the solution at RT under nitrogen. After stirring for 1 min, $AgSbF_6$ (0.02 mmol in $ClCH_2CH_2Cl$) was added to the mixture. The reaction was completed within 5 min. The reaction mixture was directly subjected to column chromatography, from which (+)-**4a** (24.9 mg, 87%, over 99% *ee*)[20] was obtained. The *ee* value was determined by HPLC with an OJ-H column (hexane:isopropanol = 95:5, 1 mL min^{-1}, 254 nm). $[\alpha]_D^{25} = +3.52$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.28$–7.16 (m, 5H), 5.85 (dt, $J = 2.2$, 5.9 Hz, 1H), 5.58–5.53 (m, 1H), 5.08–5.02 (m, 2H), 4.80–4.77 (m, 2H), 4.61 (s, 2H), 4.48 (d, $J = 14.6$ Hz, 1H), 4.35 (d, $J = 14.6$ Hz, 1H), 3.32 ppm (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) $\delta = 167.72$, 137.76, 136.57, 134.50, 129.13, 128.65, 128.07, 118.00, 96.84, 95.57, 64.04, 54.54, 50.22, 47.15, 42.17 ppm; MS *m/z*: 288.1 [M^++1]; HRMS (APCI) calcd for $C_{17}H_{22}NO_3$ [M^++1)]: 288.1600; found: 288.1603.

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Mechanistic Studies of HPP Epoxidase: Configuration of the Substrate Governs Its Enzymatic Fate**

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Non-heme iron-dependent enzymes are an important class of catalysts involved in many biological transformations of medical, pharmaceutical, and environmental significance. Although considerable progress has been made in our understanding of their catalyses, characterization of the metal centers and the modes of dioxygen activation remain a challenge because of the great structural and mechanistic diversity found among these enzymes.[1] Recently, HPP epoxidase,[2] an enzyme in the biosynthetic pathway of the antibiotic fosfomycin, was recognized as a new member of this enzyme family.[3] This epoxidase performs the final transformation in the fosfomycin biosynthesis by converting (*S*)-2-hydroxypropylphosphonic acid (HPP, (*S*)-**1**) to (1*R*,2*S*)-epoxypropylphosphonic acid (**2**), also known as fosfomycin

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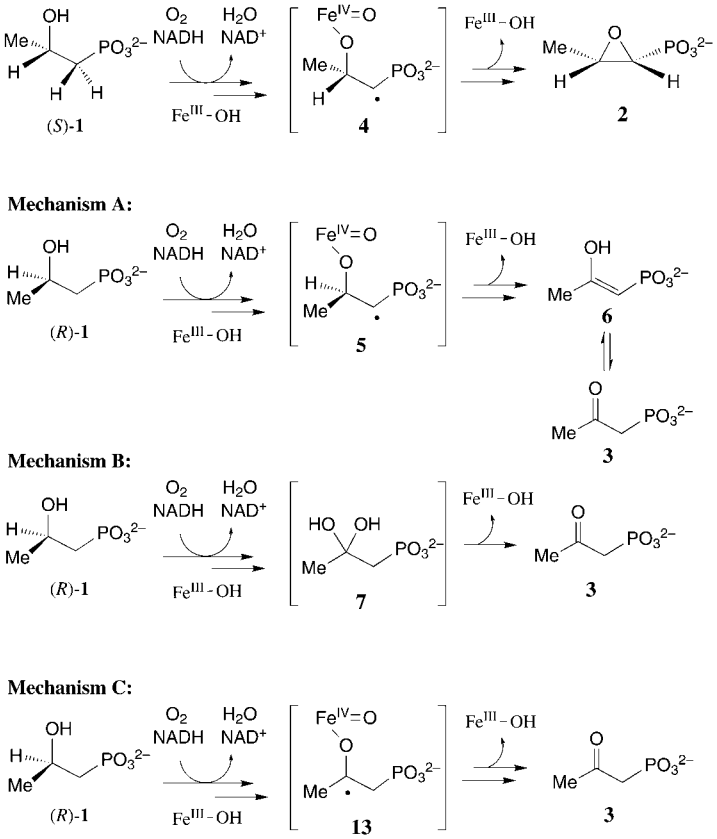
(Scheme 1). The epoxidation catalyzed by HPP epoxidase is unusual since it is effectively a dehydrogenation of a secondary alcohol ((*S*)-**1**→**2**).[3–5]

Recent studies of HPP epoxidase from *Streptomyces wedmorensis* revealed that this enzyme is a mononuclear non-heme iron-containing catalyst, and unlike most other enzymes in the same class, its activity is α-ketoglutarate-independent.[3] The conversion of (*S*)-**1** into **2** consumes NADH wherein the ultimate oxidant is dioxygen. While a reductase is required to mediate the transfer of the reducing equivalents, alternative electron carriers, such as FMN and FAD, have been shown to be competent substitutes for NADH.[3] Several mechanisms are conceivable for this intriguing transformation in which an iron–oxo intermediate has been proposed to be the reactive species that triggers the reaction, and the catalysis probably involves radical intermediates.[3] To gain more insight into the functioning of HPP epoxidase, a study of the stereospecificity of this enzyme was carried out. Reported herein are the results and the mechanistic implications of our investigation.

