The reaction was quenched by adding NH_4NO_3 and extracted as described previously. The substitution product was quantified by GLC using 4-bromobiphenyl as internal standard.

Photostimulated Reaction of *p*-Bromoanisole with Ph_2P^- and PhS^- Ions in Me_2SO. These reactions were carried out by following the same procedure as before, with the same internal standards.

General Procedure for Competition Experiments. The nucleophile Ph_2P^- and PhS^- ions were simultaneously prepared in liquid ammonia as in the preceding reactions. Then the ammonia was allowed to evaporate and dry degassed Me_2SO was added. The substrate, 1-bromoadamantane or *p*-bromoanisole, was quickly added, and the flask was irradiated as stated in Table II. The reactions were worked-up as before and quantified by GLC. Molar response factors were determined and used in the calculations of GLC results in all cases.

Calculations of Relative Reactivities of Nucleophiles. Equation 15 was employed. $[Nu_1^-]_0$ and $[Nu_2^-]_0$ are initial concentrations, and $[RNu_1]_t$ and $[RNu_2]_t$ are concentrations of products at time t. This equation is based on the assumption that both Nu_1^- and Nu_2^- reactions with the radicals are first order in nucleophile.[27]

$$\frac{kNu_1^-}{kNu_2^-} = \frac{\ln ([Nu_1^-]_0/([Nu_1^-]_0 - [RNu_1]_t))}{\ln ([Nu_2^-]_0/([Nu_2^-]_0 - [RNu_2]_t))} \quad (15)$$

Calculations of Relative Reactivities of Substrates. To calculate the relative reactivity we used eq 16:[27]

$$\frac{k(1\text{-BrAd})}{k(p\text{-BrAn})} = \frac{[p\text{-BrAn}]_0([1\text{-AdPPh}_2] + [\text{AdH}])}{[1\text{-BrAd}]_0([p\text{-AnPPh}_2] + [\text{AnH}])} \quad (16)$$

In this equation we used both products formed from 1-adamantyl radicals (1-adamantyldiphenylphosphine and adamantane) and from *p*-anisyl radicals (*p*-anisyldiphenylphosphine and anisole) because they are products derived from the radicals.

Acknowledgment. E.R.N.B. gratefully acknowledges receipt of a fellowship from the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina. INFIQC is jointly sponsored by the CONICET and the Universidad Nacional de Córdoba. This work is partially supported by the Consejo de Investigaciones Científicas y Tecnológicas de Córdoba.

Registry No. Ph_2P^-, 6396-02-7; PhS^-, 13133-62-5; 1-AdSPh, 88459-01-2; 1-bromoadamantane, 768-90-1; *p*-bromoanisole, 104-92-7; 1-adamantyl, 2819-03-6; *p*-anisyl, 2396-03-4.

(27) Bunnett, J. F. In *Investigation of Rates and Mechanisms of Reactions*, 3rd ed.; Lewis, E. S., Ed.; Wiley-Interscience: New York, 1974; Part I, p 159.

Synthesis of Polydentate Ligands with Homochiral Phosphine Centers

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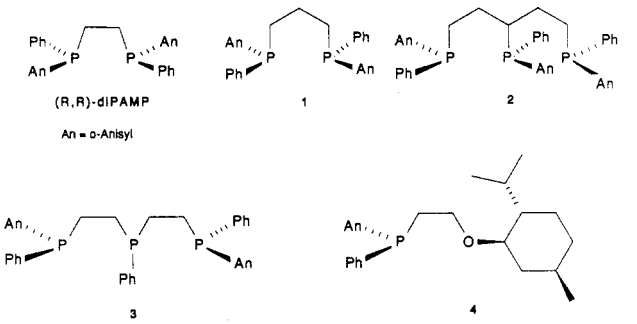
Optically pure (*S*)-(*o*-methoxyphenyl)phenylvinylphosphine oxide was prepared from (*S*)-(*o*-methoxyphenyl)methylphenylphosphine oxide and *N*,*S*-dimethyl-*S*-phenylsulfoximine and utilized in the preparation of (*S*,*S*)-1,3-propanediylbis[(*o*-methoxyphenyl)phenylphosphine], (*S*,*S*,*S*)-1,3,5-pentanetriyltris[(*o*-methoxyphenyl)phenylphosphine], (*S*,*S*)-bis[2-[(*o*-methoxyphenyl)phenylphosphinyl]ethyl]phenylphosphine, and (*SP*,1′*R*,2′*S*,5′*R*)-[2-[(2′-isopropyl-5′-methylcyclohexyl)oxy]ethyl](*o*-methoxyphenyl)phenylphosphine. These phosphines as complexes with rhodium(I) salts were used in hydrogenation of α-(acetylamino)acrylic acids to provide *N*-acetyl amino acids in optical purities ranging from 22 to 96%.

