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Catalytic asymmetric oxidation of sulfide with titanium–mandelic acid complex: practical synthesis of (*S*)-3-[1-(2-methylphenyl)imidazol-2-ylsulfinyl]propan-1-ol, the key intermediate of OPC-29030

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Abstract—An effective catalytic asymmetric oxidation of prochiral sulfide **1a** to (*S*)-**2a** has been achieved by the use of chiral titanium–mandelic acid complex. The enantioselectivity was found to be not influenced by moisture, and moderate to high selectivity (76% ee) was obtained at room temperature (25°C). Thus a practical synthetic method for the platelet adhesion inhibitor, OPC-29030, was established utilising asymmetric oxidation of **1a**.

1. Introduction

(*S*)-(+)-3,4-Dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)sulfinyl-propoxy]-2(1*H*)-quinolinone (OPC-29030, Fig. 1) is known as a sulfinyl derivative which exhibits potent inhibition of the platelet adhesion by interfering with the release of 12(*S*)-hydroxyeicosatetraenoic acid (12-HETE) from platelets.[1,2]

The present synthetic method to obtain the optically pure OPC-29030 involves Sharpless–Kagan oxidation[3,4] of 3-[1-(2-methylphenyl)imidazol-2-ylthio]propan-1-ol **1a**[5] as a key step to introduce chirality to the molecule. However, the reaction proceeded with only 54% ee and the corresponding sulfoxide **2a** was isolated in 78% yield, although the optical purity of **2a** was easily raised to more than 99.5% ee by one recrystallization from methanol. As a result, we could obtain optically pure **2a** in 42% overall yield from prochiral **1a**[1] (Scheme 1). Due to the unsatisfactory low optical yield, we tried to find out a better stereoselective mono-oxidation method for the sulfide.

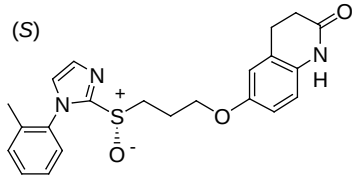

Figure 1. Inhibitor of the platelet adhesion OPC-29030.

In this article, we wish to report the details of the study regarding the practical asymmetric oxidation of **1a** to give (*S*)-**2a**, which is a key intermediate for the synthesis of OPC-29030.

2. Results and discussion

First of all, we examined some well-known asymmetric oxidation methods[6–9] on **1a**, which resulted in lower optical yields (Scheme 2). Then, we focussed on the Sharpless–Kagan method, since titanium(IV) was already claimed to be a good metal for the mono-oxidation of sulfide **1a**.[4] We examined various kinds of mono-, bi- and tridentate ligands instead of the usual tartaric ester (Table 1).[10]

As is clear from Table 1, chiral mandelic acid gave the best result.[11] The enantiomeric excess (76% ee)[12] obtained by this ligand is superior to that from the Sharpless–Kagan oxidation. As a next step, we examined the reaction with some mandelic acid derivatives and found that the presence of a free α-hydroxy carboxylic acid moiety is essential to exhibit high selectivity (Table 1).

The reaction was confirmed to proceed in catalytic way. The

Keywords: asymmetric induction; catalysts; oxidation; sulfoxides; titanium and compounds.

