-78 °C) followed by trapping with Me_2SO_4 gave the BOM ether of (*R*)-2-butanol (90% ee). A similar sequence was carried out for the reduction product of **5c**.[18] The absolute stereochemistry of the other carbinols (except **5e**, R = *t*-Bu) produced by (*S*)-BINAL-H is also expected to be *R* based on the similar (same sign and approximate magnitude) rotations of their BOM or MOM ethers.[20] The sense of asymmetric induction is also consistent with Noyori's empirical rule if one considers the tributylstannyl group to be an unsaturated group (Scheme III).[21] As expected, reductions using (*R*)-BINAL-H's gave the (*S*)-carbinols as the major products.

In the case of pivaloyltributylstannane (**5e**, R = *t*-Bu) the reduction proceeded anomalously. With MeOH or EtOH as the coligand, the reduction was exceedingly slow but proceeded more quickly with *i*-PrOH as the coligand (albeit still very slowly, entry 15).[22] Amazingly, reasonable enantioselectivity (80% ee) was observed but in the opposite sense[23] as had been observed for all the other acylstannanes. Presumably this anomalous result is a reflection of the very large steric requirements of a *tert*-butyl group.[25]

A general procedure follows. To a solution of 3.0 mmol of LAH (3.0 mL of a 1 M THF solution) in a total of 9 mL of anhydrous THF at 0 °C under Ar was added slowly a solution of anhydrous EtOH (138 mg, 3 mmol) in 1 mL of THF. After the solution was stirred at room temperature for 20 min, a solution of (*S*)-(-)-1,1′-bi-2-naphthol (859 mg, 3.0 mmol) in 6 mL of THF was added slowly via syringe. The resulting milky mixture was stirred at room temperature for 2 h then cooled to -78 °C. The acylstannane (1.0 mmol) was then added slowly as a solution in 2 mL of THF, and the mixture was stirred at -78 °C for 3 h. The disappearance of the yellow-green color of the acylstannane was a good indication of the progress of the reaction (as monitored by TLC on silica with petroleum ether-ethyl ether, 4:1). The reaction was quenched with 5 mL of saturated aqueous NH_4Cl, and the mixture was diluted with Et_2O (50 mL). The organic layer was washed with water (15 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was suspended in petroleum ether (10 mL), and undissolved binaphthol was removed by filtration (and recovered). Concentration of the filtrate afforded the crude alcohol (with nearly quantitative mass balance), which was immediately converted to the MOM (1.5 mmol of MOM-Cl, 2 mmol of *i*-Pr_2NEt, 2 mL of CH_2Cl_2, room temperature, 12 h) or BOM (1.5 mmol of BOM-Cl, 2 mmol of *i*-Pr_2NEt, 2 mL of CH_2Cl_2, room temperature, 12 h) derivative. Standard aqueous workup (Et_2O, $NaHCO_3$) followed by column chromatography on silica gel (2% ethyl ether in petroleum ether) gave the expected compound as a clear colorless oil.

In summary, we have described a general approach to simple alkyl α-alkoxystannanes of good enantiomeric purity and predictable (Scheme III) stereochemistry via reduction of acylstannanes. We anticipate that the availability of enantiomerically enriched α-alkoxystannanes will renew interest in these compounds as reagents for organic synthesis.

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Philip C.-M. Chan, J. Michael Chong*
Guelph-Waterloo Centre for Graduate Work in Chemistry
Chemistry Department
University of Waterloo
Waterloo, Ontario, Canada N2L 3G1
Received July 12, 1988

(18) Transmetalation of **10c** (96% ee, *n*-BuLi, DME, -78 °C) and reaction with Me_2SO_4 afforded the BOM ether of (*R*)-3-methyl-2-butanol $[\alpha]_D$ -26.2° (*c* 1.5, $CHCl_3$), which had the opposite rotation as the BOM ether of (*S*)-(+)-3-methyl-2-butanol[19] [90% ee $[\alpha]_D$ 25.1° (*c* 1.5, $CHCl_3$)].

