

The Improved Synthesis of OPC-29030, a Platelet Adhesion Inhibitor *via* Diastereoselective Oxidation of Chiral Non-racemic Sulfide

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An improved synthetic route of OPC-29030, the platelet adhesion inhibitor, was established *via* the diastereoselective oxidation of a chiral non-racemic sulfide (*R*)-**5** to (*S_S*)-**6** by the catalytic oxidation using VO(acac)₂ and cumene hydroperoxide (CHP) in the presence of MS4A. Under the current condition, the diastereoselectivity was not influenced by the presence of moisture, and moderate to high selectivity (72% *de*) was obtained at –30 °C. The obtained sulfoxide, which diastereomeric excess was easily raised by the recrystallization, could successfully lead to OPC-29030.

Key words oxidation; catalyst; sulfoxide; molecular sieve

(*S*)-(+)-3,4-Dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)sulfinylpropoxy]-2(1*H*)-quinolinone (OPC-29030, Fig. 1)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.²⁾

The first reported synthetic route³⁾ to obtain the optically pure OPC-29030 involves Sharpless–Kagan oxidation^{4–6)} of 3-[1-(2-methylphenyl)imidazol-2-ylthio]propan-1-ol (**1**) as a key step to introduce chirality to the molecule. However the reaction proceeded with only 54% *ee* and the corresponding sulfoxide **2** was isolated in 78% yield. To improve the low stereoselectivity, previously we have reported a modified Sharpless–Kagan method for the sulfide **1** using (*R*)-mandelic acid as a chiral auxiliary (Chart 2).^{7,8)} The other method, based on a kinetic resolution using an enzyme, was also reported for introducing the chirality to the molecule.^{9,10)}

In this note, we wish to report an alternative improved synthetic route of OPC-29030 *via* a diastereoselective oxidation by using a chiral non-racemic sulfide having an asymmetric center at the neighboring position of the sulfur atom.^{11,12)} The improved synthetic route was established based on the assumption that the use of the chiral sulfide (*R*)-**5** would arise high diastereoselective oxidation. Our hypothesis is that if there is a hydroxyl group at the neighboring position to the sulfur atom, metal catalyzed oxidation of the sulfide would proceed in a stereoselective manner *via* rigid chelating intermediate (Fig. 2).

Since a favorable sulfide to our purpose has already been reported by Uno *et al.*, we synthesized the sulfide (*R*)-**5** according to their method as shown in Chart 3.³⁾ In their report, it also provided that a corresponding (*S_S*)-sulfoxide, which was isolated by the column chromatography after the mCPBA oxidation of (*R*)-**5**, could effectively lead to OPC-29030 *via* a reductive manner using a super Hydride®. This information supported us to use (*R*)-**5** as the substrate of the diastereoselective oxidation.

First, we examined the stoichiometric oxidation of the sulfide (*R*)-**5** using cumene hydroperoxide (CHP) along with several kinds of metals that were claimed to be useful for the

mono-oxidation of sulfides (Table 1).¹³⁾

Although the stereoselectivity of the oxidation was not very high, we have found that oxovanadium(II) and titanium(IV) gave the moderate result for the stereoselectivity of the product among the metals used.

Next, we examined the possibility of the catalytic reaction using oxovanadium(II), which is easier to handle compared to titanium(IV). As clear from Table 2, both stereoselectivity

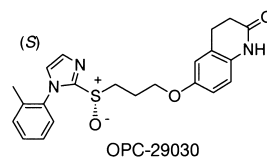


Fig. 1. Inhibitor of the Platelet Adhesion OPC-29030

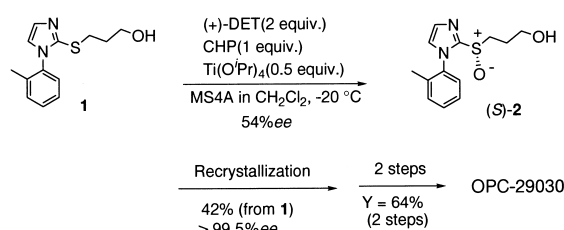


Chart 1. First Synthetic Route of OPC-29030 *via* Modified Sharpless–Kagan Oxidation

