Product **16**: IR 1770, 1731 $cm^{-1}$; $^1H$ NMR $\delta$ 1.31 (t, $J$ = 7, 3 H), 1.63 (s, 3 H), 2.72 (d, $J$ = 9, 1 H), 3.56 (d, $J$ = 9, 1 H), 4.21 (q, $J$ = 7, 2 H); MS 114 (65%, $M^+ - COS$), 99 (47%, $M^+ - COS - CH_3$), 86 (70%, $M^+ - COOC_2H_5 - CH_3$), 69 (100%, $M^+ - COS - OC_2H_5$), 45 (100%, $C_2H_5O^+$).

**Reaction of *S*-Alkyl 2-(Bromomethyl)-4-mesityl-2-methylbutanethioate and *S*-Alkyl ω-Aryl-2-(bromomethyl)-2-(ethoxycarbonyl)alkanethioate with Tributylstannane.** All the experiments were carried out in a same way, and the reaction of *S*-ethyl 2-(bromomethyl)-4-mesityl-2-methylbutanethioate is described as a representative. For the bromide corresponding to cobaloxime **1** (Br instead of [Co] in structure **1**) (0.21 g, 0.5 mmol), tributylstannane (0.17 g, 0.6 mmol) and AIBN (1 mg) were dissolved in 10 mL of benzene to make the concentration of 50 mmol/L for the bromide and 60 mmol/L for tributylstannane. The mixture was refluxed for 4 h under nitrogen, and the condensate of the reaction solution was separated by silica gel chromatography (5 × 10 cm) into hexane eluate (tributylstannyl bromide) and benzene eluate. Kugelrohr distillation of the benzene eluate gave 0.15 g (89%) of product **4** (R = Et), which was identified with the product from cobaloxime **1**.

The reactions were also carried out in different concentration (0.1 mol/L and 1.0 mmol/L) by changing the volume of the solvent, but the results were essentially same except the yields of the products. The reaction of *S*-*tert*-butyl 2-(bromomethyl)-2-(ethoxycarbonyl)-5-phenylpentanethioate (Br instead of [Co] in structure **2**), however, gave a β-thiolactone derivative **9** as a minor product.

**Acknowledgment.** This work was supported by The Annual Project 1986, Waseda University, and Grant-in-Aid for Science Research 1986, Ministry of Education. We are also indebted to the Mishima-Kaiun Foundation for research funds.

**Registry No. 1** (R = Et), 112312-33-1; **1** (R = *t*-Bu), 112312-34-2; **2** (R = Et), 114762-71-9; **2** (R = *t*-Bu), 114762-72-0; **3** (R = Et), 114762-73-1; **3** (R = *t*-Bu), 114762-74-2; **4** (R = Et), 112303-78-3; **4** (R = *t*-Bu), 112303-79-4; **5** (R = Et), 112303-81-8; **5** (R = *t*-Bu), 112303-82-9; **6**, 112303-85-2; **7** (R = Et), 114739-20-7; **7** (R = *t*-Bu), 114739-21-8; **8** (R = Et), 114739-22-9; **8** (R = *t*-Bu), 114739-23-0; **9**, 114739-24-1; **10** (R = Et), 114762-70-8; **10** (R = *t*-Bu), 114739-25-2; **11**, 114739-26-3; **12**, 114739-27-4; **13**, 114762-75-3; **14**, 114762-76-4; **15**, 16432-61-4; **16**, 114739-28-5; [Co(I)], 75699-52-4; $MeS(CH_2)_3COSEt$, 114739-05-8; $CH_3$-I, 74-88-4; $Mes(CH_2)_2CH(Me)COSEt$, 112303-88-5; $Mes(CH_2)_2C(Me)(CH_2Br)COSEt$, 112303-74-9; $CH_2Br_2$, 74-95-3; $Mes(CH_2)_3COS$-*t*-Bu, 114739-06-9; $Mes(CH_2)_2CH(Me)COS$-*t*-Bu, 112303-89-6; $Mes(CH_2)_2C(Me)(CH_2Br)COS$-*t*-Bu, 112303-75-0; $Mes(CH_2)_2CH(CO_2Et)COSEt$, 114739-08-1; EtOOC-Cl, 541-41-3; $Mes(CH_2)_2C(CO_2Et)(CH_2Br)COSEt$, 114739-09-2; $Ph(CH_2)_3C(CO_2Et)(CH_2Br)COSEt$, 114739-10-5; $Ph(CH_2)_3CH(CO_2Et)COSEt$, 114739-11-6; $Ph(CH_2)_4COSEt$, 114739-12-7; $Ph(CH_2)_3C(CO_2Et)(CH_2Br)COS$-*t*-Bu, 114739-13-8; $Ph(CH_2)_3CH(CO_2Et)COS$-*t*-Bu, 114739-14-9; $Ph(CH_2)_4COS$-*t*-Bu, 114739-15-0; $Mes(CH_2)_2C(CO_2Et)(CH_2Br)COS$-*t*-Bu, 114739-16-1; $Mes(CH_2)_2CH(CO_2Et)COS$-*t*-Bu, 114739-17-2; *S*-*tert*-butyl 2-(bromomethyl)-2-methylpropanethioate, 114739-07-0; *S*-*tert*-butyl 2-methylpropanethioate, 29786-94-5; *S*-*tert*-butyl 2-(bromomethyl)-2-(ethoxycarbonyl)propanethioate, 114739-18-3; *S*-*tert*-butyl 2-(ethoxycarbonyl)propanethioate, 114739-19-4; cobalt(II) chloride, 7646-79-9; dimethylglyoxime, 95-45-4; benzene, 71-43-2; acetonitrile, 75-05-8; methanol, 67-56-1; chloroform, 67-66-3; tributylstannane, 688-73-3.

# Highly Diastereofacial Selective Chelation of a Phosphite-Containing α,β-Unsaturated Ketone System to the $Fe(CO)_2$ Group†,[1]

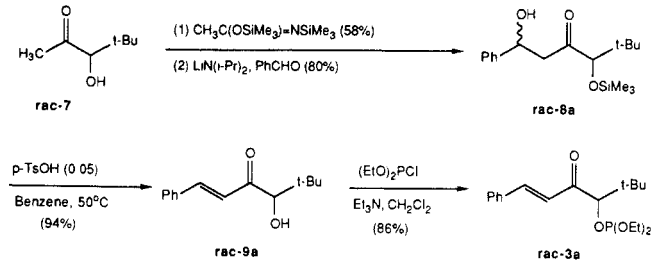
**Wei-Yuan Zhang,[2a] Dennis J. Jakiela,[2b] André Maul,[2b] Christopher Knors,[2a,b] Joseph W. Lauher,[2b] Paul Helquist,*[,2a-c] and Dieter Enders[2d]**

*Contribution from the Deparments of Chemistry, State University of New York, Stony Brook, New York 11794, University of Notre Dame, Notre Dame, Indiana 46556, and Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule Professor-Pirlet-Strasse 1, D-5100 Aachen, FRG.* *Received September 30, 1987*

**Abstract:** Chiral, phosphite-containing α,β-unsaturated ketones of the general structure $RCH{=}CHC(=O)CH(t\text{-}Bu)OP(OEt)_2$ (**3**) have been synthesized as specially designed chelating ligands that permit the highly diastereofacial selective coordination of the conjugated enone moiety to transition metals. The coordination of these ligands with iron carbonyl units has been studied in detail, and the structures of three of the resulting complexes *rac*-**5a**, *rac*-**6a**, and (*S*)-**5b** have been determined by single-crystal X-ray diffraction. Conjugate addition to one of these complexes has demonstrated the potential utility of these systems in asymmetric synthesis.

Asymmetric synthesis is an intensively studied area of chemistry.[3,4] Of special interest to us are methods that permit the diastereofacial selective coordination of a prochiral face of an alkene or other π-systems to a transition metal.[5] Subsequent addition reactions of the coordinated double bond are then expected to proceed with control of the configurations of the resulting adducts. Our goal is to design systems that employ chelation effects[6] to induce diastereofacial selective coordination in a completely predictable fashion so that the overall products of coordination and then addition will possess predictable configurations. Various aspects of chelation and functional group directing effects have been studied by others,[7,8] but especially related to our studies is recent work of Collum.[6c,f]

**Scheme I**




† This paper is dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

0002-7863/88/1510-4652$01.50/0 

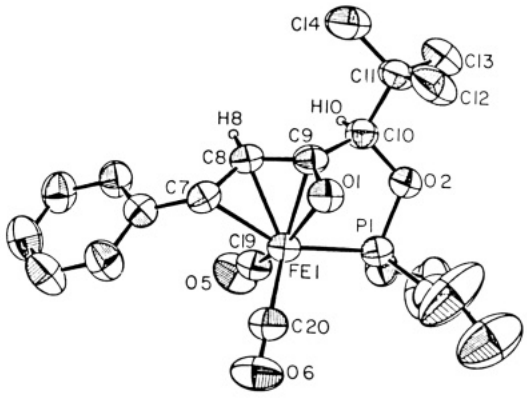
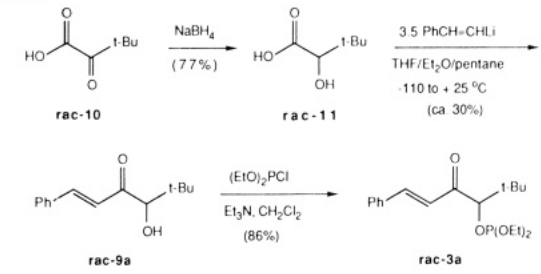



**Figure 1.** X-ray crystal structure of *rac*-**5a**.

We now report the initial stages of our investigations in this area. This first paper is concerned primarily with the design and

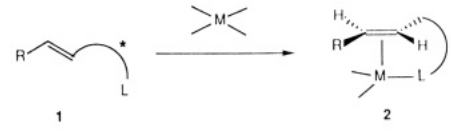
**Scheme II**




the coordination studies of a specially designed $\alpha,\beta$-unsaturated ketone system. The detailed study of the reactions of this and related $\pi$-derivatives will be the subject of subsequent papers, although in the present paper we briefly demonstrate the potential utility of our ligand system in asymmetric synthesis.

## Results and Discussion

**Design of the Ligand System.** The general concept upon which our initial investigations are based is to place a metal-coordinating group (L) in a side chain connected to the $\pi$-system of interest and also in this side chain to have an element of chirality (indicated by an asterisk in the structures below) of such a nature that coordination of a transition metal (M) is steered to one prochiral face of the $\pi$-system. This selectivity may be driven by conformational preferences of the side chain imposed by the fixed configuration of the chiral element and the requisite multipoint attachment of the chelating ligand to the metal. Ideally, the chiral side chain should be easily removable after addition reactions are performed on the coordinated substrate. We illustrate the general concepts for the case of a simple alkene derivative **1** and the resulting chelate complex **2** (eq 1).