(19) Prepared from $LiAlH_4$ opening of the epoxide derived from (*S*)-valine: Koppenhoefer, B.; Schurig, V. *Org. Synth.* **1987**, *66*, 160.

(20) Also, in the ^1H NMR (250 MHz, $CDCl_3$) spectrum of the derived (*R*)-MTPA esters, the methoxy peak of the major diastereomer is consistently the downfield one by ~0.05 ppm.

(21) One might speculate that the similarity between a tributylstannyl group and an unsaturated group is also manifested by their similar effects on the carbonyl stretching frequency in the IR: acetone, 1715 cm^{-1}; acetophenone, 1690 cm^{-1}; acetyltributylstannane (**5a**), 1638 cm^{-1}.

(22) In fact, the reactions with MeOH and EtOH did not proceed at -78 °C. At higher temperatures (-45 °C → 0 °C), some reaction occurred, but the *S* alcohol was formed with only moderate selectivity (1.5-3:1).

(23) That the major isomer produced in this reduction was the *S* isomer was suggested by the rotation (+) of the MOM ether and the relative chemical shifts of the methoxy peaks of the derived (*R*)-MTPA ester (the major peak was upfield). Confirmation was obtained by a transmetalation-trapping sequence as previously described, which gave the BOM ether of (*S*)-(+)-3,3-dimethyl-2-butanol[24] as the major product.

(24) Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1988**, *53*, 1231.

(25) A similar reversal of selectivity (from acetophenone to pivalophenone) has been reported for Ipc_2BCl[17] and rationalized on the basis of steric arguments.

Synthesis of (±)-Verrucarol Using a Remarkably Facile Alumina-Catalyzed Intramolecular Diels-Alder Reaction

Summary: The synthesis of the verrucarol skeleton **3** has been achieved in a highly efficient and diastereoselective manner through the intramolecular Diels-Alder reaction of the cyclopentyl C-ring-tethered diene-dienophile **7**. Remarkably, this intramolecular Diels-Alder reaction proceeds readily at room temperature under catalysis by neutral alumina.

Sir: Owing to their unique structures where a number of functional groups are intricately webbed onto a relatively compact sesquiterpene framework, and to their wide-ranging biological activities,[1] the synthesis of the trichothecenes has been extensively scrutinized.[2] Interestingly, most of the successful endeavors involve the biogenetically patterned C_{11}-O_1 or O_1-C_2 bond formation to regio- and stereoselectively construct the B ring of the trichothecene. Surprisingly untested, however, is the seemingly obvious intramolecular Diels-Alder approach to build both A/B rings simultaneously by using the appropriate diene-dienophile precursor based on the disection as illustrated for the archetypical trichothecene verrucarol (**1**) (Scheme I). Herein, we report the highly efficient synthesis of the verrucarol skeleton **3**, the key synthetic intermediate to verrucarol, employing this intramolecular Diels-Alder concept. Furthermore, particular reference is drawn to the unprecedented extent of catalysis exerted by neutral alumina on the reaction.

An earlier model study[3] from these laboratories had revealed the unexpected observation that cycloaddition of **4** proceeds through the transition state **5** in which incipient

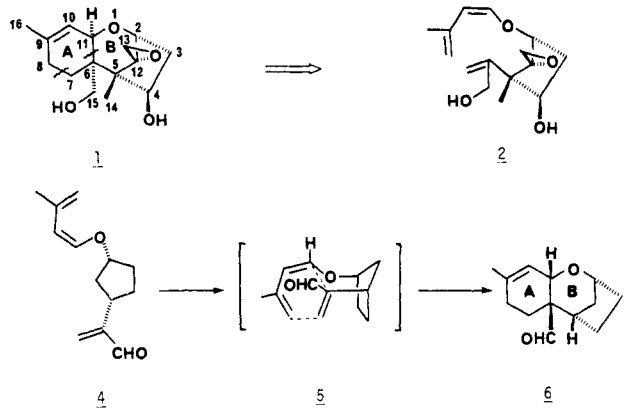
(1) For recent reviews, see: *Trichothecenes: Chemical, Biological and Toxicological Aspects*; Ueno, Y., Ed.; Elsevier: Amsterdam, 1983. Tamm, C.; Tori, M. In *Mycotoxin-Production, Isolation, Separation and Purification*; Betina, V., Ed.; Elsevier: Amsterdam, 1984; pp 131-184.

