Switching of the Direction of Enzyme-Mediated Oxidation and Reduction of Sulfur-Substituted 2-Propanols and 2-Propanones[1]

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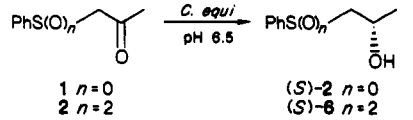
Incubation of 1-(phenylsulfenyl)- and 1-(phenylsulfonyl)-2-propanone with *Corynebacterium equi* IFO 3730 grown on hexadecane at pH 6.5 afforded the corresponding 1-substituted *S* propanols. 1-(Phenylsulfinyl)-2-propanone was also reduced by the microorganism, the product being affected by the configuration of the sulfur atom, i.e., while the *R* sulfoxide gave (R_S,S_C)-1-(phenylsulfinyl)-2-propanol, the *S* sulfoxide was oxidized first to the corresponding sulfone and then reduced to (*S*)-1-(phenylsulfonyl)-2-propanol. Adjusting the pH of the medium to 8 reversed the direction of reaction. When the *dl*-1-(phenylsulfenyl)-2-propanol was cultured with grown cells of *C. equi* in the alkaline medium, only the *S* isomer was oxidized to the corresponding ketone, the *R* enantiomer being recovered intact. On the other hand, both optical isomers of 1-(phenylsulfonyl)-2-propanol were resistant to microbial oxidation under the same conditions. A similar reactivity was observed in the case of sulfinylpropanol in that (R_C)-1-(phenylsulfinyl)-2-propanol was oxidized to the corresponding sulfone. The S_C alcohol was degraded presumably via the corresponding ketone.

In recent years, a variety of sulfur-containing chiral synthons have been utilized in asymmetric organic synthesis.[2] Chirality of sulfoxide, carbanion stabilizing effect of the sulfur atom, and facility in desulfurization after desired transformation are considered to be the main advantages of these synthons. It has been demonstrated that application of biological systems, i.e., enzymes and whole cells, is often useful in introducing chiral centers to synthetic substrates.[3] Enzyme-mediated reactions are reversible. For example, horse liver alcohol dehydrogenase has been used for oxidation of alcohols and reduction of carbonyl compounds in the presence of the appropriate cofactors.[4]. When whole cells are utilized as the enzyme source, it becomes very difficult to regulate the direction of reaction by controlling the amount of cofactors. In these cases, often other additives will influence the equilibrium to provide the desired products.[5] Changing the cultivation conditions can result in variation of reaction products.

We report here a study on the oxidation–reduction of sulfur-containing alcohols and ketones and demonstrate that the direction of reaction is very sensitive to the pH of the medium.[6] Moreover, the enzyme activity responsible for oxidation of the sulfur atom can be controlled by what is used as the carbon source for cell growth.

Reduction of α-Thio-Substituted Acetones

We have already demonstrated that *Corynebacterium equi* IFO 3730[7] oxidized a variety of sulfides to the corresponding sulfoxides and sulfones.[8] Oxidation of alkyl aryl sulfides has resulted in the formation of optically active sulfoxides.[8a,b] Because α-sulfinyl ketones are known to be synthetically useful,[2a-f,j] we tried to extend this microbial oxidation to 1-(phenylsulfenyl)-2-propanone (1). *C. equi* IFO 3730 was grown in a medium containing 1% hexadecane as the sole source of carbon. When the initial pH of the medium was adjusted to 7.2, it became 6.5 when the growth of bacterium reached its stationary phase. Then 1 was added to the cell suspension to an amount 0.1% of the medium. Unexpectedly, 1 was reduced to (*S*)-1-(phenylsulfenyl)-2-propanol ((*S*)-**2**, $[\alpha]^{20}_D$ +6.8°, *c* 0.86, MeOH) (eq 1)in a yield of 65% instead of formation



1 *n* = 0
2 *n* = 2

(*S*)-**2** *n* = 0
(*S*)-**6** *n* = 2

(1)

of the corresponding sulfoxide **3**. Its absolute configuration is *S* as determined by comparison of the specific rotation with the reported value.[9] The optical purity was determined to be over 95% after derivation as the MTPA ester.[10] It is worth mentioning that the same bacterium oxidizes aliphatic and aromatic secondary alcohols, re-

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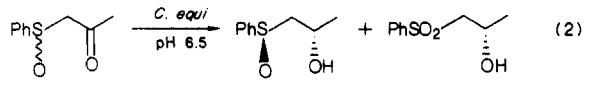
gardless of their absolute configuration, to the corresponding ketones in high yields under the same conditions.[11] The reason for this marked contrast is not clear at present, but it will be attributed to the presence of two kinds of alcohol dehydrogenase or the difference of the structure of substrates. 1-(Phenylsulfonyl)-2-propanone (**5**) was reduced in a similar manner to afford 1-(phenylsulfonyl)-2-propanol (**6**) in a yield of 97%. The value of specific rotation, $[\alpha]^{22}_D$ +7.48°, showed that it has the *S* configuration.[9] Optical yield was determined to be 76% from ^1H NMR in the presence of $Eu(TFC)_3$.

