Sharpless Asymmetric Dihydroxylation of *trans*-Propenylphosphonate by Using a Modified AD-mix-α and the Synthesis of Fosfomycin

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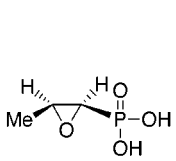
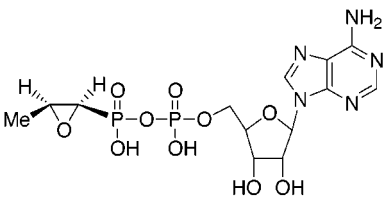
Fosfomycin (**1**) is not only a naturally occurring organophosphonic acid isolated from fermentation broths of *Streptomyces fradiae*[1] but also a component of fosfadecin (**2**) isolated recently from the culture filtrates of *Pseudomonas viridiflava* PK-5.[2] Both of these products are antibiotics against Gram-negative and Gram-positive bacteria. Due to its excellent properties as a drug, fosfomycin is manufactured by a method that involves epoxidation of the corresponding (*E*)-1-propenylphosphonate and optical resolution of the resulting racemic epoxide.[3] However, a method that does not rely upon such resolution is desirable. Several syntheses of optically active fosfomycin along this idea have been published recently.[4] The key reactions used in these syntheses are asymmetric hydrogenation of *β*-oxo-α-bromopropylphosphonate,[5a] bromohydroxylation of a chiral 1-propenylphosphonate,[5b] addition of $(TMSO)P(OR)_2$ or $HP(=O)(OR)_2$ to α-alkoxy propanal,[5c−e] reduction of an α-oxo-*β*-acyloxypropylphosphonate,[5f] and microbial epoxidation.[5g] In addition to fosfomycin, analogues probably synthesized by these methods would be useful to start a biochemical study of fosfadecin. These methods, however, suffer from low enantio-(or diastereo-)selectivity, production of byproduct(s), and/or insufficient efficiency.



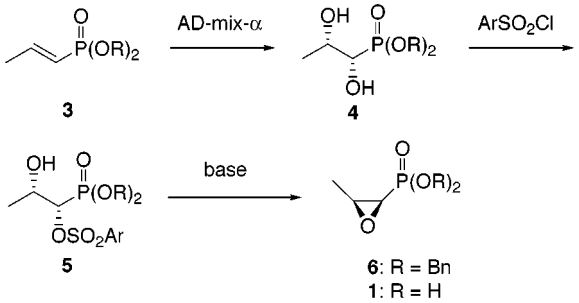
fosfomycin (**1**)



fosfadecin (**2**)

Our recent research work[6] using the Sharpless asymmetric dihydroxylation (AD) reaction[7] inspired a method illustrated in Scheme 1. The key reactions are the AD reaction of **3** and subsequent monosulfonylation of the resulting diol **4** at either the α- or *β*-side of the hydroxyl groups. High regioselection in the latter step is pivotal to transfer the enantiomeric purity of **4** into the epoxide moiety of **1**. The stereochemistry of **4** tentatively drawn in Scheme 1 assumes the sulfonylation at the α side. Investigation of the literature revealed that diethyl phosphonate **3a** (R = Et), investigated for the other purposes, is a poor substrate for the AD reaction even though the loading of the osmium catalyst and/or the chiral ligand ($(DHQ)_2PHAL$) in the AD reagent is increased from the original.[8−11] On the other hand, regioselective sulfonylation of **4** is less predictable by the fact that silyation of α,*β*-dihydroxyalkylphosphonates prefers the *β* side,[12] while sulfonylation of α,*β*-dihydroxyalkanoates prefers the α side,[13] respectively. However, the proposed short-step method (Scheme 1) was attractive enough for us to reinvestigate the AD reaction of **3** and

Scheme 1



for **3** and **4**:
a, R = Et; **b**, R = Bn
for **5**:
a, R = Bn, Ar = 4-MeC_6H_4;
b, R = Bn, Ar = 4-$NO_2C_6H_4$

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(4) Reviews: (a) Iorga, B.; Eymery, F.; Savignac, P. *Synthesis* **1999**, 207−224. (b) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237−12273.

