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New Diol Metabolites Derived by Biooxidation of Chlorostyrenes with *Pseudomonas putida:* Determination of Absolute Stereochemistry and Enantiomeric Excess by Convergent Syntheses[1]

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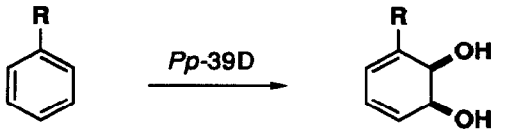
Abstract: The three isomers of chlorostyrenes were subjected to whole cell biooxidation by means of a mutant strain of *Pseudomonas putida* 39D. The metabolites were isolated and their absolute stereochemistry determined by conversion to known standards derived from 1-ethenyl-2,3-dihydroxycyclohexa-4,6-diene whose absolute configuration has been previously established. The extent of ring vs side chain oxidation of the chlorostyrene isomers was evaluated and the enantiomeric excess determined for all compounds.

Introduction

Microbial dioxygenation of aromatic substrates by mutant strains of the soil bacterium *Pseudomonas putida*[2] has furnished the synthetic chemist with a variety of enantiomerically pure cyclohexadiene-*cis*-diols (Eq. 1). To date more than two hundred of such metabolites are known, mainly due to the efforts of Gibson, Ribbons, Roberts, Boyd, and Dalton, as well as our own.[3] The synthetic community, initially slow to react to the availability of these synthons, has recently shown intense activity in using arene-*cis*-diols in enantiocontrolled synthesis. In addition, a number of novel diol synthons have been prepared synthetically from mono-halogenated arene *cis*-diols.[4] The functional diversity of diols of type **1** permits simple synthetic elaboration into a variety of oxygenated natural products. Several groups in the U. S., U. K., and Australia have used arene-*cis*-diols in expedient routes to conduritols, inositols, and other targets.[5] Following initial disclosures of a prostanoid synthesis,[6] our own group focused on a stereorational design of carbohydrates,[7] conduritols,[8] oxygenated terpenes,[9] and alkaloids,[10] and other compounds. Several recent reviews indicate the enormous potential of these compounds in enantiocontrolled sythesis.[11] Indeed, in view of the arduous

protection, deprotection, and inversion operations associated with sugar chemistry,[12] arene-*cis*-diols may soon replace carbohydrates in the chiral pool for the preparation of sugars, especially their unnatural derivatives.



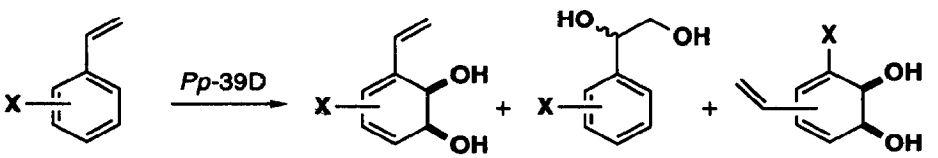
Eq. 1

1

Recently, Genencor International, Inc., made several halo-arene-*cis*-diols available on a large scale,[13] increasing the number of commercially-available diols to over twenty.[14] New diols, including those derived by the oxidation of heteroaromatic systems, continue to be identified. The recent work of Boyd[51,m] on the diols derived from benzofurans, quinolines and other ring systems is especially fascinating as it portends well for the use of such diverse compounds in the synthesis of alkaloids. Because the synthetic routes stemming from the use of diols are shorter and because the fermentation as well as some of the subsequent chemical steps are frequently performed in water, acetone, or other innocuous solvents, the potential of these diols in the manufacture of pharmaceuticals in an environmentally-benign fashion is tremendous and will no doubt lead to rapid commercialization of this field in the near future.

The current knowledge of the enzymatic transformation rests on the pioneering work of Gibson,[2,15] who provided initial insight into the transformation as well as the overall oxidative metabolism of aromatic hydrocarbons.[16] Because it appears difficult to identify the exact structure of the labile toluene or naphthalene dioxygenase systems, we embarked on a program destined to study the remarkable substrate tolerance exhibited by the bacterial dioxygenase. Such an approach would logically probe the spatial and functional limitations of

Scheme 1



2a (X = H)
2b (X = *o*-Cl)
2c (X = *m*-Cl)
2d (X = *p*-Cl)

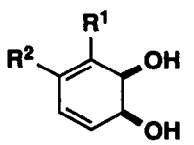
3a–d **4a–d** **5b,c**

the active site on the bacterial dioxygenase by determining several parameters of substrate specificity: a) electronic properties of the aromatic substituents, b) steric properties of these substituents, and c) the spatial

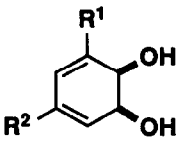
distribution of the substituents about the aromatic nucleus (i.e., *ortho*-, *meta*- and *para*-substitution patterns). In this manuscript we report on the outcome of microbial oxidation of three isomeric chlorostyrenes (Scheme 1) by the mutant bacterium *P. putida* strain 39D and identification of the metabolites whose structures may enhance the current understanding concerning topology of the active site region of the bacterial dioxygenase.

Results and Discussion

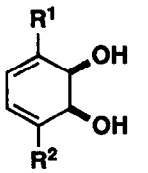
Although a variety of monosubstituted benzenes are readily oxidized by *P. putida* strain 39D with predictable regiochemistry and absolute stereochemistry, the regiochemistry of oxidation of di- and tri-substituted aromatics is more difficult to predict.[3a-c] Monosubstituted aromatics are generally oxidized with 2,3-regiochemistry with respect to the substituent and with absolute stereochemistry as indicated in **1** (Eq. 1). Exceptions are the benzoic or toluic acids, which are metabolized to the corresponding 1,2-diols.[3p] Reports of systematic studies on the dioxygenation of *ortho*- and *meta*-disubstituted benzenes by *P. putida* are less common, but generally occur with the regiochemistries as indicated in **6** and **7**.[3a,g] For example, the series of o-, m-, and p-fluorobenzoates has been investigated by Ribbons using the *Pseudomonas* B13 organism.[3i] Mutant strains of pseudomonas PL pT11/43 have oxidized a series of p-substituted benzoic acids.[3j] Gibson compared the effectiveness of Pp 39D and its more efficient *E. Coli* clone, JM109(pDTG601), in their oxidations of series of o-, m-, and p- substituted benzenes.[3k] Trifluoromethyl benzoic acids have been oxidized using Pp JT 101 mutants[3l] and trisubstituted benzoic acids have been subjected to degradation by Pp Jt 103.[3m]



6: $R^1 = CF_3$, $R^2 = F$



7: R^1, R^2 = Me



8: R^1, R^2 = Me.
R^1 = Me; R^2 = halogen.
$R^1 = CO_2H$; R^2 = H, alkyl, alkoxy, halogen.

