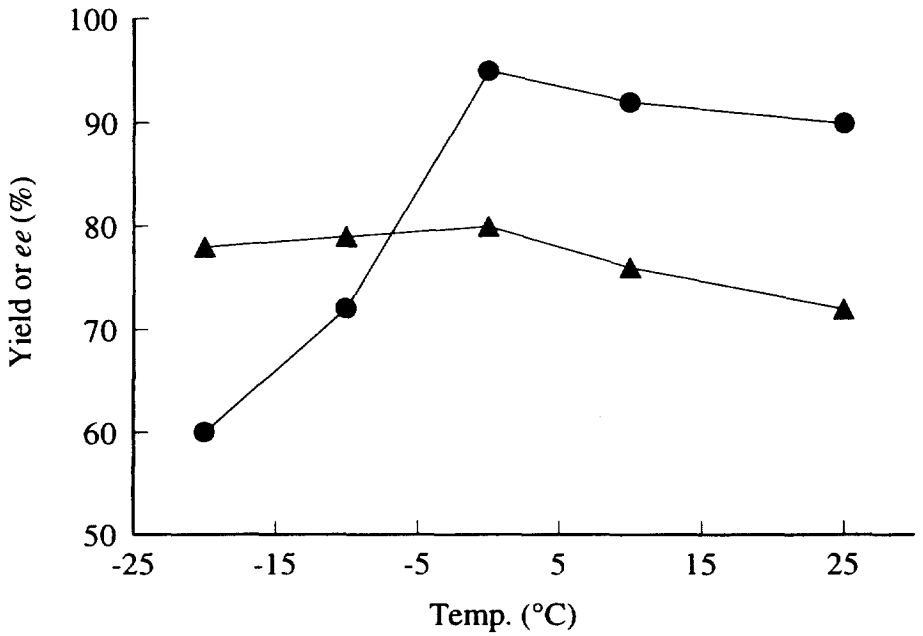


Fig. 1. Effect of temperature: • chemical yield; ▲ enantiomeric excess

Since it became obvious that lower temperatures give high enantioselectivities for this reaction, the influence of other chiral biphosphines such as (4*S*,5*S*)-MOD-DIOP and (2*S*,4*S*)-BPPM which gave similar enantiomeric excesses to (4*S*,5*S*)-DIOP in Table 1 were also investigated. The results are summarized in Table 4. Both chiral biphosphines increased enantioselectivity up to 90% *ee* at −10°C. The iridium(I) complex of (2*S*,4*S*)-BPPM in the presence of bismuth(III) iodide gave the best enantioselectivity and high reactivity in this reaction (entry 7).

Table 4
Influence of other chiral biphosphines on the reactivity and the enantioselectivity[a]

Entry	Chiral biphosphine	Temp.(°C)	Yield (%)	*ee* (%)
1	(4*S*,5*S*)-MOD-DIOP	25	82	77
2	(4*S*,5*S*)-MOD-DIOP	0	98	84
3	(4*S*,5*S*)-MOD-DIOP	-10	85	90
4	(4*S*,5*S*)-MOD-DIOP	-20	70	88
5	(2*S*,4*S*)-BPPM	25	85	79
6	(2*S*,4*S*)-BPPM	0	98	86
7	(2*S*,4*S*)-BPPM	-10	96	90
8	(2*S*,4*S*)-BPPM	-20	74	89

[a] All hydrogenation reactions were carried out with 1.26 mmol of substrate **3**, 6.28×10^{-3} mmol of $[Ir(COD)Cl]_2$, 1.38×10^{-2} mmol of ligand, and 2.51×10^{-2} mmol of BiI_3 in 5.0 ml of solvent (benzene / MeOH = 1:1) for 3hrs under initial hydrogen pressure of 40 bar.

3. Conclusion

We have established the asymmetric hydrogenation of cyclic imine **3** with the catalytic system composed of iridium(I), (2*S*,4*S*)-BPPM and bismuth(III) iodide to give (*S*)-(−)-7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **2**, which can be easily converted to levofloxacin **1** in six steps,[2] with high enantiomeric purity (90% *ee*) and a chemical yield of 96%.

4. Experimental section

4.1. General procedures

^{1}H-NMR spectra were measured on a JEOL JNM-EX 270 spectrometer. All signals are expressed in ppm (δ) with tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Horiba FT-720 and Perkin–Elmer 1600 FT-IR spectrometer. Mass spectra (MS) were obtained with a JEOL HX110 and JEOL AX505W mass spectrometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Column chromatography was performed on silica gel (Kieselgel 60, 70–230 mesh, Merck). The *ee* value of **2** was measured by HPLC [Daicel Chiralcel OD column; mobile phase hexane:*i*-PrOH=9:1; flow rate 1.0 ml/min; UV detection 254 nm; retention time t_R 8.8 min, t_S 10.5 min]. Unless otherwise noted, all reactions were carried out in anhydrous solvents.

