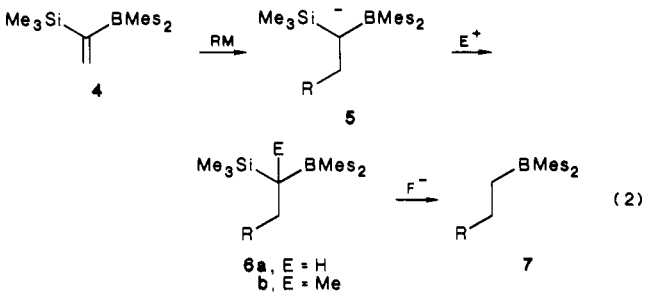
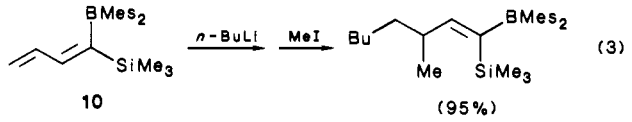
to useful organoboranes (eq 2, Table I).[14]



Additions proceed readily with a variety of nucleophiles, giving air-stable adducts **6**. Adducts were not obtained either with the lithium enolate of pinacolone or with lithium phenylacetylide, although in the latter case an ate complex derived product was obtained.[15] While not definitive, it is noteworthy that the use of 5-hexenyllithium (Table I, entry 6) as a probe for possible SET involvement[8] gives no cyclic product. Cuprate reagents[16] do undergo addition reactions (Table I, entries 2, 3), however.

β-Substitution is tolerated in the absence of allylic hydrogens (Table I, entry 11); in their presence (Table I, entry 12), allyl anion formation occurs with the more basic organolithium reagents. Interestingly, the addition to diene acceptor **10** occurs at the terminal carbon and protonation of the intermediate allylic anion gives rise to a mixture of isomers, while reaction of the intermediate with MeI results in exclusive γ-alkylation[3c] (eq 3). Attempts to alkylate the highly hindered α-carbon of addition intermediates **5** have been successful only with MeI, where **6b** (R = Bu, Ph) were obtained in 96% and 93% yield, respectively.



Functionalized silylated boranes **6a** are rapidly desilylated by Bu_4NF in moist THF in nearly quantitative yield (Table I) giving boranes **7** of a type which has been shown to be convertible to alcohols,[3] alkylatable carbanions,[3b] diols,[17] and olefins.[18] Interestingly, more highly substituted silylated borane **6b** (R = Ph) is deboronated by fluoride ion under the same conditions, giving (1-phenyl-2-propyl)trimethylsilane in 74% yield. The direct oxidation of **6a** (R = Ph) with alkaline hydrogen peroxide gives a 1.6:1 mixture of 1-(trimethylsilyl)phenethyl alcohol and phenethyl alcohol while prior treatment with Bu_4NF followed by oxidation in a one-pot procedure gives only phenethyl alcohol in 95% yield.

In summary, we have demonstrated the feasibility of using hindered boryl substituents to activate olefins to nucleophilic addition reactions. Preliminary experiments suggest that other α-substituted vinyldimesilylboranes also undergo addition reactions, and work is in progress on this new class of acceptors.

Acknowledgment. We thank the National Science Foundation for support of this work.

(12) Prepared[4] in 60% yield from (1-(trimethylsilyl)vinyl)lithium[13] and Mes_2BF[3a] in Et_2O at −78 °C. Acceptors **8**, **9**, and **10** were similarly prepared.

(13) Boeckman, R. K., Jr.; Bruza, K. S. *Tetrahedron Lett.* **1974**, 3365.

(14) Vinylsilanes undergo addition reactions with reactive alkyllithium reagents: Mulvaney, J. E.; Gardlund, Z. G. *J. Org. Chem.* **1965**, *30*, 917. Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1974**, 1133. Cason, L. F.; Brooks, H. G. *J. Org. Chem.* **1954**, *19*, 1278. Chan, T. H.; Chang, E. *Ibid.* **1974**, *39*, 3264.