Predictions of absolute stereochemistry or even regiochemistry become difficult in these instances. A variety of *para*-disubstituted benzenes undergo dioxygenation by *Pp*-mutants as indicated in **8**.[3h] Reports of absolute stereochemical determinations for polysubstituted arene *cis*-diols are scarce.[3a,b,c,f,o]

The methodology available for proof of absolute configurations includes x-ray diffraction studies of crystalline derivatives, degradation to known compounds, or the Mosher ester method of Boyd.[17] The latter method is not completely conclusive for new metabolites without an additional rigorous proof of absolute stereochemistry by other means, such as x-ray crystallography, but gives excellent results with many different diols studied to date by the Boyd group. We have successfully used this method to determine the absolute stereochemistry of a number of metabolites including those derived from iodobenzene and 2-methoxynapthalene.[18]

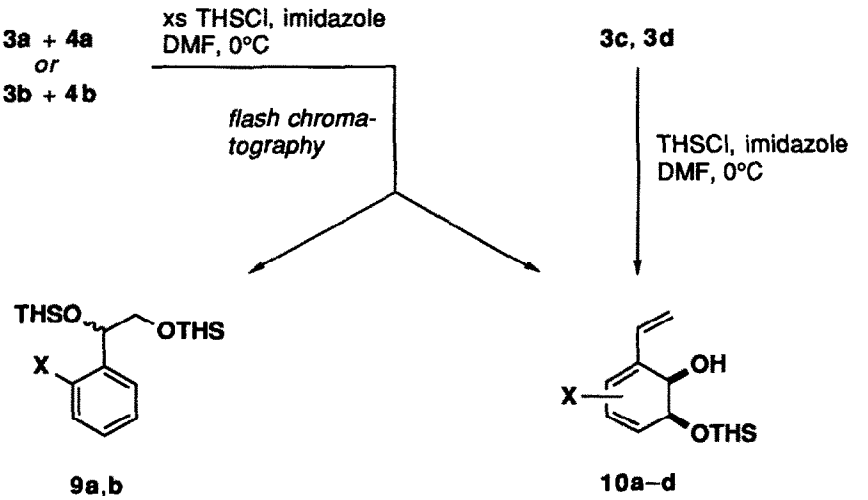
We chose to study the chlorostyrene series for two reasons. First, the oxidation of the set of *ortho*-, *meta*-, and *para*-substituted derivatives and the identification of their metabolites should reflect a pattern with regard to the regio- and stereochemical outcome of the biooxidation. This in turn may provide some insight into the topology of the active sites on the toluene dioxygenase enzyme. Second, some of the chlorostyrene metabolites may become useful in synthetic projects ongoing at the time of this research.[19]

We first set out to develop a standard fermentation protocol.[20] In *P. putida* strain 39D the gene responsible for dioxygenase expression is not activated until the bacteria are exposed to low levels of an inducing compound for a discrete period of time; only after this "induction period" will diol production commence. In our laboratories we have found that toluene, ethylbenzene, the halobenzenes, and styrene will all act as inducers in addition to serving as substrates yielding 3–8 g/L of diol. Considerably higher space-time yields are obtained with the recombinant organism *E. Coli* JM 109.[3k,15] However, our experiences with a number of disubstituted benzenes has shown that many which will serve as substrates will not act as inducers. For example, our first fermentations utilizing *o*-chlorostyrene as both inducer and substrate did not produce any diol whatsoever.

To address this difficulty several different induction methods were examined. In a typical 8L, fifty-hour fermentation, the cell population remains fairly low and steady for about 20 hours then undergoes an exponential increase before leveling out at a maximum around 27 hours and finally declining rapidly upon exhaustion of the carbon source. Introduction of an inducer to the fermentation broth at various times along the growth curve followed by substrate introduction generally gave poor results—extremely low production of substrate diol and/or excessive production of inducer diol. The best method was continuous induction achieved by saturating the air space over the broth with inducer vapor *throughout* the course of the oxidation and slowly adding the *liquid* substrate directly to the fermentation broth. This enhanced the yield of substrate diol while attenuating production of inducer diol.

The product distributions and enantiomeric excess for the microbial oxidation of styrene (**2a**) and the chlorostyrenes (**2c–d**) are shown in Table 1. The high concentrations of glycols formed (**4a–d**) caused some difficulties. The *o*-chlorostyrene metabolites **3b** and **4b** were virtually inseparable by flash chromatography. Interestingly, this problem was resolved by treating the mixture with imidazole and excess dimethylthexylsilylchloride (THSCl) in DMF. Over several days at 0 °C the glycol (**4b**) was converted to the bis-silyl ether (**9b**) while the cyclohexadiene-*cis*-diol (**3b**) was selectively protected at the C-3 hydroxyl group

Scheme 2

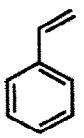
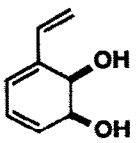
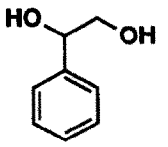
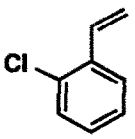
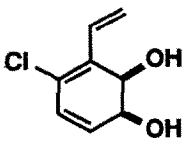
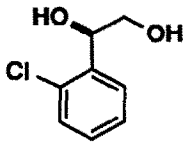
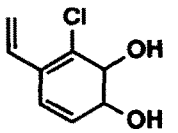
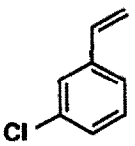
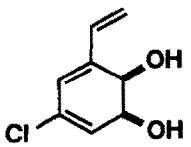
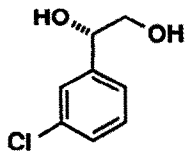
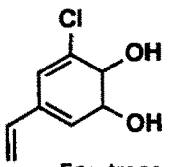
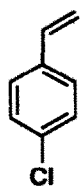
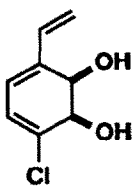
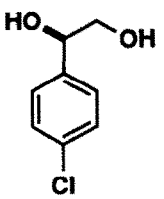


9a,b **10a–d**

only (**10b**). The mixture of styrene metabolites **3a** and **4a** was treated in a similar fashion (Scheme 2). This had the dual advantages of both allowing for an easy chromatographic separation and of regioselectively protecting the proper alcohol required for the convergent synthetic sequence. In the case of the *m*- and *p*-chlorostyrene metabolites, the glycols **4c** and **4d** were seperable from the cyclohexadiene-*cis*-diols **3c** and **3d** by flash chromatography. The purified arene *cis*-diols **3c** and **3d** were subsequently converted to their mono-THS-ethers as shown Scheme 2.

The convergent synthetic strategy employed for determining absolute stereochemistry and optical purity of arene *cis*-diols **3b** and **3c** is outlined in Scheme 3. The method utilizes an intramolecular Diels–Alder reaction with an allyl tether. As a standard we chose the styrene diol **3a**, the absolute stereochemistry of which was established previously by total synthesis.[9b,21] Alkylation of the silyl derivative **10a** with allyl bromide and

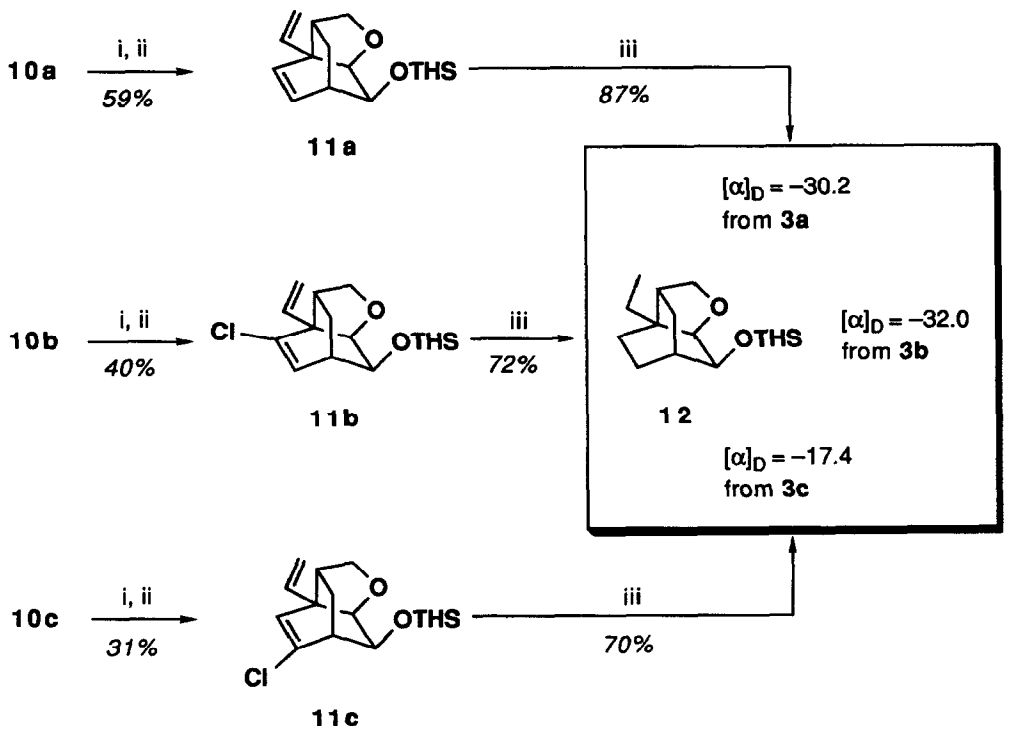
Table 1. Substrates and Metabolites for the Microbial Oxidation of Styrene (2a) and Chlorostyrenes (2b-d) by *Pseudomonas putida* Strain 39D.