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(7) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(8) Original stoichiometries for $K_2OsO_2(OH)_2$ and the chiral ligand are 0.2 and 1 mol %, respectively. Shibuya[9] added $K_2OsO_2(OH)_2$ (0.8 mol %) in AD-mix-α (from Aldrich) to obtain diol **4a** (R = Et) with 33% ee in 48% yield from **3a** (R = Et) after 2 days at 25 °C, while Lohray[10] increased concentration of OsO_4 and $(DHQ)_2PHAL$ to 1 and 2 mol % to obtain the same diol with 32% ee in 45% yield.

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Table 1. AD Reaction of 3b and 3a[a]

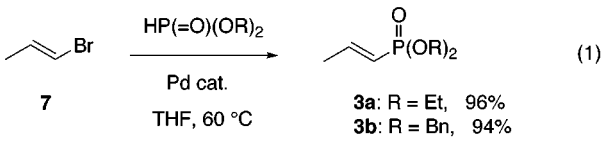
entry	substrate	reagent	*T* (°C)	time (days)	product[b]	yield (%)	% ee[c]
1	**3b**	AD-mix-α[d]	rt	8	**4b**	<30	62
2	**3b**	AD-mix-α-(x 3)[e]	rt	5	**4b**	51	72
3	**3b**	AD-mix-α-(x 3)[e]	0	6	**4b**	95	78
4	**3a**	AD-mix-α-(x 3)[e]	0	10	**4a**	62	–

[a] **3b**: R = Bn. **3a**: R = Et. [b] **4b**: R = Bn. **4a**: R = Et. [c] Calculated by ^{1}H NMR spectroscopy of the corresponding bis-MTPA ester. [d] Prepared according to ref 7a. [e] Three times standard quantity of $K_2OsO_2(OH)_4$ and $(DHQ)_2PHAL$ (0.6 and 3.0 mol %, respectively) were used.

to explore the other steps. In this paper, we present successful results with a modified AD reagent and the synthesis of fosfomycin.

We envisioned that the inefficiency of the above AD reaction of diethyl phosphonate **3a** (R = Et) arises mainly from a lack of the lipophilic part in molecule **3a**, which is a necessary part to be trapped into the cavity of the chiral ligand. Thus, dibenzyl derivative **3b** (R = Bn) was chosen as an alternative substrate for AD reaction.

Phosphonate **3b** was once synthesized by a rather tedious method because a simpler method through a base-catalyzed isomerization of dibenzyl 2-propenylphosphonate, the reaction originally reported for diethyl phosphonate,[14] was unsuccessful.[15] Among the other methods published,[3,16] the palladium-catalyzed reaction[16a] of alkenyl halides and dialkyl phosphite ($HP(=O)(OR)_2$) was investigated. Phosphonate **3b** was obtained from (*E*)-1-propenyl bromide (**7**) and $HP(=O)(OBn)_2$ in moderate yield (52%) under the reported conditions ($Pd(PPh_3)_4$ (5 mol %), Et_3N (1 equiv), toluene, 90 °C, 6 h). Although use of *i*-Pr_2NEt as a base did not improve the yield, reaction in THF at 60 °C furnished **3b** in 94% yield (eq 1). Under similar conditions, **3a** was prepared from **7** and $HP(=O)(OEt)_2$ in good yield.



(1)

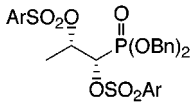
AD reaction of dibenzyl phosphonate **3b** was investigated, and the results are summarized in Table 1. For comparison, that obtained with diethyl derivative **3a** is also presented in Table 1. AD reaction of **3b**, carried out with standard AD-mix-α, was sluggish even at room temperature to produce diol **4b** (R = Bn) in <30% yield (Table 1, entry 1). However, enantiomeric purity was 62% ee, which was much higher than that of **4a** (R = Et) synthesized previously by other groups,[8−10] thus confirming our proposed effect of the benzyl ester on AD reaction (vide supra). To speed up the reaction, we prepared a reagent enriched with the catalyst: three times standard quantity of $K_2OsO_2(OH)_4$ and $(DHQ)_2PHAL$, i.e., 0.6 and 3 mol %, respectively, were loaded on a mixture of $K_3Fe(CN)_6$ (3 equiv) and K_2CO_3 (3 equiv) to give AD-mix-α-(×3). The modified reagent thus prepared not only accelerated the reaction (Table 1, entry 2) but also allowed the reaction to proceed at a lower temperature (0 °C), providing better ee (Table 1, entry 3). Enantiomeric purity of **4b** thus obtained was increased to >99% ee by recrystallization from hexane/EtOAc in 65% yield. Next, AD reaction of diethyl phosphonate **3a** with the modified reagent was examined. However, the reaction was not remarkably accelerated and the yield of **4a** was moderate even after 10 days (Table 1, entry 4).