1 2 (1)

Beyond simple alkene-containing ligands, one can extend the above concepts to other $\pi$-systems that are known to form coordination complexes with transition metals. These systems may include diene, allyl, dienyl, allene, arene, imine, hydrazone, and other derivatives. We chose to begin our investigations with

(1) Taken in part from the Ph.D. Dissertation of D.J.J., State University of New York at Stony Brook, 1986.

(2) (a) University of Notre Dame. (b) State University of New York at Stony Brook. (c) Address correspondence to this author at Notre Dame. (d) Institut für Organische Chemie.

(3) For some reviews of asymmetric synthesis, see: (a) *Stereochemistry of Optically Active Transition Metal Compounds*; Douglas, B. E., Saito, Y., Eds.; American Chemical Society: Washington, DC, 1980. (b) Bosnich, B.; Fryzuk, M. D. *Top. Stereochem.* **1981**, *12*, 119. (c) Kagan, H. B. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, pp 463–498. (d) Eliel, E. L. *Top. Curr. Chem.* **1982**, *105*, 1. (e) Consiglio, G.; Pino, P. *Ibid.* **1982**, *105*, 77. (f) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (g) Brown, J. M.; Chaloner, P. A. In *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983; pp 137–165. (h) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, 1983–1985; Vol. 1–5. (i) Meyers, A. I., Ed. *Tetrahedron* **1984**, *40*, 1213. (j) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (k) Brunner, H. *J. Organomet. Chem.* **1986**, *300*, 39. (l) Matteson, D. S. *Synthesis* **1986**, 973. (m) ApSimon, J. W.; Collier, T. l. *Tetrahedron* **1986**, *42*, 5157.

(4) For some other recent, representative developments in asymmetric synthesis, but especially methods using organometallic approaches, see: (a) Bosnich, B.; Mackenzie, P. B. *Pure Appl. Chem.* **1982**, *54*, 189. (b) Brookhart, M.; Timmers, D.; Tucker, J. R.; Williams, G. D.; Husk, G. R.; Brunner, H.; Hammer, B. *J. Am. Chem. Soc.* **1983**, *105*, 6721. (c) Reetz, M. T.; Kyung, S.-H.; Westermann, J. *Organometallics* **1984**, *3*, 1716. (d) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591. (e) Midland, M. M.; Lee, P. E. *J. Org. Chem.* **1985**, *50*, 3237. (f) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (g) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *Ibid.* **1986**, *108*, 6328. (h) Evans, D. A.; Weber, A. E. *Ibid.* **1986**, *108*, 6757. (i) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *Ibid.* **1986**, *108*, 8279. (j) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224. (k) Smaardijk, A. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135. (l) Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137. (m) Hsiao, C.-N.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201. See also several of the references in the following footnote.

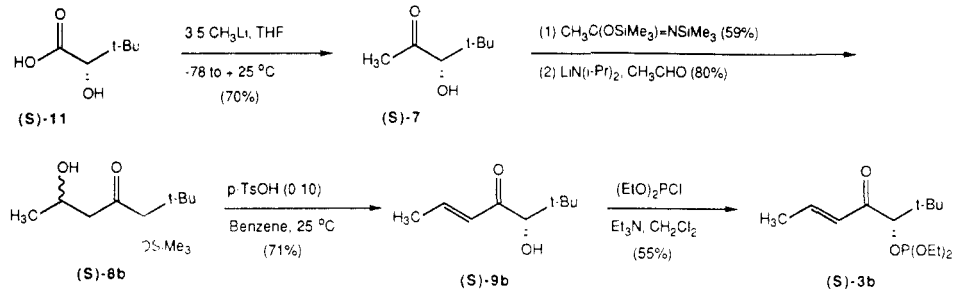
(5) For recent leading references to the work of several research groups with chiral $\pi$-complexes of alkenes and other unsaturated systems, see: (a) Meyer, A.; Hofer, O. *J. Am. Chem. Soc.* **1980**, *102*, 4410. (b) Franck-Neumann, M.; Martina, D.; Heitz, M. P. *Tetrahedron Lett.* **1982**, *23*, 3493. (c) Ammendola, P.; Ciajolo, M. R.; Panunzi, A.; Tuzi, A. *J. Organomet. Chem.* **1983**, *254*, 389. (d) Jaouen, G.; Top, S.; Laconi, A.; Couturier, D.; Brocard, J. *J. Am. Chem. Soc.* **1984**, *106*, 2207. (e) Faller, J. W.; Chao, K.-H. *Organometallics* **1984**, *3*, 927. (f) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. (g) Farrar, D. H.; Payne, N. C. *Ibid.* **1985**, *107*, 2054. (h) Birch, A. J.; Kelly, L. F. *J. Org. Chem.* **1985**, *50*, 712. (i) Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282. (j) Gree, R.; Laabassi, M.; Mosset, P.; Carrie, R. *Tetrahedron Lett.* **1985**, *26*, 2317. (k) Solladie-Cavallo, A.; Farkhani, D.; Dreyfuss, A. C.; Sanch, F. *Bull. Soc. Chim. Fr.* **1986**, 906. (l) Consiglio, G.; Morandini, F. *J. Organomet. Chem.* **1986**, *310*, C66. (m) Brocard, J.; Lebibi, J.; Pelinski, L.; Mahmoudi, M. *Tetrahedron Lett.* **1986**, *27*, 6325. (n) Moriarty, R. M.; Engerer, S. C.; Prakash, O.; Prakash, I.; Gill, U. S.; Freeman, W. A. *J. Org. Chem.* **1987**, *52*, 153. (o) Palotai, I. M.; Stephenson, G. R.; Kane-Maguire, L. A. P. *J. Organomet. Chem.* **1987**, *319*, C5. (p) Howell, J. A. S.; Squibb, A. D.; Walton, G.; McArdle, P.; Cunningham, D. *J. Organomet. Chem.* **1987**, *319*, C45. (q) Uccello-Barretta, G.; Lazzaroni, R.; Bertucci, C.; Salvadori, P. *Organometallics* **1987**, *6*, 550. (r) Uemura, M.; Minami, T.; Yamashita, Y.; Hiyoshi, K.; Hayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 641. (s) Green, M.; Greenfield, S.; Grimshire, M. J.; Kersting, M.; Orpen, A. G.; Rodrigues, R. A. *J. Chem. Soc., Chem. Commun.* **1987**, 97. For other cases and older references, see also the reviews in ref 3.

(6) With respect to related cases of chelation and coordination effects, see the following book for a general treatment of the subject: (a) Omae, I. *Organometallic Intramolecular-Coordination Compounds*; Journal of Organometallic Chemistry Library 18; Elsevier: Amsterdam, 1986. For several specific examples, see: (b) McCrindle, R.; Alyea, E. C.; Ferguson, G.; Dias, S. A.; McAlees, A. J.; Parvez, M. *J. Chem. Soc., Dalton Trans. I* **1980**, 137. (c) DePue, R. T.; Collum, D. B.; Ziller, J. W.; Churchill, M. R. *J. Am. Chem. Soc.* **1985**, *107*, 2131. (d) Cupertino, D. C.; Harding, M. M.; Cole-Hamilton, D. J. *J. Organomet. Chem.* **1985**, *294*, C29. (e) Peterleitner, M. G.; Tolstaya, M. V.; Krivikh, V. V.; Denisovich, L. I.; Ribinskaya, M. I.; Kravtsov, D. N. *Bull. Acad. Sci. USSR, Div. Chem.* **1986**, 605. (f) Collum, D. B.; Depue, R. T.; Klang, J. A. *Organometallics* **1986**, *5*, 1015. (g) Cupertino, D. C.; Cole-Hamilton, D. J. *J. Chem. Soc., Dalton Trans. I* **1987**, 443.

(7) For some examples of various types of stereoselective reactions occurring with directing effects possibly due to metal coordination of functional groups, see: (a) Groves, J. T.; Van Der Puy, M. *J. Am. Chem. Soc.* **1974**, *96*, 5274. (b) Holton, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 8083. (c) Thompson, H. W.; McPherson, E. *J. Org. Chem.* **1977**, *42*, 3350. (d) Eisch, J. J. *J. Organomet. Chem.* **1980**, *200*, 101. (e) Heumann, A.; Reglier, M.; Waegell, B. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 366. (f) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull.* **1983**, *31*, 31. (g) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458. (h) Johnson, C. R.; Barbachyn, M. R. *Ibid.* **1984**, *106*, 2459. (i) Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*, 3171. (j) Lansbury, P. T.; Mazur, D. J.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 1632. (k) Welch, S. C.; Chou, C.-Y.; Gruber, J. M.; Assercq, J.-M. *J. Org. Chem.* **1985**, *50*, 2668. (l) Hasegawa, K.; Matsuda, F.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1987**, *28*, 1671. For a recent compilation of several further examples, see ref 6c.

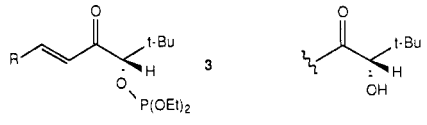
(8) For a recent review of asymmetric hydrogenation of alkenes controlled by metal-coordinated functional group directing effects, see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

**Scheme III**

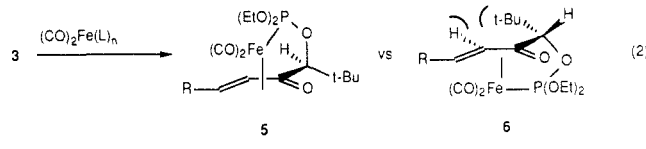



$\alpha,\beta$-unsaturated carbonyl compounds because of their well-known ability to form reasonably stable and characterizable metal complexes[9] and because of the possible use of these compounds in various conjugate addition,[10-12] Diels–Alder,[13] and other addition reactions.[14]

With all of the above considerations in mind, we chose to study the conjugated enones **3** on the basis of the chiral auxiliary **4** that has been used in other contexts by earlier workers.[15] Careful




examination of molecular models indicated that chelation, for example, with an iron dicarbonyl unit on the depicted upper face of the enone to give the complex **5** would be favorable, whereas coordination on the lower face would give the complex **6** exhibiting highly unfavorable nonbonded interactions of the sterically demanding *tert*-butyl substituent with the alkenyl portion of the enone (eq 2).[16] Therefore, having made the assumption of




(2)

thermodynamic control due to possible equilibration of the chelated

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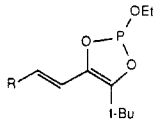
species, we expected highly diastereofacial selective formation of complex **5**. These predictions have been borne out exactly according to plan.