(15) (PhCH=C(Mes))B(Mes)(CH_2=$CSiMe_3$), mp 139-140 °C, 87% yield.

(16) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. H. *Ibid.* **1984**, *40*, 5005.

(17) Pelter, A.; Buss, D.; Pitchford, A. *Tetrahedron Lett.* **1985**, *26*, 5093. Pelter, A.; Bugden, G.; Rosser, R. *Ibid.* **1985**, *26*, 5097.

(18) Pelter, A.; Singaram, B.; Wilson, J. W. *Tetrahedron Lett.* **1983**, *24*, 635.

Avermectin Chemistry: Problems of Conjugation, Deconjugation, and Epimerization

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The able studies of Merck scientists[1,2] have shown that the remarkable biological activity[3] of the avermectins **1**[4] is strongly structure-dependent. With the oxahydrindene moiety, for example, the isomers obtained by epimerization and conjugation (i.e., **2** and **3**, Chart I) show much reduced biological activities, as also does the aromatized product **4**. Thus, the most daunting challenges confronting any synthesis of these molecules come from (a) control of configuration and (b) suppression of lability at the C2 stereocenter. Our laboratory[5] recently described a synthesis of chiron[6] (**5a**) for the "southern" half of **1**, in which these isomerizations could be examined. In subsequent studies (Scheme I), we have discovered (a) that the regioisomeric olefin **6a** was frequently easier to obtain than **5a** and (b) that the carboxylic derivative **5b** underwent conjugation to **6b**, even on standing at room temperature. It therefore seemed to us, given the conditions for the isolation of the natural product,[4] that the intact avermectins are more stable than might have been expected from the partial structure **5b**. This increased stability could conceivably be attributed to the constraints of the macrolactone, as we have surmized elsewhere.[5]

We were, therefore, intrigued by the recent report of a synthesis of avermectin B_{1a} (i.e., **1Aa**) in which a deconjugative transformation was executed as the "last major hurdle".[7] This achievement promised to simplify the synthetic challenge enormously, particularly in view of the easier formation of **6a** and **6b** (vide supra). However, rather than confront this hurdle at late stages of such a monumental undertaking, we decided to examine the comparable transformations in the Ivermectin series **1B**, since much of the groundwork had already been laid securely by Merck scientists.[2] Thus, 2-*epi*-ivermectin **2Ba** and Δ^2-ivermectin **3Ba** were prepared from Ivermectin and were converted into disilylated (**1Bb**, **2Bb**, and **3Bb**) and trisilylated (**1Bc** and **3Bc**) derivatives under standard conditions. Deconjugation of **3Bc** with LDA followed by acetic acid quench under a variety of conditions (Table I, entries a-c) gave either the 2-epi product **2Bb**, or caused the simple loss of the trimethylsilyl group (i.e., **3Bb**).

It was conceivable that the C22-C23 double bond, which is present in avermectin B_{1a} (**1A**), but not in Ivermectin (**1B**), could so alter the shape of the molecule as to change the stereochemical course of deconjugation.[8] Accordingly, the Pivnichny procedure[2]

(1) (a) Chabala, J. C.; Mrozik, H.; Tolman, R. L.; Eskola, P.; Lusi, A.; Peterson, L. H.; Woods, M. F.; Fisher, M. H. *J. Med. Chem.* **1980**, *23*, 1134. (b) Egerton, J. R.; Birnbaum, J.; Blair, L. S.; Chabala, J. C.; Conroy, J.; Fisher, M. H.; Mrozik, H.; Ostlind, D. A.; Wilkins, C. A.; Campbell, W. C. *Br. Vet. J.* **1980**, *136*, 88. (c) Mrozik, H.; Eskola, P.; Fisher, M. H.; Egerton, J. R.; Cifelli, S.; Ostlind, D. A. *J. Med. Chem.* **1983**, *25*, 658. (d) Campbell, W. C.; Burg, R. W.; Fisher, M. H.; Dybas, R. A. *ACS Symp. Ser.* **1984**, *No. 255*, 5.