Table 2. Sulfonylation of Diol 4b

entry	Ar of $ArSO_2Cl$ (equiv)	amine (equiv)	*T* (°C)	time (h)	yield of **5**[a]
1	4-Me-C_6H_4 (1.3)	Et_3N (1.8)	rt	41	**5a** (28%)[b]
2	4-Me-C_6H_4 (1.3)	pyridine (1.8)	rt	73	no reaction
3	4-Me-C_6H_4 (1.3)	*i*-Pr_2NEt (1.8)	rt	73	no reaction
4	4-Me-C_6H_4 (1.7)	Et_3N (2.0)	5	53	**5a** (49%)[b]
5	4-NO_2−C_6H_4 (1.3)	Et_3N (1.8)	5	30	**5b** (> 67%)[c]

[a] **5a**: R = Bn, Ar = 4-Me-C_6H_4 for entries 1−4. **5b**: R = Bn, Ar = 4-$NO_2C_6H_4$ for entry 5. [b] In addition to **5a**, ditosylate **8** and diol **4b** were isolated. [c] Yield of **6** from **4b** via **5b** was 67%.

Regioselective sulfonylation of diol **4b** (R = Bn) and subsequent transformation to **1** was then investigated. In this particular case, steric hindrance around the diol moiety (Me vs phoshonate group) seems to prefer sulfonylation at the β-hydroxyl group, and the electron-withdrawing nature of the phosphonate group vice versa on the basis of the related reactions.[11−13] With these tendencies in mind, sulfonylation with MsCl, TsCl, or 4-$NO_2C_6H_4SO_2Cl$ was examined. Mesylation was marginally regioselective (data not shown). On the other hand, tosylation at room temperature took place regioselectively at the α-hydroxyl group to furnish **5** of R = Bn, Ar = 4-MeC_6H_4 (Table 2, entry 1). However, more than a small quantity of ditosylation product **8** was detected by TLC analysis before **4b** was consumed completely. Reaction proceeded little with other bases, and **4b** was recovered quantitatively (Table 2, entries 2 and 3), while use of a larger quantity of TsCl and a lower temperature of 5 °C (in a refrigerator) improved the yield to 49% (Table 2, entry 4), though substantial formation of **8** was still accompanied with monotosylate **5** and diol **4b**. Efficiency of this transformation was enhanced with 4-$NO_2C_6H_4SO_2Cl$. After 30 h at the same temperature (5 °C), TLC analysis showed no diol **4b**, major production of monosulfonate **5** (R = Bn, Ar = 4-$NO_2C_6H_4$), and a trace amount of disulfonate **9**.[11,17] Subsequently, the mixture was treated with K_2CO_3 in acetone to afford the dibenzyl epoxide **6** ($[\alpha]^{30}_D$ +4.7 (*c* 0.32, $CDCl_3$) (lit.[5d] $[\alpha]^{20}_D$ +4.4 (*c* 2.15, $CDCl_3$))) in 67% yield from diol **4b**. Hydrogenolysis of this epoxide to produce **1** is reported,[5d] and hence, the method proposed in Scheme 1 was established.