**Synthesis of the Ligands.** Our initial developmental studies were done with racemic compounds. Two methods of preparation were investigated. In the first of our routes (Scheme I), 2,2-dimethyl-3-hydroxy-4-pentanone [(*rac*)-**7**], available by the method of Stacy from ethyl pyruvate diethyl ketal,[15a] is protected as the trimethylsilyl ether and subjected to an aldol condensation with benzaldehyde to give the alcohol *rac*-**8a**. Acid-catalyzed dehydration and desilylation produces the hydroxy enone *rac*-**9a**, and reaction with diethyl chlorophosphite gives the desired ligand, the phosphite-containing, phenyl-substituted enone *rac*-**3a**. The same compound is obtained by a route (Scheme II) based upon the work of Masamune.[15d] The keto acid *rac*-**10**, obtained by oxidation of pinacolone by potassium permanganate,[15b] is reduced with sodium borohydride, and in the key step of the sequence, the hydroxy acid *rac*-**11** reacts with 2-lithiostyrene to produce the hydroxy enone *rac*-**9a** once again. Although this route is shorter than the first one, it proceeds in lower overall yield.

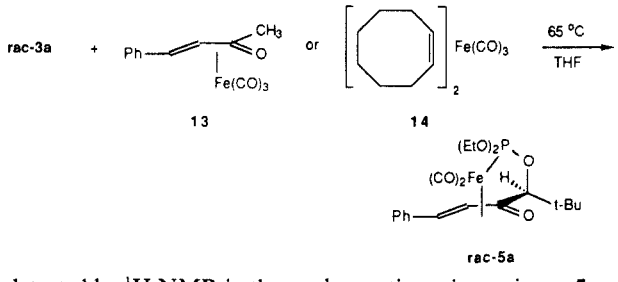
The racemic methyl-substituted enone derivative *rac*-**3b** is prepared according to the basic route in Scheme I but with acetaldehyde replacing benzaldehyde in the aldol condensation step. A more direct route patterned after Scheme II is again less efficient because of a low-yield reaction of an alkenyllithium reagent (1-propenyllithium in this case) with the hydroxy acid **11**. The preparation of the optically active ligand (*S*)-**3b** (Scheme III) is patterned after Scheme I but first involves resolution of the hydroxy acid **11** with (*S*)-1-phenylethylamine according to the procedure of Masamune.[15d]

These phosphites are somewhat air-sensitive compounds that undergo oxidation to the corresponding phosphates. Therefore, the phosphites are normally stored and handled under a nitrogen atmosphere. Also, the desired phosphites are often accompanied by minor side products (less than 5%), which we have tentatively identified as the cyclic derivatives **12** but which do not interfere with our further reactions.




**12**

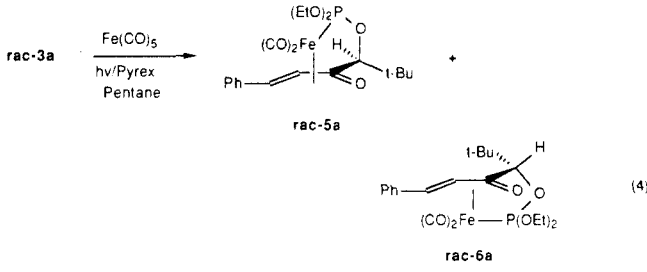
**Coordination Studies.** Our work to date in this area has concentrated mainly upon coordination of the ligands **3** to iron carbonyl groups. We first of all investigated several sets of conditions for complex formation between *rac*-**3a** and several sources of iron, including iron pentacarbonyl, diiron ennecarbonyl, tricarbonyl(benzylideneacetone)iron (**13**),[9a,b,i] and tricarbonylbis(*cis*-cyclooctene)iron (**14**).[17] The best conditions have proven to be the use of **13** in THF (eq 3). The only coordination product




(3)

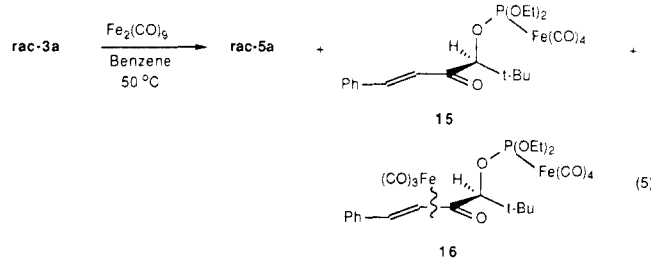
detected by $^1$H NMR in the crude reaction mixture is *rac*-**5a**. On the basis of the limits of detection and comparison with the other possible diastereomer, *rac*-**6a** (vide infra), we can claim a diastereofacial selectivity of at least 95% in this reaction. The complexation also proceeds in high chemical yield; chromatographic purification of the crude product to remove benzylideneacetone and a small amount of unreacted **13** followed by recrystallization provides pure, crystalline *rac*-**5a** in 80% yield. Similarly, the use of the cyclooctene complex **14** as the source of the iron provides *rac*-**5a** as the only detectable coordination product in 68% yield after purification. These results are consistent with our original expectations as discussed above.

When the complexation reaction is done with iron pentacarbonyl under photochemical conditions (eq 4), the two possible diastereomers, *rac*-**5a** and *rac*-**6a**, are obtained in a 1.3:1.0 ratio as determined by $^1$H NMR analysis of the crude reaction mixture. After separation by a combination of chromatography and recrystallization, these two isomers are obtained in a combined yield of 59%.




(4)

The use of diiron enneacarbonyl under thermal conditions gives a complicated mixture consisting of *rac*-**5a** and two new products tentatively identified as the simple mononuclear phosphite complex **15** and the dinuclear complex **16** (eq 5). Analysis of the crude




(5)

mixture by $^1$H NMR spectroscopy indicates that the three products are produced in a ratio of 1:4:1. Chromatographic separation permits isolation of **15** in 46% yield, whereas *rac*-**5a** and **16** are isolated in yields of only 8% and 2%, respectively. Diastereomer *rac*-**6a** could not be detected as a product in this reaction.

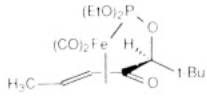
Attempts were made to convert the major product **15** from above into the desired chelated complex. When **15** is heated at 60 °C in benzene for 26 h, no reaction occurs, but when **15** is irradiated in pentane for 50 min, a 1.3:1.0 mixture of *rac*-**5a** and *rac*-**6a** is again obtained as in the earlier photochemical complexation experiment. This photochemical conversion of **15** into the enone/phosphite chelate complexes is also in accord with earlier results of other workers concerned with related ligand substitution reactions.[9c,h,i]

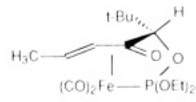
A clear pattern is seen in all of the above experiments; the originally predicted high diastereofacial selectivity is seen consistently under thermal conditions of complexation of the ligand *rac*-**3a**, but a photostationary mixture of the two possible diastereomers is seen under photochemical conditions. A similar observation was made by Collum.[6f]

The complexation behavior of the racemic and the optically active methyl-substituted ligands *rac*-**3b** and (*S*)-**3b** is consistent with the above findings. For example, reaction of (*S*)-**3b** with the benzylideneacetone complex **13** at 60–65 °C in THF for 20 h produces (*S*)-**5b** in 71% yield after isolation and purification. The alternative diastereomer (*S*)-**6b** cannot be detected in the reaction mixture by $^1$H NMR spectroscopy. However, if the above experiment is done for ca. 12 h, a 9:1 mixture of (*S*)-**5b** and (*S*)-**6b** is observed. When the minor isomer (*S*)-**6b** is isolated in pure form from this mixture and is then reheated at 100 °C in toluene, isomerization occurs to give a greater than 20:1 mixture favoring (*S*)-**5b** over (*S*)-**6b**.

**Characterization of the Chelated Complexes.** The simultaneous $\pi$-coordination of the enone moieties and the phosphite groups

(17) Fleckner, H.; Grevels, F.-W.; Hess, D. *J. Am. Chem. Soc.* **1984**, *106*, 2027.




of the ligands **3** to iron was clearly indicated by the changes in the peak positions of the alkenyl hydrogens, the alkenyl carbons, and the phosphorus in the $^1H$, $^{13}C$, and $^{31}P$ NMR spectra before and after complexation. In the free ligand *rac*-**3a**, the $\alpha$-hydrogen is observed at $\delta$ 7.14, and the $\beta$-hydrogen is obscured by the peaks of aromatic hydrogens at $\delta$ 7.15–7.75. In the complex *rac*-**5a**, these two hydrogens appear at $\delta$ 6.29 and 3.15, and in *rac*-**6a** they are seen at $\delta$ 6.77 and 3.37, respectively. This observation of a much greater upfield shift of the $\beta$-hydrogen than the $\alpha$-hydrogen upon $\pi$-coordination of the enone unit is well-precedented by previous studies of related complexes.[9c,h,i,14a] In the free ligand, the phosphorus appears at $\delta$ 138.9 in the $^{31}P$ NMR spectrum, whereas in complex *rac*-**5a** it is seen at $\delta$ 166.0, again consistent with earlier work.[9i] The $^{13}C$ NMR spectral data for our complexes also agree very well with previously reported data.[9i] Corresponding NMR data are also given for the methyl-substituted compounds **3b**, **5b**, and **6b** in the Experimental Section.

The assignment of stereochemistry to the diastereomeric complexes **5** and **6** is difficult on the basis of spectral data alone. Perhaps indicative of these structures are the $^1H$ NMR positions of the hydrogen atom of the methine carbon bearing the phosphite group. In the spectrum of *rac*-**5a**, for example, this hydrogen appears at $\delta$ 4.37, whereas for *rac*-**6a**, it appears at $\delta$ 3.81. The greater downfield shift in the former case is consistent with this hydrogen being held in the anisotropic deshielding region in the plane of the enone unit of *rac*-**5a** compared to the case of *rac*-**6a** in which this hydrogen is held well out of the enone plane as depicted in our drawings of these two compounds. A similar effect is seen for the *tert*-butyl groups; in *rac*-**5a**, this group is held out of the enone plane and appears at $\delta$ 1.10, whereas in *rac*-**6a**, the *tert*-butyl group lies more nearly in the enone plane and appears at $\delta$ 1.22 in the $^1H$ NMR spectrum.