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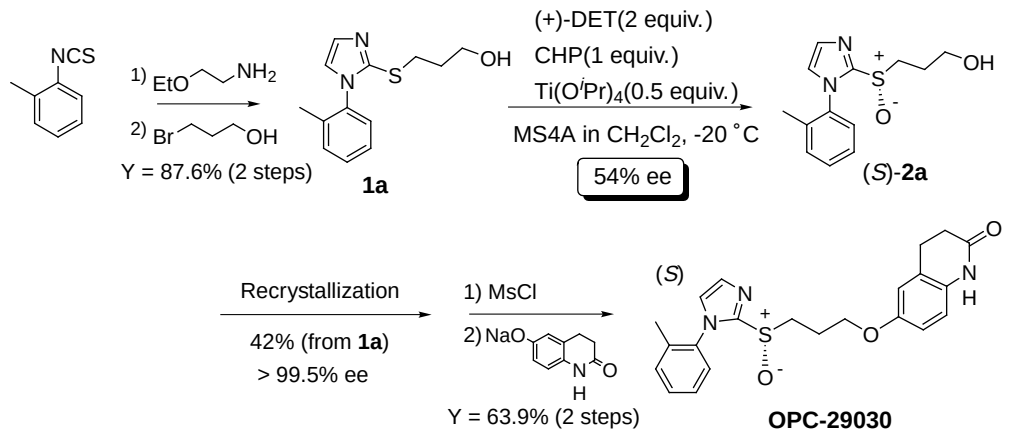
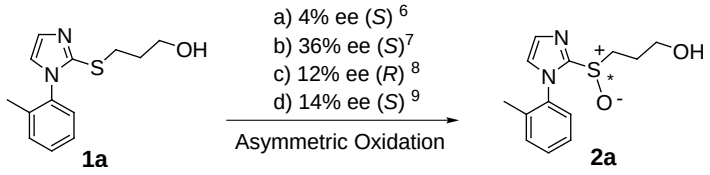
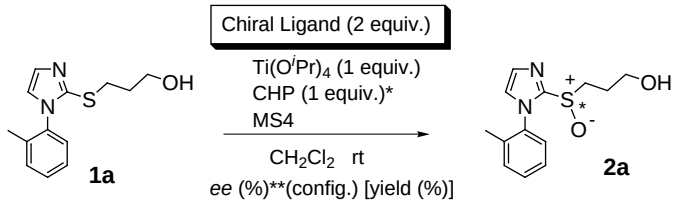


Scheme 1. Present synthetic route of OPC-29030.

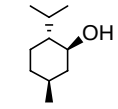
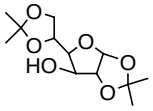
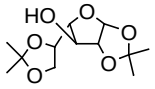
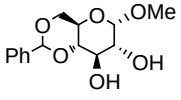
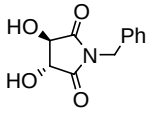
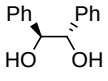
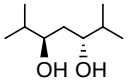
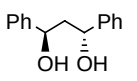
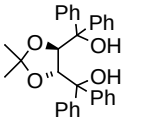
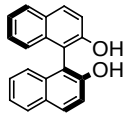
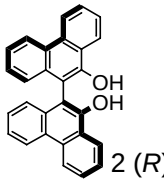
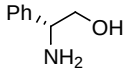
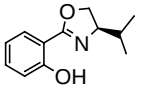
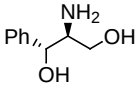
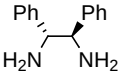
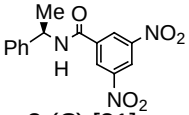
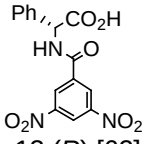
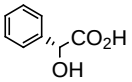
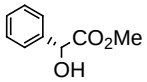
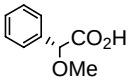
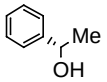
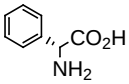
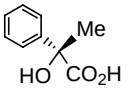


Scheme 2. Asymmetric oxidation of sulfide **1a** using known procedures. (a) (+)-DET (1 equiv.), CHP (1 equiv.), $Ti(O^iPr)_4$ (0.5 equiv.), H_2O (0.5 equiv.), MS4A in $C_2H_4Cl_2$, −30°C. (b) (+)-Binaphthol (1 equiv.), CHP (1 equiv.), $Ti(O^iPr)_4$ (0.5 equiv.), MS4A in CH_2Cl_2, 25°C. (c) (+)-(10-Camphorsulfonyl)oxaziridine (Davis reagent) in CH_2Cl_2, 25°C. (d) (−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese chloride (Jacobsen's catalyst), H_2O_2 ^{t}BuOH soln. in MeCN, 25°C.

Table 1. Asymmetric oxidation of **1a** using various titanium complexes[10]



*CHP: Cumene hydroperoxide; the commercial product was used without further purification. **Enantiomeric excess was determined by HPLC (CHIRALCEL® OJ)

					
3 (*S*) [74]	2 (*R*) [97]	1 (*S*) [75]	12 (*S*) [52]	2 (*S*) [76]	10 (*S*) [78]
					
66 (*S*) [17]	4 (*R*) [40]	22 (*R*) [35]	3 (*R*) [71]	10 (*S*) [36]	2 (*R*) [70]
					
15 (*S*) [29]	5 (*S*) [8]	0 [8]	31 (*S*) [16]	3 (*S*) [81]	13 (*R*) [62]
					