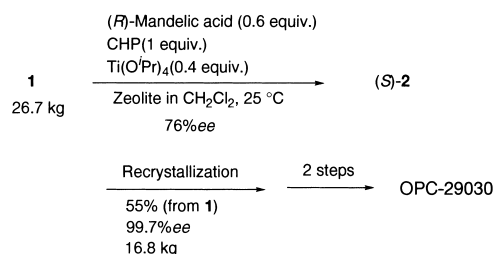


Chart 2. Large Scale Synthesis of OPC-29030 *via* Asymmetric Oxidation of **1** Using (*R*)-Mandelic Acid–Titanium Complex

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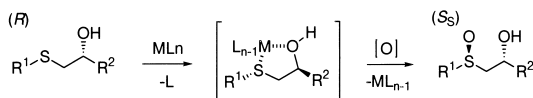
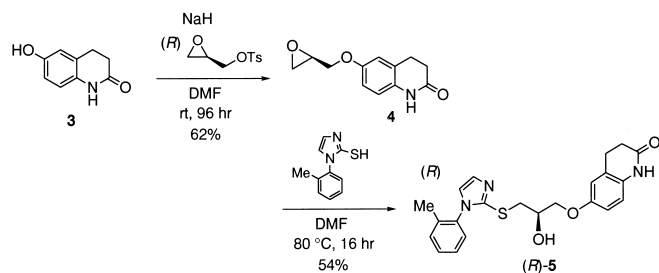
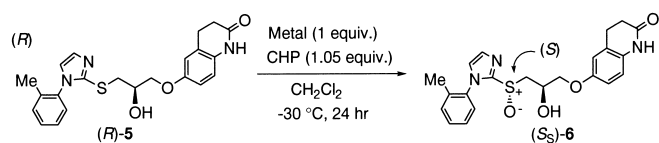


Fig. 2. Strategy of the Effective Diastereoselective Oxidation

Chart 3. Preparation of the Chiral Non-racemic Sulfide (*R*)-5Table 1. Stoichiometric Diastereoselective Oxidation of (*R*)-5 Using Various Metals

Entry	Metal	Yield (%) ^{a)}	De (%) ^{b)}
1	VO(acac) ₂	50	36
2	Ti(O ⁱ Pr) ₄	40	35
3	MoO ₂ (acac) ₂	21	20
4	Mn(acac) ₂	3	6
5	Ni(acac) ₂	trace	—

a) Calculated yield by HPLC. b) De was determined by HPLC.

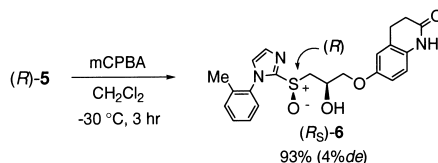
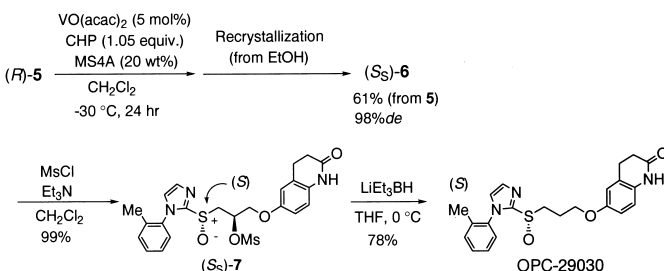
Table 2. Catalytic Diastereoselective Oxidation of (*R*)-5 Using VO(acac)₂

Entry	Additive	Yield (%) ^{a)}	De (%) ^{b)}
1	None	81	46
2	MS4A	91	72
3	MS4A + H ₂ O (10 mol%)	93	68

a) Calculated yield by HPLC. b) De was determined by HPLC.

and product yield were higher than those in the reaction that was carried out by a stoichiometric way (Table 2, Entries 1, 2). It is noteworthy that the addition of the MS4A, which is an essential step to carry out the catalytic reaction in Sharpless–Kagan oxidation, made the stereoselectivity remarkably high (72% *de*). At this moment, the role of the MS4A for the selectivity is not clear, but it is suggested that the MS4A, which is known as the acid-base characteristic compound¹⁴⁾ participates in the formation of the active species in the transition-state.