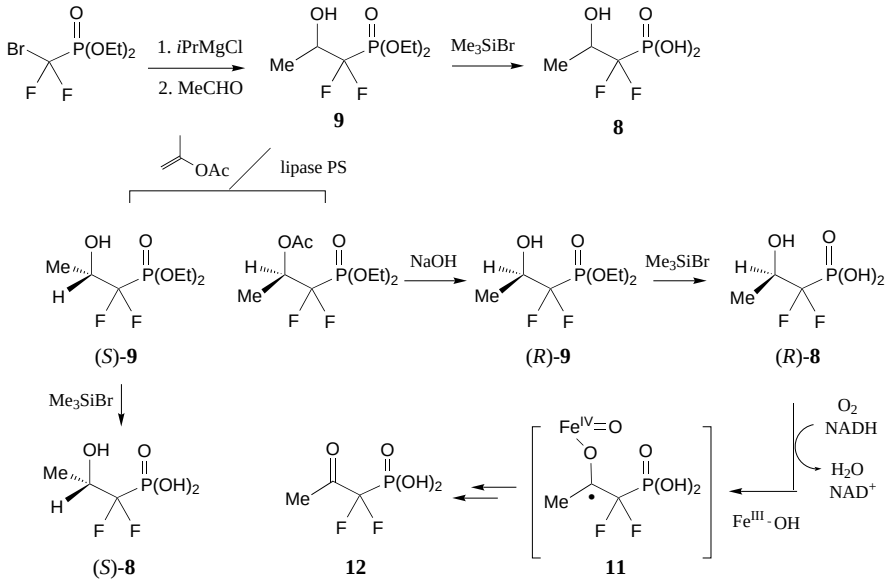
Our interest in this subject was inspired by the observation that incubation of racemic HPP with HPP epoxidase in high concentration resulted in the total consumption of all substrate to generate fosfomycin and a new product in 1:1 ratio. Since it has been established that (*S*)-HPP ((*S*)-**1**) is the immediate precursor of fosfomycin (**2**), the new product is probably derived from the oxidation of (*R*)-HPP ((*R*)-**1**) by HPP epoxidase. Subsequently, enantiomerically pure (*R*)-**1** was chemically prepared (> 97 % *ee*),[6] which, upon incubation with the epoxidase, led to 2-oxopropylphosphonic acid (**3**) as the sole product (Scheme 1).[7] The turnover rates for (*R*)-**1** and (*S*)-**1** were determined to be (162 ± 7) and (149 ± 2) nmol mg^{-1} min^{-1}, respectively, under our assay conditions.[8] Clearly, HPP epoxidase is not selective with regard to substrate recognition, but can stereospecifically convert each enantiomer into a unique product with similar efficiency.

As depicted in Scheme 1, the key step in the formation of fosfomycin from (*S*)-HPP may involve the abstraction of an α-H atom from (*S*)-**1** by a reactive iron–oxo species (formation of **4**), followed by a radical-induced homolytic cleavage of the Fe–O bond in **4** to produce **2**. Thus, an analogous route initiated by the generation of the α radical **5**, followed by the abstraction of a β-H atom and tautomerization of the resulting enol **6** can be envisioned for the conversion of (*R*)-**1** into **3** (Scheme 1, mechanism A). Alternatively, a direct hydroxylation–dehydration at β-C of (*R*)-**1** via a *gem*-diol intermediate (**7**) could also explain the formation of **3** (Scheme 1, mechanism B).[9] To probe these possibilities, an HPP sample ^{13}C-labeled at β-C ([2-^{13}C]HPP)[10] and an HPP analogue carrying two fluorine atoms at α-C (1,1-difluoro-HPP, **8**)[11] were prepared (Scheme 2). The ^{13}C-labeled HPP was designed to facilitate the detection of hydroxy incorporation at C-2, and the difluoro derivative **8** was expected to be an inhibitor if α radical formation is a prerequisite for the catalysis.



Scheme 1. The oxidation of (*S*)-**1** by HPP epoxidase and three possible mechanisms for the oxidation of (*R*)-**1** by the same enzyme. The phosphonic acids are shown as dianions although strictly speaking the formula numbers refer to the protonated forms.