(2) Pivnichny, J. V.; Shim, J.-S. K.; Zimmerman, L. A. *J. Pharm. Sci.* **1983**, *72*, 1447.

(3) For a recent thorough review: Davies, H. G.; Green, R. H. *Natural Prod. Rep.* **1986**, *3*, 87. For some recent chemistry, see: Baker, R.; Swain, C. J.; Head, J. C. *J. Chem. Soc., Chem. Commun.* **1985**, 309. Kozikowski, A. P.; Huss, E. M. *Tetrahedron Lett.* **1985**, *26*, 5759. Smith, A. B., III; Thomspon, A. S. *Tetrahedron Lett.* **1985**, *26*, 4279. Crimmins, M. T.; Lever, T. G. *Tetrahedron Lett.* **1986**, *27*, 291.

(4) Campbell, W. C.; Fisher, M. H.; Stapley, O.; AlbersSchonberg, G.; Jacob, T. A. *Science (Washington, D.C.)* **1983**, *221*, 823.

(5) Prashad, M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1564.

(6) Hanessian, S. In *Total Synthesis of Natural Products: The 'Chiron' Approach*; Baldwin, J. E., Ed.; Pergamon: Oxford, 1983.

(7) Hanessian, S.; Ugolini, A.; Dube, D.; Hodges, P. J.; Andrē, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776.

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Table I. Behavior of Δ^2-Avermectins in Base

entry	substrate	deconjugation conditions	quench[e]	products
	Ivermectin			
a	**3Bc**	LDA/TMSCl/THF, −78 °C	HOAc, −78 °C → rt; H_2O, rt	**2Bb** + **3Bb**
b	**3Bc**	LDA/TMSCl/THF, −78 °C	HOAc/H_2O, −78 °C → rt	**2Bb** + **3Bb**
c	**3Bc**	LDA/THF, −78 °C	HOAc, −78 °C → rt; H_2O, rt	**4Bb**
	avermectin B_{1a}			
d	**3Ac**	LDA/TMSCl/THF, −78 °C	HOAc, −78 °C → rt	**2Ac** (52%) + **4Ab** (10%) + **3Ac** (7%)
e[b]	**3Ac**	LDA/TMSCl/THF, −78 °C	HOAc/THF, −78 °C → rt; H_2O, rt	**2Ab** or **3Ab** (variable ratios)
f	**3Ac**	LDA/TMSCl[a]/THF, −78 °C	HOAc, −78 °C → rt	**2Ac** (64%) + **3Ac** (30%)
g	**3Ac**	LDA/TMSCl[a]/THF/HMPA, −78 °C	HOAc, −78 °C → rt	**3Ac**
h	**3Ac**	LDA/TMSCl[a]/THF, −78 °C	HOAc/THF, −78 °C → rt	**3Ac**
i	**3Ac**	$LiN(TMS)_2$/TMSCl/THF, 78 °C	HOAc, −10 °C → rt	**3Ac**
j[c]	**3Ac**	LDA/TMSCl(−78 °C)/HMPA/THF, −78 °C	HOAc, rt	**2Ac** + **4Ab**
k	**2Ac**	NaOH(0.1 M)/MeOH/H_2O (9:1), rt,[e] 3 h		**2Ab** (90%) + **3Ab** (6%)
l[d]	**2Aa**	NaOH(0.05 M)/MeOH/H_2O (1:1), rt,[e] 1 h		**1Aa** (25%) + **2Aa** (70%) + **3Aa** (trace)