Furthermore, we found that the presence of water in the reaction medium had no significant influence on the stereoselectivity and also the yield (Table 2, Entry 3). This result is

Chart 4. Diastereoselective Oxidation of (*R*)-5 Using mCPBAChart 5. Derivation to OPC-29030 from (*S*)-6

rather surprising, because in the usual Sharpless–Kagan oxidation, even the presence of a small amount of water greatly influences the stereoselectivity by changing the aggregation state of the chiral titanium complex.¹⁵⁾ The noted feature that the presence of water does not affect the stereoselectivity of the product is particularly useful for a large-scale synthesis.

In this oxidation, it is obvious that the metal salt plays an essential role to exhibit high selectivity. Although the stereoselectivity of the mCPBA oxidation of (*R*)-5 was not mentioned in the previous report,³⁾ we have confirmed that the mCPBA oxidation in methylene chloride provided the corresponding sulfoxide with a lower stereoselectivity (only 4% *de*) and the sense of the chirality was opposite as shown in Chart 4.

In addition, when the substrate, whose hydroxyl function was protected by the mesyl group was used in the VO(acac)₂ oxidation, the reaction afforded the corresponding sulfoxide with lower selectivity (78% yield, 9% *de*), suggesting that the free hydroxyl function is also an essential feature to achieve the high selectivity.

Finally, we carried out the derivation of the sulfoxide to the optically active OPC-29030 according to Uno's report³⁾ (Chart 5). The recrystallization of the sulfoxide from ethanol provided an almost optically pure sulfoxide (98% *de*) in a good yield (61% from 5). Then the hydroxyl function was converted to the corresponding mesylate function, followed by reduction to methylene function by super Hydride[®] to afford OPC-29030.

It is likely that the presented synthetic route is highly practical, since the key reaction of the oxidation gives a good yield of the product with moderate to high stereoselectivity, and need not to care for the atmospheric moisture.

Experimental

Melting points are uncorrected. ¹H-NMR spectra were measured on 270 or 500 MHz spectrometers with SiMe₄ as the internal standard. E. Merck silica gel 60 (70–230 mesh ASTM) and YMC SIL 60A were used for column chromatography. The *de* values of 6 were determined by HPLC on a TSK-80TM column (eluent: MeCN/H₂O=30/70) and *ee* values of OPC-29030 were determined by HPLC on a Ultaron ES-OVM (eluent: MeCN/20 mM KH₂PO₄ aq.=10/90). Chiral non-racemic sulfide (*R*)-5 was prepared by the published method.³⁾

(*R*)-6-[2-Hydroxy-3-(1-*o*-tolyl-1*H*-imidazol-2-ylsulfanyl)-propoxy]-3,4-

dihydro-1*H*-quinolin-2-one [(*R*)-**5**]³: Colorless crystals; mp 65.0–66.0 °C (EtOH). [α]_D²⁴ +8.0° (*c*=0.54, MeOH). ¹H-NMR (CDCl₃, 270 MHz) δ : 2.10 (3H, s), 2.57–2.62 (2H, m), 2.89–2.94 (2H, m), 3.24–3.31 (1H, dd, *J*=6.3, 15.0 Hz), 3.38–3.44 (1H, dd, *J*=2.6, 15.0 Hz), 3.94–4.00 (1H, m), 4.06–4.11 (1H, m), 4.35–4.37 (1H, m), 6.62–6.73 (3H, m), 6.98 (1H, d, *J*=1.3 Hz), 7.11 (1H, d, *J*=1.3 Hz), 7.19–7.42 (4H, m), 7.62 (1H, br s).

