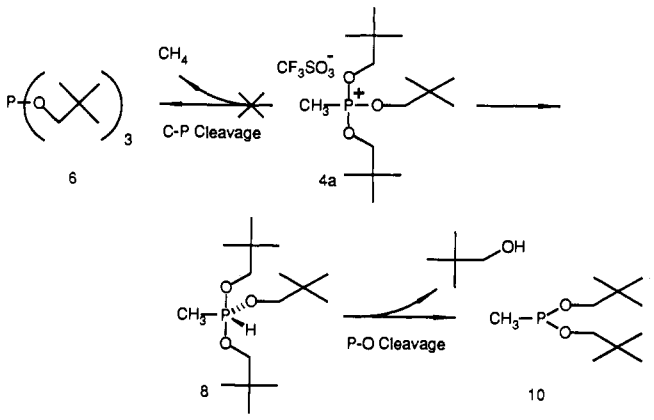
Scheme III



propane and propene with the alkane in substantial excess.[1a]

Phosphoranyl radical **5** is likely produced[7] by the single-electron reduction (Scheme II) leading to both carbon to oxygen (C–O) and C–P bond cleavage. On the basis of the yields of phosphorus-containing products (Table I), C–O and C–P bond cleavage are the only major reactions that occur during single-electron reduction of the phosphonium ions. Thermodynamically favored[8] C–O bond cleavage dominates the single-electron reductions. Carbon to phosphorus bond homolysis competes with C–O bond homolysis as the kinetically favored fragmentation when the resultant carbon-centered radical is stabilized as in the single-electron reductions of allyl- and benzyltrineopentoxyphosphonium ion. Low levels (1–3%) of trineopentyl phosphate are detected during all single-electron reductions of phosphonium ions.

Reaction with lithium triethylborohydride provides a gauge of organophosphonate and organophosphonium reactivity with a hydride reductant. Organophosphonate diesters are unreactive while methyltrineopentoxyphosphonium trifluoromethanesulfonate (**4a**) is rapidly reduced with complete loss of phosphonium ion.[9] Fragmentation via C–P bond cleavage was initially anticipated (Scheme III), given the precedented dealkylations observed during reaction of quaternary ammonium ions with hydride reagents.[10] However, no methane or trineopentyl phosphite is produced. Instead, a quantitative conversion to dineopentyl methylphosphonite (**10**) indicative of P–O bond cleavage (Scheme III) is observed. Suggestion of phosphorane **8** as an intermediate follows from reactions of phosphonium ions with nucleophiles which proceed through or produce phosphoranes.[11]

Mechanisms proposed for microbial cleavage of organophosphonate C–P bonds include organophosphonate oxidation to a phosphonyl radical[1] or reduction to an organophosphonite ($RCH_2P(OH)_2$) followed by phosphoranyl radical formation.[2] Organophosphonium ion intermediacy and C–P bond fragmentation (Scheme I) differs from these proposals by virtue of the phosphorus-containing metabolites predicted to form during biodegradation. Phosphonium ion but not phosphonyl radical intermediacy should lead to phosphorous acid as the immediate product of C–P bond cleavage. All reductive mechanisms postulate intermediacy of a phosphoranyl radical and a phosphorous acid. However, an organophosphonite is absent from Scheme I where phosphonium ion is directly reduced to phosphoranyl radical.

The chemistry of organophosphonates and organophosphonium ions under reducing conditions significantly expands the chemical data base relevant to organophosphonate C–P bond cleavage. Even hydride reduction of organophosphonium ions, which does not lead to C–P bond cleavage, provides potential insights. Organophosphonate stability toward hydride reduction relative to the facile reduction of phosphonium ion indicates how a biological system could catalyze organophosphonite formation. Phosphonium ion fragmentation can thus be considered as a new, free-standing mechanism (as in the case of single-electron reduction) or an adjunct (like hydride reduction) to an extant mechanism. Which is the correct viewpoint awaits identification of the phosphorus-containing metabolites present during organophosphonate biodegradation.

Acknowledgment. Research was partially supported by NIH GM36558. NMR services were funded through NIH RR01077 and NSF/BBS-88714258.

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(8) (a) Bentrude, W. G.; Hansen, E. R.; Khan, W. A.; Rogers, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 2867. (b) Pobedimskii, D. G.; Mukmeneva, N. A.; Kirpichnikov, P. A. *Russ. Chem. Rev. (Engl. Transl.)* **1972**, *41*, 555.