76 (*S*) [74]	39 (*S*) [39]	- [6]	2 (*R*) [34]	5 (*R*) [43]	48 (*S*) [63]

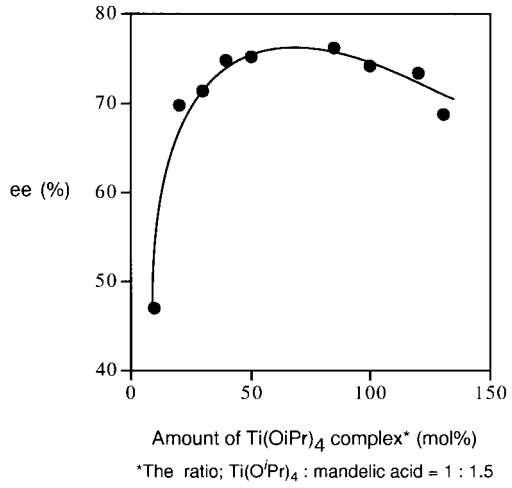


Figure 2. The correlation between the amount of titanium complex and ee of the product.

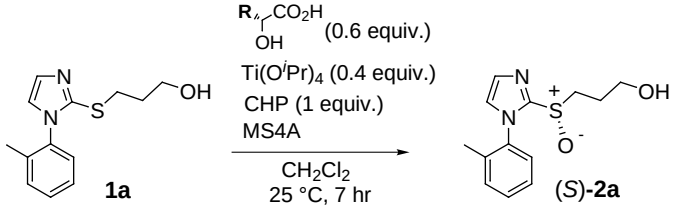
correlation between the amount of the titanium complex and ee of the product is shown in Fig. 2. The optimised molar ratio, that is, sulfide/Ti(O^iPr)$_4$/mandelic acid is 1:0.4:0.6.

The presence of water in the reaction medium has no significant influence on the stereoselectivity, however, the reaction rate is slightly reduced (Table 2, entry 2). This result is surprising, because in the usual Sharpless oxidation, even the presence of a small amount of water greatly influences the stereoselectivity by changing the aggregation state of the chiral titanium complex[13] The remarkable feature that the presence of water does not affect the stereoselectivity of the product in the present study is particularly useful for large-scale synthesis.

In our reaction, the substituent group (*R*) attached to the α-hydroxy carboxylic acid moiety plays an important role to exhibit the high enantioselectivity. It is also found that the electron-donating ability of the aryl function is a more important factor than the steric effect (Table 2, entries 3–6). These trends suggest that π-stacking effect is probable[14] in the enantioselectivity determining step.

Terminal hydroxyl function of **1a** is observed to be essential

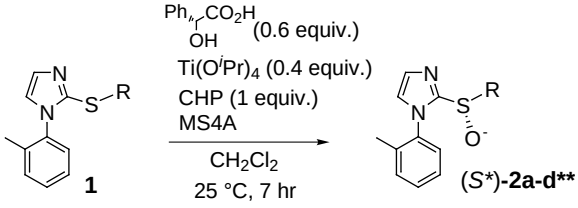
Table 2. Catalytic oxidation using various titanium–α-hydroxycarboxylic acid complexes



Entry	R	Yield of **2** (%)	Ee of **2** (%)[a]
1	Ph	89	76
2[b]	Ph	56	75
3	*p*-Methoxyphenyl	63	77
4	*p*-Chlorophenyl	70	51
5	Cyclohexyl	89	48
6	Isopropyl	69	31

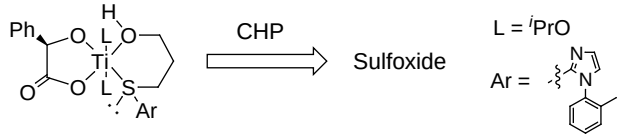
[a] Enantiomeric excess was determined by HPLC (CHIRALCEL® OJ).
[b] In the presence of H_2O (1 equiv.) instead of MS4A.