Typical Procedure for the Diastereoselective Oxidation of (*R*)-5**** To a suspension of molecular sieves 4A in dry dichloromethane was added vanadyl acetylacetonate (0.49 g, 1.8 mmol) at room temperature. To the mixture was added 6-[2-hydroxy-3-(1-*o*-tolyl-1*H*-imidazol-2-ylsulfanyl)propoxy]-3,4-dihydro-1*H*-quinolin-2-one [(*R*)-**5**] (15.1 g, 36.8 mmol) and then 80% cumene hydroperoxide (7.35 g, 38.6 mmol) was added to the above mixture at –30 °C and the mixture was stirred for 24 h. After the filtration of molecular sieves 4A, 8.3% sodium thiosulfate solution was added and the mixture was stirred for 0.5 h at room temperature. The organic layer was separated, dried (MgSO₄) and concentrated *in vacuo* to give (*S*_S)-**6** of 72% *de* (14.2 g) in 92% yield.

Recrystallization of (*S*_S)-6**** A solution of 14.2 g of (*S*_S)-**6** (33.4 mmol, 72% *de*) in 113.6 ml of ethylalcohol was heated to reflux. Then the solution was cooled down to 2 °C by degrees under stirring and the stirring was continued for 30 min at 2 °C. The white precipitate was collected to give (*S*_S)-**6** of 98% *de* (9.55 g) in 67.3% yield.

(*S*_S)-**6**-[2-Hydroxy-3-(1-*o*-tolyl-1*H*-imidazol-2-ylsulfanyl)propoxy]-3,4-dihydro-1*H*-quinolin-2-one [(*S*_S)-**6**]³: Colorless solid; mp 128.0–130.0 °C. ¹H-NMR (CDCl₃, 270 MHz) δ : 2.11 (3H, br s), 2.57–2.63 (2H, m), 3.54–3.69 (2H, m), 4.05–4.16 (2H, m), 6.65–6.75 (3H, m), 7.18 (1H, m), 7.38–7.49 (4H, m), 8.06 (1H, m). *t*_R 15.8 min (flow rate, 0.5 ml/min).

(*S*_S)-Methanesulfonic Acid 1-(2-Oxo-1,2,3,4-tetrahydro-quinolin-6-yloxy-methyl)-2-(1-*o*-tolyl-1*H*-imidazol-2-ylsulfanyl)-ethyl Ester [(*S*_S)-**7**]³: Colorless solid; mp 87.0–89.0 °C. [α]_D²⁵ –2.9° (*c*=0.41, CHCl₃). ¹H-NMR (CDCl₃, 270 MHz) δ : 2.11 (3H, s), 2.58–2.64 (2H, m), 2.90–2.98 (2H, m), 3.07 (3H, s), 3.57 (1H, m), 4.23–4.33 (2H, m), 4.41–4.46 (1H, m), 5.32–5.40 (1H, m), 6.66–6.75 (3H, m), 7.20 (1H, m), 7.36–7.50 (5H, m), 7.97 (1H, br s). HR-MS Calcd for C₂₃H₂₆N₃O₆S₂: 504.1263. Found: 504.1271.

(*S*)-(+)-3,4-Dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)sulfinylpropoxy]-2(1*H*)-quinolinone (OPC-29030)³: Colorless solids; mp 124.0–126.0 °C. [α]_D²⁰ +19.0° (*c*=1.0, MeOH). ¹H-NMR (DMSO-*d*₆, 500 MHz) δ : 1.93–

2.06 (2H, m), 2.02 (3H, s), 2.39 (2H, t, *J*=7.3 Hz), 2.82 (2H, t, *J*=7.3 Hz), 3.38 (1H, ddd, *J*=13.8, 8.4, 6.5 Hz), 3.47 (1H, ddd, *J*=13.8, 8.4, 6.5 Hz), 4.00 (2H, t, *J*=6.1 Hz), 6.67 (1H, dd, *J*=8.6, 2.7 Hz), 6.72 (1H, d, *J*=2.7 Hz), 6.75 (1H, d, *J*=8.6 Hz), 7.34–7.38 (2H, m), 7.36 (1H, d, *J*=1.2 Hz), 7.47 (1H, ddd, *J*=7.4, 5.9, 2.4 Hz), 7.43 (1H, bd, *J*=7.4 Hz), 7.58 (1H, bd, *J*=1.2 Hz), 9.73 (1H, s). *t*_R 24.5 min (flow rate, 1.0 ml/min).

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