4.2. 7,8-Difluoro-3-methyl-2H-1,4-benzoxazine 3

To the mixture of compound **4** (10.0 g, 54.0 mmol) in ethyl acetate (AcOEt) (100 ml) and triethylamine (75.3 ml, 54.0 mmol), a solution of bromine (3.06 ml, 59.4 mmol) in AcOEt (15 ml) was added dropwise over 15 min at −78°C under an argon atmosphere. The mixture was then allowed to slowly warm to 0°C (1 h). The reaction was quenched with water (100 ml), and the aqueous layer was extracted with AcOEt (2×100 ml). The combined organic layers were washed with water (2×50 ml) and brine (50 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with chloroform as an eluent to afford **3** (8.1 g, 81.9%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ=2.16 (3H, s), 4.60 (2H, s), 6.28 (1H, *J*=2.3, 4.7, 8.9 Hz, ddd), 6.50–6.80 (1H, m); MS *m/z* 183 (M^+). Other analytical data are identical to those of an authentic sample.[4]

4.3. Typical procedure for (S)-7,8-difluoro-2,3-dihydro-3-methyl-4H-1,4-benzoxazine 2

A mixture of di-μ-chlorobis(1,5-cyclooctadiene)diiridium(I), $[Ir(COD)Cl]_2$ (4.2 mg, 6.28×10^{-3} mmol), (2*S*,4*S*)-BPPM (7.6 mg, 1.38×10^{-2} mmol) in a mixed solvent of degassed benzene and methanol (1:1, 5 ml) was stirred for 5 min under an argon atmosphere. Bismuth(III) iodide (14.8 mg, 2.51×10^{-2} mmol) was added to the mixture, and the whole was stirred for another 5 min. This catalyst solution together with compound **3** (230 mg, 1.26 mmol) was placed in an autoclave (50 ml), pressurized with hydrogen to 40 bar, and stirred for 3 h at −10°C. After concentration of the reaction mixture, the residue was purified by column chromatography on silica gel with chloroform as an eluent to afford **2** (224 mg, 96%, 90% *ee*) as a colorless oil. $[\alpha]_D^{26}$ −5.5 (*c* 3.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ=1.18 (3H, d, *J*=6.3 Hz), 3.43–3.54 (1H, m), 3.64 (1H, brs), 3.77 (1H, dd, *J*=8.3, 10.4 Hz), 4.26 (1H, dd, *J*=2.7, 10.4 Hz), 6.25 (1H, ddd, *J*=2.3, 4.7, 8.9 Hz), 6.54 (1H, m); MS *m/z* 185 (M^+); IR (neat) 3388, 2976, 2871, 1716, 1683, 1610, 1558 cm^{-1}.

Acknowledgements

The authors wish to thank Assistant Professor Kimito Funatsu (Toyohashi University of Technology) for permission to use the computer-assisted synthesis design system AIPHOS (Artificial Intelligence for Planning and Handling Organic Synthesis)[14,15] in developing this procedure.

References

1. Atarashi, S.; Yokohama, S.; Yamazaki, K.; Sakano, K.; Imamura, M.; Hayakawa, I. *Chem. Pharm. Bull. Jpn* **1987**, *35*, 1896–1902.
2. Hayakawa, I.; Atarashi, S.; Yokohama, S.; Imamura, M.; Sakano, K.; Furukawa, M. *Antimicrob. Agents. Chemotherap.* **1986**, *29*, 163–164.
3. Sakano, K.; Yokohama, S.; Hayakawa, I.; Atarashi, S.; Kadoya, S. *Agric. Biol. Chem.* **1987**, *51*, 1265–1270.
4. Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, I. *J. Heterocycl. Chem.* **1991**, *28*, 329–331.
5. Xie, L. J. *Chin. Chem. Lett.* **1995**, *6*, 857–860.
6. Kang, S. B.; Ahn, E. J.; Kim, Y.; Kim Y. H. *Tetrahedron Lett.* **1996**, *37*, 9317–9320.
7. Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 558–559.
8. Morimoto, T.; Nakajima, N.; Achiwa, K. *Chem. Pharm. Bull. Jpn* **1994**, *42*, 1951–1953.
9. Togni, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1475–1477.
10. Tani, K.; Onouchi, J.; Yamagata, T.; Kataoka, Y. *Chem. Lett.* **1995**, 955–956.
11. During the course of our work, Morimoto and his co-workers reported that addition of bismuth(III) iodide to the catalytic system composed of iridium(I)–BCPM and its analog was effective in the asymmetric hydrogenation of cyclic ketimines.[15] Prior to their publication, we had presented in part at the *112th Annual Meeting of the Pharmaceutical Society of Japan*, Fukuoka, Japan, March 1992; Abstracts Vol. 2, p. 109.
12. Hayakawa, I.; Hiramatsu, T.; Tanaka, Y. *Chem. Pharm. Bull. Jpn* **1984**, *32*, 4907–4913.
13. Kang, G.-J.; Cullen, W.; Fryzuk, M.; James, B.; Kutney, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1466–1467.
14. (a) Funatsu, K.; Sasaki, S. *Tetrahedron Comput. Method.* **1988**, *1*, 27–38. (b) Funatsu, K. *AIPHOS konpyuta ni yoru yukigouseikeirotansaku*, Kyoritsushuppan, Tokyo, 1994.
15. Morimoto, T.; Nakajima, N.; Achiwa, K. *Synlett* **1995**, 748–750.