(9) Lithium triethylborohydride in tetrahydrofuran was added dropwise under a nitrogen atmosphere to a tetrahydrofuran solution of **4a** at −78 °C. After quenching with water, product yield was determined by gas chromatography relative to decane as an internal standard. Reaction product and independently synthesized dineopentyl methylphosphonite coinjected and had identical mass spectra.

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(11) (a) Kumli, K. F.; McEwen, W. E.; Vander Werf, C. A. *J. Am. Chem. Soc.* **1959**, *81*, 3805. (b) Zanger, M.; Vander Werf, C. A.; McEwen, W. E. *J. Am. Chem. Soc.* **1959**, *81*, 3806. (c) Phillips, D. I.; Szele, I.; Westheimer, F. H. *J. Am. Chem. Soc.* **1976**, *98*, 184.

The Synthesis and Absolute Configuration of Mycosporins. A Novel Application of the Staudinger Reaction

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Received July 24, 1989

The mycosporins, e.g., **1** and **2**, represent a structurally unique class of fungal metabolites[2] that are believed to exercise a regulatory effect on sporulation.[3] Although ubiquitous among both terrestrial and marine species,[4] mycosporins and their imino derivatives, e.g., **3** and **4**,[5] are notoriously unstable substances, suffering dehydration and consequent aromatization as well as hydrolysis to a meso cyclohexane-1,3-dione with facility. Further, in spite of the fact that mycosporins possess optical activity, their absolute configurations are unknown. We now report the first syntheses of **1** and **2** by a route that defines the configuration of the stereogenic centers in these two mycosporins as *S*. Our synthetic strategy illustrates a novel application of the Staudinger reaction[6] of an iminophosphorane for introducing the appropriate mycosporin side chain.

(1) Guggenheim Fellow, 1988–1989.

(2) (a) Leach, C. M. *Can. J. Bot.* **1965**, *43*, 187. (b) Trione, E. J.; Leach, C. M.; Mutch, J. T. *Nature* **1966**, *212*, 163. (c) Trione, E. J.; Leach, C. M. *Phytopathology* **1969**, *59*, 1077. Mycosporins were originally known as P-310's due to their characteristic UV absorbance at this wavelength.

(3) (a) Dehorter, B. *Can. J. Bot.* **1976**, *54*, 600. (b) Dehorter, B.; Bernillon, J. *Can. J. Bot.* **1983**, *61*, 1435.

(4) (a) Arpin, N.; Curt, R.; Favre-Bonvin, J. *Rev. Mycol.* **1979**, *43*, 247. (b) Arpin, N.; Bovillant, M.-L. *The Fungal Spore*; Turian, G., Hohl, H. R., Eds.; Academic Press: London, 1981.

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(6) Gololobor, Y. G.; Zhmurova, I. N.; Kasuklim, L. F. *Tetrahedron* **1981**, *37*, 437.

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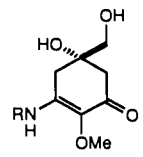
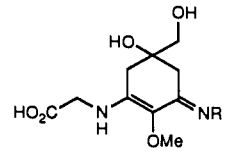


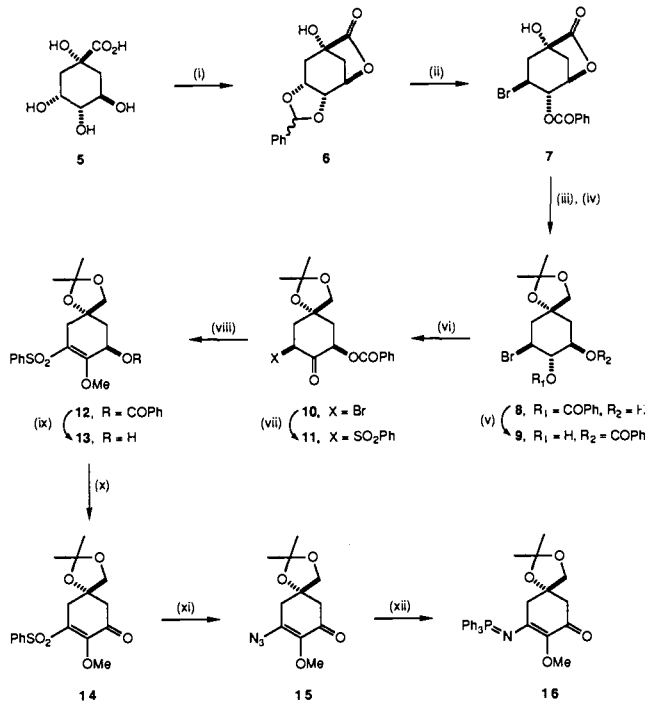


1, R = CH_2CO_2H (Mycosporin-Gly)
2, R = $CH(CH_2OH)_2$ (Mycosporin I)
3, R = H (Palythine)
4, R = CH_2CH_2OH (Asterina-330)
18, R = CH_2CO_2Me