The above stereochemical arguments are tenuous at best, and therefore, we have determined the structures of *rac*-**5a**, *rac*-**6a**, and (*S*)-**5b** by single-crystal X-ray diffraction. The resulting ORTEP diagrams are shown in Figures 1–3, and selected bond lengths and bond angles are listed in Tables I–III (supplementary material). The results clearly confirm our initial stereochemical assignments and lend strong support to our original prediction of diastereofacial selective coordination of our ligands. (In order to minimize confusion, readers should realize that the ORTEP diagram for *rac*-**5a** is enantiomeric relative to the other drawings in this paper. Also, the ORTEP drawing of (*S*)-**5b** is rotated ca. 180° about an axis perpendicular to the page compared to the earlier drawings.)

The bond distances within the enone moieties and between these groups and the iron atoms correspond very well with one another for each of the two diastereomeric complexes *rac*-**5a** and *rac*-**6a**. The agreement is within 0.01 Å for each of the pairs of corresponding bonds. Furthermore, these values are consistent with X-ray data reported previously for several related iron complexes of enones.[9d,h] However, an important difference between our two diastereomeric complexes is seen upon comparison of their C9–C10–C11 bond angles, i.e. the angles for bonding of the *tert*-butyl groups to the enone units. In the favored isomer *rac*-**5a**, it is 115.4°, but in the less stable diastereomer *rac*-**6a**, it is opened up to 120.0°. Likewise, the C8–C9–C10 bond angles are 124.2° and 130.7° for these two complexes, respectively. The greater values for the less stable complex *rac*-**6a** may be attributed to the nonbonded steric interaction, which we had originally anticipated (see **6** in eq 2).

**Preliminary Study of Reactivity.** Although the main emphasis of our initial work in this area has been placed upon the preparation of ligands and the study of their complexation behavior, we would like to close this paper with a brief indication of the potential utility of our complexes in asymmetric synthesis.

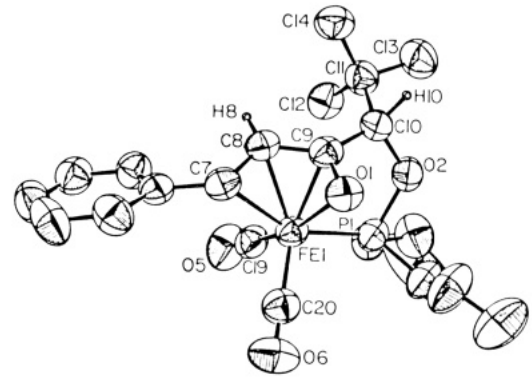



**Figure 2.** X-ray crystal structure of *rac*-**6a**.

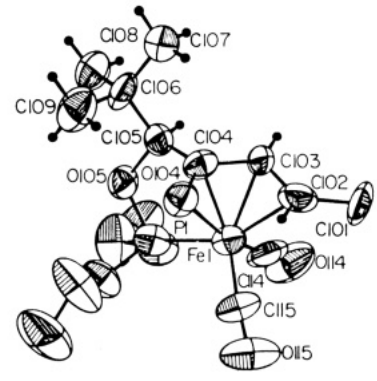
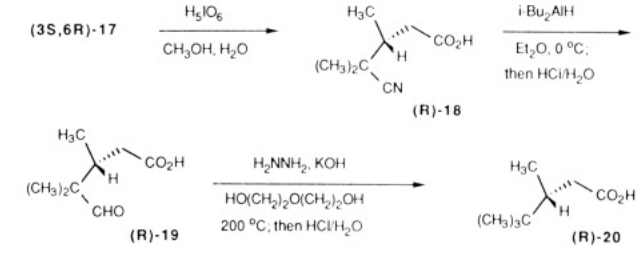
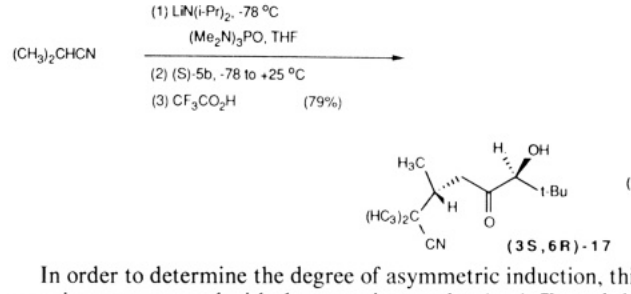



**Figure 3.** X-ray crystal structure of (*S*)-**5b**.

**Scheme IV**




Specifically, we wished to explore carbanionic addition reactions of the optically active complex (*S*)-**5b**, although there are conflicting reports in the literature concerning the possibility of effecting Michael-type additions to related complexes.[14] However, we believed that a good choice of a nucleophile for these reactions would be $\alpha$-lithioisobutyronitrile. This choice was based upon the work of Semmelhack concerned with carbanionic addition to simple diene complexes.[18] Indeed, (*S*)-**5b** undergoes the desired reaction to give the adduct (3*S*,6*R*)-**17** after acidic hydrolysis of the reaction mixture (eq 6).




(6)

In order to determine the degree of asymmetric induction, this reaction was repeated with the racemic complex (*rac*)-**5b**, and the resulting product was compared with the optically active adduct through use of the chiral NMR shift reagent, tris[3-[(hepta-

(18) (a) Semmelhack, M. F.; Herndon, J. W.; Springer, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 2497. (b) Semmelhack, M. F.; Le, H. T. M. *J. Am. Chem. Soc.* **1984**, *106*, 2715.

fluoropropyl)hydroxymethylene]-(+)-camphorato]europium [Eu(hfc)$_3$]. None of the enantiomer of our optically active product could be detected in the reaction mixture resulting from addition of isobutyronitrile to (*S*)-**5b**. On the basis of the minimum amount of the enantiomer that could be detected by $^1$H NMR analysis, we are able to report an enantiomeric excess of at least 99% for the addition to (*S*)-**5b**.

The absolute configuration of our adduct was proven by a classical degradation approach (Scheme IV). Periodate cleavage[15c] gives the cyano acid (*R*)-**18**, reduction with diisobutylaluminum hydride[19] gives the carboxyaldehyde (*R*)-**19**, and Wolff–Kishner reduction[20] gives the acid (*R*)-**20**, having the same optical rotation as the compound for which the configuration is known from previous work.[21]

## Conclusion

We have succeeded in our original goal of designing metal-chelating ligands that undergo diastereofacial selective coordination of carbon–carbon double bonds in a highly predictable manner. We believe that the principles delineated in this paper will be applicable in general to $\pi$-complexes of several types of unsaturated organic compounds including other alkene, diene, allene, allyl, pentadienyl, and arene systems. Furthermore, several other coordinating groups besides phosphites may conceivably be employed. Also, other chiral auxiliaries beyond what we have used to date may be derived from many sources, including amino acids,[22] carbohydrates, terpenes, and other members of the chiral pool.[23] We intend to explore each of these points as we investigate modifications of our ligand systems. With the more finely tuned systems that will result, we will be in a position to study applications in asymmetric synthesis in greater detail.

## Experimental Section

**General Remarks.** All reactions and other manipulations of air-sensitive compounds were performed under a nitrogen atmosphere with double-manifold techniques or in a Vacuum Atmospheres Dri-Lab glovebox. Solutions of air- and/or water-sensitive compounds were transferred with double-ended needles (cannulas) or hypodermic syringes and were concentrated by using a vacuum line equipped with a liquid nitrogen or dry ice cooled trap. Glassware was flame-dried or taken directly from a drying oven into the glovebox before use.

Other general comments, the preparations of previously known compounds **8a**[15c] and **11**,[15b,d] and the details for the X-ray diffraction studies of *rac*-**5a**, *rac*-**6a**, and (*S*)-**5b** may be found in the supplementary material.

**5,5-Dimethyl-4-hydroxy-1-phenyl-1-hexen-3-one (9a). Dehydration of 8a.** A solution of **8a** (7.09 g, 23.0 mmol), and *p*-toluenesulfonic acid monohydrate (0.219 g, 1.15 mmol), and benzene (115 mL) was stirred at 50 °C for 12 h. The mixture was then cooled to 25 °C and washed with 5% aqueous sodium carbonate. The aqueous layer was extracted with ether (2 × 100 mL), and the combined organic layers were washed with 5% aqueous sodium carbonate (50 mL) and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated under reduced pressure to give 4.72 g (94%) of **9a** as a yellow solid, which was pure by $^1$H NMR spectroscopy but which contained minor impurities by TLC analysis. Highly polar impurities were removed by filtration through a 70 × 30 mm column of silica gel (0.040–0.063 mm, 230–400 mesh ASTM) with ether as the solvent. The eluate was concentrated under reduced pressure, and a 1.21-g portion of the residue was further purified by radial chromatography (4-mm layer of silica gel) with 400 mL of 7:1 hexanes/ether acetate (v/v). The major band afforded 0.94 g (78% recovery) of **9a** as a pale yellow solid. Alternatively, 2.08 g of the solid from the filtration through silica gel was recrystallized from hexanes (6 mL) to give 1.57 g (75% recovery) of **9a**: mp 64–71 °C; IR (Nujol) 3425, 2930, 1683, 1613 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 7.70 (d, $J$ = 16 Hz, PhC*H*=CH), 7.35–7.70 (m, $C_6H_5$), 6.86 (d, $J$ = 16 Hz, PhCH=C*H*), 4.14 (d, $J$ = 7 Hz, C*H*OH, collapses to a singlet in acetone-$d_6$ containing a trace of $H_2O$), 3.42 (d, $J$ = 7 Hz, O*H*, exchanges with $H_2O$ in acetone-$d_6$), 1.05 (s, C(C$H_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 201.15 (*C*=O), 143.09. (PhCH=CH), 134.15 (ipso-*C*), 130.83 (para-*C*), 128.90 (ortho-*C*), 128.49 (meta-*C*), 123.29 (PhCH=*C*H), 83.28 (*C*HOH), 35.25 (*C*(CH$_3$)$_3$), 26.37 (C(*C*H$_3$)$_3$); MS, *m/e* (relative intensity) 218 (1.6, M$^+$), 162 (M – $H_2C$=C(CH$_3$)$_2$), 132 (48.3, M – (CH$_3$)$_3$CHO), 131 (100, PhCH=CHC=O$^+$), 104 (23.5), 103 (29.3, PhCH=CH$^+$), 87 ((CH$_3$)$_3$CCHOH$^+$), 57 ((CH$_3$)$_3$C$^+$); exact mass for $C_{14}H_{18}O_2$ calcd 218.1307, found 218.1302. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.68; H, 8.10.