Among the large number of optically active phosphine ligands that have been used in catalytic asymmetric reactions,[1] only several possess chiral centers at phosphorus.[2] Knowles and co-workers made the initial breakthrough in this chemistry with their synthesis of a C_2-symmetric chiral bisphosphine, (*R*,*R*)-1,2-ethanediylbis[(*o*-methoxyphenyl)phenylphosphine] (diPAMP), and demonstration that the ligand is exceptionally effective in catalytic asymmetric hydrogenation of α-(acylamino)acrylic acids.[2a,b] Although the synthesis of such ligands is laborious, they are usually effective at very low concentrations. Herein we describe new methods for the production of polydentate phosphine ligands and their application to the synthesis of the novel, optically pure phosphine ligands **1**–**4** that are chiral at phosphorus. Ligand **1**, the next higher homologue of the celebrated diPAMP was of particular interest. The results of our investigation of the use of these ligands in the production of optically active α-amino acids by asymmetric hydrogenation are also summarized.



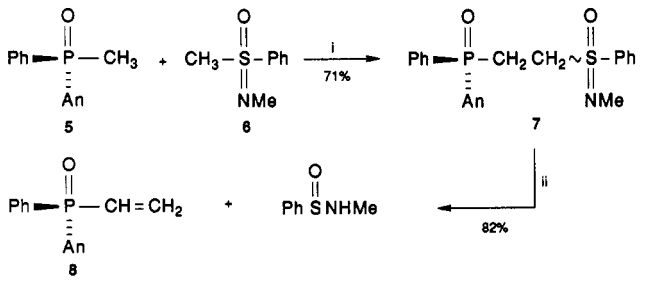
Our methods for the synthesis of ligands **1**–**4** utilize

† Wayne State University.
‡ Chiba University.

(1) For reviews, see: Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. Caplar, V.; Comisso, G.; Sunjic, V. *Synthesis* **1981**, *85*. Brown, J. M.; Chaloner, P. A. In *Homogeneous Catalysis with Metal Phosphine Complexes*; Fackler, J. P., Jr., Ed.; Plenum: New York, 1983; pp 137–165. Ojima, I. *Pure Appl. Chem.* **1984**, *56*, 99. Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395. Morrison, J. D., Ed.; *Asymmetric Synthesis*; Academic: New York, 1985; Vol. 5, Chapters 1–6.

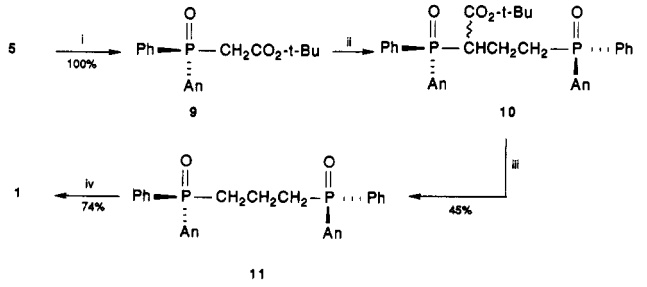
0022-3263/87/1952-2170$01.50/0

Scheme I[a]



[a] Key: (i) LDA followed by $CuCl_2$; (ii) xylene, reflux.

Scheme II[a]

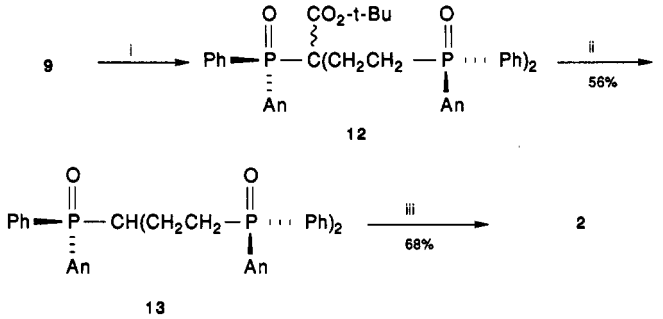


[a] Key: (i) $(t\text{-BuOCO})_2O$; (ii) **8**, catalytic NaH, benzene, rt, 6 h; (iii) *p*-TsOH, xylene, reflux; (iv) $HSiCl_3$/c-$C_6H_{11}NEt_2$, MeCN.

homochiral vinylphosphine oxide **8** as a key intermediate. Compound **8** was prepared by the sequence shown in Scheme I. Oxidative cross-coupling of (*S*)-(*o*-methoxyphenyl)methylphenylphosphine oxide (**5**) with racemic *N*,*S*-dimethyl-*S*-phenylsulfoximine (**6**) was conducted by a modification of a Mislow procedure for the dimerization of phosphine oxides.[3] Treatment of a 1:2 mixture of **5** and **6** with lithium diisopropylamide (LDA), followed by oxidation with copper(II) chloride, gave cross-coupling products **7** as mixture of diastereomers that were inseparable by thin-layer chromatography (TLC). (The reason for the preponderance of the cross-coupling product remains obscure.) The mixture, as a solution in xylene, was heated to reflux to furnish optically pure vinylphosphine oxide **8** as a stable crystalline solid.[4] (The difficulty of separation of diastereomers **7** by chromatography on silica gel thwarted our original goal of preparing optically pure **8** by a route involving the coupling of *dl*-**5** with optically pure **6**.)