D-(−)-Quinic acid (**5**) was chosen as the starting point (Scheme I) with the goal of elevating its contiguous triol system to the oxidation level of the mycosporins without aromatization or transit through an achiral intermediate that would erase its stereochemical content. Acid-catalyzed acetalization of **5** with benzaldehyde was accompanied by γ-lactonization to afford the quinide **6**,[7] which, upon treatment with *N*-bromosuccinimide, gave a single bromo benzoate **7**.[8] Reduction of **7** with sodium borohydride,[9] followed by ketalization of the resultant mixture of triols, afforded isomeric acetonides **8** and **9** in which partial migration of the benzoate ester to the peripheral oxygen had occurred. Advantage was taken of this serendipitous rearrangement by forcing the mixture toward **9** and then oxidizing this alcohol to **10**. The bromo substituent of **10** underwent clean displacement with sodium benzenesulfinate to give **11** with retention of configuration.[10] An X-ray crystallographic analysis of **11** established its structure as shown in Figure 1.[11]

The enol tautomer of **11** was methylated quantitatively with diazomethane to furnish **12**, from which the benzoate was removed by reduction. The resulting allylic alcohol **13** was carefully oxidized to **14**. Attempts to effect an addition–elimination sequence with **14** that would replace the sulfonyl moiety with an intact mycosporin side chain invariably led to benzenoid products. However, sodium azide accomplished net displacement[12] to yield **15** and thereby provided an alternative means for introducing the pendant amino function. A Staudinger reaction of **15** with triphenylphosphine afforded the stable iminophosphorane **16** in excellent yield, and this species was reacted with benzyl glyoxylate[13] to give initially an imine,[14] which was promptly reduced with sodium cyanoborohydride to **17** (Scheme II). Trifluoroacetic acid cleaved the acetonide quantitatively from **17** to produce a diol that, upon hydrogenolysis, afforded labile mycosporin-Gly (**1**). The properties of **1** were in excellent agreement with those recorded for the natural product.[5b] Treatment of synthetic **1** with diazomethane gave the stable methyl ester **18** ($[\alpha]_D$ −11.3°), the optical rotation of which matched that of the naturally derived ester ($[\alpha]_D$ −12°).[5b] The stereogenic center of **1** is thereby defined as *S*, in agreement with a proposed biosynthesis of mycosporins via the shikimate pathway.[15]

Scheme I[a]



[a] Reagents and conditions: (i) C_6H_5CHO, *p*-TsOH, C_6H_6, reflux, 19 h, 97%; (ii) *N*-bromosuccinimide, CCl_4, reflux, 1.3 h, 76%; (iii) $NaBH_4$, *i*-PrOH; (iv) $(MeO)_2CMe_2$, *p*-TsOH, acetone, reflux, 2 h, 45% of **8**, 41% of **9** (from **7**); (v) NH_4Cl (saturated), NH_4OH, *i*-PrOH, 25 °C, 15 h, 49% with 35% recovered **8**; (vi) PCC, CH_2Cl_2, reflux, 11 h, 64%; (vii) $C_6H_5SO_2Na$, DMF, 25 °C, 15 h, 88%; (viii) CH_2N_2, Et_2O–EtOAc (1:1), 0 °C, 15 h, 99%; (ix) $(i\text{-Bu})_2AlH$, CH_2Cl_2, 0 °C, 3 h, 62%; (x) PCC, NaOAc, CH_2Cl_2, 25 °C, 13 h; (xi) NaN_3, LiCl (cat.), DMF, 25 °C, 15 h, 59% from **13**; (xii) Ph_3P, Et_2O, 25 °C, 3 h, 94%.