Substrate	Metabolites[a,b]		
			
2a	**3a**: >95%, >98%ee	**4a**: <5%	
			
2b	**3b**: 35%, >98%ee	**4b**: 65%, 73%ee	**5b**: trace
			
2c	**3c**: 29%, 54%ee	**4c**: 71%, 95%ee	**5c**: trace
			
2d	**3d**: 83%, 15%ee	**4d**: 17%, 79%ee	

[a] Percentages represent relative amounts of these metabolites present in the crude diol extract. [b] % ee's are based on $[\alpha]_D$ values obtained by convergent syntheses.

subsequent Diels–Alder reaction in CCl_4 (room temperature→80 °C) provided the tricyclic ether **11a** in an overall yield of 59%. Hydrogenation of this material gave the saturated tricyclooxadecane **12**, which exhibited a specific rotation of –30.2 . The protected *o*-chlorostyrene diol **10b** and the *m*-chlorostyrene diol **10c** were

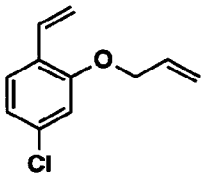
Scheme 3



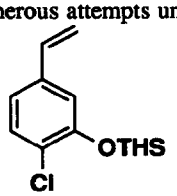
(i) NaH, allyl bromide, THF, –20°C; (ii) CCl_4, rt → 80°C; (iii) H_2, Pd/C, EtOH, 45 psi.

similarly converted to their Diels–Alder adducts **11b** and **11c**, respectively. Subsequent hydrogenations provided the saturated adduct **12**, which gave specific rotations of –32.0 (from **10b**)[1b] and –17.4 (from **10c**). These specific rotations correspond to enantiomeric excesses of >98% for the *o*-chlorostyrene diol **3b** and *ca.* 54% for the *m*-chlorostyrene diol **3c**.

The determination of optical purity and absolute stereochemistry of **3d** by this method proved troublesome because of extensive aromatization problems encountered during allylation of **10d**. The aromatic ethers **13** and **14** were isolated as the only products during numerous attempts under a variety of conditions



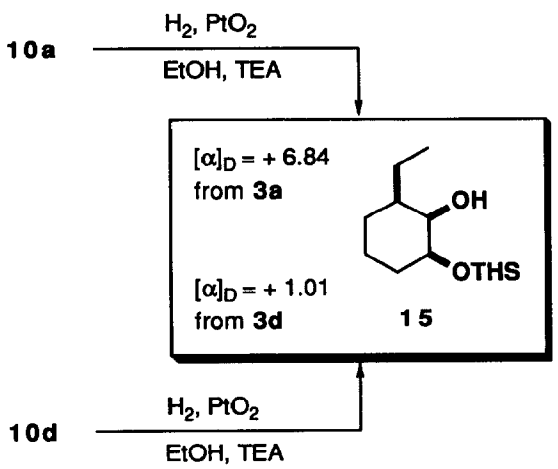
13



14

including performing the reaction at temperatures as low as –50 °C employing butyl lithium and potassium amide bases. Because of the high propensity of **10d** to aromatize, we examined a more direct method. Preliminary attempts at hydrogenation of both **10a** and **10d** with Pd/C met with significant aromatization; however, we found that both **10a** and **10d** could be fully hydrogenated with Adams' catalyst (PtO_2) in the presence of triethylamine in EtOH (Scheme 4). By means of this method, **10a** was converted to the cyclohexanol **15** in

Scheme 4

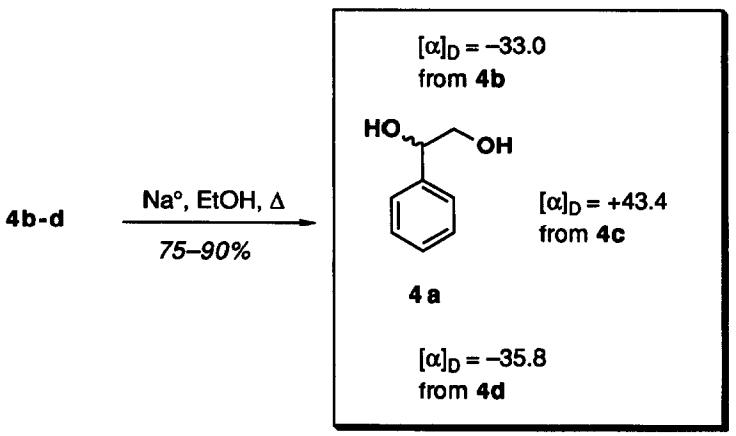


20% isolated yield, the latter giving a specific rotation of +6.84 . Conversion of **10d** to **15** was accomplished in 34% yield, the product exhibiting a specific rotation of +1.01 . Although this method is more expedient than the one shown in Scheme 3, it does suffer from rather low yields, difficult purification, and a weak $[\alpha]_D$ of the product (**15**). Nevertheless, the specific rotations of **15** prepared from **10a** and **10d** indicate an enantiomeric

excess of *ca.* 15% for the *p*-chlorostyrene diol **3d**. These results completed the analysis of regio- and stereochemistry (including enantiomeric excess) of the three "ring" diols (**3b–d**) from the chlorostyrenes.

The absolute configuration of the glycols (**4b–d**) were determined by convergent synthesis through their reduction with sodium metal in EtOH to 1-phenyl-1,2-ethanediol (**4a**) (Scheme 5). Comparison of specific rotations with the literature value for **4a**[23] established enantiomeric excesses and absolute configurations of 72% ee[24] for *R*-(–)-**4a** synthesized from the *o*-chloroglycol **4b**, 95% ee for *S*-(+)-**4a** synthesized from **4c**, and 79% ee for *R*-(–)-**4a** synthesized from **4d**. It is important to note that *m*-chlorostyrene was converted to a glycol

Scheme 5



with the opposite configuration at the benzylic position relative to the glycols obtained from *o*- and *p*-chlorostyrene. Finally, the products of "chlorine-directed" ring oxidation (**5b** and **5c**) were detected in trace amounts only. The results of the entire study are summarized in Table 1.