(2) For a recent review on the chemical synthesis of the trichothecenes, see: McDougal, P. G.; Schmuff, N. R. *Prog. Chem. Org. Nat. Prod.* **1985**, *47*, 153.

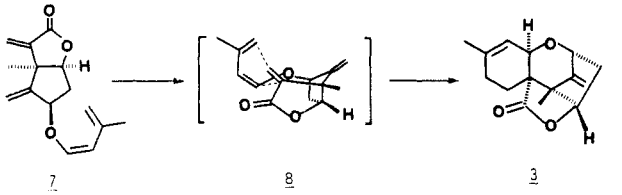
(3) Koreeda, M.; Leungo, J. I. *J. Org. Chem.* **1984**, *49*, 2079.

0022-3263/88/1953-5586$01.50/0

Scheme I



Scheme II



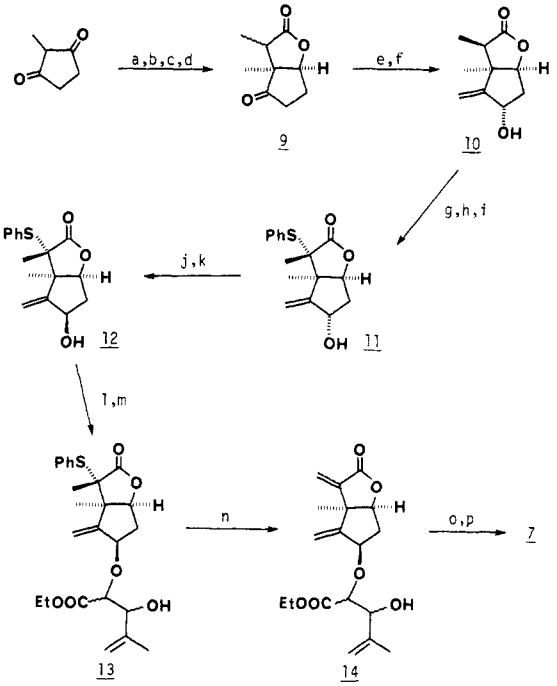
B ring adopts a boat-like conformation, giving rise to a novel, stereoisomeric cis-fused hydrochromane (**6**). Therefore, it was envisaged that the use of a conformationally restricted dienophile fused to the cyclopentyl ring with a tethered *Z*-dienol ether, i.e., **7**, would lead to the formation of the tetracyclic adduct **3**, possessing the natural type of stereochemistry (Scheme II).

The synthesis of the requisite tetraene **7** was achieved in a highly expeditious manner from 2-methyl-1,3-cyclopentanedione, as detailed in Scheme III.[4] The bicyclic lactone nucleus **9** was readily obtained in four steps commencing from the dione. Methylenation of **9**, followed by Sharpless allylic oxidation,[5] afforded allylic alcohol **10** as a single stereoisomer. The stereochemistry was validated by a single-crystal X-ray analysis of the benzoate derivative of **10**.[6] Procurement of the exo orientation of the allylic alcohol was not unexpected but necessitated an eventual inversion of its configuration. Subsequent to alcohol protection as its TBDMS ether, the dienophile unit, masked as an α-methyl-α-phenylthio lactone, was secured by the standard enolate formation–sulfenylation sequence.[7] Deprotection of the TBDMS ether afforded allylic alcohol **11**. The hydroxy stereochemistry of the exo allylic alcohol **11** was cleanly inverted to the desired **12** by employing the Mitsunobu protocol[8] with PPh_3/DEAD/PhCOOH, followed by hydrolysis of the resulting benzoate. It is noteworthy that the Mitsunobu reaction product was found to be virtually void of that from the potential S_N2' process. Apparently, steric congestion imposed by the adjoining two quaternary carbon centers considerably impedes the nucleophilic attack onto the exo-methylene carbon.