**5,5-Dimethyl-4-hydroxy-1-phenyl-1-hexen-3-one (9a). Reaction of 11 with 2-Lithiostyrene.** On the basis of the procedure of Seebach,[24] a solution of *trans*-2-bromostyrene (0.45 mL, 3.51 mmol) in 4:1:1 THF/ether/pentane (the Trapp mixture, 12 mL) was stirred at −110 °C (liquid nitrogen in 4:1:1 petroleum ether/2-propanol/acetone) under nitrogen. A 1.41 M solution of *tert*-butyllithium (5.0 mL, 7.1 mmol) in pentane was added over 15 min. The solution became bright yellow, and a thick precipitate formed. The mixture was stirred for 2 h, and a solution of **11** (0.134 g, 1.01 mmol) in 1:1 pentane/ether (1 mL) was added over 5 min. The mixture was then allowed to warm to 25 °C; during this warming, the precipitate dissolved, and an orange-red solution was formed at −90 °C. After being stirred at 25 °C for ca. 12 h, the resulting red-violet solution was added dropwise with a cannula to stirred 1.5 N hydrochloric acid (5 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 15 mL). The combined layers were washed with saturated aqueous sodium chloride, dried, and concentrated under reduced pressure to give 0.37 g of a viscous yellow green oil. This material was shown by $^1$H NMR analysis to be a 2:1 mixture of **11** and **9a** (see data above for **9a**).

**Diethyl 5,5-Dimethyl-3-oxo-1-phenyl-1-hexen-4-yl Phosphite (*rac*-3a).** All operations in this procedure were performed under nitrogen. To a solution of **9a** (0.27 g, 1.2 mmol) and methylene chloride (20 mL) at −78 °C were added triethylamine (1.5 mL, 11 mmol) and then diethyl chlorophosphite (0.19 mL, 1.3 mmol) dropwise. The mixture was then warmed to 25 °C, stirred for 4 h, and concentrated under reduced pressure. The residue was extracted with pentane, the extracts were filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure to give 0.38 g (91%) of *rac*-**3a**. The amount of **12** as an impurity varied each time this procedure was followed but was generally less than 5–10%. For the purpose of characterization, the two compounds were isolated in pure form by radial chromatography (silica gel, 5:1 hexanes/ethyl acetate or 20:1 pentane/ether). *rac*-**3a**: $^1$H NMR ($CDCl_3$, 80 MHz) $\delta$ 7.15–7.75 (m, $C_6H_5$C*H*=CH), 7.14 (d, $J$ = 16.0 Hz, PhCH=C*H*), 4.30 (d, $J$ = 10.2 Hz, C*H*OP), 3.86 (apparent quintet, $J$ = 7.4 Hz, P(OC$H_2$CH$_3$)$_2$), 1.21 (t, $J$ = 7.0 Hz, P(OCH$_2$C$H_3$)$_2$), 1.01 (s, C(C$H_3$)$_3$); $^{13}$C NMR (acetone-$d_6$, 20 MHz) $\delta$ 198.26 (*C*=O), 142.25 (PhCH=CH), 135.93 (ipso-*C*), 131.21 (para-*C*), 129.80 (ortho-*C*), 129.19 (meta-*C*), 124.31 (PhCH=*C*H), 84.68 (d, $J$ = 7.2 Hz, $CH_{OP}$), 59.06 (d, $J$ = 12.2 Hz, P(O$CH_2$CH$_3$)$_2$), 35.50 (d, $J$ = 4.9 Hz, *C*(CH$_3$)$_3$), 26.71 (C(*C*H$_3$)$_3$), 17.14 (d, $J$ = 5.0 Hz, P(OCH$_2$*C*H$_3$)$_2$); $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 138.91 (sextet, $J$ = 8.4 Hz); MS, *m/e* (relative intensity) 339 (0.1, M + 1), 338 (M$^+$), 155 (61), 131 (100), 121 (90), 93 (71); exact mass for $C_{18}H_{27}O_4P$ calcd 338.1647, found 338.1681. **12** (R = Ph): mp (sealed tube) 45–51 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.19–7.45 (m, $C_6H_5$), 7.02 (d, $J$ = 15.5 Hz, C*H*=CH), 6.86 (d, $J$ = 15.6 Hz, CH=C*H*), 3.63–3.79 (m, POC$H_2$CH$_3$), 1.35 (s, C(C$H_3$)$_3$), 1.21 (t, $J$ = 7.1 Hz, POCH$_2$C$H_3$); $^{31}$P NMR ($CDCl_3$, 121 MHz) $\delta$ 117.20 (t, $J$ = 6.2 Hz).

**(3*S*)-2,2-Dimethyl-3-hydroxy-4-pentanone [(*S*)-7].** 2-Hydroxy-3,3-dimethylbutyric acid (*rac*-**11**) was resolved with (*S*)-1-phenylethylamine according to the procedure of Masamune.[15d] Obtained was (*S*)-**11**, $[\alpha]^{25}_D$ 4.5° (*c* 1, $H_2O$) [lit.[15d] $[\alpha]^{20}_D$ 4.5° (*c* 4, $H_2O$). To a solution of (*S*)-**11** (1.32 g, 10.0 mmol) in THF (20 mL) at −78 °C under nitrogen was added a 1.4 M solution of methyllithium (25 mL, 35 mmol) in ether over 30 min, during which time a white solid precipitated. The mixture was stirred at −78 °C for 30 min and then at 25 °C for 5 h until the solid dissolved. The mixture was then transferred with a cannula to a rapidly stirred mixture of ice and 1 N hydrochloric acid. The organic solvents were removed from this mixture by rotary evaporation, and the remaining aqueous mixture was extracted with ether (3 × 50 mL). The combined extracts were washed with 10% aqueous sodium carbonate and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated by rotary evaporation. The crude product was purified by flash chromatography (silica gel, 10:1 hexanes/ethyl acetate) (or alternatively, by vacuum distillation) to give 0.91 g (70%) of (*S*)-**7** as a colorless oil: bp 45–50 °C (1 torr) [lit.[15a] for *rac*-**7** bp 26 °C (0.35 torr)]; $[\alpha]^{25}_D$ 133.2° (*c* 1, $CHCl_3$); IR (neat) 3435 (br), 2955, 2870, 1709 cm$^{-1}$; $^1$H NMR ($CDCl_3$ 200 MHz) $\delta$ 3.88 (d, $J$ = 6 Hz, C*H*OH), 3.30 (d, $J$ = 6 Hz, intramo-

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lecularly hydrogen bonded O*H*), 2.25 (s, C*H*$_3$C=O), 0.99 (s, C(C*H*$_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 210.97 (*C*=O), 84.44 (*C*HOH), 35.40 (*C*(CH$_3$)$_3$), 29.31 (*C*H$_3$C=O), 26.23 (C(*C*H$_3$)$_3$).

**2,2-Dimethyl-6-hydroxy-3-[(trimethylsilyl)oxy]-4-heptanone [(*S*)-8b].** According to the same procedure that was used in the initial part of the conversion of *rac*-**7** to *rac*-**8a**, the hydroxy ketone (*S*)-**7** was converted into its *O*-trimethylsilyl derivative (82% yield), $[\alpha]^{25}_D$ −59.8° (*c* 4, $CHCl_3$). A solution of this silyl derivative (2.02 g, 10 mmol) was added dropwise to a solution of lithium diisopropylamide [prepared from 1.5 M *n*-butyllithium solution (7 mL, 10 mmol) in hexane and diisopropylamine (1.4 mL, 10 mmol) in 30 mL of THF] at −75 °C under nitrogen. After the mixture was stirred for 2.5 h at −78 °C, freshly distilled acetaldehyde (0.56 mL, 10 mmol) was added dropwise. The mixture was stirred at −75 °C for 30 min, saturated aqueous sodium bicarbonate (30 mL) was added, and the mixture was warmed to 25 °C. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with cold 0.1 N hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated under reduced pressure. The remaining yellow oil was purified by flash chromatography (silica gel, 20:1 pentane/ethyl acetate), giving 2.0 g (80%) of a mixture of diastereomeric alcohols (*S*)-**8b** as a yellow oil: $[\alpha]^{25}_D$ −58.5° (*c* 1.6, $CHCl_3$); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 4.35 (m, C*H*OH), 3.79 (s, C*H*(OSi)-*t*-Bu), 3.73 (d, *J* = 3 Hz) and 3.54 (d, *J* = 3 Hz, hydrogen-bonded O*H* of two diastereomers), 2.70 (m) and 2.96 (m, diastereotopic C(=O)C*H*$_2$), 1.38 (d, *J* = 6.0 Hz) and 1.36 (2 d, *J* = 6.0 Hz, C*H*$_3$CH(OH)), 1.11 (s) and 1.09 (s, C(C*H*$_3$)$_3$), 0.31 (s) and 0.28 (s, Si(C*H*$_3$)$_3$). On a larger preparative scale (13.0 g of the silyloxy ketone) in the racemic series, the product was purified by distillation to give 12.17 g (77%) of (*rac*)-**8b**: bp 103–106 °C (4 torr).

**2,2-Dimethyl-4-oxo-5-hepten-3-ol [(*S*)-9b].** A solution of (*S*)-**8b** (0.74 g, 3 mmol) and *p*-toluenesulfonic acid monohydrate (0.06 g, 0.3 mmol) in benzene (10 mL) was stirred at 25 °C for 12 h. The brown mixture was then washed with 5% aqueous sodium carbonate, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with 5% aqueous sodium carbonate and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated under reduced pressure. The remaining yellow oil was purified by radial chromatography (silica gel, 10:1 pentane/ethyl acetate) to give 0.33 g (71%) of (*S*)-**9b** as a pale yellow oil: $[\alpha]^{25}_D$ 168.9° (*c* 0.72, $CHCl_3$) [lit.[15d] $[\alpha]^{20}_D$ 178.1° (*c* 0.96, $CHCl_3$)]; $^1$H NMR ($CDCl_3$, 200 MHz; lit.[15d]) $\delta$ 7.02 (dq, *J* = 16.5, 7.5 Hz, CH$_3$C*H*=CH), 6.30 (dd, *J* = 16.5, 2 Hz, CH$_3$CH=C*H*), 4.03 (d, *J* = 7.5 Hz, C*H*OH), 3.40 (d, *J* = 7.5 Hz, hydrogen-bonded O*H*), 1.96 (dd, *J* = 7.5, 2 Hz, C*H*$_3$), 0.98 (s, C(C*H*$_3$)$_3$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 200.98 (*C*=O), 143.74 (CH$_3$*C*H), 129.29 (*C*HC=O), 82.48 (*C*HOH), 35.87 (*C*(CH$_3$)$_3$), 26.29 (C(*C*H$_3$)$_3$), 18.29 (*C*H$_3$).