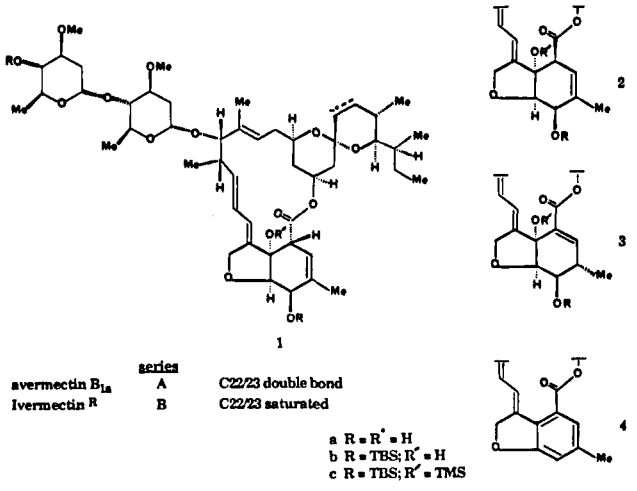
[a] In these experiments the silylating agent was obtained from the supernatant of the centrifugate of TMSCl/Et_3N (3:1).[11] [b] This experiment was carried out as described for the published work.[7] [c] In this experiment, the cold reaction mixture was cannulated into the acetic acid solution. [d] The conditions for this experiment are similar to those developed by Merck scientists for Ivermectin.[2] [e] rt = room temperature.

Table II. Key ^1H NMR Signals (ppm) for Identifying Avermectin B_{1a} Isomers[a,b]

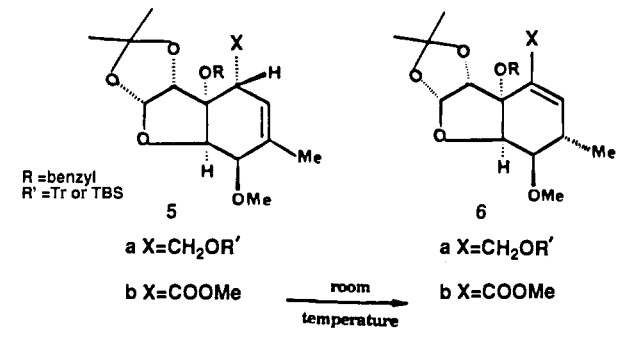
1Ab	5.827 (H-11)	4.984 (H-15)	3.432, 3.332 (2 OMe)	3.208, 3.130 (H4′, H4″)	1.777 (C4–Me)
2Ab	5.917 (H-11)[c]	4.904 (H-15)[c]	3.492, 3.53 (2 OMe)	3.216, 3.142 (H4′, H4″),[c] partially resolved	1.854 (C4–Me)
3Ab	6.119 (H-11)[c]	4.932 (H-15)[c]	3.487, 3.353 (2 OMe)	3.215, 3.139 (H4′, H4″)	

[a] From 300-MHz spectra run in $CDCl_3$ ($CHCl_3$ standard). [b] These parameters allow for each isomer to be recognized and differentiated from the other two in *crude reaction mixtures*. [c] These assignments are tentative.

Chart I



Scheme I



was applied to avermectin B_{1a} (**1Aa**), and the products **2Aa** and **3Aa** were silylated.

The transformation of interest, **3Ac** → **1Ab**, could be readily monitored by thin-layer chromatography,[9] and separation by flash chromatography[10] was readily carried out. The salient NMR parameters, shown in Table II, enabled us to identify the isomers unambiguously and also to determine their ratios in the crude mixtures *prior to* the chromatographic fractionation.

A variety of deconjugation experiments were carried out with subtle changes in the conditions. For example, entry f differs from d (Table I) in that the trimethylsilylating agent was prepared, as described by Ireland.[11] The addition of HMPA (entry g) again follows Irelands' specific recommendation,[11] and in entry i, a different base was tried. *As seen, if there was any deconjugation at all, the product was the 2-epi isomer* ***2Ab*** *or* ***2Ac***. There was no mention[7] of the 2-epi isomer having been encountered under any conditions or even of it being a possible (or improbable) product of deconjugation.