The reaction of *dl*-1-(phenylsulfinyl-2-propanone (**3**, is more complicated than those of the above two in that the reaction was divided into two paths, depending on the configuration of the sulfinyl group. While (*R*)-3 was smoothly reduced to afford (R_S,S_C)-4 in good yield (eq 2),

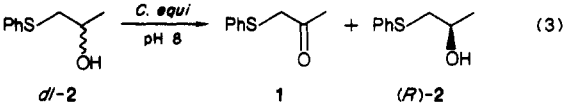


dl-3 (R_S,S_C)-4 (*S*)-6 (2)

(*S*)-**3** resulted in the formation of (*S*)-1-(phenylsulfonyl)-2-propanol ((*S*)-**6**). The stereochemistry of the resulting sulfinyl alcohol **4** was determined as follows. The alcohol **4** was oxidized with active manganese dioxide to afford 1-(phenylsulfinyl)-2-propanone of $[\alpha]^{22}_D$ +269° (MeOH) in a quantitative yield,[12] which indicates that the absolute configuration of the sulfinyl group is *R*.[9] On the other hand, deoxygenation with low-valent titanium chloride resulted in the formation of (*S*)-1-(phenylsulfenyl)-2-propanol[13] as indicated from the specific rotation: $[\alpha]^{22}_D$ +6.45° (MeOH. Diastereomeric purity of **4** was confirmed to be 95% by HPLC analysis. Two intermediates are supposed in the pathway for the formation of (*S*)-**6**; One is via (S_S,S_C)-1-(phenylsulfinyl)-2-propanol (S_S,S_C-**4**), and the other is via sulfonyl ketone **5**. To confirm this point, sulfinylpropanol (S_S,S_C)-4 was prepared via kinetic resolution of 1-(phenylsulfinyl)-2-propanone **3** by yeast reduction,[9] followed by reduction of the remaining (*S*)-**3** with diisobutylaluminum hydride in the presence of zinc chloride.[2d,f] Incubation of (S_S,S_C)-**4** with grown cells of *C. equi* for 7 days at 30 °C resulted in quantitative recovery of the substrate, which shows that this sulfinyl alcohol is only slightly oxidized by the enzyme system of *C. equi*. Thus, it is concluded that (*S*)-**3** is first oxidized to the sulfone **5** and then is reduced to *S* sulfonyl alcohol (*S*)-**6**. The above observed order for reactivities of α-thio-substituted 2-propanones is parallel to that of bakers' yeast reduction.[9]

Oxidation of α-Thio-Substituted Alcohols

In the above studies, it has become clear that the alcohol dehydrogenase system of *C. equi* catalyzed the reduction of α-thio-substituted acetones to afford *S* alcohols when incubation was carried out at pH 6.0–6.5. Then are there any methods for obtaining *R* alcohols by using the same bacterium? Alcohol dehydrogenases are capable of catalyzing both reduction of carbonyl compounds and oxidation of the corresponding alcohols, thus it might be possible to reverse the direction of reaction by some alteration of reaction (cultivation) conditions. To our surprise, the solution involved simply a change in the pH of the medium to weakly alkaline (8). When *dl*-1-(phenylsulfenyl)-2-propanone (**2**) was added to the suspension of grown cells of *C. equi* in the medium adjusted to pH 8 by the addition of aqueous sodium hydroxide (eq 3), it resulted in the



dl-2 1 (*R*)-2 (3)

formation of ketone **1** (50%) and (*R*)-1-(phenylsulfenyl)-2-propanol ((*R*)-**2**) (50%). This result might be ascribed to the action of the same enzyme that catalyzed the reduction of the carbonyl group. When the substrate is incorporated in the active site of the enzyme system, it is supposed that the configuration of the substrate will be the same in the transition state of the reduction/oxidation of the substrate (alcohol or ketone) and the direction of attacking and leaving hydride (or an electron) will be the same (Figure 1). In the case of reduction of **1**, hydride attacks on the *re* face of the carbonyl group to form *S* alcohol. In the case of oxidation of alcohol **2**, hydride will leave on the *re* face of developing carbonyl group. Thus, *S* alcohol **2** will be oxidized preferentially, the *R* alcohol being recovered intact. This was observed in the experiment. The optical purity of recovered (*R*)-**2** was over 95%. Under the same conditions, (*S*)-1-(phenyl sulfonyl)-2-propanol ((*S*)-**6**), as well as its antipode (*R*)-**6**, was not oxidized to the ketone **5**. The equilibrium is presumed to lie to the reduced form, regardless of the pH of the medium.

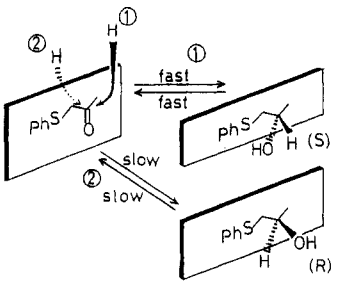
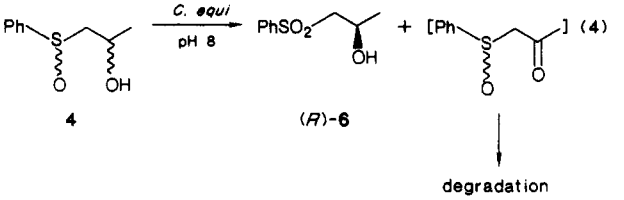


Figure 1.