From a synthetic viewpoint, the most useful result is the high stereospecificity of ring oxidation observed in production of the *o*-chlorostyrene diol (**3b**) provided the selectivity between the aromatic versus vinylic dioxygenation can be improved. One possibility is to investigate oxidation of substrates with a substituent on the α-carbon of the styrene. This would not only create a steric deterrent to oxidation at the vinylic position, but would also provide a more functionalized arene-*cis*-diol. Efforts in this area are currently under investigation in our labs. Screening of other organisms or use of the overexpressed mutant *E. coli* JM109[15] may also serve to enhance the regioselectivity. Organisms that impart selectivity for *only* the styrene olefin moiety may also be identified through screening. The production of enantiopure glycols through biooxidation of olefins may prove

quite useful in view of recent reports on enantiocontrolled syntheses utilizing optically active ketals and acetals.[25] Such optimization endeavors lie in the domain of microbiology and molecular biology and may be addressed in due course.[26] The availability of bridged tricyclic ethers of type **11** may also find expression in potential chiral auxiliary development.[27]

Conclusion

The diversity of monosubstituted benzenes that are oxidized to *cis*-diols (**1**) with 2,3-regiochemistry (eq. 1) is consistent with a predominant steric effect. The fact that substituents as electronically disparate as chlorine and ethyl groups give arene *cis*-diols with identical regiochemistry, absolute stereochemistry, and enantiomeric excess[17] is consistent with this postulate. Interestingly, the arene *cis*-diol obtained from fluorobenzene, although displaying similar regiochemistry and absolute stereochemistry, has an enantiomeric excess of *ca.* 60%.[28] Our results from the biooxidations of the series of chlorostyrene isomers indicate that steric disposition of the substrate is probably the dominant factor determining regiochemistry of the oxidation. Based on the analysis of known metabolites and the results of this study, we would favor the proposition of an "open" active site for binding of the arene as shown in Figure 1.

Gibson has shown that the multicomponent enzyme system—designated toluene dioxygenase—is responsible for the formation of arene-*cis*-diols (**1**) by various strains of *P. putida*.[2,15] Toluene dioxygenase is

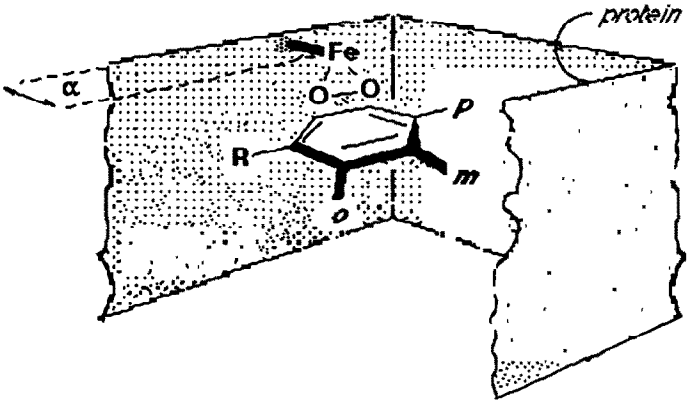


Figure 1. A generalized topology proposed for the active site region on the ISP_{TOL} enzyme responsible for incorporating molecular oxygen into aromatic substrates.

comprised of a flavoprotein ($reductase_{TOL}$), a small iron–sulfur protein ($ferredoxin_{TOL}$), and a terminal dioxygenase iron–sulfur protein (ISP_{TOL}) which is responsible for the addition of molecular oxygen to the

aromatic substrate. If the ISP_{TOL} active site contains the iron-based oxidizing species at a distance α from the protein that would bind the aromatic ring, this "open" active site model would explain why fluorobenzene displays only 80:20 stereospecificity for oxidation[17] and why large groups can be tolerated at C-1. The testing of this model can be effected by designing substrates that could not "fit" in any orientation to the corner pocket—alkyl benzenes, *p*-substituted with large groups, or *m*-functionalized benzoic acids. Covalent attachment to the active site of substrates containing appropriately activated functionality may be used in the future to further probe the topology of this extraordinary enzyme and to aid in the design of a mimicking reagent that would accomplish such oxidation in the laboratory. These endeavors form the current focus of our research and will be reported in due course.

Experimental Section

General: Proton NMR spectra were recorded in $CDCl_3$ (ref. 7.24 ppm) at 200, 270, and 400 MHz on Brüker WP-200, Brüker WP-270, and Varian Unity 400 instruments, respectively. Coupling constants (*J*) are given in hertz. Carbon NMR spectra were recorded in $CDCl_3$ (ref. 77.0 ppm) at 50 and 100 MHz on Brüker WP-200 and Varian Unity 400 instruments, respectively, and multiplicities were determined by DEPT experiments. IR spectra were obtained from neat oils unless noted otherwise. THF and Et_2O were distilled from sodium/benzophenone. Hexanes and DMF were distilled from CaH_2. EtOAc and CCl_4 were HPLC grade. Flash column chromatography was performed on Merck silica gel (grade 60, 230-400 mesh). Air- and moisture-sensitive reactions were carried out in flame-dried reaction vessels under argon and with oven-dried syringes. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

***Pp*-39D Oxidations of 2a-d.** *P. putida* strain 39D (*Pp* 39D) were grown in a B. Braun Biostat E 15 L fermenter in 10 L of mineral salts broth slightly modified from that of Gibson.[20] Throughout the course of the oxidation, the pH was maintained at nominally 7.2 by the automated addition of 5M NH_3 or 1M H_2SO_4, and oxygen gas was bubbled through the broth to maintain the dissolved oxygen level at about 50% of the initial dissolved oxygen content. The rate of stirring was 250 rpm. Compound **2a** was passed as a vapor through the broth. For the chlorostyrenes, the air space *over* the broth was saturated with toluene vapor while the substrate was passed as vapor (**2b** and **2c**) or a liquid (**2d**) *through* the broth. Once the oxidation was complete (i.e., massive cell death or exhaustion of substrate), the broth was processed by continuous centrifugation to remove the solids, basification with 10M NaOH to pH=8.8, saturation with NaCl, and extraction with base-washed EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a crude diol

mixture (for the chlorostyrenes this included a large amount the toluene diol metabolites). *Pp*-39D oxidation of **2a** (*ca.* 50 g) provided a 95:5 mixture of **3a** and **4a** (17 g) which was protected *immediately* with dimethylthexylsilyl chloride (THSCl). The crude diol extracts obtained from microbial oxidation of the chlorostyrenes **2b-d** were chromatographed on silica gel (deactivated with 10 % w/w H_2O) eluting with 1:1 base-washed EtOAc/hexanes. Microbial oxidation of **2b** (*ca.* 20 g) gave **3b** and **4b** (980 mg, total ratio of 7:13) with a trace of **5b**; **2c** (*ca.* 9 g) gave **3c** and **4c** (330 mg, 2:5) with a trace of **5c**; **2d** (*ca.* 29 g) provided **3d** and **4d** (7.41 g, 5:1). The isolated *cis*-dihydrodiols (**3**) were susceptible to aromatization and were fully characterized as their mono-THS-ethers (**10**).

(2*R*,3*S*)-*cis*-6-Chloro-1-vinylcyclohexa-4,6-diene-2,3-diol (3b): UV (λ_{max}, EtOH) 292 nm; ^{1}H NMR (270 MHz) δ 6.85 (1H, dd, *J*=17, 10), 5.95 (1H, dd, *J*=12, 4), 5.89 (1H, dd, *J*=12, 3), 5.60 (1H, d, *J*=17), 5.37 (1H, d, *J*=10), 4.5 (2H, br), 3.24 (1H, bd), 2.50 (1H, bs). ^{13}C NMR δ 134.1 (CH), 131.4 (CH), 130.1 (C), 129.7 (C), 127.1 (CH), 116.8 (CH_2), 70.1 (CH), 66.9 (CH).

(2-Chlorophenyl)-1,2-ethanediol (4b): $[\alpha]_D$ = –47.2 (*c* 1.9, EtOH), $[\alpha]_{5461}$ = –56.3 (*c* 1.9, EtOH); ^{1}H NMR (200 MHz, CD_3OD) δ 7.60 (1H, d, *J*=7.4), 7.37-7.16 (3H, m), 5.14 (1H, dd, *J*=7.7, 3.2), 3.71 (1H, dd, *J*=11.4, 3.2), 3.47 (1H, dd, *J*=11.4, 7.7); ^{13}C NMR (CD_3OD) δ 140.6 (C), 133.1 (C), 130.2 (CH), 129.7 (CH), 129.1 (CH), 128.0 (CH), 72.4 (CH), 67.2 (CH_2).