Table 3. Effect of hydroxyl function and chain length (**the absolute configuration was estimated by the retention time observed in chiral HPLC)

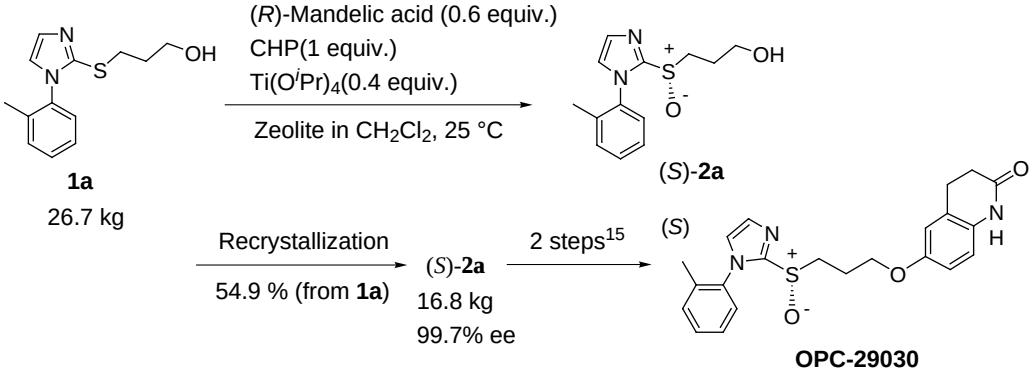


Entry	R		Yield of **2** (%)	Ee of **2** (%)[a]
1	Me:	**1b**	91	6
2	OH:	**1c**	91	49
3	OH:	**1a**	89	76
4	OH:	**1d**	48	27

[a] Enantiomeric excess was determined by HPLC (CHIRALCEL® OJ).



Scheme 3. Speculated structure of titanium complex.



Scheme 4. Large-scale synthesis of OPC-29030 via practical asymmetric oxidation.[15]

to obtain the high enantioselectivity (Table 3, entry 1) and the length of carbon chain attached to the hydroxyl also influences the stereoselectivity (Table 3, entries 2–4).

From the following two facts, (1) the necessity of a free α-hydroxyl carboxylic acid function in the ligand, and (2) no significant influence of water regarding the selectivity, it is suggested that the reaction may proceed via rigid chelate complex as shown in Scheme 3.

Finally, the present method was scaled-up in pilot plant and satisfactory results were obtained (Scheme 4).[15] Several beneficial aspects of the present oxidation method in large-scale production are obvious from the following observations. (1) The reaction proceeds at ambient temperature (25°C) affording products with moderate to high enantioselectivity. (2) The chiral ligand, i.e. mandelic acid, is cheap enough and could be recovered readily by extracting with a weak base. (3) No care is necessary for atmospheric moisture.

Attempts to extend the reaction to other substrates are the next theme that will be studied in the near future.

3. Experimental

3.1. General

Melting points were determined on a Yamato Melting Point Apparatus MP-21 and uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-200 (200 MHz) and JEOL JMN-A500 (500 MHz) using $CDCl_3$ or DMSO-d_6 as the solvent with TMS as internal standard. Mass spectra were obtained on a Shimadzu GCMS QP1000 or JEOL JMS SX-102A spectrometer. The ee values were determined by HPLC on a CHIRALCEL® OJ (DAICEL) column (eluent: EtOH/hexane=1/4). Optical rotations were measured on a JASCO DIP-360 polarimeter. E. Merck silica gel 60 (70–230 mesh ASTM) was used for column chromatography.

3.1.1. 1-*o*-Tolyl-1*H*-imidazole-2-thiol.[1] This compound was essentially prepared by the published method.[1] To a solution of 1100 g of 2-methylphenyl isothiocyanate (7.37 mol) in 556 ml of methanol was added 780 g of 2,2-dimethoxyethylamine (7.42 mol) at 6°C under stirring. Stirring was continued for 1 h at 6–38°C and then conc. HCl (780 g) was added to the mixture. Stirring was continued for 1 h at 37–50°C. After the addition of 12.0 kg of water, the mixture was heated at 90°C for 4 h and allowed to reach room temperature and resulted precipitate was collected by filtration. After washing with 3.30 kg of water followed by drying at 60°C gave 1292 g (92.1%) of 1-*o*-tolyl-1*H*-imidazole-2-thiol. This was employed in the next step without further purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.14 (s, 3H), 6.72 (d, *J*=1.6 Hz, 1H), 6.83 (d, *J*=1.6 Hz, 1H), 7.29–7.40 (m, 4H), 12.31 (bs, 1H). Anal. calcd for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; found: C, 62.97; H, 5.24; N, 14.42.