Construction of the *Z*-dienol ether group was realized through stereospecific anti-dehydrative decarboxylation of the β-hydroxy-α-alkoxy-γ-pentenoic acid by using the previously established procedure.[9] Thus, the (ethoxycarbonyl)methyl unit was first appended onto **12** by etherification of its thallium alkoxide derivative.[10] Deprotonation of the resulting α-alkoxy ester with LDA[11] followed by treatment with methacrolein afforded two *erythro*-β-hydroxy-α-alkoxy esters **13** as a 5:3 mixture of diastereomers originating form preexisting bicyclic lactone nucleus. Exclusive generation of the erythro relative stereochemistry across the newly formed C–C bond was unequivocally ascertained by 300-MHz ^1H NMR analysis of the dienol ether formed from a base hydrolysis/dehydrative decarboxylation sequence. Namely, stereospecific anti-dehydrative decarboxylation with DMF dineopentyl acetal of a 5:3 mixture of β-hydroxy-α-alkoxy carboxylic acids from **13** gave rise to a single *Z*-dienol ether whose ^1H NMR spectrum in $CDCl_3$ showed a diagnostic one proton doublet (J = 7.2 Hz) at δ 5.903 ppm (the α-alkoxy-vinylic hydrogen).

With both the latent diene and dienophile groups embodied in the two erythro diastereomers **13**, realizing them

Scheme III[a]



[a] Reagents and conditions: (a) crotyl alcohol (excess), *p*-TsOH (catalytic), toluene, reflux, 72 h (95%[15]); (b) $KMnO_4$ (4 equiv), CH_2Cl_2/H_2O/AcOH (35/30/7), 0 °C, 10 h; (c) CH_2N_2, diethyl ether, room temperature, 2 h (77% overall yield for steps b and c); (d) $LiAl(OBu^t)_3H$ (1.15 equiv), THF, −78 to 20 °C, 12 h (95%); (e) Ph_3PCH_3Br, $KOBu^t$, Bu^tOH (1.1 equiv of each), THF, 20 °C (93%); (f) SeO_2 (0.1 equiv), Bu^tOOH (2 equiv), $ClCH_2CH_2Cl$, reflux, 6 h (75%); (g) TBDMS-OTf (1.25 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 20 °C, 0.5 h (98%); (h) LDA (1.3 equiv), THF, −78 °C, 0.75 h; Ph_2S_2 (1.5 equiv), HMPA (1.5 equiv), THF, −78 to 20 °C, 2 h (95%); (i) $(n\text{-Bu})_4NF$ (1.2 equiv), THF, 20 °C, 10 h (90%); (j) Ph_3P, DEAD, PhCOOH (1.1 equiv of each), THF, 20 °C, 12 h (91%); (k) K_2CO_3 (5 equiv), CH_3OH/H_2O (5/1), 20 °C, 10 h (95%); (l) TlOEt (2 equiv), benzene, 20 °C, 10 h; $BrCH_2COOEt$ (5 equiv), CH_3CN, 20 °C, 3 h (95%); (m) LDA (1.3 equiv), THF, −78 °C, 0.25 h; methacrolein (5 equiv), −78 °C, 1 h (80%); (n) MCPBA (1.1 equiv), $NaHCO_3$ (2 equiv), CH_2Cl_2, 0 to 20 °C, 1 h; $CaCO_3$, CCl_4, reflux, 3 h (75% overall yield); (o) LiOH (3 equiv), THF/H_2O (8/1), 20 °C, 2 h (98%); (p) DMF dineopentyl acetal (1.5 equiv), CH_2Cl_2, 0 °C, 0.5 h.