(2*R*,3*S*)-*cis*-5-Chloro-1-vinylcyclohexa-4,6-diene-2,3-diol (3c): ^{1}H NMR (200 MHz) δ 6.36 (1H, dd, *J*=17.5, 10.8), 5.88 (2H, bs), 5.58 (1H, d, *J*=17.5), 5.30 (1H, d, *J*=10.8), 4.47 (1H, bs), 4.35 (1H, bd, *J*=5.8), 3.1 (1H, bs), 2.4 (1H, bs).

(1*S*)-1-(3-Chlorophenyl)-1,2-ethanediol (4c): $[\alpha]_D$ = +24.05 (*c* 1.24, EtOH), $[\alpha]_{5461}$ = +28.18 (*c* 1.24, EtOH); ^{1}H NMR (400 MHz) δ 7.36 (1H, m), 7.27 (2H, m), 7.21 (1H, m), 4.77 (1H, dd, *J*=8.2, 3.3), 3.73 (1H, dd, *J*=11.4, 3.3), 3.60 (1H, dd, *J*=11.4, 8.2), 3.35 (1H, bs), 2.81 (1H, bs); ^{13}C NMR δ 142.5 (C), 134.4 (C), 129.8 (CH), 128.0 (CH), 126.2 (CH), 124.2 (CH), 74.0 (CH), 67.8 (CH_2); MS (CI): 174 (2), 172 (5), 157 (38), 155 (100), 143 (8), 141 (22); HRMS (CI): $C_8H_9ClO_2$ [M] calcd. 172.0291, found 172.0288.

***cis*-1-Chloro-5-vinylcyclohexa-4,6-diene-2,3-diol (5c):** ^{1}H NMR (200 MHz) δ 6.37 (1H, dd, *J*=17.5, 10.9), 6.14 (1H, dd, *J*=6.3, 2.2), 5.89 (1H, dd, *J*=6.3, 0.6), 5.50 (1H, d, *J*=17.5), 5.23 (1H, d, *J*=10.9), 4.55 (1H, bd, *J*=5.6), 4.44 (1H, bm), 2.85 (1H, bd, *J*=9), 2.01 (1H, bs).

***cis*-4-Chloro-1-vinylcyclohexa-4,6-diene-2,3-diol (3d):** ^{1}H NMR (270 MHz) δ 6.40 (1H, dd, *J*=17.6, 10.9), 6.13 (1H, dd, *J*=6.2, 2.2), 5.91 (1H, d, *J*=6.2), 5.49 (1H, d, *J*=17.6), 5.15 (1H, d,

J=10.9), 4.45 (1H, d, *J*=5.7), 4.33 (1H, dd, *J*=5.7, 2.2); ^{13}C NMR δ 138.3 (C), 138.2 (C), 137.0 (CH), 124.7 (CH), 123.0 (CH), 114.5 (CH_2), 72.7 (CH), 68.2 (CH).

(*1R*)-1-(4-Chlorophenyl)-1,2-ethanediol (4d): $[\alpha]_D$ = -27.60 (*c* .96, EtOH), $[\alpha]_{5461}$ = -32.71° (*c* .96, EtOH); ^{1}H NMR (400 MHz) δ 7.36-7.29 (4H, m), 4.81 (1H, dt, *J*=8.1, 3.4), 3.76 (1H, ddd, *J*=11.1, 7.3, 3.4), 3.62 (1H, ddd, *J*=11.1, 8.1, 4.8), 2.57 (1H, d, *J*=3.4), 2.03 (1H, dd, *J*=7.3, 4.8); ^{13}C NMR δ 138.9 (C), 133.8 (C), 128.7 (CH, 2x), 127.4 (CH, 2x), 74.0 (CH), 67.9 (CH_2).

Preparation of 1-Phenyl-1,2-ethanediol (4a) from 4b–d: Typically, the chlorostyrene glycol (**4b–d**) (100 mg, 0.58 mmol) was dissolved in absolute EtOH (2 ml) and refluxed under argon. Sodium metal was added in *ca.* 25 mg portions to the stirring solution, and EtOH was added as needed to maintain the volume at *ca.* 2 ml. The reaction was monitored by TLC (2:1 EtOAc/hexanes) or ^{1}H NMR and upon completion was evaporated to near dryness and neutralized with aqueous HCl. The aqueous was extracted with EtOAc; the extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield **4a** in 75-90% yield. Recrystallization from EtOAc/hexanes provided white crystals: $[\alpha]_{5461}$ = -33.0 (*c* .46, EtOH) from **4b**, $[\alpha]_{5461}$ = +43.4 (*c* .44, EtOH) from **4c**, $[\alpha]_{5461}$ = -35.8 (*c* .36, EtOH) from **4d**, lit. $[\alpha]_{5461}$ = -45.5 (EtOH)[23] for *R*-(–)-**4a**; ^{1}H NMR (400 MHz) δ 7.36-7.30 (4H, m), 7.28 (1H, m), 4.77 (1H, dd, *J*=8.3, 3.4), 3.72 (1H, dd, *J*=11.4, 3.4), 3.62 (1H, dd, *J*=11.4, 8.3), 3.10 (1H, bs), 2.75 (1H, bs); ^{13}C NMR δ 140.4 (C), 128.5 (CH, 2x), 127.9 (CH), 126.0 (CH, 2x), 74.6 (CH), 68.0 (CH_2).

(2*R*,3*S*)-*cis*-3-Dimethyl(1,1,2-trimethylpropyl)siloxy-1-vinylcyclohexa-4,6-diene-2-ol (10a). Dimethylthexylsilyl chloride (21.4 g, 119.7 mmol, neat) was added *via* syringe over a period of 5 min to a solution of the diol **3a** (13.79 g, 99.80 mmol) and imidazole (8.82 g, 129.74 mmol) in DMF (130 ml) and the resulting solution allowed to stand at 0°C overnight. The solution was diluted with ether (150 ml) and washed with brine (1 x 100 ml). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 ml). The combined organic layers were washed with sat. $CuSO_4$ (3 x 50 ml), water (1 x 50 ml) and brine (1 x 50 ml) and dried over Na_2SO_4. Filtration and concentration *in vacuo* followed by flash chromatography on silica gel (deactivated with 10% w/w H_2O) eluting with 5% EtOAc/hexanes provided **10a** (16.48 g, 58.75 mmol, 59% yield) as a colorless oil: $[\alpha]_D$ = +108.44 (*c* 4.29, $CHCl_3$); IR (v) 3554, 2958, 2868, 1252, 1090, 874, 832, 777, 671 cm^{-1}; ^{1}H NMR (400 MHz) δ 6.41 (1H, dd, *J*=17.4, 10.8), 5.94 (1H, m), 5.92 (1H, ddd, *J*=5.6, 2.4, 0.5), 5.70 (1H, m), 5.50 (1H, d, *J*=17.4), 5.17 (1H, d, *J*=10.8), 4.56 (1H, bd, *J*=5.8), 4.21 (1H, dt, *J*=5.8, 1.6), 2.69 (1H, d, *J*=1.6), 1.66 (1H, heptet, *J*=6.9), 0.91 (3H, d, *J*=6.9), 0.90 (3H, d, *J*=6.9), 0.883 (3H, s), 0.881 (3H, s), 0.17 (3H, s), 0.16 (3H, s); ^{13}C NMR δ 136.6(CH), 136.3(C), 132.1(C),

124.8(CH), 123.6(CH), 113.9(CH_2), 71.8(CH), 65.8(CH), 34.2(CH), 25.0(C), 20.3(CH_3), 20.2(CH_3), 18.61(CH_3), 18.56(CH_3), -2.6(CH_3), -2.9(CH_3); HRMS (CI): $C_{16}H_{27}O_2Si$ [M–1] calcd. 279.1780, found 279.1782.