4. Sulfides (1a–d)

4.1. General procedure, preparation of 1a[2]

To a solution of 10.01 g of 1-*o*-tolyl-1*H*-imidazole-2-thiol (52.61 mmol) in 80 ml of isopropylalcohol was added 5.31 g of 3-chloro-1-propanol (56.12 mmol), 2.30 g of sodium hydroxide and 20 ml of deionized water at 25°C under stirring. Stirring was continued for 2.5 h under reflux. The mixture was allowed to reach room temperature and then 70 ml of water and 50 ml of toluene were added to the mixture. The organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by short silica-gel column chromatography [eluent: *n*-hexane–AcOEt (3:1, v/v)] to give 3-(1-*o*-tolyl-1*H*-imidazol-2-ylsulfanyl)-propan-1-ol (13.04 g) in 99.8% yield.

4.1.1. 3-(1-*o*-Tolyl-1*H*-imidazol-2-ylthio)propan-1-ol (1a). Colorless crystals from Et_2O–*n*-hexane); mp 47–48°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.84–1.91 (m, 2H), 2.09 (s, 3H), 3.32 (t, *J*=5.5 Hz, 2H), 3.73 (t, *J*=5.3 Hz, 2H), 5.86 (bs, 1H), 6.96 (d, *J*=1.4 Hz, 1H), 7.12 (d, *J*=1.4 Hz,

1H), 7.19–7.42 (m, 4H). Anal. calcd for $C_{18}H_{14}N_4O_3S$: C, 59.00; H, 3.85; N, 15.29; found: C, 58.74; H, 3.55; N, 14.99.

4.1.2. 2-Methylthio-1-*o*-tolyl-1*H*-imidazole (1b). 98% yield, colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.09 (s, 3H), 2.57 (s, 3H), 6.98 (d, J=1.4 Hz, 1H), 7.19 (d, J=1.4 Hz, 1H), 7.21–7.43 (m, 4H). Anal. calcd for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71; found: C, 64.45; H, 5.93; N, 13.77.

4.1.3. 2-(1-*o*-Tolyl-1*H*-imidazol-2-ylthio)ethanol (1c). 94.5% yield, colorless crystals from AcOEt; mp 84–85°C. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.10 (s, 3H), 3.17 (t, J=4.6 Hz, 2H), 4.02 (t, J=4.6 Hz, 2H), 5.99 (s, 1H), 6.98–7.40 (m, 6H). Anal. calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96; found: C, 61.47; H, 5.94; N, 11.96.

4.1.4. 4-(1-*o*-Tolyl-1*H*-imidazol-2-ylthio)butan-1-ol (1d). 59% yield, pale yellow viscous oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65 (dt, J=6.4, 12.8 Hz, 2H), 1.84 (dt, J=7.3, 12.8 Hz, 2H), 2.08 (s, 3H), 3.09 (t, J=7.3 Hz, 2H), 3.84 (s, 1H), 3.72 (t, J=6.4 Hz, 2H), 6.98 (d, J=1.4 Hz, 1H), 7.17 (d, J=1.4 Hz, 1H), 7.20 (d, J=8.5 Hz, 1H), 7.27–7.39 (m, 3H).

4.2. General procedure for the asymmetric oxidation

To a suspension of molecular sieves 4A in dry dichloromethane was added titanium tetraisopropoxide and (*R*)-(−)-mandelic acid at room temperature and stirred for 0.5 h. To the mixture was added 3-(1-*o*-tolyl-1*H*-imidazol-2-ylthio)propan-1-ol, stirred for 1 h, and then added cumene hydroperoxide. The mixture was stirred for 2–6 h. After concentration of the reaction mixture in vacuo, the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH as eluent) to give chiral sulfoxide.

4.2.1. (*S*)-3-(1-*o*-Tolyl-1*H*-imidazol-2-ylsulfinyl)propan-1-ol (2a). 89% yield, colorless powder from AcOEt; mp 110–111°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.03 (m, 2H), 2.04 (s, 3H), 3.03 (bs, 1H), 3.41–3.53 (m, 2H), 3.72 (m, 2H), 7.15 (d, J=1.2 Hz, 1H), 7.37 (d, J=1.2 Hz, 1H), 7.27–7.46 (m, 4H); $[\alpha]_D^{24}$=+67.5° (c 1.0, MeOH). Anal. calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; found: C, 58.86; H, 5.92; N, 10.30.