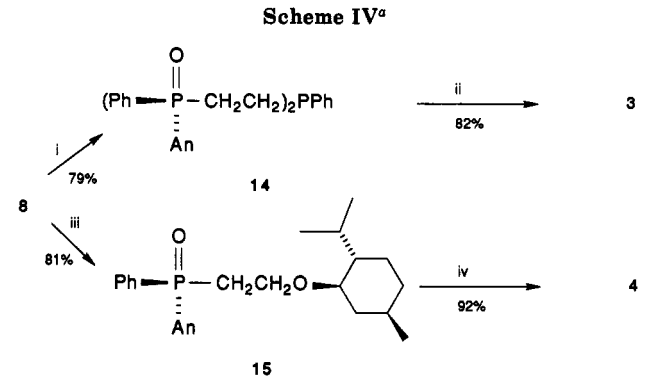
Compound **5** in the presence of di-*tert*-butyl dicarbonate was treated with LDA to give (*S*)-[(*tert*-butoxycarbonyl)methyl](*o*-methoxyphenyl)phenylphosphine oxide (**9**). The addition of **9** to **8** proceeded at room temperature in the presence of a catalytic amount of sodium hydride to yield **10**, which was converted to (*S*,*S*)-1,3-bis[(*o*-methoxyphenyl)phenylphosphinyl]propane (**11**) upon refluxing in xylene in the presence of *p*-toluenesulfonic acid. Bis(phosphine oxide) **11** was reduced to (*S*,*S*)-1,3-propanediylbis[(*o*-methoxyphenyl)phenylphosphine] (**1**) employing a combination of trichlorosilane and cyclohexyldiethylamine, a reaction known to proceed with inversion of configuration[5] at phosphorus (Scheme II).

Scheme III[a]



[a] Key: (i) 2 equiv of **8**, catalytic NaH, benzene, rt, 3 days; (ii) *p*-TsOH, xylene, reflux; (iii) $HSiCl_3$/c-$C_6H_{11}NEt_2$, MeCN.

Scheme IV[a]



[a] Key: (i) $PhPH_2$, catalytic KOH, rt, 5 h; (ii) $HSiCl_3$/c-$C_6H_{11}NEt_2$, MeCN, rt, 2 h; (ii) (−)-menthol, catalytic NaH, 60 °C, 14 h; (iv) $HSiCl_3$/c-$C_6H_{11}NEt_2$, MeCN, rt, 1 h.

Tridentate phosphine ligand **2** was synthesized by the sequence shown in Scheme III. Compound **9** was treated with 2 equiv of **8** in the presence of sodium hydride to give **12**, which was converted to **13**. The latter was deoxygenated to **2** under the conditions mentioned above.

Phosphine ligands **3** and **4** were prepared by the reactions summarized in Scheme IV. The addition of phenylphosphine to 2 equiv of **8** proceeded smoothly at room temperature in the presence of a catalytic amount of potassium hydride to provide **14**. The addition of (−)-menthol to **8** was accomplished in the presence of sodium hydride to provide **15**. Oxides **14** and **15** were reduced with trichlorosilane to phosphines **3** and **4**, respectively.

Rhodium(I) complexes of **1** and **2** were prepared by their treatment with rhodium 1,5-cyclooctadiene chloride dimer in the presence of sodium tetrafluoroborate. The catalysts thus prepared were employed for the asymmetric hydrogenation of several α-(acetylamino)acrylic acids using moderate pressures. The results are given in Table I. Optical yields of 78–96% were obtained by use of **1** as a chiral ligand. These results are comparable to those obtained by the use of diPAMP[2a,b] and related ligands.[6]

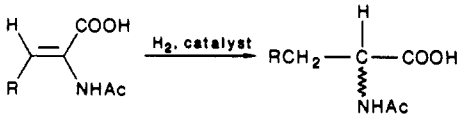
(2) (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. (c) Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1968**, 1445. (d) Horner, L.; Siegel, H.; Buthe, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942. (e) Roberts, N. K.; Wild, S. B. *J. Am. Chem. Soc.* **1979**, *101*, 6254. (f) Fisher, C.; Mosher, H. S. *Tetrahedron Lett.* **1977**, 2487. (g) Valentine, D., Jr.; Blount, J. F.; Toth, K. *J. Org. Chem.* **1980**, *45*, 3691. (h) Valentine, D., Jr.; Johnson, K. K.; Priester, W.; Sun, R. C.; Toth, K.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 3698.

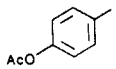
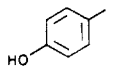
(3) Maryanoff, C. A.; Maryanoff, B. E.; Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 5839.