***(1S, 2S, 3R, 6R, 7S)*-2-Dimethyl(1,1,2-trimethylpropyl)siloxy-7-vinyl-4-oxatricyclo-[4.3.1.$0^{3,7}$]dec-8-ene (11a).** A solution of **10a** (1.00 g, 3.56 mmol) in THF (5 ml) was added slowly to a stirring slurry of NaH (0.43 g, 17.9 mmol) in THF (5 ml) cooled to –20°C. A solution of allyl bromide (2.15 g, 17.8 mmol) in THF (3 ml) was then added slowly, and the mixture stirred at -15°C for 4 d at which point TLC showed complete disappearance of **10a**. The reaction was quenched at –20°C with H_2O (3 ml), diluting with Et_2O (30 ml) and the mixture poured into a separatory funnel. The layers were separated and the aqueous layer extracted with Et_2O (2 x 10 ml). The combined organic layers were washed with brine (2 x 15 ml) and dried over Na_2SO_4. Filtration and concentration *in vacuo* provided 2.5 g of the crude allyl ether. The latter was dissolved in CCl_4 (360 ml) and the solution allowed to stand at room temperature for 4 d followed by an additional 2.5 h at reflux. Concentration *in vacuo* and flash chromatography on silica gel eluting with 2% EtOAc/hexanes provided the adduct **11a** (0.677 g, 2.11 mmol, 59% yield) as a colorless oil: $[\alpha]_D = -67.76$ (*c* 1.27, $CHCl_3$); IR (ν) 3051, 2952, 2878, 1639, 1250, 1118, 1102, 914 cm^{-1}; ^1H NMR (400 MHz) δ 6.26 (1H, dd, *J*=8.4, 6.9), 6.08 (1H, dd, *J*=17.6, 10.9), 5.80 (1H, dd, *J*=8.4, 1.3), 5.24 (1H, dd, *J*=17.6, 1.2), 5.16 (1H, dd, *J*=10.9, 1.2), 3.91 (1H, ddd, *J*=7.5, 4.7, 0.6), 3.59 (1H, d, *J*=7.5), 3.55 (1H, d, *J*=6.8), 3.45 (1H, dt, *J*=6.8, 2.1), 2.32 (1H, m), 1.94 (1H, dd, *J*=10.1, 4.7), 1.79 (1H, ddd, *J*=12.6, 3.6, 1.3), 1.61 (1H, heptet, *J*=6.8), 1.52 (1H, bm), 0.90 (3H, d, *J*=6.8), 0.88 (3H, d, *J*=6.8), 0.844 (3H, s), 0.837 (3H, s), 0.09 (3H, s), 0.05 (3H, s); ^{13}C NMR δ 141.4(CH), 134.9(CH), 129.7(CH), 114.4(CH_2), 76.1(CH), 74.2(CH_2), 71.8(CH), 52.0(C), 40.4(CH), 37.0(CH), 34.4(CH), 33.0(CH_2), 25.1(C), 20.6(CH_3), 20.2(CH_3), 18.7(CH_3), 18.5(CH_3), -2.6(CH_3), -3.4(CH_3); Anal. Calcd for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06. Found: C, 71.44; H, 10.11.

***(1S, 2S, 3R, 6R, 7S)*-2-Dimethyl(1,1,2-trimethylpropyl)siloxy-7-ethyl-4-oxatricyclo-[4.3.1.$0^{3,7}$]decane (12) from 11a.** A solution of **11a** (52.8 mg, 0.165 mmol) in absolute EtOH (1.5 ml) was hydrogenated over 10% Pd/C (4.5 mg) at 45 psi for 1.5 h. The mixture was vacuum filtered through celite and the filtrate concentrated *in vacuo*. Flash chromatography on silica gel eluting with a 0 → 4% EtOAc/hexanes solvent gradient provided **12** (46.4 mg, 0.143 mmol, 87% yield) as a colorless oil: $[\alpha]_D = -30.2$ (*c* 0.265, $CHCl_3$); IR (ν) 2940, 2867, 1464, 1249, 1129, 1102, 831 cm^{-1}; ^1H NMR (400 MHz) δ 3.94 (1H, ddd, *J*=7.5, 4.9, 0.9), 3.66 (1H, dt, *J*=6.7, 1.5), 3.63 (1H, d, *J*=6.7), 3.37 (1H, d, *J*=7.5), 1.89 (1H, dd, *J*=9.0,

5.0), 1.67 (1H, m), 1.64-1.56 (2H), 1.60 (1H, pentet, *J*=6.8), 1.49-1.37 (4H), 1.30 (1H, dd, *J*=7.6, 3.8), 1.26 (1H, dd, *J*=7.6, 3.4), 0.89 (3H, d, *J*=6.8), 0.88 (3H, d, *J*=6.8), 0.84 (3H, s), 0.83 (3H, s), 0.77 (3H, t, *J*=7.6), 0.10 (3H, s), 0.05 (3H, s); ^{13}C NMR δ 79.9(CH), 75.7(CH_2), 74.0(CH), 44.3(C), 37.3(CH), 34.5(CH), 32.3(CH_2), 31.2(CH), 28.3(CH_2), 25.8(CH_2), 25.1(C), 20.6(CH_3), 20.26(CH_3), 20.24(CH_2), 18.7(CH_3), 18.5(CH_3), 8.4(CH_3), -2.6(CH_3), -3.3(CH_3); Anal. Calcd for $C_{19}H_{36}O_2Si$: C, 70.31; H, 11.18. Found: C, 70.46; H, 11.17.

(2*R*,3*S*)-*cis*-6-Chloro-3-dimethyl(1,1,2-trimethylpropyl)siloxy-1-vinylcyclohexa-4,6-diene-2-ol (10b). Dimethylthexylsilyl chloride (1.05 g, 5.85 mmol, neat) was added dropwise to a solution of **3b** and **4b** (0.416 g, *ca.* 0.8 mmol **3b**, *ca.* 1.6 mmol **4b**) and imidazole (0.361 g, 5.30 mmol) in DMF (2 ml) and the solution stored at 0°C for 4 d. The mixture was diluted with Et_2O (10 ml) and washed with brine (1 x 5 ml). The aqueous layer was extracted with Et_2O (3 x 10 ml), and the combined organic layers were washed with sat. $CuSO_4$ (2 x 10 ml) and brine (1 x 10 ml) and dried over Na_2SO_4. Filtration and concentration *in vacuo* provided a crude mixture of the bis-protected glycol **9b** and **10b** which were separated by flash chromatography on silica gel (deactivated with 10% w/w H_2O) eluting with 5% EtOAc/hexanes to provide pure **10b** (0.215 g, 0.683 mmol, *ca.* 85% yield) as a colorless oil: $[\alpha]_D$ = +101.1 (*c* 1.12, $CHCl_3$); UV (λ_{max}, EtOH) 290 nm; IR (ν) 3555, 3094, 2958, 2867, 1626, 1466, 1389, 1254, 1108, 1074, 879 cm^{-1}; ^{1}H NMR (200 MHz) δ 6.89 (1H, dd, *J*=17.5, 11.0), 5.91 (1H, dd, *J*=10.0, 2.7), 5.75 (1H, dt, *J*=10.0, ~1.5), 5.62 (1H, d, *J*=17.5), 5.37 (1H, d, *J*=11.0), 4.60 (1H, m), 4.32 (1H, dt, *J*=5.5, ~1.5), 2.70 (1H, d, *J*=1.6), 1.66 (1H, pentet, *J*=6.8), 0.90 (6H, bd, *J*=6.8), 0.88 (6H, bs), 0.17 (3H, s), 0.16 (3H, s); ^{13}C NMR δ 133.5(CH), 132.0(CH), 129.6(C), 129.4(C), 127.1(CH), 116.6(CH_2), 71.0(CH), 67.3(CH), 34.2(CH), 25.0(C), 20.3(CH_3), 20.2(CH_3), 18.6(CH_3), 18.5(CH_3), -2.6(CH_3), -2.9(CH_3); HRMS (CI): $C_{16}H_{26}ClOSi$ [M–17] calcd. 297.1441, found 297.1435.