8: Ar = C_6H_4-Me-4
9: Ar = C_6H_4-NO_2-4

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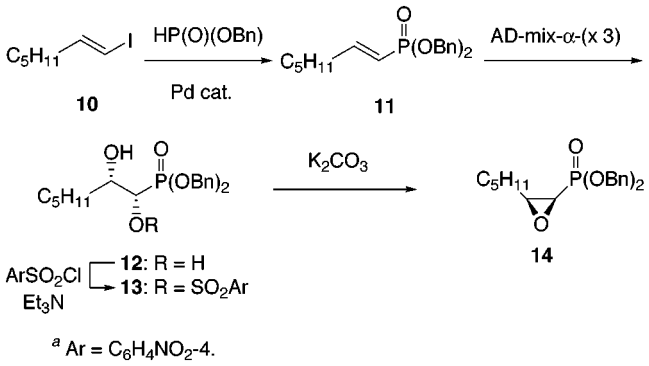
(17) The inherent low regioselectivity of diol **4b** for sulfonylation with TsCl is likely to be improved by the high reactivity of 4-$NO_2C_6H_4SO_2Cl$.

Scheme 2



[a] Ar = $C_6H_4NO_2$-4.

Since the Me group in substrate **3b** (R = Bn) is the smallest alkyl group, homologues of **3b** would surely be better substrates than **3b** for the AD reaction due to the increased lipophilic property provided by the alkyl chain. In fact, dibenzyl phosphonate **11**, prepared from iodide **10** and $HP(O)(OBn)_2$ under the palladium catalysis in 78% yield, was converted into diol **12** with 96% ee in 85% yield by using the modified reagent (AD-mix-α-(×3)). This result is better than that of entry 3 in Table 1 for **3b**. Subsequently, diol **12** was transformed into epoxide **14** in 75% yield through monosulfonate **13**, which was produced with high regioselectivity. In summary, synthesis of fosfomycin was achieved through the AD reaction of dibenzyl (*E*)-1-propenylphosphonate (**3**) with modified AD-mix-α-(×3) and the highly regioselective sulfonylation of **4b** at the α-hydroxyl group. High efficiency in the AD reaction was realized not only by the lipophilic nature of the benzyl group in the substrate but also by the modification of the AD reagent. In addition, conditions for regioselective α-sulfonylation were established. α-Sulfonyloxyalkyl phosphonates available by the present method would be useful for synthesis of α-amino-*β*-hydroxy- or *β*-amino-α-hydroxyalkylphosphonic acids, which are important analogues of the corresponding carboxylic acids.[12,18]

Experimental Section

General Methods. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}). ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ ($\delta = 0$ ppm) and the center line of $CDCl_3$ triplet ($\delta = 77.1$ ppm) as internal standards, respectively. Coupling constants between carbon and phosphorus atom in ^{13}C NMR spectra are given in hertz (Hz) with indication of d (doublet). THF and Et_2O were distilled from Na/benzophenone before use. After the reactions, products were extracted with given solvents, and the extracts were dried over $MgSO_4$ and concentrated by using a rotary evaporator unless otherwise specified. The crude products were purified by chromatography on silica gel using a mixture of solvents as eluents.

Modified AD-mix-α (AD-mix-α-(×3)). $K_2OsO_2{\cdot}2H_2O$ (11 mg, 0.030 mmol) and $(DHQ)_2PHAL$ (117 mg, 0.150 mmol) were added to a mixture of powdered $K_3Fe(CN)_6$ (4.90 g, 15 mmol) and K_2CO_3 (2.06 g, 15 mmol). The resulting mixture was grounded to afford AD-mix-α-(×3).

Dibenzyl (*E*)-1-Propenylphosphonate (3b) (R = Bn). To a solution of bromide **7** (0.78 mL, 9.15 mmol, 99% trans), $HP(O)(OBn)_2$ (1.68 mL, 7.61 mmol), and Et_3N (1.06 mL, 7.56 mmol) in THF (15 mL) was added $Pd(PPh_3)_4$ (452 mg, 0.391 mmol) under argon atmosphere. The resulting mixture was stirred at 60 °C for 8 h. After being cooled to 0 °C, the mixture was quenched with EtOAc and saturated $NaHCO_3$ (1:1, 30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried and concentrated to afford an oil, which was purified by chromatography (EtOAc/hexane) to furnish **3b** (2.16 g, 94%): bp 190 °C (1 Torr); IR (neat) 3033, 1637, 1254, 996 cm^{-1}; ^1H NMR δ 1.84 (dm, $J = 7$ Hz, 3 H), 5.01 (d, $J = 8$ Hz, 4 H), 5.68 (ddq, $J = 22$, 17, 2 Hz, 1 H), 6.78 (ddq, $J = 22$, 17, 7 Hz, 1 H), 7.32 (br s, 10 H); ^{13}C NMR δ 20.0 (d, $J = 24$ Hz), 67.0 (d, $J = 5$ Hz), 118.0 (d, $J = 188$ Hz), 127.6, 128.0, 128.3, 136.1 (d, $J = 7$ Hz), 149.2 (d, $J = 5$ Hz). Anal. Calcd for $C_{17}H_{19}O_3P$: C, 67.54; H, 6.33. Found: C, 67.16; H, 6.40.