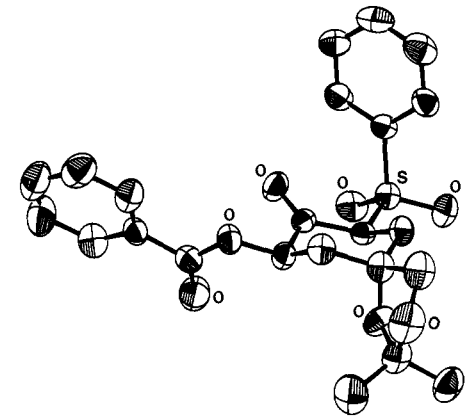


Figure 1. ORTEP plot of **11** with heteroatoms labeled. Thermal ellipsoids are drawn at the 50% probability level.

A second sequence, in which **16** was reacted with diethyl ketomalonate and the intermediate imine reduced with sodium cyanoborohydride, led to **19**. Directed reduction of the α-amino diester moiety,[16] followed by unmasking of the acetonide, produced a polar substance **2**, identical chromatographically and spectroscopically with a sample of natural mycosporin I.[17] A final confirmation of identity was made by converting both natural and synthetic compounds to the same bis(acetonide) **20**.[18] Attempts

(7) DePooter, H.; DeBrucker, J.; Van Sumere, C. F. *Bull. Soc. Chim. Belg.* **1975**, *84*, 835.
(8) The regiospecificity observed in the trans diaxial opening of the dioxolane ring of **6** is probably associated with the rigidity enforced by the bridging γ-lactone on this framework (cf.: Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1053). We are indebted to Dr. Klaus Thirring for initial studies of this reaction.
(9) Mercier, D.; Leboul, J.; Cleophax, J.; Gero, S. D. *Carbohydr. Res.* **1971**, *20*, 299.
(10) Enolization, with preference of the sulfonyl substituent for an equatorial orientation, accounts for this result.
(11) Monoclinic crystals of **11** (space group $P2_12_12_1$) had lattice parameters a = 12.550 (4) Å, b = 7.165 (2) Å, and c = 12.659 (2) Å, with two independent molecules per unit cell. A total of 1486 reflections ($\theta < 50°$) were considered observed ($I > 3.00\sigma(I)$]. The structure was solved by a multiple solution procedure and was refined by full-matrix least squares. The final discrepancy index was R = 0.036.
(12) Nesmeyanov, A. N.; Rybinskaya, M. I. *Dokl. Akad. Nauk SSSR* **1966**, *170*, 600; *Chem. Abstr.* **1967**, *66*, 55440.
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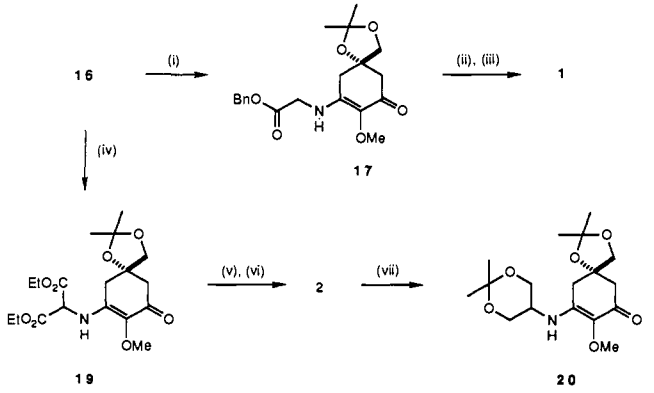
(14) For an elegant application of the little-used Staudinger reaction, see: Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.
(15) Favre-Bonvin, J.; Bernillon, J.; Salin, N.; Arpin, N. *Phytochemistry* **1987**, *26*, 2509.
(16) Seki, H.; Koga, K.; Matsuo, H.; Ohki, S.; Matsuo, I.; Yamada, S. *Chem. Pharm. Bull. Jpn.* **1965**, *13*, 995.
(17) Favre-Bonvin, J.; Arpin, N.; Brevard, C. *Can. J. Chem.* **1976**, *54*, 1105. Mycosporin I was observed to undergo mutarotation associated with cyclization of the amino diol side chain to an oxazolidine.
(18) Synthesized **20** had $[\alpha]_D$ −2.4° whereas the compound derived from natural material had $[\alpha]_D$ −3.8°. This discrepancy is believed to be due to mutarotation of **2**.