The reactions of sulfinyl alcohol **4** were again disappointing, because four stereoisomers are possible for this alcohol. When a stereoisomeric mixture of sulfinyl alcohol **4** was incubated with the grown cells of *C. equi* for 7 days, the only product isolated was (*R*)-1-(phenylsulfonyl)-2-propanol (yield 25%, 95% ee $[\alpha]^{23}_D$ −13° in methanol) (eq 4). As mentioned above, both enantiomers of sulfonyl



4 (*R*)-**6**

alcohol **6** are stable under the cultivation conditions; the results indicate that the sulfinyl group of only the R_C epimer have been oxidized to the corresponding sulfone (*R*)-**6**. It is not clear whether both (S_S,R_C)-**4** and (R_S,R_C)-**4** afford (*R*)-**6** or either diastereomer of the two results the product **6**, but the chemical yield of (*R*)-**6** and the fact that racemic sulfinyl ketone **3** gave (R_S,S_C)-**4** and (*S*)-**6** suggest that the origin of (*R*)-**6** in this experiment would be (S_S,R_C)-**4**. Products that are expected to be generated from other diastereomers of sulfinyl alcohol **4** could not be isolated from the broth. The most probable primary products are *R* and *S* sulfinyl ketones **3**. These ketones are estimated to be degraded enzymatically under the

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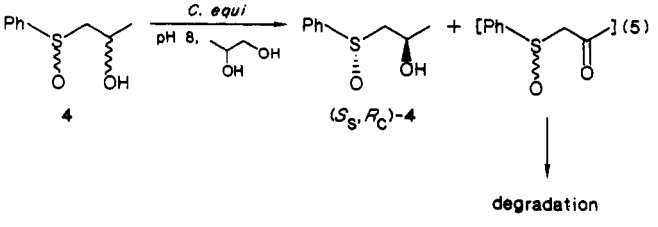
cultivation conditions employed via unidentified intermediates. In a control experiment, incubation of *dl*-**3** with grown cells of *C. equi* at pH 8 showed that the substrate is completely metabolized in 7 days. On the other hand, when *dl*-**3** was shaken under the same conditions but without the microorganism, 95% of the ketone was recovered intact.

Effect of Carbon Sources

Studies have so far revealed that not only alcohol dehydrogenase but also a sulfoxide oxidizing enzyme acts on some isomers of 1-(phenylsulfinyl)-2-propanone and -propanol. This enzyme is assumed to be induced in the cell in the process of metabolizing hexadecane. Because metabolism of hydrocarbon requires a number of oxidizing enzymes, such as monooxygenase and dehydrogenase, it is natural to suppose that the activity of the enzyme responsible for the oxidation of the sulfoxide moiety will increase during the hydrocarbon degradation. If this is correct, the use of a carbon source that is higher in oxidation state than the hydrocarbons will bring about a change in reaction course. 1,2-Propanediol was selected for this purpose because *C. equi* shows good growth by assimilating this diol. As it already has C–O bonds, this diol may then not require oxygenases in its metabolic pathway. Thus, it is expected that the activity of the enzymes of interest may be relatively low for the diol-grown cells. *erythro*- and *threo*-1-(phenylsulfinyl)-2-propanols **4** were prepared and subjected separately to the microbial transformation. The starting materials were obtained readily by the reduction of 1-(phenylsulfinyl)-2-propanone (**3**) with diisobutylaluminum hydride[2d,f] in the presence or absence of zinc chloride. As expected, some products having the sulfoxide moiety were isolated by the incubation with *C. equi* grown on 1,2-propanediol. *erythro*-1-(Phenylsulfinyl)-2-propanol (mixture of (R_S,R_C)-**4** and (S_S,S_C)-**4**) afforded on 3-day incubation a mixture of (*S*)-1-(phenylsulfinyl)-2-propanone ((*S*)-**3** 12% ee) and (R_S,R_C)-1-(phenylsulfinyl)-2-propanol ((R_S,R_C)-**4**, 23% ee) totaling 53%. The low optical purities of resulting (*S*)-**3** and recovered (R_S,R_C)-**4** show that a part of (R_S,R_C)-**4** is also oxidized to ketone **3** in 3 days. Low total yield of recovered material is ascribed to the degradation of **3** without the intermediary formation of sulfonyl ketone **5**. On the other hand the reactivity of *threo*-1-(phenylsulfinyl)-2-propanol ((R_S,S_C)-**4** and (S_S,R_C-**4**)) is relatively low. Under the same conditions, virtually all the starting alcohol was recovered intact after incubation for 3 days. Then a mixture of four diastereomeric isomers was subjected to the microbial reaction for 7 days. In this case, about 30% of starting sulfinyl alcohol **4** was recovered, and no sulfonyl compounds were detected in the broth. The obtained **4** was revealed to be diastereomerically pure *threo* isomer, demonstrating that all *erythro*-**4** was degraded regardless of the configuration of the hydroxyl-linked carbon. The configuration of the recovered **4** was found to the S_S,R_C (eq 5) of 90% purity by derivation to (*S*)-1-



propanone ((*S*)-**3**) and (*R*)-1-(phenylsulfonyl)-2-propanol ((*R*)-**6**) as described above. The antipode of this diastereomer has been already obtained by reduction of racemic sulfinyl ketone **3** (vide supra).