Dibenzyl (1*S*,2*S*)-1,2-Dihydroxypropylphosphonate (4b) (R = Bn). To an ice-cold suspension of the modified AD-mix-α-(×3) (2.31 g) and $MeSO_2NH_2$ (157 mg, 1.65 mmol) in *t*-BuOH (8 mL) and H_2O (8 mL) was added **3b** (500 mg, 1.65 mmol). The resulting mixture was stirred at 0 °C for 6 days. Brine (10 mL) was added, and the mixture was extracted with EtOAc twice. The combined organic layers were dried and concentrated. The residue obtained was purified by chromatography (EtOAc/hexane) to afford **4b** (526 mg, 95%), which was 78% ee by ^1H NMR spectroscopy of the corresponding bis-MTPA ester. This product was recrystallized from hexane and EtOAc to obtain **4b** (mp 90−91 °C) in 65% yield with >99% ee: $[\alpha]^{28}_D$ −1.2 (*c* 1.0, $CHCl_3$); IR (Nujol) 3392, 1189, 991 cm^{-1}; ^1H NMR δ 1.28 (dd, $J = 7$, 1.5 Hz, 3 H), 3.46 (d, $J = 5$ Hz, 1 H), 3.70−3.84 (m, 2 H), 4.10−4.24 (m, 1 H), 4.98−5.19 (m, 4 H), 7.34 and 7.35 (2s, 10 H); ^{13}C NMR δ 19.3 (d, $J = 11$ Hz), 66.6 (d, $J = 3$ Hz), 68.1 (d, $J = 7$ Hz), 68.8 (d, $J = 7$ Hz), 72.1 (d, $J = 157$ Hz), 128.03, 128.09, 128.52, 128.61, 128.64, 135.8 (d, $J = 6$ Hz), 136.0 (d, $J = 6$ Hz). Anal. Calcd for $C_{17}H_{21}O_5P$: C, 60.71; H, 6.29. Found: C, 60.85; H, 6.42.

Dibenzyl (1*R*,2*S*)-1,2-Epoxypropylphosphonate (6). To an ice-cold solution of diol **4b** (30 mg, 0.089 mmol, > 99% ee) and Et_3N (0.022 mL, 0.16 mmol) in CH_2Cl_2 (0.5 mL) was added 4-nitrobenzenesulfonyl chloride (26 mg, 0.117 mmol). The flask was kept in a refrigerator (5 °C) for 30 h. The solution was diluted with EtOAc and saturated NH_4Cl. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined extracts were dried and concentrated to afford a an oil, which was a mixture of monosulfonate **5b** (R = Bn, Ar = 4-$NO_2C_6H_4$) and a trace of **9** by TLC analysis. This mixture was subjected to the next reaction without further purification. Analytically pure monosulfonate **5b** was obtained from a crude product of another run by chromatography (hexane/EtOAc): ^1H NMR δ 1.35 (dd, $J = 6$, 1 Hz, 3 H), 2.70 (br d, $J = 6$ Hz, 1 H), 4.21−4.34 (m, 1 H), 4.83−5.15 (m, 5 H), 7.18−7.38 (m, 10 H), 7.96 (dt, $J = 9$, 2 Hz, 2 H), 8.11 (dt, $J = 3$, 2 Hz, 2 H).