Scheme II[a]



[a] Reagents and conditions: (i) $PhCH_2O_2CCHO$ (25 equiv), THF, 25 °C, 7 h, then $NaBH_3CN$, MeOH, 25 °C, 57%; (ii) 50% aqueous TFA–$CHCl_3$ (3:10), 0 °C, 20 min; (iii) H_2, 10% Pd/C, 58% from **17**; (iv) EtO_2CCOCO_2Et (5 equiv), Et_2O, reflux, 2 h, then $NaBH_3CN$, MeOH, 25 °C, 1 h, 73%; (v) $NaBH_4$, MeOH–H_2O (5:1), 0 °C, 3 h; (vi) 50% aqueous TFA, 0 °C, 20 min, 59% from **19**; (vii) $(MeO)_2CMe_2$, pyridinium *p*-toluenesulfonate, acetone, 25 °C, 3 days, 44%.

to prepare iminomycosporins by condensation of **1** with various amines have been unsuccessful.

Acknowledgment. We are grateful to Dr. Noël Arpin, Université de Lyon, France, for a sample of natural mycosporin I and to Professor Shosuke Ito, Fujita-Gakuen Health University, Toyoake, Japan, for UV, IR, and ^1H NMR spectra of **18**. Financial support was provided by the National Science Foundation (CHE-8619029).

Supplementary Material Available: Spectroscopic data (IR, ^1H NMR, ^{13}C NMR, MS), optical rotations ($[\alpha]_D$), and analytical data for **1**, **2**, and **6–20** (4 pages). Ordering information is given on any current masthead page.

Regioselective and Diastereoselective Addition of Methyl Anion to Chiral (Pentadienyl)ruthenium Complexes[1]

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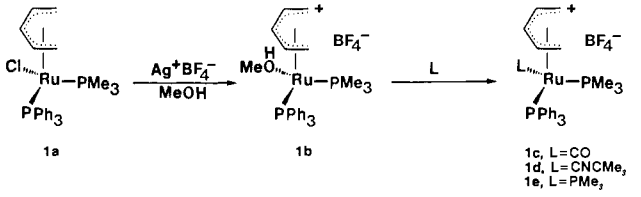
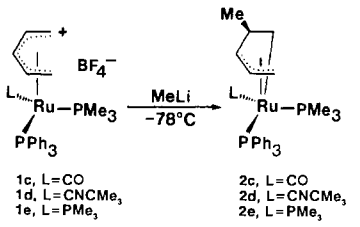
Received July 31, 1989

During the past two decades, there has been considerable interest in the reactions of acyclic pentadienyl ligands with nucleophiles.[2] Virtually all of these studies have involved complexes

Scheme I



Scheme II



in which the pentadienyl ligand is bonded to an electron-poor $Fe(CO)_3^+$ moiety and have, with few exceptions, resulted in nucleophilic attack at the pentadienyl termini (C1/C5).

We are interested in promoting nucleophilic attack at the *internal* carbons (C2/C4) of pentadienyl ligands in order to produce (pentenediyl)metal complexes, a relatively unexplored compound class[3] with potential applications to organic synthesis. Following the thesis of Davies, Green, and Mingos,[4] who assert that electron-rich ML_n moieties will promote nucleophilic attack at the even-numbered carbon atoms of odd open polyenyl ligands (i.e., C2/C4 in pentadienyl ligands), we have synthesized a family of electron-rich (pentadienyl)ruthenium complexes. We report herein the regio- and diastereoselective nucleophilic addition of methyl anion to the C2 position of the pentadienyl ligands in these complexes.[5]

As shown in Scheme I, treatment of (η^5-pentadienyl)Ru(PMe_3)(PPh_3)(Cl) (**1a**)[1a] with $Ag^+BF_4^-$ in methanol produces [(η^5-pentadienyl)Ru(PMe_3)(PPh_3)(MeOH)]$^+BF_4^-$ (**1b**). The weakly coordinated methanol ligand in **1b** is readily displaced by a series of 2e ligands, including carbon monoxide, *tert*-butyl isocyanide, and trimethylphosphine, producing a family of complexes of formula [(η^5-pentadienyl)Ru(PMe_3)(PPh_3)(L)]$^+BF_4^-$ (L = CO, **1c**; L = $CNCMe_3$, **1d**; L = PMe_3, **1e**).[6] Each of these complexes exists in solution as a *single detectable rotamer*,[7] in which the smaller phosphine ligand, PMe_3, resides under the open pentadienyl "mouth", while PPh_3 and L reside under the pentadienyl "edges". Furthermore, the *barrier* to pentadienyl ligand rotation is quite high. For example, line-shape simulations of the variable-temperature $^{31}P(^1H)$ NMR spectra of **1e** yield a $\Delta G^{\ddagger}$ for rotation of >18 kcal/mol. Finally, each of the complexes (**1c–e**) is *chiral* with a stereogenic center at ruthenium.[8]