Thus, six of eight possible stereoisomers of 1-sulfur-substituted 2-propanol of various oxidation states on the sulfur atom were obtained by microbial oxidation–reduction with *C. equi* IFO 3730. The remaining two isomers, i.e., two *erythro* isomers of sulfinyl alcohol **4**, can be prepared by reduction of *R* and *S* sulfinyl ketone **3** with a diisobutylaluminum hydride–zinc chloride system.[2d,f] In conclusion, it is interesting to note that various stereoisomers of sulfur-containing propanol and propanone derivatives can be prepared by using one bacterium in slightly different cultivation conditions.

Experimental Section

General Procedures. ^{1}H NMR spectra were measured with Me_4Si as internal standard on Varian EM-390. IR spectra were recorded with a Jasco A-202 spectrophotometer. Mass spectra were obtained with a Hitchi M-80 instrument. Optical rotations were measured with a Jasco DIP-4 polarimeter. HPLC data were taken on a Schimadzu LC-5A high-performance liquid chromatograph. The assays were performed by using a Develosil ODS-5 column, with H_2O/MeOH/THF (35:10:0.5) as the mobile phase and detection by UV absorption at 254 nm. The following silica gels were used: Kieselgel 60 F_{254} (Merck) for analytical TLC, Wakogel B-5F (Wako Chemical) for preparative TLC, and Wakogel C-200 for column chromatography. Melting points and boiling points were not corrected.

Basal Medium for Microbial Transformation. The composition of the basal medium was as follows: $(NH_4)_2HPO_4$, 10 g; K_2HPO_4, 2 g; $MgSO_4 \cdot 7H_2O$, 0.3 g; $FeSO_4 \cdot 7H_2O$, 10 mg; $ZnSO_4 \cdot 7H_2O$, 8 mg; $MnSO_4 \cdot nH_2O$, 8 mg; and yeast extract, 0.2 g in 1 L of distilled water. The initial pH of the medium was adjusted to 7.2 with 2 N HCl.

Seed Culture. To a sterilized 500-mL Sakaguchi flask containing 100 mL of the basal medium was added 2 mL of hexadecane as the sole carbon source. The mixture was inoculated with a loopful of *C. equi* IFO 3730 from a nutrient slant. The flask was shaken on a reciprocatory shaker at 30 °C for 3 days. This suspension was used as the seed culture for further reactions. In the case of the enzymatic reaction carried out with cells grown on 1,2-propanediol, the same diol was employed as the carbon source for the seed culture.

Microbial Reduction of 1-(Phenylsulfenyl)-2-propanone (1). Preparation of (*S*)-1-(Phenylsulfenyl)-2-propanol ((*S*)-2). To a 500-mL Sakaguchi flask were added the sterilized basal medium (95 mL), hexadecane (2 mL), and a suspension of the seed culture of *C. equi* (5 mL). The mixture was incubated for 2 days at 30 °C on a reciprocatory shaker. To the resulting suspension of grown cells, 1-(phenylsulfenyl)-2-propanone (**1**; 100 mg, 0.60 mmol) was added, and the incubation was continued for additional 7 days. The broth was extracted with a 200-mL portion of ethyl acetate three times. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The mixture was subjected to column chromatography on silica gel to remove unaffected hexadecane by elution with hexane. The sulfur-containing compounds were obtained (total yield, 102 mg) as fractions eluted with ethyl acetate and further purified by preparative TLC on silica gel. The product was identified as 1-(phenylsulfenyl)-2-propanol (**2**; yield, 65%) by comparison of its IR and ^{1}H NMR spectra with those of racemic specimen. The optical purity of (*S*)-**2** was determined by derivatization to Mosher's ester ((*R*)-(+)-MTPA ester).[10] The CH_3 signal (δ 1.42) due to only one diastereomer was observed in the ^{1}H NMR spectrum compared with that of *dl*-**2** (δ 1.36 and 1.42). Thus, the optical purity of (*S*)-**2** was determined to be over 95%. The absolute configuration of **2** was determined to be *S* from its specific rotation: $[\alpha]^{20}_D$ +6.75° (*c* 0.86, MeOH), +8.20° (*c* 0.59, MeOH, 94% ee);[9] ^{1}H NMR of (*R*)-(+)-MTPA ester of *dl*-**2** δ 1.36 and 1.42 (d, J = 7 Hz, 3 H), 3.01 (m, 2 H), 3.56 (br s, 3 H), 5.17 (m, 1 H), 7.02–7.65 (m, 10 H); from (*S*)-**2** δ 1.42 (d, J = 7 Hz, 3 H), 3.00 (m, 2 H), 3.52 (br s, 3 H), 5.10 (m, 1 H), 7.00–7.70 (m, 10 H).