4.2.2. (*S)-2-Methylsulfinyl-1-*o*-tolyl-1*H*-imidazole (2b).** 91% yield, 6% ee, colorless viscous oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.10 (bs, 3H), 3.09 (s, 3H), 7.15 (d, J=1.2 Hz, 1H), 7.37 (d, J=1.2 Hz, 1H), 7.31–7.41 (m, 4H); Anal. calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72; found: C, 60.11; H, 5.59; N, 12.63.

4.2.3. (*S)-2-(1-*o*-Tolyl-1*H*-imidazol-2-ylsulfinyl)ethanol (2c).** 91% yield, 49% ee, colorless powder from AcOEt; mp 103–105°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.11 (bs, 3H), 3.40–3.64 (m, 2H), 4.06–4.14 (m, 1H), 4.33–4.40 (m, 1H), 7.15 (d, J=1.1 Hz, 1H), 7.29 (d, J=1.1 Hz, 1H), 7.36–7.47 (m, 4H). Anal. calcd for $C_{12}H_{14}N_2O2S$: C, 57.58; H, 5.64; N, 11.19; found: C, 57.41; H, 5.70; N, 11.08.

4.2.4. (*S)-4-(1-*o*-Tolyl-1*H*-imidazol-2-ylsulfinyl)butan-1-ol (2d).** 48% yield, 27% ee, pale yellow viscous oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65–1.95 (m, 4H), 2.10 (bs, 3H), 2.36 (bs, 1H), 3.43–3.47 (m, 2H), 3.69 (m, 2H), 7.15 (d, J=1.1 Hz, 1H), 7.29 (d, J=1.1 Hz, 1H), 7.36–7.47 (m, 4H); HRMS calcd for $C_{14}H_{19}N_2O_2S$: 279.1167; found: 279.1152.

4.2.5. Large-scale synthesis of 2a. To a suspension of zeolite 3A (28.65 kg) in dichloromethane (286.5 L) was added 3-(1-*o*-tolyl-1*H*-imidazol-2-ylsulfanyl)-propan-1-ol (28.65 kg, 115.36 mol), titanium tetraisopropoxide (13.13 kg, 46.19 mol) and (*R*)-(−)-mandelic acid (10.53 kg, 69.21 mol) at room temperature and stirred for 0.5 h. Then, cumenehydroperoxide (21.4 kg, 140.6 mol) was added to the above mixture below 25°C and stirred for 2 h at 22–27°C. After the filtration of zeolite, 10% (+)-tartaric acid solution[16] (286.5 L) was added and stirred for 1 h. Then, 20% NaOH solution (85.95 L) and 8.3% sodium thiosulfate solution (85.95 L) were added in succession to the reaction mixture and further stirred for 0.5 h at room temperature. The organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized from ethyl acetate (57.3 L) to give 16.77 kg of almost enantiomerically pure **2a** (54.9%, 99.7% ee) as colorless crystals.

4.2.6. (*S*)-(+)-3,4-Dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)-sulfinylpropoxy]-2(1*H*)-quinolinone (OPC-29030). Mp 265–268°C (dec.). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.93–2.06 (m, 2H), 2.02 (s, 3H), 2.39 (t, J=7.3 Hz, 2H), 2.82 (t, J=7.3 Hz, 2H), 3.38 (ddd, J=13.8, 8.4, 6.5 Hz, 1H), 3.47 (ddd, J=13.8, 8.4, 6.5 Hz, 1H), 4.00 (t, J=6.1 Hz, 2H), 6.67 (dd, J=8.6, 2.7 Hz, 1H), 6.72 (d, J=2.7 Hz, 1H), 6.75 (d, J=8.6 Hz, 1H), 7.34–7.38 (m, 2H), 7.36 (d, J=1.2 Hz, 1H), 7.47 (ddd, J=7.4, 5.9, 2.4 Hz, 1H), 7.43 (bd, J=7.4 Hz, 1H), 7.58 (bd, J=1.2 Hz, 1H), 9.73 (s, 1H); $[\alpha]_D^{20}$=−174° (c 0.5, DMF). Anal. calcd for $C_{22}H_{23}N_3O_3S$: C, 64.53; H, 5.66; N, 10.26; found: C, 64.45; H, 5.65; N, 10.03.

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