(4) For routes to optically pure vinylphosphine oxides see: Bodalski, R.; Rutkowska-Olma, E.; Pietrusiewicz, K. M. *Tetrahedron* **1980**, *36*, 2353. Pietrusiewicz, K. M.; Zablocka, M.; Monkiewicz, J. *J. Org. Chem.* **1984**, *49*, 1522.

(5) Horner, L.; Balzer, W. D. *Tetrahedron Lett.* **1965**, 1157. Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012.

Table I. Asymmetric Hydrogenation of α-(Acetylamino)acrylic Acids



substrate R	catalyst	substrate/ catalyst	solvent	temp, °C	pressure, atm	time, h	opt yield,[a] %	abs confign
Ph	1-Rh[b]	500	EtOH	rt	3	21	94	*R*
	1-Rh[b]	10000	EtOH	rt	13	16	87	*R*
	2-Rh[c]	1000	*i*-PrOH/PhH (2:1)	45	5	9	90	*R*
	2-Rh[d]	600	EtOH	50	5	1	83	*R*
	3-Rh[e]	200	MeOH	rt	9	13	47	*R*
	4-Rh[f]	200	MeOH	rt	10	12	22	*S*
	1-Rh[b]	500	EtOH	rt	3	12	91	*R*
	2-Rh[c]	500	EtOH/PhH (1:2)	50	13	12	86	*R*
H	1-Rh[b]	500	EtOH	rt	3	2	78	*R*
	2-Rh[d]	800	*i*-PrOH/PhH (2:1)	50	5	3	80	*R*
	1-Rh[b]	500	EtOH	45	15	24	96	*R*
	2-Rh[d]	1000	*i*-PrOH/PhH (2:1)	50	15	21	88	*R*
	2-Rh[c]	1000	*i*-PrOH/PhH (2:1)	50	5	26	79	*R*

[a] Optical yields were determined from the following literature values for the optically pure compounds: (*S*)-*N*-acetylphenylalanine, $[\alpha]^{26}_D$ + 46.0° (*c* 1, EtOH) (Poulin, J. C.; Kagan, H. B. *J. Organomet. Chem.* **1975**, *91*, 105); (*R*)-*N*-acetyl-3,4-(methylenedioxy)phenylalanine, $[\alpha]^{19}_D$ −53.4° (*c* 1.8, EtOH) (Yamada, S.; Fujii, T.; Shiori, T. *Chem. Pharm. Bull* **1962**, *10*, 680; (*R*)-*N*-acetylalanine, $[\alpha]_D$ +66.5° (*c* 2, H_2O) (Birbaum, S. M.; Levintow, L.; Kingsley, R. B.; Greenstein, J. P. *J. Biol. Chem.* **1952**, *194*, 455); (*R*)-*O*,*N*-diacetyltyrosine, $[\alpha]^{27}_D$ +40.4° (*c* 0.5, H_2O) (Sealcock, R. R. *J. Biol. Chem.* **1946**, *166*, 1); (*S*)-*N*-acetyltyrosine, $[\alpha]^{27}_D$ +51.1° (*c* 1, MeOH) (Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262). [b] (1,5-Cyclooctadiene)[(*S*,*S*,)-1,3-propanediylbis[[(*o*-methoxyphenyl)phenylphosphine]]rhodium tetrafluoroborate. [c] (1,5-Cyclooctadiene)[(*S*,*S*,*S*)-1,3,5-pentanetriyltris[[(*o*-methoxyphenyl)phenylphosphine]]rhodium tetrafluoroborate. [d] Prepared in situ by the reaction of **2** with $[Rh(COD)Cl]_2$. [e] Prepared in situ by the reaction of **3** with $[Rh(COD)Cl]_2$. [f] Prepared in situ by the reaction of **4** with $[Rh(COD)Cl]_2$.

Both (*S*,*S*)-diPAMP and its higher homologue (*S*,*S*)-**1** result in the production of (*R*)-*N*-acetylphenylalanine. Tridentate ligand (*S*,*S*)-**2** under the conditions noted above also leads to the production of (*R*)-*N*-acetyl amino acids with optical yields in the 79–90% range. The phosphine ligands **3**[7] and **4** in the presence of $[Rh(COD)_2Cl]_2$ were considerably less effective in asymmetric hydrogenations.

In summary, we have prepared the methylene homologue **1** of diPAMP and several other novel ligands homochiral at phosphorus by taking advantage of an unusual method for the conversion of a *P*-methyl to a *P*-vinyl group. In amino acid synthesis by asymmetric hydrogenation, ligand **1** provides results comparable to those of diPAMP. The procedures herein described could be utilized for the production of a variety of homochiral polyphosphines by the coupled use of recently developed methods for the synthesis of optically pure methyl- and vinylphosphine oxides.[4,8]

Experimental Section

(*S*)-(*o*-Methoxyphenyl)methylphenylphosphine oxide (5) was prepared according to literature procedures[9,10] and purified by bulb to bulb distillation: bp 210 °C (0.5 mmHg); mp 77–79 °C; $[\alpha]^{20}_D$ −25.5° (*c* 1.0, MeOH) [lit.[2b] mp 70–75 °C; $[\alpha]^{20}_D$ +25.9° (*c* 1.0, MeOH)].