Microbial Reduction of 1-(Phenylsulfonyl)-2-propanone (5). Preparation of (*S*)-1-(Phenylsulfonyl)-2-propanol

((*S*)-6). To 100 mL of 2-day-old culture broth of *C. equi* was added 1-(phenylsulfonyl)-2-propanone (**5**; 100 mg, 0.51 mmol), and the incubation was continued for 7 days at 30 °C. After extraction with ethyl acetate, products were purified by preparative TLC on silica gel to give reduced product (*S*)-**6** (98 mg, 97%), which showed the same peaks on IR and ^{1}H NMR spectra with those of racemic 1-(phenylsulfonyl)-2-propanol (**6**). Its ^{1}H NMR spectrum in the presence of chiral shift reagent Eu(TFC)$_3$ revealed its optical purity to be 76%. The ortho protons on the benzene ring of *dl*-**6** split in two multiplets centered at δ 8.65 and 8.90 in the presence of 0.3 equiv of Eu(TFC)$_3$. The peak at lower field was stronger for the optically active **6**. Absolute configuration of the product **6** was determined to be *S* from its positive specific rotation: $[\alpha]^{22}_D$ +7.48° (*c* 6.05, MeOH), $[\alpha]^{28.5}_D$ +15° (*c* 1.1, MeOH, 95% ee).[9]

Microbial Reduction of *dl*-1-(Phenylsulfinyl)-2-propanone (3). Preparation of (R_S,S_C)-1-(Phenylsulfinyl)-2-propanol ((R_S,S_C)-4) and (*S*)-1-(Phenylsulfonyl)-2-propanol ((*S*)-6). To 100-mL of 2-day-old culture broth of *C. equi* was added *dl*-1-(phenylsulfinyl)-2-propanone (*dl*-**3**; 100 mg, 0.55 mmol). Incubation of the mixture for 7 days, followed by the usual extraction and column chromatography on silica gel using a mixture of hexane and ethyl acetate as eluent, afforded 110 mg of crude sulfur-containing products. After further purification with preparative TLC, the products were identified as (R_S,S_C)-1-(phenylsulfinyl)-2-propanol ((R_S,S_C)-**4**; 38.4 mg, 38%) and (*S*)-1-(phenylsulfonyl)-2-propanol ((*S*)-**6**; 68.2 mg, 62%) by comparison of IR and ^{1}H NMR spectra with those of racemic ones. The diastereomeric ratio of sulfinyl alcohol **4** was determined to be threo:erythro = 95:5 by HPLC analysis; retention time threo, 12.9 min, erythro, 11.5 min. Specific rotation was $[\alpha]^{22}_D$ +214% (*c* 1.09, EtOH).

The sulfonyl alcohol (*S*)-**6** exhibited specific rotation of $[\alpha]^{22}_D$ +7.4° (*c* 4.7, MeOH). The optical purity of **6** was revealed to be 84% by its ^{1}H NMR spectra using chiral shift reagent Eu(TFC)$_3$ (vide supra).

Oxidation of (R_S,S_C)-1-(Phenylsulfinyl)-2-propanol ((R_S,S_C)-4) Obtained by Microbial Reaction with Active Manganese Dioxide.[12] To a stirred solution of excess active manganese dioxide (400 mg, 4.5 mmol) in dry acetone (5 mL) was added a solution of (R_S,S_C)-**4** (83 mg, 0.45 mmol) in dry acetone (5 mL) at room temperature. The stirring was continued overnight at room temperature. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was purified by preparative TLC on silica gel to give (*R*)-**3** as colorless powders (82 mg, 100%): mp 65–67 °C; $[\alpha]^{22}_D$ +269° (*c* 0.8, MeOH); −254° (*c* 1, MeOH for (*S*)-**3**).[9]

Reduction of (R_S,S_C)-1-(Phenylsulfinyl)-2-propanol ((R_S,S_C)-4) Obtained by Microbial Reaction with Low-Valent Titanium Chloride.[13] To a stirred solution of 46 mg (0.25 mmol) of (R_S,S_C)-**4** obtained by reduction with *C. equi* in a mixture of diethyl ether and dichloromethane (4:1 v/v, 5 mL) were added zinc powder (65 mg, 1 mmol) and titanium tetrachloride (0.1 mL, 1 mmol) dropwise, with cooling in an ice–water bath. After 1 min, the reaction was quenched by the addition of excess water. The mixture was extracted with diethyl ether (3 × 5 mL). The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure afforded reduced alcohol (*S*)-1-(phenylsulfenyl)-2-propanol ((*S*)-**2**) in a yield of 41 mg (90%) as identified by IR and ^{1}H NMR spectra : $[\alpha]^{25}_D$ +6.45° (*c* 0.8, MeOH).