(4) All new compounds reported herein have spectral (300-MHz ^1H and 75-MHz ^{13}C NMR, IR, and MS) and microanalytical (except **7**) data consistent with the assigned structure.

(5) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

(6) Performed by Dr. W. M. Butler (The University of Michigan).

(7) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(8) Mitsunobu, O. *Synthesis* **1981**, 1.

(9) Luengo, J. I.; Koreeda, M. *Tetrahedron Lett.* **1984**, *25*, 4881.

(10) Kalinowsji, H. O.; Seebach, D.; Crass, G. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 762.

(11) Interestingly, no products originating from the [2,3]-Wittig rearrangement of the carbanion were observed at −78 °C.

from 13 in a controlled manner required a judicious choice of reaction sequence. In view of the extreme acid lability of dienol ethers, it was deemed prudent to generate the dienophile first. A standard oxidation followed by thermal elimination cleanly secured exo-methylene lactone 14.[7] Transformation of the *Z*-dienol ether entailed ester hydrolysis ensued by stereospecific anti-dehydrative decarboxylation (vide supra); the intensely UV-active tetraene 7 was thus obtained in 95% yield as a crude oil. Remarkably, attempts to purify this extremely acid-sensitive tetraene by neutral alumina chromatography (Brockmann 1 from Aldrich, hexanes/ethyl acetate, 20 °C, 1 h) resulted in the unexpected formation of the desired cycloadduct 3 in 83% yield from 14.[12] The tetracyclic lactone 3, the key, advanced intermediate in the synthesis of (±)-verrucarol by Trost and McDougal,[13] was identical by 300-MHz ^{1}H NMR, IR, and MS comparisons to authentic 3.

The formal total synthesis of (±)-verrucarol delineated above features the highly expedient production of the tetracyclic lactone 3, 17 steps in 16.6% overall yield from 2-methyl-1,3-cyclopentanedione. The efficient intramolecular Diels–Alder approach allows simultaneous and diastereoselective construction of the unique A/B rings of the trichothecene skeleton and may be applicable to the synthesis of the A-ring-oxygenated trichothecenes with a small modification. Furthermore, the serendipitously discovered room-temperature alumina-catalyzed cycloaddition should add a new dimension to Diels–Alder methodologies by potentiating the cycloaddition of thermally unstable and/or acid-labile components. Current efforts in these laboratories include probing applicability of this heretofore unprecedented[14] catalysis of the intramolecular Diels–Alder reaction by neutral alumina.

Acknowledgment. We are grateful to the National Institutes of Health (ES-02851) for the support of this work. We thank Professor B. M. Trost for the spectra of the authentic 3.

(12) Purification of the crude tetraene 7 by flash column chromatography on neutral alumina gave, in addition to the cycloadduct 3 (ca. 30% yield from 14), pure tetraene 7, which did not undergo intramolecular Diels–Alder cycloaddition upon heating to 250 °C.

(13) Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110; **1984**, *106*, 383.

(14) In one case neutral alumina was reported to affect the endo/exo ratio of an intermolecular Diels–Alder reaction conducted at 50 °C for 4 h. See: Parler, H.; Baumann, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1014.

(15) Yield based on recovered starting material.

Masato Koreeda,* Daniel J. Ricca,† Juan I. Luengo

Department of Chemistry
The University of Michigan
Ann Arbor, Michigan 48109

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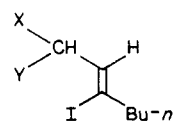
†Interdepartmental Medicinal Chemistry Program Participant. National Institutes of Health Medicinal Chemical Predoctoral Fellowship recipient, 1984–1986.