***(1S, 2S, 3R, 6R, 7S)*-8-Chloro-2-dimethyl(1,1,2-trimethylpropyl)-siloxy-7-vinyl-4-oxatricyclo[4.3.1.0^{3,7}]dec-8-ene (11b).** A solution of **10b** (41 mg, 0.130 mmol) in THF (0.5 ml) was added slowly to a stirring slurry of NaH (16 mg, 0.65 mmol) in THF (0.5 ml) cooled to –20°C. A solution of allyl bromide (79 mg, 0.65 mmol) in THF (0.5 ml) was then added slowly and the mixture stirred at -20°C for 3 d at which point TLC showed complete disappearance of **10b**. The reaction was quenched at –20°C with brine (3 ml), and extracted with Et_2O (3 x 5 ml). The combined organic layers were vacuum filtered through Na_2SO_4, and the filtrate was diluted to 25 ml with Et_2O and the resulting solution was stored at room temperature for 3 d. The Et_2O was removed *in vacuo* and the residue dissolved in CCl_4 (25 ml) and refluxed for 1.5 h.

Concentration *in vacuo* and flash chromatography on silica gel eluting with a 0 → 5% EtOAc/hexanes solvent gradient provided the adduct **11b** (18.4 mg, 0.052 mmol, 40% yield) as a colorless oil: $[\alpha]_D = -53.7$ (*c* 0.27, $CHCl_3$); IR (ν) 2955, 1250, 1120, 832, 668 cm^{-1}; ^1H NMR (400 MHz) δ 6.27 (1H, d, *J*=7.6), 5.96 (1H, dd, *J*=17.6, 11.0), 5.32 (1H, dd, *J*=11.0, 1.0), 5.27 (1H, dd, *J*=17.6, 1.0), 3.85 (1H, ddt, *J*=7.6, 4.5, 0.4), 3.81 (1H, d, *J*=6.8), 3.58 (1H, d, *J*=7.6), 3.53 (1H, dt, *J*=6.8, 2.1), 2.40 (1H, m), 2.19 (1H, bdd, *J*=10.1, 5.1), 1.85 (1H, bddd, *J*=12.8, 3.6, 1.5), 1.62 (1H, bm), 1.61 (1H, heptet, *J*=6.8), 0.90 (3H, d, *J*=6.8), 0.88 (3H, d, *J*=6.8), 0.84 (3H, s), 0.83 (3H, s), 0.10 (3H, s), 0.06 (3H, s); ^{13}C NMR δ 136.9(CH), 130.7(C), 130.1(CH), 116.1(CH_2), 74.4(CH), 74.1(CH_2), 71.2(CH), 55.8(C), 39.0(CH), 37.8(CH), 34.4(CH), 32.5(CH_2), 25.1(C), 20.5(CH_3), 20.2(CH_3), 18.7(CH_3), 18.5(CH_3), -2.6(CH_3), -3.4(CH_3); HRMS (CI): $C_{19}H_{32}ClO_2Si$ [M+1] calcd. 355.1860, found 355.1734.

Synthesis of 12 from 11b. A solution of **11b** (11.4 mg, 0.032 mmol) in absolute EtOH (1 ml) was hydrogenated over 10% Pd/C (1 mg) at 45 psi for 1.5 h. The mixture was vacuum filtered through celite and the filtrate concentrated *in vacuo*. Flash chromatography on silica gel eluting with a 0 → 4% EtOAc/hexanes solvent gradient provided **12** (7.5 mg, 0.023 mmol, 72% yield) as a colorless oil: $[\alpha]_D = -32.0$ (*c* 0.375, $CHCl_3$). The spectral data were identical to that shown for **12** above.

(2*R*,3*S*)-*cis*-5-Chloro-3-dimethyl(1,1,2-trimethylpropyl)siloxy-1-vinylcyclohexa-4,6-diene-2-ol (10c). A solution of the crude, partially aromatized diol (**3c**) (91 mg, 0.53 mmol) and imidazole (50 mg, 0.74 mmol) in DMF (1.5 ml) was stored at 0°C for 2 d. The solution was diluted with Et_2O (20 ml) and washed with brine (10 ml). The aqueous layer was extracted with Et_2O (2 x 15 ml), and the combined organic layers were washed with sat. $CuSO_4$ (2 x 10 ml), H_2O (1 x 10 ml) and brine (1 x 10 ml) and dried over Na_2SO_4. Filtration and concentration *in vacuo* followed by flash chromatography on silica gel (deactivated with 10% w/w H_2O) eluting with 5% EtOAc/hexanes gave pure **10c** (33 mg, 0.105 mmol, 20% yield) as a colorless oil: $[\alpha]_D = +82.9$ (*c* 0.42, $CHCl_3$); UV (λ_{max}, EtOH) 299 nm; IR (ν) 3552, 2958, 1254, 1103, 1049, 859, 832, 778, 668 cm^{-1}; ^1H NMR (400 MHz) δ 6.38 (1H, dd, *J*=17.4, 10.9), 5.87 (1H, m), 5.72 (1H, m), 5.59 (1H, d, *J*= 17.4), 5.28 (1H, d, *J*= 10.9), 4.55 (1H, dd, *J*=5.7, 2.7), 4.21 (1H, ddd, *J*=5.7, 2.4, 1.0), 2.71 (1H, dd, *J*=2.4, 0.4), 1.64 (1H, pentet, *J*=6.9), 0.892 (3H, d, *J*=6.9), 0.887 (1H, d, *J*=6.9), 0.87 (6H, s), 0.17 (3H, s), 0.15 (3H, s); ^{13}C NMR δ 138.5 (C), 135.2 (CH), 127.9 (C), 126.5 (CH), 126.2 (CH), 116.5 (CH_2), 71.7 (CH), 65.3 (CH), 34.2 (CH), 25.0 (C), 20.3 (CH_3), 20.1 (CH_3), 18.6 (CH_3), 18.5 (CH_3), –2.6 (CH_3), –2.9 (CH_3); HRMS (CI): $C_{16}H_{26}ClOSi$ [M–17] calcd. 297.1441, found 297.1436.