Upon treatment with HPP epoxidase under an $^{18}O_2$ atmosphere, the racemic [2-^{13}C]HPP was converted into **3** the ^{13}C NMR spectrum of which is superimposable on that of



Scheme 2. Synthesis and reactions of a difluoro analogue of HPP.

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3 produced under an $^{16}O_2$ atmosphere (air). Since no additional keto signal arising from the ^{18}O isotope shift[12] is discernible and no ^{18}O washout from **3** to solvent is expected under the incubation conditions (pH 7.5, 60 min), these results do not support a hydroxylation–dehydration mechanism as predicted in mechanism B.[13] It should be noted that fosfomycin formation via α hydroxylation of HPP (**1**) followed by the attack of β-OH at α-C to displace the newly introduced hydroxyl group had already been ruled out by early feeding experiments.[4b] Thus, the current observation is consistent with the fact that HPP epoxidase lacks hydroxylation ability.

To our surprise, when **8** was incubated with HPP epoxidase, partial turnover occurred with concomitant loss of enzyme activity. Further experiments were conducted using (*R*)- and (*S*)-1,1-difluoro-HPP ((*R*)-**8** and (*S*)-**8**) the syntheses of which involved a lipase-catalyzed stereoselective acylation to resolve the diethyl ester intermediate **9** (Scheme 2).[14] The absolute configurations of the resolved phosphonic acid esters were assigned based on NMR analysis of their Mosher ester derivatives,[15] and the enantiomeric purity of (*R*)-**9** and (*S*)-**9** was determined by NMR to be greater than 99 and 95%, respectively. When these pure enantiomers were incubated with HPP epoxidase, (*S*)-**8** was found to be a tight-binding inhibitor, while (*R*)-**8** was converted into 1,1-difluoro-2-oxopropylphosphonic acid (**12**).[16] The identity of this product was unambiguously confirmed by comparison to a synthetic standard. Expectedly, this product exists in aqueous solution as a mixture of its keto (major) and hydrate form, and the turnover rate for (*R*)-**8** (76 nmol mg^{-1} min^{-1}) is comparable to the rates for the nonfluorinated substrates (*R*)-**1** and (*S*)-**1**.

The fact that (*R*)-**8** can be processed by HPP epoxidase is mechanistically revealing. On the basis of this result, an enol–keto tautomerization mechanism initiated by an α-H atom abstraction as outlined in mechanism A (Scheme 1) can be excluded. Since the turnover rates of (*R*)-**1** and (*R*)-**8** under our assay conditions are similar, the involvement of a β carbocation intermediate in the reaction may be ruled out because of the insensitivity of the catalysis to the electronic effect imposed by the α-difluoromethylene group. Pathways involving C-2 deprotonation are also unlikely as β carbanion formation in (*R*)-**8** may prompt fluorine anion release.[17] Thus, oxidation of the *R* isomers of HPP ((*R*)-**1**) and 1,1-difluoro-HPP ((*R*)-**8**) by HPP epoxidase most probably involves the formation of a carbon-centered ketyl radical, such as **13**/**11** (Scheme 1, mechanism C/Scheme 2),[18] which is distinct from the α radical intermediate **4** proposed for the oxidation of (*S*)-HPP ((*S*)-**1**).

In summary, this study provides strong evidence for the radical nature of reactions catalyzed by HPP epoxidase. The fact that each enantiomer is stereospecifically converted into a single product suggests that a unique and specific enzyme–substrate binding mode must take place for (*S*)-**1** and (*R*)-**1** turnover. While the hydroxyl and the phosphonate group from both isomers are expected to be similarly anchored in the active site, the chirality at C-2 may allow only α-H in (*S*)-**1** or β-H in (*R*)-**1** to be productively poised for abstraction by the yet-elusive, reactive iron–oxo species, leading to the corresponding products. Thus, the regiospecificity of the initial hydrogen atom abstraction appears to be determined not by the chemical reactivity but by the relative orientation of the C–H bond to be cleaved in each enzyme–substrate complex. Such a distinct outcome from a pair of enantiomers catalyzed by a single enzyme is rare.[19] In addition, it is noteworthy that the conversion of (*S*)-**1** and (*R*)-**1** by HPP epoxidase into their respective products, **2** and **3**, is exclusive.[20] Our results also imply that oxidation of (*S*)-**1** and (*R*)-**1** involves different substrate-based radical intermediates (**4** and **13**). Such findings lend further credence to the participation of a highly reactive species, such as an iron–oxo intermediate, capable of abstracting a hydrogen atom from HPP in the catalytic mechanism. A variety of biochemical and biophysical techniques are currently employed to further elucidate this unique enzyme transformation.