(*PS*,*SS*)- and (*PS*,*SR*)-*S*-[2-[(*o*-Methoxyphenyl)-phenylphosphinyl]ethyl]-*N*-methyl-*S*-phenylsulfoximine (7). A mixture of (*S*)-**5** (3.69 g, 15 mmol) and *N*,*S*-methyl-*S*-phenylsulfoximine (**6**,[10] 5.07 g, 30 mmol) in 30 mL of THF was cooled to −78 °C in a dry ice–acetone bath under argon. To this mixture was slowly added a solution of LDA prepared from diisopropylamine (5.5 g, 54 mmol) and butyllithium (32 mL of 1.7 M hexane solution) in THF (50 mL). After the mixture was stirred for 1 h at the same temperature, anhydrous copper(II) chloride (7.9 g, 59 mmol) was added in one portion. The mixture was warmed over 1 h to room temperature with mechanical stirring and held at ambient temperature for 0.5 h prior to quenching with aqueous ammonia. The mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residual oil was chromatographed on silica gel. Elution with benzene, benzene-/ethyl acetate (2:1), ethyl acetate, and finally ethyl acetate/methanol (10:1) afforded a mixture (ca. 2:3) of diastereomers of **7** [4.42g (71% yield)] as a pasty yellow oil:[12] ^1H NMR ($CDCl_3$)

(6) For notable examples of asymmetric hydrogenation, see: Dang, T.-P.; Kagan, H. B. *J. Am. Chem. Soc.* **1972**, *94*, 6429. Lauer, M.; Samuel, O.; Kagan, H. B. *J. Organomet. Chem.* **1979**, *177*, 309. Hayashi, T.; Yamamoto, K.; Mise, T.; Mitachi, S.; Kumada, M. *Tetrahedron Lett.* **1976**, 1133. Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265. Bosnich, B.; Fryzuk, M. D. *J. Am. Chem. Soc.* **1977**, *99*, 6262. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. Brunner, H.; Pieronczyk, W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 620. Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728.

(7) Nonionic complexes of RhCl and tridentate phosphine ligands are often catalytically inactive. The modest activity observed in this case might be attributed to the ligand acting in a bidentate manner. For discussions concerning such matters see: Niewahner, J.; Meek, D. W. *Adv. Chem. Ser.* **1982**, *No. 196*, 257; *Inorg. Chim. Acta* **1982**, *64*, L123. DuBois, D. L.; Meek, D. W. *Inorg. Chim. Acta* **1976**, *19*, L29.

(8) Imamoto, T.; Sato, K.; Johnson, C. R. *Tetrahedron Lett.* **1985**, *26*, 783.

(9) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *Adv. Chem. Ser.* **1974**, *No. 132*, 274.

(10) Korpiun, O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4842.

(11) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594. Johnson, C. R.; Shroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424.

δ 2.65 (s, 3 H), 2.3–3.5 (m, 4 H), 3.66 (s, ca. 0.4 × 3 H), 3.74 (s, ca. 0.6 × 3 H), 6.70–7.95 (m, 14 H); IR (neat) 1580, 1480, 1245, 1285, 1020 cm^{-1}; MS, m/z 413 (M^+), 258 ($M^+ - 155$), 155 ($M^+ - 258$). Anal. Calcd for $C_{22}H_{24}NO_2PS$: C, 63.91; H, 5.85; N, 3.38. Found: C, 64.06; H, 5.59; N, 3.36.

(*S*)-(*o*-Methoxyphenyl)phenylvinylphosphine Oxide (8). The diastereomeric mixture **7** (3.72 g, 9 mmol) was dissolved in 40 mL of xylene, and the solution was refluxed under argon for 1 h. The solvent was removed under reduced pressure, and the residual oil was subjected to chromatography on silica gel using benzene/ethyl acetate (11:1) as eluent to give **8** [1.91 g (82%)] was white solid. Recrystallization from ethyl acetate/hexane (1:3) gave crystals: mp 85–86 °C $[\alpha]^{20}_D$ +8.8° (*c* 3.0, C_6H_6); ^1H NMR ($CDCl_3$) δ 3.59 (s, 3 H), 5.8–8.0 (m, 12 H); IR (KBr) 1580, 1480, 1280, 1190, 1005 cm^{-1}; MS, m/z 258 (M^+). Anal. Calcd for $C_{15}H_{15}O_2P$: C, 69.76; H, 5.85. Found: C, 69.87; H, 5.81.