Palladium-Catalyzed Procedures for [3 + 2] Annulation via Intramolecular Alkenylpalladation and Arylpalladation[1]

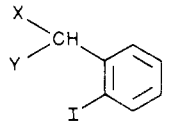
Summary: Treatment of dienolates derived from cyclohexenes activated by carbonyl groups with γ-iodoallyl electrophiles 1 and *o*-iodobenzyl electrophiles 2 followed by cyclization catalyzed by Pd complexes, e.g., $Pd(PPh_3)_4$, can produce the corresponding [3 + 2] annulated bicyclic and polycyclic derivatives.

Sir: Annulation, i.e., building a ring onto a preexisting system,[2] is an important synthetic operation. Particularly useful are those involving fusion of a new ring onto a preexisting ring in which all new ring constructing components other than those at the bridgeheads are externally introduced. There are a number of satisfactory methods for the [4 + 2] annulation[2] of this class, such as the Robinson annulation sequence and the Diels–Alder reaction.[3] The aldol cyclization and the Nazarov reaction[4] are two of the classical procedures for the [3 + 2] annulation. In addition, a fair number of procedures[5–7] for the [3 + 2] annulation have recently been developed. Despite these developments, the current scope of the [3 + 2] annulation methodology is considerably more limited than its [4 + 2] counterpart. Some desirable [3 + 2] annulation types are schematically shown (Scheme I) using cyclohexene derivatives as representative substrates.

Herein described are some examples of type I and type II annulation reactions via intramolecular carbopalladation,[8,9] which feature the use of 1 and 2 as three-carbon synthons. Experimental results are shown in eq 1–8 (Chart I).



1a: X = H, Y = Br
b: X = H, Y = I
c: X, Y = O



2a: X = H, Y = Br
b: X = H, Y = I
c: X, Y = O

Treatment of methyl 1-cyclohexenecarboxylate (3) with lithium diisopropylamide (LDA) and HMPA, followed by addition of **1a** and **1c**, gave **4** and **5**, respectively, in 70–80% yields.[10] The reaction of the lithium enolate of 3 with **2c**, followed by oxidation with CrO_3 and pyridine, provided **6**. Cyclic carbopalladation of **4–6** in the presence of 3–5 mol % of $Pd(PPh_3)_4$ and 1.5–2.0 equiv of NEt_3 in refluxing THF–MeCN (100 °C bath temperature) pro-

(1) Metal-Promoted Cyclization. 21. Part 20: O'Connor, B.; Zhang, Y.; Negishi, E.; Luo, F. T.; Cheng, J. W. *Tetrahedron Lett.* **1988**, *29*, 3903.

(2) For a review, see: Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

(3) For a review, see: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.

(4) For a review, see: Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429.

(5) Noteworthy recent developments of type I [3 + 2] annulation procedures include the following: (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (b) Bucheister, A.; Klemarzyk, P.; Rosenblum, M. *Organometallics* **1982**, *1*, 1679. (c) Piers, E.; Karunaratue, V. *J. Chem. Soc., Chem. Commun.* **1983**, 935. (d) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315, 2326. (e) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805.

(6) For papers on type II [3 + 2] annulation, see: (a) Macdonald, T. L.; Mahalingam, S. *J. Am. Chem. Soc.* **1980**, *102*, 2113. (b) Majetich, G.; Desmond, R.; Casares, A. M. *Tetrahedron Lett.* **1983**, *24*, 1913. (c) Majetich, G.; Hull, K.; Defauw, J.; Shawe, T. *Tetrahedron Lett.* **1985**, *26*, 2755.

(7) For papers on type III [3 + 2] annulation, see: (a) Corey, E. J.; Kuwajima, I. *J. Am. Chem. Soc.* **1970**, *92*, 395. (b) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61. (c) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

(8) For a review of the Heck-type carbopalladation–dehydropalladation reaction, including many references on the synthesis of heterocycles, see: (a) Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic: New York, 1985.

(9) (a) Narula, C. K.; Mak, K. T.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 2792. (b) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073; *Tetrahedron* **1988**, *44*, 2033. (c) Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, *107*, 8289. (d) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133. (e) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. (f) Negishi, E.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915. (g) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919.

(10) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

0022-3263/88/1953-5588$01.50/0