**Diethyl 2,2-Dimethyl-4-oxo-5-hepten-3-yl Phosphite [(*S*)-3b].** To a solution of diethyl chlorophosphite (0.31 g, 2.0 mmol) in methylene chloride (10 mL) at −78 °C under nitrogen was added a solution of (*S*)-**9b** (0.31 g, 2.0 mmol) and triethylamine (2.8 mL, 20 mmol) in methylene chloride (5 mL) over 10 min. The solution was warmed to 25 °C over 30 min and was then concentrated under reduced pressure. The residue was extracted with pentane, and the extracts were concentrated under reduced pressure. Purification of the residue by radial chromatography (silica gel, 20:1 ethyl acetate/pentane) gave 0.30 g (55%) of (S)-**3b** as a pale yellow oil: $[\alpha]^{25}_D$ −17.1° (*c* 1.58, $CHCl_3$); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.03 (dq, *J* = 15.7, 7.2 Hz, CH$_3$C*H*=CH), 6.46 (dd, *J* = 15.7, 5.8 Hz, CH$_3$CH=C*H*), 4.34 (d, *J* = 7.9 Hz, C(=O)C*H*OP), 4.05 (apparent quintet, *J* = 7.2 Hz, P(OC*H*$_2$CH$_3$)$_2$), 1.86 (dd, *J* = 7.0, 2.0 Hz, C*H*$_3$CH=CH), 1.23 (t, *J* = 7.3 Hz, P(OCH$_2$C*H*$_3$)$_2$), 0.94 (s, C(C*H*$_3$)$_3$); IR (film) 2960, 1740, 1690, 1480 cm$^{-1}$.

**Complexation of *rac*-3a with Tricarbonyl(benzylideneacetone)iron (13) or Tricarbonylbis(*cis*-cyclooctene)iron (14). Formation of Chelate Complex *rac*-5a.** A mixture of keto phosphite *rac*-**3a** (0.17 g, 0.50 mmol) and tricarbonyl(benzylideneacetone)iron (**13**, 0.14 g, 0.50 mmol)[9a,b,i] in THF (10 mL) was stirred at reflux under nitrogen for 8 h. The mixture was concentrated under reduced pressure. Analysis of the crude produce by $^1$H NMR spectroscopy revealed only one isomer as the chelation product. The crude product was subjected to flash chromatography (silica gel, 20:1 pentane/ethyl acetate), and the orange solid obtained from the yellow band was recrystallized from pentane to give 0.18 g (80%) of *rac*-**5a** as orange crystals: mp 107–109 °C; IR (pentane or $CDCl_3$) 2070, 2030, 2000, 1967 cm$^{-1}$; $^1$H NMR (benzene-$d_6$, 300 MHz) $\delta$ 7.26 (d, 2 H, *J* = 7.4 Hz, ortho-Ar *H*), 7.09 (t, 2 H, *J* = 7.4 Hz, meta-Ar *H*), 6.94 (t, 1 H, *J* = 7.4 Hz, para-Ar *H*), 6.29 (d, *J* = 9.4 Hz, PhCH=C*H*), 4.37 (d, *J* = 1.6 Hz, C(=O)C*H*OP), 3.75–4.15 (m, P(OC*H*$_2$CH$_3$)$_2$), 3.15 (dd, *J* = 9.4, 6.7 Hz, PhC*H*=CH), 1.10 (s, C(C*H*$_3$)$_3$), 1.07 (t, *J* = 7.0 Hz, POCH$_2$C*H*$_3$), 1.04 (t, *J* = 7.1 Hz, POCH$_2$C*H*$_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 215.66 and 212.05 (Fe*C*O), 140.49 (*C*(=O)CH), 132.96 (ipso-*C*), 128.43 and 126.09 (ortho- and meta-*C*), 125.53 (para-*C*), 92.03 and 85.11 (PhCH=*C*H and C(=O)-*C*HOP), 62.50 (Ph*C*H=CH), 61.04 and 56.35 (P(O*C*H$_2$CH$_3$)$_2$), 34.44 (*C*(CH$_3$)$_3$), 26.21 (C(*C*H$_3$)$_3$), 16.20 and 16.04 (P(OCH$_2$*C*H$_3$)$_2$); $^{31}$P NMR (benzene-$d_6$, 121 MHz) $\delta$ 166.0 (sextet, *J* = 7.2 Hz); MS, *m/e* (relative intensity) 452 (0.1, M + 2), 451 (0.4, M + 1), 450 (1.3, M$^+$), 422 (M − CO), 394 (M − 2CO), 287 (14.3), 259 (17.1), 258 (100), 243 (15.8); exact mass for $C_{20}H_{27}FeO_6P$ calcd 450.0895, found 450.0897.

The reaction of *rac*-**3a** (0.17 g, 0.5 mmol) and **14** (0.18 g, 0.5 mmol) in THF (10 mL) at 65 °C under nitrogen for 24 h also gave *rac*-**5a** (0.153 g, 68%) after flash chromatography and recrystallization.

**Complexation of *rac*-3a with Iron Pentacarbonyl under Photochemical Conditions. Formation of Chelate Complexes *rac*-5a and *rac*-6a.** A 110-mL, three-necked, Pyrex Schlenk tube was equipped with a cold finger, a magnetic stirring bar, a rubber septum, and a three-way stopcock connected to a double manifold. A nitrogen atmosphere was established, and *rac*-**3a** (0.539 g, 1.59 mmol), iron pentacarbonyl (0.23 mL, 1.75 mmol), and pentane (100 mL) were added sequentially by syringe. The reaction vessel was placed in a Srinivasan–Griffin photochemical reactor equipped with a cylindrical array of 12 75-W 350-nm lamps. The reactor lamps and fan were turned on, and cold water was circulated through the cold finger while the reaction mixture was irradiated for 22 h. The solution was then concentrated under reduced pressure. The residue was dissolved in ether, and polar impurities were removed by filtration of the solution under nitrogen through a short column (55 × 30 mm) of silica gel (0.040–0.063 mm). The filtrate was concentrated under reduced pressure. Analysis of the viscous, orange-red oily residue by $^1$H NMR spectroscopy indicated that it consisted mainly of a 1.3:1.0 mixture of two components, identified below as *rac*-**5a** and *rac*-**6a**, respectively. The mixture was purified further by radial chromatography (4-mm layer of silica gel) under nitrogen. The first broad, yellow band was eluted with 12:1 pentane/ether, and concentration of this fraction gave 0.235 g (33%) of *rac*-**5a** having the same $^1$H NMR parameters as the material isolated in the previous experiment. The second yellow band was eluted with 6:1 pentane/ether. Concentration of this fraction gave 0.185 g (26%) of *rac*-**6a** as an oil, which slowly solidified to give a pale orange solid: mp 105–109 °C (sealed capillary); $^1$H NMR (benzene-$d_6$, 80 MHz) $\delta$ 6.89–7.80 (m, C$_6$*H*$_5$), 6.77 (d, *J* = 9 Hz, PhCH=C*H*), 3.63–4.00 (m, C(=O)C*H*OP and P(OC*H*$_2$CH$_3$)$_2$), 3.37 (dd, *J* = 9.6, 7 Hz, PhC*H*=CH), 1.22 (s, C(C*H*$_3$)$_3$), 1.13 (t, *J* = 7 Hz, POCH$_2$C*H*$_3$), 1.01 (t, *J* = 7 Hz, POCH$_2$C*H*$_3$), $^{13}$C NMR (acetone-$d_6$, 75 MHz) $\delta$ 217.02 and 213.14 (Fe*C*O), 141.62 (*C*(=O)CH), 134.69 (ipso-*C*), 129.24 and 127.15 (ortho- and meta-*C*), 126.38 (para-*C*), 92.46 and 87.49 (PhCH=*C*H and C(=O)*C*HOP), 63.22 (Ph*C*H=CH), 61.74 and 57.66 (P(O*C*H$_2$CH$_3$)$_2$), 35.14 (*C*(CH$_3$)$_3$), 26.89 (C(*C*H$_3$)$_3$), 16.44 and 16.38 (P(OCH$_2$*C*H$_3$)$_2$); MS, *m/e* (relative intensity) 450 (3.6, M$^+$), 422 (19.6, M − CO), 394 (30.5, M − 2CO), 258 (100); exact mass for $C_{20}H_{27}FeO_6P$ calcd 450.0895, found 450.0880.

**Complexation of *rac*-3a with Diiron Enneacarbonyl under Thermal Conditions. Formation of Complexes *rac*-5a, 15, and 16.** A mixture of *rac*-**3a** (0.669 g, 1.98 mmol), diiron enneacarbonyl (0.793 g, 2.17 mmol), and benzene was stirred at 50 °C under nitrogen for 17 h. The mixture was cooled to 25 °C, stirred for an additional 2.5 h, and concentrated under reduced pressure. The residue was extracted with pentane (3 × 4 mL), and the combined pentane extracts were filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure. Analysis of the residue by $^1$H NMR spectroscopy indicated a 1:4:1 mixture of three principal components, identified below as *rac*-**5a**, **15**, and **16**, respectively. Polar impurities were removed by filtration under nitrogen through a short column (40 × 25 mm) of silica gel (0.040–0.63 mm) with 40 mL of ether. The filtrate was concentrated under reduced pressure. Further purification was accomplished with radial chromatography (4-mm layer of silica gel) under nitrogen. The first two yellow bands were eluted with 33:1 pentane/ether and were collected together. Concentration of this combined fraction gave a mixture enriched in *rac*-**5a** and **16**. The next major band was observed by short-wavelength ultraviolet light only and was eluted with 6.7:1 pentane/ether. Concentration of this fraction gave 0.461 g (46%) of a pale yellow, soft solid tentatively identified as **15**: homogeneous by TLC (silica gel, 9:1 pentane/ether, $R_f$ 0.51); mp 75–79.5 °C (sealed capillary); IR (pentane) 2070, 1989, 1949, 1690, 1610 cm$^{-1}$; $^1$H NMR (benzene-$d_6$, 300 MHz) $\delta$ 7.88 (d, *J* = 15.9 Hz, PhC*H*=CH), 7.41 (m, 2 H, Ar *H*), 7.38 (d, *J* = 15.9 Hz, PhCH=C*H*), 7.01 (m, 3 H, Ar *H*), 4.71 (d, *J* = 10.6 Hz, C(=O)C*H*OP), 3.81 and 3.75 (two overlapping apparent quintets, *J* = 6.97 and 6.95 Hz, respectively, P(OC*H*$_2$CH$_3$)$_2$, both collapse to doublets, *J* = 6.63 Hz, and 6.78 Hz, respectively, upon irradiation at $\delta$ 0.90), 1.03 (s, C(C*H*$_3$)$_3$), 0.94 and 0.86 (two t, both *J* = 7.0 Hz, P(OCH$_2$C*H*$_3$)$_2$, both collapse to singlets upon irradiation at $\delta$ 3.75); $^{13}$C NMR (acetone-$d_6$, 75 MHz) $\delta$ 213.45 (d, *J* = 24.7 Hz, Fe(*C*O)$_4$), 196.06 (*C*(=