(*S*)-[(*tert*-Butoxycarbonyl)methyl](*o*-methoxyphenyl)phenylphosphine Oxide (9). A mixture of **5** (2.46 g, 10 mmol) and di-*tert*-butyl dicarbonate (2.62 g, 12 mmol) in THF (10 mL) was cooled to −78 °C under argon. A solution of LDA (25 mmol) in THF/hexane was added over 10 min. After being stirred for 30 min, the mixture was quenched with aqueous NH_4Cl solution. The product was extracted into dichloromethane. The combined extracts were dried over Na_2SO_4 and concentrated. Trituration of the residual oil with hexane afforded the product as a solid, which was collected and washed with hexane. Yield of the crude product (mp 118–119 °C) was 3.3 g (100%). Recrystallization from 1,2-dichloroethane/hexane (1:5) gave pure **9** as colorless cubes: mp 119–120 °C; $[\alpha]^{20}_D$ −38.5° (*c* 1.0, C_6H_6); ^1H NMR ($CDCl_3$) δ 1.20 (s, 9 H), 3.48 (d, J = 12 Hz, 2 H), 3.76 (s, 3 H), 6.7–8.0 (m, 9 H); IR (KBr) 1720, 1480, 1280, 1110 cm^{-1}. Anal. Calcd for $C_{19}H_{23}O_4P$: C, 65.88; H, 6.69. Found: C, 65.77; H, 6.85.

(*S,S*)-1,3-Propanediylbis[(*o*-methoxyphenyl)phenylphosphine Oxide] (11). A mixture of **8** (258 mg, 1 mmol), **9** (346 mg, 1 mmol), and sodium hydride (50% oil dispersion) (4.8 mg, 0.1 mmol) in dry benzene (3 mL) was stirred under argon for 6 h. The solvent was evaporated under reduced pressure. Xylene (5 mL) and *p*-toluenesulfonic acid (285 mg, 1.5 mmol) were added, and the mixture was stirred at reflux under argon for 3 h. The solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. The solution was washed with aqueous $NaHCO_3$ solution and dried over Na_2SO_4. Evaporation and preparative thin-layer chromatography (PTLC) on silica gel (5:1 AcOEt/MeOH) afforded recovered **8** (51 mg) and **11** [228 mg (45%)] as an amorphous solid: $[\alpha]^{20}_D$ +2.9° (*c* 3.0, MeOH); ^1H NMR ($CDCl_3$) δ 1.65–2.15 (m, 2 H), 2.35–2.70 (m, 4 H), 3.63 (s, 6 H), 6.55–7.90 (m, 18 H); IR (KBr) 1585, 1475, 1275, 1180, 1025 cm^{-1}. Anal. Calcd for $C_{29}H_{30}O_4P_2$: C, 69.04; H, 5.99. Found: C, 68.69; H, 5.97.

(*S,S*)-1,3-Propanediylbis[(*o*-methoxyphenyl)phenylphosphine] (1). A mixture of **11** (252 mg, 0.5 mmol), trichlorosilane (0.75 mL, 7 mmol), and cyclohexyldiethylamine (1.6 mL, 9 mmol) in dry acetonitrile (8 mL) was stirred at 70 °C under argon for 2 h. The reaction mixture was vigorously stirred with 20% aqueous NaOH solution under argon, and organics were extracted into degassed benzene. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a short column packed with silica gel with benzene as eluent under argon to remove most of the cyclohexyldiethylamine. The filtrate was concentrated, and the residue was subjected to PTLC on silica gel using benzene under argon. The pasty oil [175 mg (74%)] obtained was dissolved in hot methanol, and the solution was cooled to −20 °C. The solvent was removed by the use of a pipet, and the residue was dried in vacuo to give **1** as a glass: $[\alpha]^{20}_D$ −15.1° (*c* 2.0, C_6H_6); ^1H NMR ($CDCl_3$) δ 1.4–1.9 (m, 2 H), 2.1–2.4 (m, 4 H), 3.67 (s, 6 H), 6.65–7.50 (m, 18 H); IR (neat) 2905, 1570, 1460, 1240, 1030 cm^{-1}. Anal. Calcd for $C_{29}H_{30}O_2P_2$: C, 73.72; H, 6.40. Found: C, 73.60; H, 6.29.

(*S,S,S*)-1,3,5-Pentanetriyltris[(*o*-methoxyphenyl)phenylphosphine Oxide] (13). A mixture of **8** (516 mg, 2 mmol), **9** (346 mg, 1 mmol), and sodium hydride (0.2 mmol) in dry benzene (4 mL) was stirred at room temperature under argon for 3 days. The benzene was evaporated, and xylene (8 mL) and *p*-toluenesulfonic acid (1.5 mmol) were added. The mixture was stirred at reflux under argon for 3 h. The reaction mixture was worked up in a similar manner as described above for **11** to give **11** [151 mg (30%)], **8** (70 mg), and **13** [425 mg (56%)] as an amorphous solid: $[\alpha]^{20}_D$ −13.8° (*c* 2.0, MeOH); ^1H NMR ($CDCl_3$) δ 1.6–3.1 (m, 9 H), 3.52 (s, 3 H), 3.66 (s, 3 H), 3.72 (s, 3 H), 6.4–8.0 (m, 27 H); IR (KBr) 1585, 1470, 1270, 1170, 1020 cm^{-1}. Anal. Calcd for $C_{44}H_{45}O_6P_3$: C, 69.28; H, 5.95. Found: C, 68.38; H, 5.87.