The discovery of the "kinetic isomer" in this tripartite system (**3**, **2**, and **1**) is nontrivial, particularly since the influence of the macrocyclic ring is unclear (see the first paragraph). *However, on the basis of the isolated oxahydrindene moiety, compound* ***2*** *is the expected kinetic product since the proton is being added to the exo surface.* Actually, the conditions in the report[7] and in entries d–i might not be the best for kinetic control. A better approach is that in entry j, where the enolate was cannulated into excess acetic acid. However, it is seen that the effect is the same, with the exception of the formation of the aromatized material **4**—not a surprising result.

Thus, **2Ac** appears to be the kinetic *epimer*, but can this product be epimerized to **1Ac**?—(a transformation which could conceivably have happened in situ in the reported synthesis). To evaluate this possibility, we applied a variation of the Pivnichny conditions[2] (entry k) to **2Ac**, but the product obtained was the conjugated isomer **3Ab**. Very significantly, however, the effect of protecting groups on this process should be noted. Thus, when the unprotected 2-*epi*-avermectin B_{1a} (**2Aa**) was examined (entry l) some of the natural isomer **1Ac** could be detected, as noted in Table I.

(8) For example, it is known that saturation of the C3/C4 double bond attenuates the activity of the molecule.[1b]

(9) Thin-layer chromatography was carried out as follows. *For the silylated Ivermectins*, hexane/ethyl acetate (9:1), four runs (R_F): **1Bb** (0.157); **2Bb** (0.165); **1Bc** (0.174); **3Bb** (0.193); **3Bc** (0.226). *For the silylated avermectins* B_{1a}, hexane/diethyl ether (4:1), two runs (R_F): **3Ab** (0.23); **3Ac** (0.27); **1Ab** (0.19); **2Ab** (0.18); **1Ac** (0.19); **2Ac** (0.22); **4** (0.31). *For the unsilylated avermectins*, hexane/ethyl acetate (1:3), one run: **1Aa** (0.46); **2Aa** (0.35), **3Aa** (0.50).

(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(11) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279.

From these studies we concluded (a) that deconjugation of the Δ^2-isomer **3**, under kinetic control leads to the 2-epi isomer **2** exclusively, and (b) that partial isomerization, **2** → **1**, can be achieved, but only in a *protic medium and* only if the polarity of the molecule is appropriate. *Furthermore, an important* Corrolary *of our studies is that 3,4-alkenes, such as* ***6a*** *and* ***6b****, must be regarded as unreliable synthons for the "southern" oxahydrindene moiety of these molecules.*

Acknowledgment. We are grateful to the National Institutes of Health for support of this work (GM 32569). We are greatly indebted to Merck, Sharp, and Dohme for generous samples of Ivermectin and avermectin B_{1a}. We are much obliged to Drs. Mrozik, Christensen, and Pivnichny for numerous helpful discussions and for providing us with ^1H NMR spectra and unpublished information. We thank Professor Hanessian for providing us with details of his experimental procedures.

Supplementary Material Available: ^1H NMR spectra, 300 MHz, of pure specimens of **1Ab**, **2Ab**, and **3Ab**, spectra of admixtures of isomers and of the crude product from a deconjugation experiment, and experimental conditions for the deconjugation and chromatographic isolation (9 pages). Ordering information is given on any current masthead page.

Coupling of 1,3-Dienes with (Carbene)iron Complexes To Give Substituted (1,3-Diene)$Fe(CO)_3$ Derivatives

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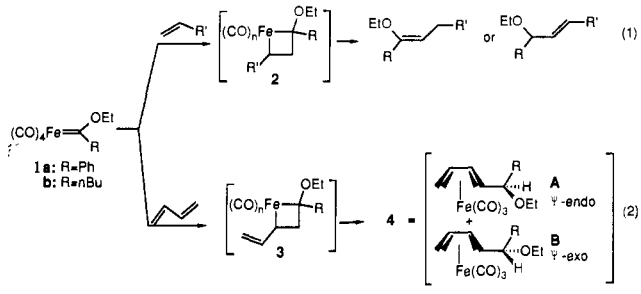
Fischer-type carbene complexes of chromium react with alkenes by several pathways but the processes are not very general and no useful synthesis methodology has appeared.[1] Recent studies of simple iron analogues (i.e., **1**) demonstrated a one-carbon homologation process, according to eq 1. A ferracyclobutane