Microbial Oxidation of *dl*-1-(Phenylsulfenyl)-2-propanol (2). Preparation of (*R*)-1-(Phenylsulfenyl)-2-propanol ((*R*)-2). A 2-day-old culture broth of *C. equi* (100 mL) grown on hexadecane was adjusted to pH 8.0 with 2 N NaOH. To this broth was added *dl*-1-(phenylsulfenyl)-2-propanol (*dl*-**2**: 100 mg, 0.59 mmol), and the incubation was continued for an additional 7 days at 30 °C. After the usual extraction, the products were purified by preparative TLC on silica gel. Oxidized ketone **1** and unreacted substrate **2** were obtained in yields of 50%, respectively. Recovered substrate was confirmed to have *R* configuration by its sign of specific rotation: $[\alpha]^{22}_D$ −6.42° (*c* 0.87, MeOH). The optical purity was determined to be over 95% by the ^{1}H NMR spectrum of (*R*)-(+)-MTPA ester: δ 1.33 (d, J = 7 Hz, 3 H), 3.00 (m, 2 H), 3.52 (br s, 3 H), 5.15 (m, 1 H), 7.05–7.60 (m, 10 H). The signals due to the methyl group of the (*R*)-(+)-MTPA ester of *dl*-**2** were observed at δ 1.36 and 1.42 as mentioned above.

Microbial Oxidation of 1-(Phenylsulfinyl)-2-propanol. Preparation of (*R*)-1-(Phenylsulfonyl)-2-propanol ((*R*)-6). A suspension of 2-day-old culture broth of *C. equi* (100 mL) was adjusted to pH 8.0 with 2 N NaOH. *dl*-1(Phenylsulfinyl)-2-propanol (*dl*-**4**; 100 mg, 0.54 mmol) was added to this broth, and the incubation was continued for an additional 7 days. Extraction with ethyl acetate, washing with brine, and removal of solvent afforded an oily product, which was purified by preparative TLC on silica gel. Sulfonyl alcohol (*R*)-**6** was obtained as a major product (24.5 mg, 23%). It was identified by comparison of IR, NMR, and mass spectra with those of racemic **6**. Optical purity of **6** was determined to be over 95% by its ^{1}H NMR spectra using chiral shift reagent Eu(TFC)$_3$ (vide supra). The absolute configuration of this sulfonyl alcohol was unambiguously determined to be *R* from its specific rotation: $[\alpha]^{25}_D$ −13.9° (*c* 0.36, MeOH).

Microbial Oxidation of *erythro*-1-(Phenylsulfinyl)-2-propanol (*erythro*-4) by *C. equi* Grown on 1,2-Propanediol. To 100 mL of 2-day-old culture broth of *C. equi* grown on 1,2-propanediol as a sole source of carbon was added *erythro*-1-(phenylsulfinyl)-2-propanol (*erythro*-**4**; 100 mg, 0.55 mmol), and the incubation was continued for 3 days at 30 °C. After the usual extraction and chromatography, oxidized sulfinyl ketones **3** (22.4 mg, 22%) and unreacted substrate **4** (31.7 mg, 31%) were obtained as identified by IR and ^{1}H NMR spectroscopic comparison with authentic samples. Oxidized product **3** was determined to have absolute configuration of *S* by its specific rotation: $[\alpha]^{27}_D$ −84.5° (*c* 1.12, MeOH). Recovered substrate *erythro*-**4** was confirmed to be enriched by *R*,*R* configuration by its specific rotation: $[\alpha]^{27}_D$ +18.1° (*c* 1.58, MeOH).

Oxidation of 1-(Phenylsulfinyl)-2-propanol (4) with *C. equi* Grown on 1,2-Propanediol. Preparation of (S_S,R_C)-1-(Phenylsulfinyl)-2-propanol ((S_S,R_C)-4). To a 500-mL Sakaguchi flask were added 95 mL of the sterilized basal medium, 0.5 mL of 1,2-propanediol, and 5 mL of the seed culture of *C. equi*. This mixture was incubated for 2 days at 30 °C on a reciprocatory shaker. The pH of the resulting suspension of grown cells was adjusted to 8 by addition of 2 N NaOH. To this broth was added a stereoisomeric mixture of 1-(phenylsulfinyl)-2-propanol (**4**; 100 mg, 0.55 mmol), and shaking was continued for additional 7 days at 30 °C. After the usual extraction, the products were purified by preparative TLC on silica gel to give (S_S,R_C)-**4** as an oil (31.3 mg, 60%): $[\alpha]^{22}_D$ −287° (*c* 1.6, MeOH). Its diastereomeric ratio was determined to be >99:1 (threo:erythro) by HPLC analysis. Reduction of this sulfinyl alcohol with titanium tetrachloride–zinc gave (*R*)-1-(phenylsulfenyl)-2-propanol ((*R*)-**2**)): $[\alpha]^{20}_D$ −6.12° (*c* 0.85, MeOH). Optical purity of the resulting (*R*)-**2** was revealed to be 90% by ^{1}H NMR spectrum of its (*R*)-(+)-MTPA ester (vide supra).