(*S,S,S*)-1,3,5-Pentanetriyltris[(*o*-methoxyphenyl)phenylphosphine] (2). A mixture of **13** (305 mg, 0.4 mmol), trichlorosilane (0.75 mL, 7 mmol), and cyclohexyldiethylamine (1.6 mL, 9 mmol) in dry acetonitrile (8 mL) was stirred at 70 °C under argon for 2 h. The reaction mixture was worked up in a similar procedure as the preparation of **1** to give crude **2** [198 mg (68%)]. Recrystallization from hot methanol gave a colorless powder: mp 61–63 °C; $[\alpha]^{20}_D$ −18.2° (*c* 2.3, C_6H_6); ^1H NMR ($CDCl_3$) δ 1.3–2.4 (m, 8 H), 2.45–2.75 (m, 1 H), 3.62 (s, 9 H), 6.6–7.6 (m, 27 H); IR (KBr) 2905, 1570, 1460, 1240, 1030 cm^{-1}. Anal. Calcd for $C_{44}H_{45}O_3P_3$: C, 73.94; H, 6.35. Found: C, 73.84; H, 6.29.

(*S,S*)-Bis[2-[(*o*-methoxyphenyl)phenylphosphinyl]ethyl]phenylphosphine (14). Freshly distilled phenylphosphine (88 μL, 0.8 mmol) was added through a microsyringe to a solution of **8** (459 mg, 1.78 mmol) in acetonitrile (1 mL) under argon. An aqueous 10 N potassium hydroxide solution (16 μL, 0.16 mmol) was then added, and the solution was stirred at room temperature for 5 h. The reaction mixture was subjected to PTLC (10:1 AcOEt/MeOH) to give **14** [396 mg (79% yield based on phenylphosphine)]. The colorless amorphous solid was very hygroscopic; we were unable to obtain satisfactory elemental analyses of this compound: $[\alpha]^{20}_D$ +24.1° (*c* 2.6, MeOH); ^1H NMR ($CDCl_3$) δ 1.5–2.5 (m, 8 H), 3.42 (s, 3 H), 3.55 (s, 3 H), 6.50–7.90 (m, 23 H); IR (KBr) 1585, 1475, 1275, 1170, 1025 cm^{-1}.

(*S,S*)-Bis[2-[(*o*-methoxyphenyl)phenylphosphinyl]ethyl]phenylphosphine (3). A mixture of **14** (313 mg, 0.5 mmol), trichlorosilane (0.75 mL, 7 mmol), cyclohexyldiethylamine (1.6 mL, 9 mmol), and dry acetonitrile (8 mL) was stirred at room temperature under argon for 2 h. The reaction mixture was worked up in a similar manner as described above for **1** to give **3**: 243 mg (82%); $[\alpha]^{20}_D$ +29.0° (*c* 2.8, C_6H_6); ^1H NMR ($CDCl_3$) δ 1.3–2.3 (m, 8 H), 3.52 (s, 3 H), 3.56 (s, 3 H), 6.45–7.30 (m, 23 H); IR (neat) 2905, 1580, 1460, 1245, 1030 cm^{-1}. Anal. Calcd for $C_{36}H_{37}O_2P_3$: C, 72.72; H, 6.27. Found: C, 73.05; H, 6.18.

(*SP,1′R,2′S,5′R*)-[2-[(2′-Isopropyl-5′-methylcyclohexyl)oxy]ethyl](*o*-methoxyphenyl)phenylphosphine Oxide (15). A mixture of **8** (258 mg, 1 mmol), (−)-menthol (1.56 g, 10 mmol), and sodium hydride (50% oil dispersion) (96 mg, 2 mmol) was stirred under argon at 60 °C for 14 h. The reaction mixture was chromatographed on silica gel using hexane/ethyl acetate (1:5) followed by ethyl acetate to give unchanged (−)-menthol (ca. 1.3 g) and crude **15**. The crude product was purified by PTLC on silica gel (1:1 AcOEt/hexane) to obtain **15** [336 mg (81%)] as a colorless oil: $[\alpha]^{20}_D$ −51.1° (*c* 1.3, MeOH); ^1H NMR ($CDCl_3$) δ 0.5–2.1 (m, 18 H), 2.45–3.05 (m, 4 H), 3.3–3.8 (m, 1 H), 3.62 (s, 3 H), 6.50–7.85 (m, 9 H); IR (neat) 1590, 1480, 1275, 1180, 1110, 1085, 1025 cm^{-1}. Anal. Calcd for $C_{25}H_{35}O_3P$: C, 72.44; H, 8.51. Found: C, 72.33; H, 8.37.