intermediate (**2**) was suggested.[2] Following the same pathway, conjugated dienes would lead to an intermediate (**3**) with new opportunities for further reaction involving the additional double bond. In this paper we describe the first examples of coupling **1a** with 1,3-dienes, which results in a new preparation of (η^4-1,3-diene)$Fe(CO)_3$ complexes **4** bearing an allylic ethoxy group, as shown for 1,3-butadiene in eq 2.

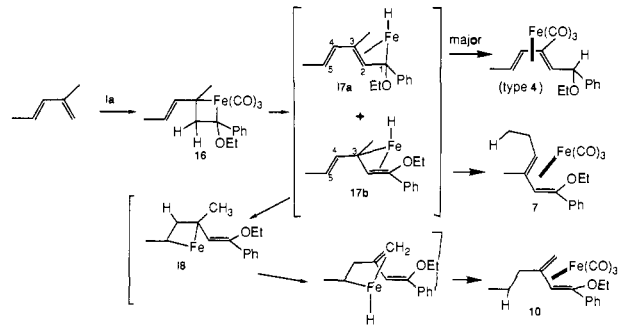


Figure 1. Suggested mechanism illustrated with **1a** and 2-methyl-1,3-pentadiene. CO ligands are deleted to simplify the intermediates.

Table I displays the results with a series of simple 1,3-dienes, following a standard procedure.[3] Coupling of **1a** with dienes which bear one monosubstituted olefin unit (entries 1-6) occurs at 25 °C to give high yields of coupled products as 5-ethoxy 1,3-diene complexes **4**. In one case (entry 1), the ligand is partially detached (20% yield) from the iron during the coupling and/or isolation process, but generally the coupled product appears as a mixture of diastereomeric iron complexes (**4A**/**B** in eq 2), in a ratio of 2:1 to 4:1. The major isomer can be tentatively assigned configuration **4B**, based on consistent chromatographic elution behavior and closely related examples in the literature.[4] The diasteromeric complexes are readily separated by preparative TLC, and the yields are based on weighed amounts of the separated isomers. The 1-ethoxy 1,3-diene double bond positional isomer can be a significant byproduct, either as the free ligand (**5** and **6**; Table I) or as the $Fe(CO)_3$ complex (**7** and **8**). Further rearrangement occurred to a minor extent in two cases (**9** and **10**, Table I).

Complexes of 1,3-dienes with $Fe(CO)_3$ provide starting points for useful synthesis methodology via direct nucleophile addition[5] and by conversion to (η^5-pentadienyl)$Fe(CO)_3$ cationic complexes

(1) For a review, see: (a) Dötz, K.-H. In *Transition Metal Carbene Complexes*; Verlag Chemie: Weinheim, 1983; pp 204 ff. (b) Fischer, E. O.; Kiener, V. *Adv. Organomet. Chem.* **1976**, *14*, 1-32. (c) Cardin, D. J.; Cetinkaya, B.; Doyle, M. T.; Lappert, M. F. *Chem. Rev.* **1972**, *72*, 545-574. (d) Brown, F. J. *Prog. Inorg. Chem.* **1981**, *27*, 1-122. (e) Fischer, E. O. *Angew. Chem.* **1974**, *86*, 651.

(2) (a) For reactions of **1** with simple alkenes, see: Semmelhack, M. F.; Tamura, R. *J. Am. Chem. Soc.* **1983**, *105*, 6730. (b) For preparation of **1**, see: Semmelhack, M. F.; Tamura, R. *J. Am. Chem. Soc.* **1983**, *105*, 4099.