O)CH), 143.41 (PhCH=CH), 135.62 (ipso-*C*), 131.57 (para-*C*), 129.82 and 129.44 (ortho- and meta-*C*), 123.68 (PhCH=*C*H), 87.68 (d, $J$ = 11.5 Hz, C(=O)*C*HOP), 64.40 (d, $J$ = 3.9 Hz, P(O*C*$H_2$CH$_3$)$_2$), 35.83 (d, $J$ = 6.4 Hz, *C*(CH$_3$)$_3$), 16.57 (C(*C*H$_3$)$_3$), 15.92 (P(OCH$_2$*C*H$_3$)$_2$); $^{31}$P NMR (benzene-$d_6$, 121 MHz) $\delta$ 172.5; MS, $m/e$ (relative intensity) 478 (0.8, M - CO), 450 (M - 2CO), 422 (30.7, M - 3CO), 394 (45.8, M - 4CO), 259 (17.3), 258 (100); exact mass for $C_{21}H_{27}FeO_7P$ (M - CO) calcd 478.0844, found 478.0817. Anal. Calcd for $C_{22}H_{27}FeO_8P$: C, 52.19; H, 5.38; P, 6.12. Found: C, 52.29; H, 5.69; P, 5.80.

The mixture enriched in *rac*-**5a** and **16** from above was further purified by radial chromatography (2-mm layer of silica gel, 25:1 pentane/ether) under nitrogen. The first yellow band gave 0.023 g (1.8%) of a pale yellow-orange solid that was recrystallized from pentane (0.4 mL) under nitrogen to give orange crystals tentatively identified as **16**: mp 112–115 °C (sealed capillary); $^1$H NMR (benzene-$d_6$, 80 MHz) $\delta$ 6.90–7.47 (m, 5 H, Ar *H*), 6.74 (d, $J$ = 9.2 Hz, PhCH=C*H*), 5.04 (d, $J$ = 12.1 Hz, C(=O)C*H*OP), 3.77–4.27 (m, P(OC$H_2$CH$_3$)$_2$), 3.23 (d, $J$ = 9.4 Hz, PhC*H*=CH), 1.18 (t, $J$ = 7 Hz, P(OCH$_2$C$H_3$)$_2$), 1.13 (s, C(C$H_3$)$_3$); $^{31}$P NMR (benzene-$d_6$, 121 MHz) $\delta$ 172.4; MS, $m/e$ (relative intensity) 618 (0.9, M - CO), 590 (M - 2CO), 562 (M - 3CO), 534 (M - 4CO), 506 (M - 5CO), 478 (M - 6CO), 450 (100, M - Fe(CO)$_5$), 422 (M - Fe(CO)$_5$ - CO), 404 (25.7), 394 (29.7, M - Fe(CO)$_5$ - 2CO), 258 (78.1); exact mass for $C_{22}H_{27}Fe_2O_8P$ (M - 3CO) calcd 562.0142, found 562.0191. The second yellow band to elute gave 0.068 g (7.6%) of *rac*-**5a** having the same spectroscopic parameters as the materials isolated previously.

**Complexation of (*S*)-3b with Tricarbonyl(benzylideneacetone)iron (13). Formation of Chelate Complex (*S*)-5b.** A mixture of (*S*)-**3b** (0.700 g, 2.54 mmol) and **13** (0.730 g, 2.55 mmol) in THF (15 mL) was stirred at 60 °C under nitrogen for 20 h. The mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 20:1 pentane/ethyl acetate), and the material obtained from the yellow band was recrystallized from pentane to give 0.70 g (71%) of (*S*)-**5b** as orange crystals: mp 59–60 °C; $[\alpha]^{25}_D$ 292.3° ($c$ 0.68, CHCl$_3$); IR (CDCl$_3$) 2970, 2020, 1950, 1480, 1380, 1020 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 5.97 (d, $J$ = 9 Hz, CH$_3$CH=C*H*), 4.58 (d, $J$ = 1.5 Hz, C(=O)C*H*OP), 3.98 (m, P(OC$H_2$CH$_3$)$_2$), 1.92 (dq, $J$ = 9, 6.3 Hz, CH$_3$C*H*=CH), 1.43 (t, $J$ = 6 Hz, C$H_3$CH=CH), 1.29 (apparent q, $J$ = 7.2 Hz, P(OCH$_2$C$H_3$)$_2$), 1.06 (s, C(C$H_3$)$_3$); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 216.87 (Fe*C*O), 213.18 (Fe*C*O), 132.67 (C(=O)C), 98.52 (CH$_3$CH=*C*HC(=O)), 84.95 (C(=O)*C*HOP), 62.34 and 60.71 (P(O*C*H$_2$CH$_3$)$_2$), 52.61 (CH$_3$*C*H=CH), 34.32 (*C*(CH$_3$)$_3$), 26.23 (*C*H$_3$)$_3$), 17.66 (*C*H$_3$CH=CH), 16.10 (P(OCH$_2$*C*H$_3$)$_2$); MS, $m/e$ (relative intensity) 388 (6, M$^+$), 360 (22.2, M - CO), 332 (1.8, M - 2CO), 288 (100). Anal. Calcd for $C_{15}H_{25}FeO_6P$: C, 46.41; H, 6.49. Found: C, 46.64; H, 6.73.

Similarly, (*rac*)-**5b** was obtained from (*rac*)-**3b**. When the reaction was performed for only 12 h, a 9:1 mixture of (*rac*)-**5b** and (*rac*)-**6b** is obtained on the basis of $^1$H NMR analysis of the crude mixture. Purification by flash chromatography (silica gel, 20:1 pentane/ethyl acetate) and recrystallization from pentane of the material from the second yellow band gave (*rac*)-**6b** as yellow crystals: mp 103–104 °C; IR (CDCl$_3$) 2975, 2900, 2950, 1980, 1960, 1620, 1480, 1400, 1280 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 3.83–4.30 (m, C*H*OP(OC$H_2$CH$_3$)$_2$), 3.52 (m, C*H*=C*H*), 1.69 (dd, $J$ = 7, 2 Hz, CHC$H_3$), 1.40 (t, $J$ = 7 Hz) and 1.30 (t, $J$ = 7 Hz, P(OCH$_2$C$H_3$)$_2$), 1.02 (s, C(C$H_3$)$_3$); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 210.9 (Fe*C*O), 201.25 (Fe*C*O), 87.72, 62.82, and 61.77 (P(O-*C*H$_2$CH$_3$)$_2$), 59.47, 49.72 (CH$_3$*C*H=CH), 35.48 (*C*(CH$_3$)$_3$), 26.4 (C-(*C*H$_3$)$_3$), 24.26 (*C*H$_3$CH=CH), 15.87 (P(OCH$_2$*C*H$_3$)$_2$); MS, $m/e$ (relative intensity) 388 (2.8, M$^+$), 360 (23.5, M - CO), 332 (5.8, M - 2CO), 288 (100). Heating a solution of (*rac*)-**6b** in toluene at 100 °C under nitrogen for 12 h gave a greater than 20:1 mixture of (*rac*)-**5b** and (*rac*)-**6b** according to $^1$H NMR analysis.

**Addition of α-Lithioisobutyronitrile to (*S*)-5b. Formation of Adduct (3*S*,6*R*)-17.** To a solution of diisopropylamine (0.04 mL, 0.3 mmol) in THF (4 mL) at −78 °C under nitrogen was added a solution of *n*-butyllithium (0.3 mmol) in hexane. The mixture was stirred for 20 min, and isobutyronitrile (0.027 mL, 0.3 mmol) was added followed by the addition of hexamethylphosphoric triamide (0.20 mL, 1.1 mmol). The mixture was stirred at −78 °C for 20 min, and a solution of (*S*)-**5b** (0.039 g, 0.10 mmol) in THF was added rapidly. The cooling bath was removed, and the mixture was stirred at 25 °C for 2 h. The mixture was recooled to −78 °C, trifluoroacetic acid (0.15 mL, 2.0 mmol) was added over 30 s, and the mixture was stirred at 25 °C for 1 h. The mixture was poured into saturated aqueous sodium carbonate solution at 25 °C, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with saturated aqueous sodium chloride, dried (MgSO$_4$), and concentrated by rotary evaporation. Purification of the residue by column chromatography (silica gel, 7:3 pentane/ethyl acetate) gave 0.0178 g (79%) of (3*S*,6*R*)-**17** as a yellow oil: $[\alpha]^{25}_D$ 130.9° ($c$ 0.2, CHCl$_3$); IR (CDCl$_3$) 3500, 2980, 2880, 2245, 1700, 1460, 1360 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 3.84 (s, C(=O)C*H*OH), 3.05 (s, O*H*), 2.76 (dd, $J$ = 18, 3 Hz) and 2.50 (dd, $J$ = 16, 10 Hz, C(=O)C$H_2$CH), 2.26 (m, C(=O)CH$_2$C*H*CH$_3$), 1.36 (s) and 1.34 (s, C(C$H_3$)$_2$CN), 1.00 (s, C(C$H_3$)$_3$), 1.00 (d, $J$ = 6 Hz, C$H_3$CHCH$_2$); $^{13}$C NMR (CDCl$_3$) $\delta$ 190.70 (*C*=O), 124.25 (*C*N), 85.27 (*C*HOH), 45.17 (C(=O)*C*H$_2$), 37.66, 36.13, and 35.63 (*C*HCH$_2$, *C*(CH$_3$)$_2$CN, and *C*(CH$_3$)$_3$), 26.48, 25.25, 24.16, and 15.38 (C(*C*H$_3$)$_3$ and other CH$_3$ groups); MS (CI), $m/e$ (relative intensity) 226 (8.6, M$^+$ + 1), 197 (1.3), 169 (5.9), 138 (12.4), 69 (100). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29. Found: C, 69.36; H, 10.09.