(*SP,1′R,2′S,5′R*)-[2-[(2′-Isopropyl-5′-methylcyclohexyl)oxy]ethyl](*o*-methoxyphenyl)phenylphosphine (4). Phosphine oxide **15** (310 mg, 0.75 mmol) was treated with a mixture of trichlorosilane (0.3 mL, 3 mmol), cyclohexyldiethylamine (0.64 mL, 3.5 mmol), and dry acetonitrile (5 mL) under argon at room temperature for 1 h. The reaction mixture was worked up in a similar manner as described for **1** to give **4** [275 mg (92%)] as a colorless oil: $[\alpha]^{20}_D$ −56.0° (*c* 2.9, C_6H_6); ^1H NMR ($CDCl_3$) δ 0.5–1.7 (m, 15 H), 1.7–2.6 (m, 5 H), 2.70–3.05 (m, 1 H), 3.05–3.70 (m, 2 H), 3.56 (s, 3 H), 6.40–7.35 (m, 9 H); IR (neat) 2880, 1575, 1455, 1235, 1090, 1025 cm^{-1}. Anal. Calcd for $C_{25}H_{35}O_2P$: C, 75.35; H, 8.85. Found: C, 75.62; H, 8.63.

(1,5-Cyclooctadiene)[(*S,S*)-1′,3′-propanediylbis[(*o*-methoxyphenyl)phenylphosphine]]rhodium Tetrafluoroborate and (1,5-Cyclooctadiene)[(*S,S,S*)-1′,3′,5′-pentanetriyltris[(*o*-methoxyphenyl)phenylphosphine]]rhodium Tetrafluoroborate. These rhodium complexes were prepared by the reaction of **1** or **2** with rhodium 1,5-cyclooctadiene chloride dimer and sodium tetrafluoroborate, according to the procedure described in literature.[2b] The orange complexes obtained were stored under argon.

(12) After standing for 1 week, one of the diastereomers (mp 143–144 °C) crystallized.

Hydrogenation Procedure. The requisite substrate (0.5–1 g) was accurately weighed into a 60-mL pressure bottle equipped with a magnetic stirrer. The rhodium/phosphine complex and solvent were then added. The flask was successively evacuated and filled with hydrogen. The solution was stirred until gas uptake ceased. The reduction solution was diluted to a known volume, and the optical yield was determined on a polarimeter by comparison with a standard.

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Synthesis of an Isosteric Phosphonate Analogue of Cytidine 5′-Monophospho-3-deoxy-D-*manno*-2-octulosonic Acid

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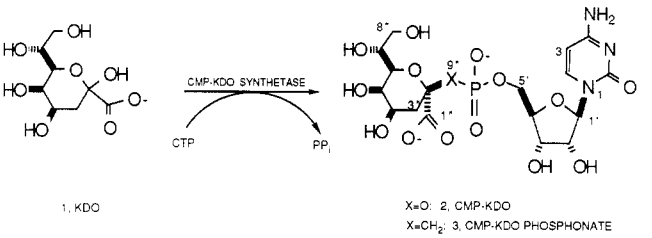
A stereoselective synthesis of **3**, a stable, isosteric phosphonate analogue of cytidine 5′-monophospho-3-deoxy-D-*manno*-2-octulosonic acid (CMP-KDO, **2**), is described. Key steps include alkylation of an ester enolate, Arbuzov reaction of a β-lactone, and esterification of a phosphonate under Mitsunobu conditions. Compound **3** is a modest inhibitor of CMP-KDO synthetase, a key enzyme in bacterial lipopolysaccharide biosynthesis.

3-Deoxy-D-*manno*-2-octulosonic acid (KDO, **1**; Scheme I) is a vital component of the outer membrane lipopolysaccharide (LPS) of all Gram-negative bacteria.[1] Several groups have pursued inhibition of KDO metabolism as a strategy for the development of novel antiinfective agents.[2] Condensation of KDO with CTP to form the extremely labile cytidine 5′-monophospho-3-deoxy-D-*manno*-2-octulosonic acid (**2**, CMP-KDO; Scheme I) may be the rate-limiting step in LPS biosynthesis.[3] The stereochemistry of this reaction was recently elucidated by Kohlbrenner and Fesik[4] and provides a basis for the rational design of enzyme inhibitors. A stable, β-linked CMP-KDO analogue could conceivably inhibit both the synthetase and the subsequent transferase[5] that catalyze displacement of CMP by a lipid A precursor.[6] Here we report the synthesis and preliminary biological evaluation of the CMP-KDO phosphonate **3**.[7]

Scheme I. Biosynthesis of CMP-KDO



Cornforth condensation[8] of D-arabinose and oxaloacetate provided multigram quantities of crystalline (+)-KDO (**1**) in a single step (Scheme II).[9] The desired pyranose ring isomer[10] was secured by acid-catalyzed isopropylidenation,

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