Reduction of *dl*-1-(Phenylsulfinyl)-2-propanone (*dl*-3) with Bakers' Yeast. Preparation of (R_S,S_C)-1-(Phenylsulfinyl)-2-propanol ((R_S,S_C)-4) and (*S*)-1-(Phenylsulfinyl)-2-propanone ((*S*)-3). According to the procedures described by Iriuchijima et al., (R_S,S_C)-**4** and (*S*)-**3** were obtained by reduction of *dl*-**3** with bakers' yeast.[9] Bakers' yeast (*Saccharomyces cerevisiae*, purchased from Oriental Yeast Co., 7.5 g), and sucrose (20 g) were stirred in tap water (50 mL). Fifteen minutes later, *dl*-**3** (1.5 g, 8.2 mmol) was added with vigorous stirring, and the mixture was stirred overnight at room temperature. The mixture was filtered through Celite, and the filtrate was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The mixture was subjected to flash column chromatography on silica gel. (R_S,S_C)-1-(Phenylsulfinyl)-2-propanol ((R_S,S_C)-**4**) and unaffected (*S*)-1-(phenylsulfinyl)-2-propanone ((*S*)-**3**) were obtained in yields of 35% and 11%, respectively. ^{1}H NMR and IR spectra of these compounds were identical with those of the reported values.

Preparation of (S_S,R_C)-1-(Phenylsulfinyl)-2-propanol ((S_S,R_C)-4).[2d] To a solution of (*S*)-1-(phenylsulfinyl)-2-propanone ((*S*)-**3**; 54.6 mg, 0.3 mmol) in THF (5 mL) was added a solution of diisobutylaluminum hydride in hexane (0.29 mL, 0.3 mmol) dropwise with stirring at −78 °C under an atmosphere of argon. After 15 min, phosphate buffer (pH 7) and NaF (0.5 g) were added to quench the reaction. The mixture was stirred for 2 h at 0 °C and filtered through Celite. The organic layer was washed with

brine and a 3% aqueous solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced presure gave an oily residue, which was purified on silica gel chromatography to afford (S_C,R_C)-1-(phenylsulfinyl)-2-propanol ((S_S,R_C)-4) in a yield of 48 mg (95%) as a colorless powder: mp 134–135 °C. ^1H NMR and IR spectra were identical with that obtained by yeast reduction. The diastereomeric ratio was determined to be 95:5 (threo:erythro) by HPLC analysis.

Preparation of (S_S,S_C)-1-(Phenylsulfinyl)-2-propanol ((S_S,S_C)-4).[2d,f] To a solution of (*S*)-**3** (54.6 mg, 0.3 mmol) and zinc chloride (61 mg, 0.45 mmol) in THF (5 mL) was added a solution of diisobutylaluminum hydride in hexane (0.29 mL, 0.3 mmol) dropwise at −78 °C under an atmosphere of argon. After 15 min, phosphate buffer (pH 7) was added to quench the reaction. The same treatment as for (S_S,R_C)-4 afforded (S_S,S_C)-1-(phenylsulfinyl)-2-propanol ((S_S,S_C-4) as a colorless powder in a yield of 90%: mp 40 °C; ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 6 Hz, 3 H), 2.83 (m, 2 H), 3.73 (br s, 1 H), 4.48 (m, 1 H), 7.56 (m, 5 H); IR (film) 3350, 2945, 1470, 1315, 1125, 1092, 1055, 1005, 760, 680 cm^{-1}. The diastereomeric ratio was 95:5 (erythro:threo) as determined by HPLC analysis.

1-(Phenylsulfenyl)-2-propanone (1). To a stirred solution of sodium benzenethiolate (80 mmol) in methanol (80 mL) was added chloroacetone (7.4 g, 80 mmol) dropwise over a period of 5 min. The mixture was stirred overnight at room temperature. After the usual workup, the crude oily product was distilled under reduced pressure to give 11.9 g (90%) of **1** as a colorless oil: bp 117 °C (5 mmHg); ^1H NMR (CCl_4) δ 2.20 (s, 3 H), 3.50 (s, 2 H), 7.00–7.40 (m, 5 H); IR (film) 3070, 3000, 2910, 1710, 1580, 1480, 1360, 1230, 1150, 740, 690 cm^{-1}; MS, m/e (rel intensity) 77 (15), 109 (26), 123 (100), 166 (78, M^+).

1-(Phenylsulfenyl)-2-propanol (2). To a stirred solution of thiophenol (5.5 g, 50 mmol) and triethylamine (5.56 g, 55 mmol) in diethyl ether (140 mL) was added 1,2-epoxypropane (2.90 g, 50 mmol) at room temperature over a period of 5 min. The resulting mixture was stirred overnight. After the usual workup, the crude oily mixture was distilled in vacuo to give 7.30 g (87%) of **2** as a colorless oil: bp 95–98 °C (0.45 mmHg); ^1H NMR (CCl_4) δ 1.23 (d, J = 7.2 Hz, 3 H), 2.30 (br s, 1 H), 3.27 (m, 2 H), 3.80 (m, 1 H), 7.15–7.50 (m, 5 H); IR (film 3400, 2985, 1585, 1480, 1440, 1375, 1130, 1070, 935, 740, 690 cm^{-1}; MS, m/e (rel intensity) 45 (100), 77 (50), 109 (87), 123 (33), 168 (38, M^+).