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[8] The reaction mixture contained 22.5 mM NADH, 12.0 mM substrate, 62.5 μM FMN, and 24.7 μM reconstituted enzyme in 200 μL of 25 mM Tris·HCl buffer (pH 7.5). The reaction was incubated with shaking at 250 rpm for 30 min at 30 °C, quenched by adding EDTA to a final concentration of 100 mM. D_2O was added to a final volume of 600 μL, and the mixture analyzed by ^{1}H NMR spectroscopy. Reaction rates were estimated based on the integrals of the well-resolved methyl signals associated with substrate and product.

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[11] Spectral data for 1,1-difluoro-HPP (**8**): ^{1}H NMR (D_2O): $\delta = 3.98$ (m, 1H), 1.15 ppm (d, $J = 6.6$ Hz, 3H); ^{19}F NMR (D_2O): $\delta = -119.8$ (ddd, $J = 281.1$, 83.7, 9.9 Hz, 1F), −128.8 ppm (ddd, $J = 283.4$, 81.8, 18.0 Hz, 1F,); ^{31}P NMR (D_2O): $\delta = 5.44$ ppm (t, $J = 82.4$ Hz).

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[16] The incubation conditions were similar to those in ref. [8]. Spectral data of **12** in the keto form (74 %): ^1H NMR (D_2O): $\delta = 2.29$ ppm (s, 3H); ^{19}F NMR (D_2O): $\delta = -118.59$ ppm (d, $J = 77.8$ Hz); ^{31}P NMR (D_2O): $\delta = 2.90$ (t, $J = 76.0$ Hz); high resolution MS (CI) calcd for $C_3H_6F_2PO_4$ [M^++H]: m/z: 174.9972, found 174.9979. Spectral data of **12** in the hydrate form (26 %): ^1H NMR (D_2O): $\delta = 1.32$ ppm (s, 3H); ^{19}F NMR (D_2O): $\delta = -124.17$ ppm (d, $J = 79.8$ Hz); ^{31}P NMR (D_2O): $\delta = 5.69$ ppm (t, $J = 79.0$ Hz); high resolution MS (CI) calcd for $C_3H_8F_2PO_5$ [M^++H]: m/z: 193.0077, found 193.0072.

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Novel Achiral Biphenol-Derived Diastereomeric Oxovanadium(IV) Complexes for Highly Enantioselective Oxidative Coupling of 2-Naphthols**

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Optically pure 1,1′-binaphthol and its derivatives have been evaluated as versatile chiral auxiliaries and ligands in asymmetric transformations. Research in this area has provided many efficient and useful methods for the preparation of key chiral building blocks, some of which have been used for the construction of complex natural products.[1] They have also been extensively applied to the preparation of chiral organic materials.[2] The wide-ranging and important applications of such compounds in organic synthesis have stimulated great interest in developing efficient methods for their preparation.[3] Compared to the well-established resolution of racemic binaphthol for the preparation of optically pure BINOL,[3a–f] catalytic asymmetric preparation of chiral binaphthols has developed much more slowly. The discovery of efficient catalysts for the highly enantioselective formation of optically active binaphthol and its derivatives is an attractive target. The oxidative coupling of 2-naphthols in the presence of a catalytic amount of a copper complex of a chiral amine has provided several promising results, but high enantioselectivity has been achieved only for the coupling of 3-carboalkoxyl-2-naphthols (93 % *ee*).[4] A photo-activated chiral [Ru^{II}(salen)(NO)] complex catalyzes the aerobic oxidative coupling of 2-naphthols with 33–71 % *ee*.[5] Chen et al. and Uang et al. independently designed similar oxovanadium(IV) complexes of chiral Schiff bases for the asymmetric oxidative coupling of 2-naphthols with moderate enantioselectivities of up to 62 % *ee*.[6]

We developed the catalyst (*R*,*S*)-**1c** for the oxidative coupling of 2-naphthol with high enantioselectivity, and found that the chiral centers on the amino acid part and the axially chiral binaphthyl unit are both crucial to stereocontrol by the catalyst.[7] However, a drawback is that the chiral oxovanadium complex must be prepared from an optically pure 3,3′-diformyl-2,2′-dihydroxy-1,1′-binaphthol and (*S*)-amino acid. The catalyst is only highly enantioselective when the two

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Supporting information for this article (general procedures for the preparation of chiral oxovanadium catalysts and asymmetric couplings of 2-naphthols; HRMS spectra of **2a–d**; HPLC spectra of **6a–c**, **6e**, and **6g–k**) is available on the WWW under http://www.angewandte.org or from the author.

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