(3) General procedure: a sample of complex **1** (1.5 mmol) and the diene (6-10 mmol) in 25 mL of *n*-hexane was allowed to stir under argon at 60-70 °C for 0.5-10.0 h. The mixture was concentrated at reduced pressure, and the residue was purified by preparative TLC on silica gel. Elution with hexane/ether 8:1 provided complete separation of the isomeric adducts. All structures of type **4** listed in Table I show satisfactory IR, ^1H NMR, and low-resolution MS data. In addition, evidence for composition (high-resolution MS or combustion analysis) has been obtained for at least one member of each diastereomeric pair **4**. The minor product **5** is a mixture of geometrical isomers (^1H NMR), while **6** is homogeneous by chromatographic and spectral analysis; the *cis*-ethoxy configuration shown is based on the special chemical shift of "inner" proton at C-4, δ 2.0-2.1. In the absence of the *cis*-ethoxy, the "inner" proton appears near δ 1.0. Complexes **9**, **12**, and **14** were characterized primarily by spectral data, while spectral and composition data have been obtained for complexes **7**, **8**, **10**, **11**, **13**, and **15**. Representative characterization data from Table I, entry 3. Eluted first was the minor diastereoisomer, 117 mg, 18% yield, as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4-7.2 (m, 5 H, Ar H), 5.06 (d, J = 8.4 Hz, 1 H), 3.96 (d, J = 7.5 Hz, 1 H), 3.40-3.20 (m, 2 H), 2.06 (s, 3 H), 1.38 (d, J = 6.3 Hz, 3 H), 1.18 (t, J = 7.0 Hz), 1.04 (q, J = 6.3 Hz, 1 H), 0.98 (dd, J = 8.4, 7.5 Hz, 1 H). IR (neat): 2980 (m), 2880 (m), 2040 (s), 1965 (s), 1450 (m), 1390 (m) cm^{-1}. Mass spectrum (EI): *m/e* 356 (parent, 13% of base), 328 (15), 300 (32), 272 (29), 228 (100), 226 (91), 174 (45), 95 (59). Eluted next was the major diastereomer, 353 mg, 54% yield as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4-7.2 (m, 5 H, Ar H), 5.06 (d, J = 8 Hz, 1 H, H at C-3), 3.96 (d, J = 7.5 Hz, 1 H, H at C-1), 3.4-3.2 (m, 2 H), 2.06 (s, 3 H, C-9 Me), 1.38 (d, J = 6.3 Hz, 3 H, C-6 Me), 1.18 (t, J = 7.0 Hz, 3 H, C-8 Me), 1.04 (q, J = 6.3 Hz, 1 H, H at C-5), 0.98 (dd, J = 8.4, 7.5 Hz, 1 H, H at C-2). IR (neat): 2980 (m), 2880 (m), 2040 (s), 1965 (vs), 1450 (m), 1390 (m) cm^{-1}. Mass spectrum (EI): *m/e* 356 (parent, 8% of base), 338 (9), 300 (24), 272 (15), 228 (83), 226 (72), 170 (87), 155 (80), 143 (61), 115 (44), 91 (100). Anal. Calcd for $C_{18}H_{20}O_4Fe$: C, 60.70; H, 5.66; Fe 15.68. Found: C, 60.80; H, 5.48; Fe 15.90.

(4) The separation and identification of isomers referred to as ψ-endo (**4A**) and ψ-exo (**4B**) have been studied carefully in closely related systems: (a) Greshan, D. G.; Lillya, C. P.; Uden, P. C.; Walters, F. H. *J. Organomet. Chem.* **1977**, *142*, 123. (b) Clinton, N. A.; Lillya, C. P. *J. Am. Chem. Soc.* **1970**, *92*, 3058. (c) Kahn, D. E.; Lillya, C. P. *Ibid.* **1972**, *94*, 1682.

(5) (a) Semmelhack, M. F.; Herndon, J. W. *Organometallics* **1983**, *2*, 363. (b) Semmelhack, M. F.; Herndon, J. W.; Springer, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 2497. (c) Semmelhack, M. F.; Herndon, J. W.; Liu, J. K. *Organometallics* **1983**, *2*, 1885.

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