9-Chloro-2-dimethyl(1,1,2-trimethylpropyl)siloxy-7-vinyl-4-oxatricyclo-[4.3.1.$0^{3,7}$]dec-8-ene (11c). A solution of **10c** (28.6 mg, 0.091 mmol) in THF (0.8 ml) was added slowly to a stirring slurry of NaH (11 mg, 0.45 mmol) in THF (0.2 ml) cooled to –20°C. A solution of allyl bromide (55 mg, 0.45 mmol) in THF (0.5 ml) was then added slowly, and the mixture stirred at -20°C for 5 d at which point TLC showed complete disappearance of **10c**. The reaction was quenched at –20°C with H_2O (0.5 ml) and extracted with Et_2O (4 x 3 ml). The combined organic layers were washed with brine (1 x 5 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude allyl ether was dissolved in CCl_4 (30 ml) and the solution stored at room temperature for 5 d. Concentration *in vacuo* and flash chromatography on silica gel eluting with a 0 → 5% EtOAc/hexanes solvent gradient provided the adduct **11c** (10 mg, 0.028 mmol, 31% yield) as a colorless oil: ^{1}H NMR (400 MHz) δ 6.01 (1H, dd, *J*=17.6, 10.8), 5.75 (1H, d, *J*=2.5), 5.25 (1H, dd, *J*=17.6, 0.9), 5.19 (1H, dd, *J*=10.8, 0.9), 3.91 (1H, *J*=7.6, 4.8, 0.3), 3.65 (1H, dt, *J*=6.7, 2.0), 3.61 (1H, d, *J*=6.7), 3.59 (1H, d, *J*=7.6), 2.42 (1H, m), 2.03 (1H, bdd, *J*=9.5, 4.8), 1.86 (1H, ddd, *J*=12.8, 3.6, 1.7), 1.82-1.75 (1H, m), 1.61 (1H, pentet, *J*=6.9), 0.90 (3H, d, *J*=6.9), 0.88 (3H, d, *J*=6.9), 0.85 (3H, s), 0.84 (3H, s), 0.10 (3H, s), 0.09 (3H, s); ^{13}C NMR δ 140.1 (CH), 134.9 (C), 124.3 (CH), 115.2 (CH_2), 76.5 (CH), 74.1 (CH_2), 71.5 (CH), 54.4 (C), 45.6 (CH), 41.0 (CH), 34.4 (CH), 33.3 (CH_2), 25.1 (C), 20.5 (CH_3), 20.2 (CH_3), 18.7 (CH_3), 18.5 (CH_3), –2.6 (CH_3), –3.4 (CH_3); MS (CI): [M+1] 355.

Synthesis of 12 from 11c. A solution of **11c** (7 mg, 0.020 mmol) in absolute EtOH (0.5 ml) was hydrogenated over 10% Pd/C (1 mg) at 45 psi for 3.5 h. The mixture was vacuum filtered through celite and the filtrate concentrated *in vacuo*. Flash chromatography on silica gel eluting with a 0 → 1% EtOAc/hexanes solvent gradient provided **12** (4.6 mg, 0.014 mmol, 70% yield) as a colorless oil: $[\alpha]_D$ = -17.4 (*c* 0.27, $CHCl_3$). The spectral data were identical to that shown for **12** above.

(2*R*,3*S*)-*cis*-4-Chloro-3-dimethyl(1,1,2-trimethylpropyl)siloxy-1-vinylcyclohexa-4,6-diene-2-ol (10d). Dimethylthexylsilyl chloride (2.46 g, 18.1 mmol, neat) was added *via* syringe to a solution of the diol **3d** (2.84 g, 16.45 mmol) and imidazole (2.46 g, 36.2 mmol) in DMF (36 ml) at 0°C. The resulting solution was stored at 0°C for 3 d. The solution was diluted with ether (35 ml) and washed with brine (1 x 25 ml). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 ml). The combined organic layers were washed with sat. $CuSO_4$ (2 x 25 ml), water (1 x 50 ml) and brine (1 x 50 ml) and dried over Na_2SO_4. Filtration and concentration *in vacuo* followed by flash chromatography on silica gel (deactivated with 10% w/w H_2O) eluting with 5% EtOAc/hexanes provided **10d** (2.50 g, 7.94 mmol, 48% yield) as a colorless oil: $[\alpha]_D$ = +12.4 (*c* 0.645, $CHCl_3$); ^{1}H NMR (400 MHz) δ 6.39 (1H, dd, *J*=17.6, 10.8),

6.10 (1H, dd, *J*=6.3, 2.3), 5.88 (1H, dd, *J*=6.3, 0.6), 5.48 (1H, d, *J*= 17.6), 5.20 (1H, d, *J*= 10.8), 4.50 (1H, dd, *J*=5.5, 2.3), 4.36 (1H, dd, *J*=5.5, 2.3), 2.73 (1H, d, *J*=2.3), 1.68 (1H, pentet, *J*=6.9), 0.93 (3H, d, *J*=6.9), 0.91 (3H, d, *J*=6.9), 0.91 (6H, s), 0.25 (3H, s), 0.19 (3H, s); ^{13}C NMR δ 136.2 (C), 135.8 (CH), 135.6 (C), 123.9 (CH), 122.1 (CH), 114.5 (CH_2), 72.6 (CH), 67.5 (CH), 34.1 (CH), 25.3 (C), 20.5 (CH_3), 20.0 (CH_3), 18.8 (CH_3), 18.4 (CH_3), -2.7 (CH_3), –2.9 (CH_3); HRMS (CI): $C_{16}H_{26}ClOSi$ [M–17] calcd. 297.1441, found 297.1448.

(1*S*,2*R*,3*S*)-1-dimethyl(1,1,2-trimethylpropyl)siloxy-3-ethylcyclohexan-2-ol (15). The mono-protected styrene diol **10a** (57.6 mg, 0.205 mmol) was dissolved in absolute EtOH (1.1 ml), and triethylamine (0.30 ml) and Adams' catalyst (6.5 mg) were added. The mixture was hydrogenated at 45 psi for 24 h. It was then filtered and concentrated to a residue which was chromatographed (flash column on silica gel, 2% EtOAc/hexanes) to give **15** as a clear oil (12 mg, 0.042 mmol, 20% yield): $[\alpha]_D$ = +6.84 (*c* 0.76, $CHCl_3$); IR (ν) 3580, 3400 (br), 2980, 2965, 2860, 1470, 1380, 1260, 1105, 1065, 990, 965, 865, 830, 775 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.71 (1H, bs), 3.55 (1H, ddd, *J*=10.4, 5.7, 3.0), 2.23 (1H, bs), 1.67 (1H, dt, *J*= 9.5, 3.2), 1.62 (1H, heptet, *J*= 6.9), 1.58-1.53 (2H, m), 1.49 (1H, dd, *J*=14.0, 7.1), 1.40 (1H, t, *J*=7.2), 1.35 (1H, m), 1.27 (1H, dd, *J*=12.0, 2.8), 1.22 (1H, dd, *J*=9.0, 2.4), 1.16 (1H, dt, *J*=12.2, 3.9), 0.92 (3H, t, *J*=7.5), 0.89 (3H, d, *J*=6.9), 0.88 (3H, d, *J*=6.9), 0.84 (6H, s), 0.10 (6H, s); ^{13}C NMR δ 73.6 (CH), 72.1 (CH), 42.42 (CH), 42.40 (C), 34.3 (CH), 28.9 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 23.6 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), 11.8 (CH_3), -2.5 (CH_3), –2.9 (CH_3). Treatment of **10d** (62 mg, 0.197 mmol) in a similar manner gave **15** (18 mg, 0.063 mmol, 32% yield) identical to that from **10a** by ^{1}H and ^{13}C NMR: $[\alpha]_D$ = +1.01 (*c* 1.39, $CHCl_3$).

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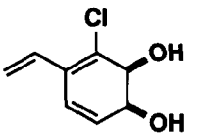

16

20. For make-up of the mineral salts broth, see reference 19.

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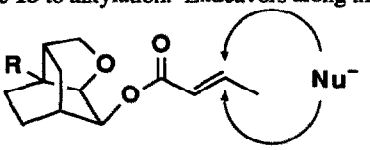
27. The structural and spatial relationship of **10** to known auxiliary groups[29] indicates the potential for testing the face selectivities of both unsaturated esters of type **17** toward conjugate addition and ester dienolate anions of type **18** to alkylation. Endeavors along these lines form current research in our laboratories.



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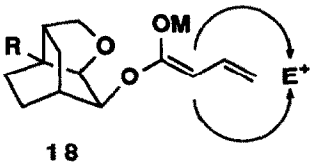

18

28. Boyd and co-workers[17] have reported the enantiomeric excess of **1** (R = F) obtained from *Pp*-UV4 to be *ca.* 60% ($[\alpha]_D = -33$). We have performed the microbial oxidation of fluorobenzene with *Pp*-39D and the optical rotation of **1** (R = F) obtained was identical to that reported above.

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