1-(Phenylsulfinyl)-2-propanone (3). A solution of perbenzoic acid in chloroform (0.33 M, 30.3 mL, 10 mmol) was reacted with 1-(phenylsulfenyl)-2-propanone (1.66 g, 10 mmol) at 0 °C for 1 h. The mixture was poured into 50 mL of an aqueous solution of $NaHCO_3$ and extracted with dichloromethane (150 mL × 3). The organic layer was washed sequentially with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by recrystallization from hexane–dichloromethane afforded **3** as colorless crystals in a yield of 1.76 g (97%): mp 69–70 °C; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.80 (s, 2 H), 7.20–7.70 (m, 5 H); IR (KBr disk) 2950, 1705, 1440, 1360, 1340, 1040, 995, 750, 730, 690 cm^{-1}; MS, m/e (rel intensity) 27 (20), 43 (42), 51 (55), 77 (59), 97 (49), 125 (100), 182 (26, M^+).

1-(Phenylsulfinyl)-2-propanol (4). To a solution of 1-(phenylsulfenyl)-2-propanol (**2**; 3.36 g, 20 mmol) in acetic acid (20 mL) was added 35% hydrogen peroxide (1.97 g, 20 mmol) dropwise with stirring in an ice–water bath. The resulting mixture was stirred for 3 h at the same temperature and poured into an aqueous solution of K_2CO_3. The mixture was extracted with dichloromethane (100 mL × 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude crystalline mixture was purified by column chromatography to afford 3.68 g (100%) of a diastereomeric mixture of **4** as colorless powders: mp 42–140 °C; ^1H NMR ($CDCl_3$) δ 1.18, 1.35 (d, J = 6.3 Hz, 3 H), 2.89 (m, 2 H), 4.37 (m, 1 H), 4.68 (s, 1 H), 7.32–7.96 (m, 5 H); IR (KBr disk) 3355, 2947, 1450, 1315, 1120, 1090, 1050, 1020, 755, 690 cm^{-1}; MS, m/e (rel intensity) 28 (60), 51 (45), 59 (36), 78 (92), 91 (27), 126 (100), 187 (12, $(M + H)^+$).

1-(Phenylsulfonyl)-2-propanone (5). To a stirred solution of 1-(phenylsulfenyl)-2-propanone (**1**); (1.54 g, 10 mmol), catalytic amounts of Na_2WO_4, and cetyltrimethylammonium chloride in dichloromethane (50 mL) was added dropwise 35% hydrogen peroxide (2.42 g, 25 mmol) with vigorous stirring at room temperature. The resulting mixture was stirred at room temperature for 24 h. After the usual workup, recrystallization from hexane–dichloromethane afforded 1.97 g (99%) of **5** as colorless powders: mp 46–47 °C, ^1H NMR ($CDCl_3$) δ 2.43 (s, 3 H), 4.17 (s, 2 H), 7.40–8.00 (m, 5 H); IR (KBr disk) 2735, 1730, 1585, 1295, 1150, 840, 745, 725, 690, 625 cm^{-1}; MS, m/e (rel intensity) 43 (49), 51 (23), 77 (100), 91 (26), 134 (87), 141 (58), 156 (36), 199 (25, $(M + H)^+$).

1-(Phenylsulfonyl)-2-propanone (6). To a stirred solution of 1-(phenylsulfenyl)-2-propanol (**2**; 3.36 g, 20 mmol) in acetic acid (20 mL) was added 35% hydrogen peroxide (4.8 g, 50 mmol) at room temperature. The resulting mixture was stirred overnight and treated in a similar manner as in the case of **4** to afford **6** as colorless powders: mp 39–41 °C; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.6 Hz, 3 H), 2.05 (br s, 1 H), 3.96 (m, 2 H), 4.38 (m, 1 H), 7.50–8.11 (m, 5 H); IR (KBr disk) 3530, 2985, 1585, 1495, 1450, 1300, 1140, 1080, 940, 750, 690 cm^{-1}; MS, m/e (rel intensity) 58 (54), 77 (100), 91 (53), 125 (32), 141 (85), 156 (77); 183 (33), 201 (44, $(M + H)^+$).

Addition of Organometallic Reagents to Cyclooctenyl Phenyl Sulfones[1]

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A series of cyclooctenyl and cyclooctadienyl phenyl sulfones were prepared and exposed to various organometallic reagents. The regio- and stereochemical results of these reactions are outlined below. The cuprate-induced reduction of epoxy vinyl sulfones **17** and **29** was explored; a mechanism involving two one-electron transfers was implicated.

Molecules containing an eight-membered carbocyclic ring remain a synthetic challenge. The theoretical and medicinal interest in compounds such as dactylol (**1**), albolic acid (**2**), stegnanacin (**3**), pleuromutilin (**4**), and acetoxycrenulide (**5**) has resulted in a plethora of synthetic approaches to these[2-6] and other similar targets (Scheme

(1) Synthesis via Vinyl Sulfones. 23. For the previous paper in this series, see: Hutchinson, D. K.; Fuchs, P. I., submitted for publication in *J. Am. Chem. Soc.*

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