A mixture of crude **5b** and K_2CO_3 (37 mg, 0.27 mmol) in acetone (0.8 mL) was stirred at room temperature for 30 h and filtered through a pad of Celite with EtOAc. The filtrate was concentrated, and the residue was purified by chromatography to afford **6** (19 mg, 67% from diol **4b**): $[\alpha]^{30}_D$ +4.7 (*c* 0.32, $CDCl_3$) (lit.[5d] $[\alpha]^{20}_D$ +4.4 (*c* 2.15, $CDCl_3$)). The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra of **6** were identical with the data reported.[5d]

Diethyl (*E*)-1-Propenylphosphonate (3a) (R = Et). According to the procedure for preparation of **3b**, bromide **7** (0.75 mL, 8.73 mmol, 99% trans) was converted into **3a**[14] (1.23 g, 96%) by using $HP(O)(OEt)_2$ (0.93 mL, 7.22 mmol), Et_3N (1.0 mL, 7.17 mmol), and $Pd(PPh_3)_4$ (430 mg, 0.372 mmol) in THF (15 mL) at 60 °C for 8 h: bp 55 °C (1 Torr); IR (neat) 1239, 1027, 964 cm^{-1}; ^1H NMR δ 1.33 (t, $J = 7$ Hz, 6 H), 1.92 (dt, $J = 7$, 2 Hz, 3 H), 4.07 (quintet, $J = 7$ Hz, 4 H), 5.68 (ddq, $J = 21$, 17, 2 Hz, 1 H), 6.80 (ddq, $J = 22$, 17, 7 Hz, 1 H); ^{13}C NMR δ 16.3 (d, $J = 7$ Hz), 20.0 (d, $J = 24$ Hz), 61.4 (d, $J = 6$ Hz), 118.3 (d, $J = 187$), 148.6 (d, $J = 5$ Hz).

Diethyl (1*S*,2*S*)-1,2-Dihydroxypropylphosphonate (4a) (R = Et). Asymmetric dihydroxylation of **3a** (100 mg, 0.561 mmol) was carried out according to the procedure for preparation of **4b** by using the modified AD-mix-α-(×3) (785 mg) and $MeSO_2NH_2$ (53 mg, 0.56 mmol) in *t*-BuOH (3 mL) and H_2O (3 mL) at 0 °C for 10 days to afford a 1:1.6 mixture of **3a** and **4a** (determined by ^1H NMR spectroscopy), which was separated by

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chromatography. The ^{1}H NMR (300 MHz) spectrum of **4a** thus synthesized was identical with that reported.[9b,10]

Dibenzyl (*E*)-1-Heptenylphosphonate (11). According to the procedure for preparation of **3b**, iodide **10** (1.53 g, 6.85 mmol) was converted into **11** (1.59 g, 78%) by using $HP(O)(OBn)_2$ (1.26 mL, 5.71 mmol), Et_3N (0.79 mL, 5.67 mmol), and $Pd(PPh_3)_4$ (339 mg, 0.293 mmol) in THF (12 mL) at 60 °C for 8 h: IR (neat) 3033, 1630, 1253, 996 cm^{-1}; ^{1}H NMR δ 0.88 (t, J = 7 Hz, 3 H), 1.18−1.46 (m, 6 H), 2.11−2.22 (m, 2 H), 5.03 (d, J = 8 Hz, 4 H), 5.65 (ddt, J = 22, 17, 1.5 Hz, 1 H), 6.78 (ddt, J = 22, 18, 7 Hz, 1 H), 7.34 (br s, 10 H); ^{13}C NMR δ 14.0, 22.4, 27.3 (d, J = 1 Hz), 31.2, 34.1 (d, J = 22 Hz), 67.1 (d, J = 5 Hz), 116.2 (d, J = 187 Hz), 127.7, 128.1, 128.3, 136.2 (d, J = 7 Hz), 154.3 (d, J = 5 Hz). Anal. Calcd for $C_{21}H_{27}O_3P$: C, 70.37; H, 7.59. Found: C, 70.21; H, 7.73.