This addition reaction was also done with *rac*-**5b** to give the racemic adduct *rac*-**17**. Peaks due to both enantiomers could readily be seen when the chiral shift reagent, tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium [Eu(hfc)$_3$, Aldrich 16,474-7], was added to an $^1$H NMR sample of *rac*-**17** in CDCl$_3$. Especially prominent were the sharp, intense singlets for the *tert*-butyl and C(CH$_3$)$_2$CN groups of the two enantiomers. In order to set a lower limit for the enantiomeric purity of the (3*S*,6*R*)-**17** obtained above, small portions of *rac*-**17** were added to an $^1$H NMR sample of (3*S*,6*R*)-**17** in CDCl$_3$ containing the chiral shift reagent. The enantiomeric compound, (3*R*,6*S*)-**17**, could be detected when the sample contained ca. 0.5% of this compound.

**Degradation of (3*S*,6*R*)-17 to (3*R*)-3,4,4-Trimethylpentanoic Acid [(*R*)-20].** A solution of periodic acid ($H_5IO_6$, 0.456 g, 2.00 mmol) and water (4 mL) was added to a solution of (3*S*,6*R*)-**17** (0.096 g, 0.043 mmol) and methanol (10 mL) at 25 °C.[15c] The mixture was stirred for 12 h and was then evaporated to dryness under reduced pressure. The residue was extracted with ether, and the extracts were evaporated by rotary evaporation. The remaining yellow oil was extracted with 1 N aqueous sodium hydroxide, the extracts were acidified with 1 N hydrochloric acid, and the aqueous mixture was extracted with ether to give 0.048 g (73%) of the cyano acid (*R*)-**18** as an oil: $[\alpha]^{25}_D$ 15.6° ($c$ 0.95, CHCl$_3$); IR (film) 2600–3460 (br, OH), 2980 and 2940 (CH), 2230 (CN), 1720 (C=O) cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 2.14–2.75 (m, C*H*C*H*CO$_2$H), 1.38 (s) and 1.36 (s, CHC(C$H_3$)$_2$CN), 1.13 (d, $J$ = 4 Hz, CHC$H_3$); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 178.27 (*C*=O), 123.90 (*C*N), 37.83, 37.39, and 36.10 (*C*H$_2$*C*H(CH$_3$)*C*(CH$_3$)$_2$CN), 24.65 and 24.06 (C(*C*H$_3$)$_2$CN), 15.39 (*C*HCH$_3$); MS (CI), $m/e$ (relative intensity) 156 (M + 1), 138 (100). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44. Found: C, 61.75; H, 8.26.

To a solution of (*R*)-**18** (0.052 g, 0.33 mmol) in ether (10 mL) at 0 °C under nitrogen was added a 1 M solution of diisobutylaluminum hydride (1.2 mL, 1.2 mmol).[19] The mixture was stirred at 0 °C for 1 h, 1 N hydrochloric acid (20 mL) was added, and the aqueous layer was extracted with ether (2 × 20 mL). The crude product obtained from the combined organic layers was extracted with aqueous sodium hydroxide, and reacidification with hydrochloric acid gave 0.017 g (40%) of the carboxyaldehyde (*R*)-**19** as an oil: $[\alpha]^{25}_D$ 17.6° ($c$ 0.31, CHCl$_3$); IR (film) 2600–3300 (br, OH), 2990 and 2940 (CH), 2700 (C(O)—H), 1720 (C(=O)H), 1710 cm$^{-1}$ (C(=O)OH); $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 9.47 (s, CO$_2$*H*), 2.02–2.46 (m, C*H*C*H*$_2$CO$_2$H), 1.03 (s, C-(C$H_3$)$_2$CHO), 0.97 (d, $J$ = 8 Hz, CHC$H_3$); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 205.67 (*C*HO), 178.8 (*C*O$_2$H), 48.50 (*C*(CH$_3$)$_2$CHO), 36.69 (*C*HCO$_2$H), 33.99 (*C*HCH$_2$), 18.53 and 18.32 (C(*C*H$_3$)$_2$CHO), 14.81 (*C*H$_3$CH).

A mixture of (*R*)-**19** (80 mg, 0.5 mmol), diethylene glycol (10 mL), 85% hydrazine hydrate (1 mL), and potassium hydroxide (0.5 g) was heated gently to dissolve the potassium hydroxide and was then heated at reflux for 4 h.[20] Water and excess hydrazine were distilled from the mixture heated in an oil bath at 240 °C. Additional hydrazine hydrate (1 mL) was added, and the mixture was heated at reflux for an additional 12 h. The mixture was cooled to 0 °C, 1 N hydrochloric acid (20 mL) was added, and the mixture was extracted with ether. The organic layer was washed with water, dried (MgSO$_4$), and concentrated by rotary evaporation. Kugelrohr distillation of the residue gave 0.040 g (55%) of the acid (*R*)-**20** as a clear, colorless oil: $[\alpha]^{25}_D$ 21.7° ($c$ 0.9, EtOH) [lit.[21] $[\alpha]^{25}_D$ 20.6° ($c$ 2.5, EtOH); IR (film) 2600–3300 (br, OH), 2960 and 2930 (CH), 1710 (C=O), 1465, 1410, 1399 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 11.0 (s, CO$_2$*H*), 1.81–2.60 (m, C*H*C*H*$_2$CO$_2$H), 0.92 (d, $J$ = 9 Hz, CHC$H_3$), 0.88 (s, C(C$H_3$)$_3$); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 180.74 (*C*O$_2$H), 39.82 (*C*HCH$_2$), 37.33 (*C*H$_2$CO$_2$H), 32.73 (*C*(CH$_3$)$_3$), 27.08 (C(*C*H$_3$)$_3$), 15.01 (*C*H$_3$CH).

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**Supplementary Material Available:** Further experimental data, including general remarks, procedures for preparation of *rac*-**8a** and *rac*-**11**, detailed description of X-ray structure determinations, supplementary literature references for these procedures, and Tables I-VII of X-ray diffraction bond lengths, bond angles, refinement data, thermal parameters, and hydrogen atom coordinates for *rac*-**5a**, *rac*-**6a**, and (*S*)-**5b** (41 pages). Ordering information is given on any current masthead page.

# Chemistry of Amphotericin B. Degradation Studies and Preparation of Amphoteronolide B†

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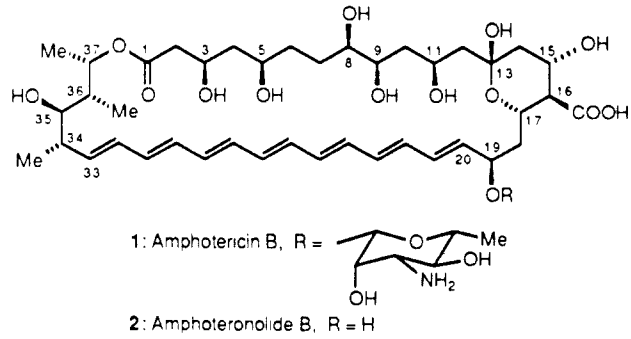
**Abstract:** Amphotericin B (**1**) was converted to a series of protected derivatives (**3–5, 27**). Compound **5** was degraded by ozonolysis and further elaborated to fragments **8, 14,** and **15**, three potential intermediates in a projected total synthesis of amphotericin B (**1**). A novel oxidative deglycosidation procedure based on radical bromination was devised and applied to the degradation of **5** and **27** to heptaenones **21** and **28**, respectively. These heptaenones were stereospecifically reduced with sodium borohydride to amphoteronolide B derivatives **23** and **29**, respectively. The *R* stereochemistry of the C-19 hydroxyl group arising from the reduction of these polyenones was confirmed by using Nakanishi's CD method on derivative **26** obtained by appropriate chemical manipulations of the reduction products. The aglycon of amphotericin B, amphoteronolide B (**2**), was obtained from **29** by desilylation followed by methyl ester hydrolysis.

The polyene macrolide class of antibiotics, encompassing hundreds of compounds, is one of the most challenging areas of natural products chemistry due to the complexity and biomedical importance of its members.[1] Amphotericin B (**1**),[2] the most prominent member of this class and a widely used antifungal agent, is produced by *Streptomyses nodosus* and is the only member of this family of compounds whose structure has been fully established by X-ray crystallographic analysis.[3] Serious difficulties in the chemistry of these natural products have long been recognized and are responsible for the notable scarcity of full structural elucidations and the lack of semisynthetic materials for biological and chemical investigations. The origin of these problems rests in the high molecular weight of these compounds and their lack of crystallinity and solubility in common organic solvents, as well as high chemical and photosensitivities. It is, therefore, not surprising that despite many attempts, this field remains largely unexplored. With the long term intention of opening the field to chemical and biological investigations, we recently embarked on a program directed toward the exploration of the chemistry of amphotericin B (**1**). Our immediate goals were the derivatization and degradation of amphotericin B (**1**) and the preparation of its aglycon, amphoteronolide B (**2**), as a prelude to eventual total syntheses of these and other potentially bioactive materials.




1: Amphotericin B, R =

2: Amphoteronolide B, R = H

† This paper is dedicated with respect and affection to Professor E. J. Corey on the occasion of his 60th birthday.

Amphoteronolide B (**2**) and its derivatives are important chemical entities from a number of perspectives, including (a) possible biological activity and natural occurrence, (b) potential starting points for enzymatic and chemical preparation of amphotericin B analogues, and (c) advanced intermediates and comparison/relay stages for an eventual total synthesis of amphotericin B (**1**) itself. In this paper we describe our studies on the chemistry of amphotericin B (**1**), including protection and degradation,[4] oxidative deglycosidation, and conversion to amphoteronolide B (**2**).[5]

## Results and Discussion

**Protection and Degradation of Amphotericin B (1).** After a brief encounter with amphotericin B (**1**) it was soon recognized that a prerequisite to the development of its chemistry was to produce derivatives that were soluble in common organic solvents, facilitating both chromatographic and spectroscopic work. Previous work[6] has shown that selective acetylation of the amino group ($Ac_2O$) followed by methylation of the carboxyl group ($CH_2N_2$) leads to the *N*-acetylamphotericin B methyl ester (**3**) with improved physical properties over **1** but still presenting solubility and chromatographic problems. Further protection, preferably differentiating the various hydroxyl groups, was, therefore, sought.

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