Treatment of **1c–e** with methyllithium at −78 °C leads cleanly to the production of the (2-methyl-1,3,4,5-η-pentenediyl)Ru(PMe_3)(PPh_3)(L) complexes (**2c–e**)[9] (see Scheme II). In each

(1) Pentadienyl–Metal–Phosphine Chemistry. 19. For recent papers in this series, see: (a) Bleeke, J. R.; Rauscher, D. J. *Organometallics* **1988**, *7*, 2328. (b) Bleeke, J. R.; Earl, P. L. *Ibid.*, in press.

(2) (a) Maglio, G.; Musco, A.; Palumbo, R. *J. Organomet. Chem.* **1971**, *32*, 127. (b) Maglio, G.; Palumbo, R. *Ibid.* **1974**, *76*, 367. (c) Bonner, T. G.; Holder, K. A.; Powell, P. *Ibid.* **1974**, *77*, C37. (d) Birch, A. J.; Pearson, A. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 954. (e) Whitesides, T. H.; Neilan, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 63. (f) Bayoud, R. S.; Biehl, E. R.; Reeves, P. C. *J. Organomet. Chem.* **1978**, *150*, 75. (g) Bayoud, R. S.; Biehl, E. R.; Reeves, P. C. *Ibid.* **1979**, *174*, 297. (h) Powell, P. *Ibid.* **1979**, *165*, C43. (i) Pearson, A. J.; Roy, T. *Tetrahedron* **1985**, *41*, 5765. (j) Gree, R.; Laabassi, M.; Mosset, P.; Carrie, R. *Tetrahedron Lett.* **1985**, *26*, 2317. (k) Uemura, M.; Minami, T.; Yamashita, Y.; Hiyoshi, K.; Hayashi, Y. *Ibid.* **1987**, *28*, 641. (l) Semmelhack, M. F.; Park, J. *J. Am. Chem. Soc.* **1987**, *109*, 935. (m) Bleeke, J. R.; Hays, M. K. *Organometallics* **1987**, *6*, 1367. (n) Donaldson, W. A.; Ramaswamy, M. *Tetrahedron Lett.* **1988**, *29*, 1343. (o) Donaldson, W. A.; Ramaswamy, M. *Ibid.* **1989**, *30*, 1339. (p) Donaldson, W. A.; Ramaswamy, M. *Ibid.* **1989**, *30*, 1343. (q) Pinsard, P.; Lellouche, J.-P.; Beaucourt, J.-P.; Toupet, L.; Schio, L.; Gree, R. *J. Organomet. Chem.* **1989**, *371*, 219.

(3) (a) The first (pentenediyl)metal complexes were obtained by Aumann via metal-centered vinylcyclopropane ring opening: Aumann, R. *J. Organomet. Chem.* **1973**, *47*, C29. Aumann, R. *J. Am. Chem. Soc.* **1974**, *96*, 2631. (b) See ref 2e,m,p,q for other examples of (pentenediyl)metal complexes.

(4) (a) Davies, S. G.; Green, M. L. H.; Mingos, D. M. P. *Tetrahedron* **1978**, *34*, 3047. (b) These rules are particularly applicable to nucleophilic additions involving hard nucleophiles where charge control is anticipated.

(5) Pearson has previously reported nucleophilic attack at C2 of the dienyl moiety in [(η^5-cycloheptadienyl)$Fe(CO)_2(L)]^+$ (L = PPh_3 and $P(OPh)_3$) complexes. See: Pearson, A. J.; Kole, S. L.; Ray, T. *J. Am. Chem. Soc.* **1984**, *106*, 6060.

(6) Representative Synthesis of **1c**. Carbon monoxide was bubbled rapidly through a 75-mL solution of compound **1b** (0.63 g, 1.0×10^{-3} mol) in methanol for 5 min. The solution volume was reduced in vacuo to approximately 10 mL and then cooled to −30 °C, to yield pale yellow crystals of **1c** overnight (0.42 g, 67%).

(7) If other rotamers are present, they must represent <1% of the mixture.

(8) The two PMe_3 ligands in **1e** are different by virtue of their orientation with respect to the pentadienyl ligand.

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