Dibenzyl (1*S*,2*S*)-1,2-Dihydroxyheptylphosphonate (12). Asymmetric dihydroxylation of olefin **11** (200 mg, 0.56 mmol) was carried out according to the procedure for preparation of **4b** by using the modified AD-mix-α-(×3) (780 mg) and $MeSO_2NH_2$ (53 mg, 0.56 mmol) in *t*-BuOH (3 mL) and H_2O (3 mL) at 0 °C for 2 days to afford diol **12** as a solid (185 mg, 85%), which was 96% ee by ^{1}H NMR spectroscopy of the corresponding bis-MTPA ester. This diol was recrystallized from hexane and EtOAc (mp 76−77 °C): $[\alpha]^{23}_D$ −2.4 (*c* 0.21, $CHCl_3$); IR (Nujol) 3400, 1189, 1012, 992 cm^{-1}; ^{1}H NMR δ 0.87 (t, J = 7 Hz, 3 H), 1.2−1.8 (m, 8 H), 3.37 (d, J = 5 Hz, 1 H), 3.62 (dd, J = 10, 2 Hz, 1 H), 3.83 (ddd, J = 10, 8, 2 Hz, 1 H), 3.90−4.01 (m, 1 H), 4.98−5.19 (m, 4 H), 7.34 and 7.35 (2s, 10 H); ^{13}C NMR δ 14.2, 22.7, 25.5, 31.8, 33.1 (d, J = 11 Hz), 68.2 (d, J = 7 Hz), 68.8 (d, J = 7 Hz), 70.4, 70.9 (d, J = 157 Hz), 128.0, 128.07, 128.45, 128.56,-128.60, 135.9 (d, J = 6 Hz), 136.1 (d, J = 6 Hz). Anal. Calcd for $C_{21}H_{29}O_5P$: C, 64.27; H, 7.45. Found: C, 63.93; H, 7.27.

Dibenzyl (1*R*,2*S*)-1,2-Epoxyheptylphosphonate (14). By using the same procedure described for the preparation of **5b**, diol **12** (50 mg, 0.127 mmol) was converted into α-sulfonate **13** (62 mg, 85%) by using 4-$NO_2C_6H_4SO_2Cl$ (36 mg, 0.16 mmol) and Et_3N (0.032 mL, 0.23 mmol) in CH_2Cl_2 (1 mL) at 0 °C for 20 h: ^{1}H NMR δ 0.88 (t, J = 7 Hz, 3 H), 1.20−1.90 (m, 8 H), 2.82 (d, J = 6 Hz, 1 H), 3.98−4.15 (m, 1 H), 4.80−5.13 (m, 5 H), 7.17−7.42 (m, 10 H), 7.95 (dt, J = 9, 2 Hz, 2 H), 8.07 (dt, J = 9, 2 Hz, 2 H).

A mixture of the above sulfonate **13** (62 mg, 0.107 mmol) and K_2CO_3 (45 mg, 0.33 mmol) in acetone (1 mL) was stirred at room temperature to furnish **14** (35 mg, 88%): $[\alpha]^{23}_D$ −2.4 (*c* 0.67, $CHCl_3$); IR (neat) 3033, 1457, 1262, 996 cm^{-1}; ^{1}H NMR δ 0.87 (t, J = 7 Hz, 3 H), 1.20−1.54 (m, 6 H), 1.80−1.92 (m, 2 H), 2.98 (dd, J = 28, 5 Hz, 1 H), 3.13 (ddd, J = 12, 7, 5 Hz, 1 H), 4.97−5.17 (m, 4 H), 7.34 (br s, 10 H); ^{13}C NMR δ 14.2, 22.7, 26.5, 28.5, 31.6, 50.2 (d, J = 204 Hz), 58.2 (d, J = 1 Hz), 67.8 (d, J = 6 Hz), 68.3 (d, J = 6 Hz), 128.0, 128.1, 128.52, 128.56, 128.59, 135.79, 135.8 (d, J = 6 Hz), 135.9 (d, J = 6 Hz). Anal. Calcd for $C_{21}H_{27}O_4P$: C, 67.37; H, 7.27. Found: C, 67.65; H, 7.47.

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Supporting Information Available: The ^{1}H NMR spectra of the bis-MTPA esters derived from racemic **4b**, enantiomerically enriched **4b** of 78% ee, and recrystallized **4b** of >99% ee. This material is available free of charge via the Internet at http://pubs.acs.org.

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