($CDCl_3$, δ) 0.91 (d, J = 6.5 Hz, 3 H), 1.02 (s, 3 H), 1.10 (s, 3 H), 1.2-2.05 (band, 9 H), 2.32 (m, 1 H), 2.61 (m, 1 H), 3.27 (d, J = 6 Hz, 1 H), 3.74 (s, 3 H), 4.33 (m, 1 H); IR (film) 3460, 1735, 1445 cm^{-1}.

Mesylation and Elimination of 37. A solution of 0.15 mL (2 mmol) of methanesulfonyl chloride in 5 mL of dichloromethane was added dropwise to a stirred solution of triethylamine (6.28 mL, 2.0 mmol) and 180 mg (0.68 mmol) of alcohol **37** in 5 mL of dichloromethane. The mixture was stirred overnight, then washed with 10% HCl and saturated $NaHCO_3$, dried, and concentrated. This crude material was dissolved in 5 mL of dichloromethane to which 1 mL of DBU was added. The mixture was stirred for 12 h, diluted with ether, washed with 10% HCl and saturated $NaHCO_3$, dried, and concentrated. The residue was flash chromatographed (10% ethyl acetate in hexanes) to provide 96 mg (56% from **34**) of ester **38**: 250-MHz ^1H NMR ($CDCl_3$, δ) 0.92 (d, J = 6 Hz, 3 H), 0.99 (s, 3 H), 1.02 (s, 3 H), 1.2-2.1 (band, 9 H), 2.88 (m, 1 H), 3.06 (d, J = 9.5 Hz, 1 H), 3.74 (s, 3 H), 6.64 (m, 1 H); IR ($CDCl_3$) 1730, 1629, 1468, 1432 cm^{-1}.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.10; H, 9.69.

Deoxypentalenic Acid (3b). A solution of 34 mg (0.14 mmol) of methyl ester **38** and 2 mL of 10% KOH in 4 mL of methanol was heated at reflux for 48 h and cooled to room temperature. The methanol was removed in vacuo, and the residue was partitioned between ether-10% HCl. The aqueous layer was extracted several times with ether, and the combined ether extracts were dried and concentrated to yield 32 mg (100%) of crystalline deoxypentalenic acid (**3b**): mp 107-111 °C; 250-MHz ^1H NMR ($CDCl_3$, δ) 0.96 (d, J = 6 Hz, 3 H), 1.03 (S, 3 H) 1.05 (s, 3 H), 1.2-2.1 (band, 9 H), 2.93 (m, 1 H), 3.09 (d, J = 8.5 Hz, 1 H), 6.82 (brs, 1 H); IR ($CDCl_3$) 1678, 1628, 1282. M^+ calcd for $C_{15}H_{22}O_3$: 234.1620. Found: 234.1598.

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Total Synthesis of Mycophenolic Acid

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Abstract: A convergent aromatic annulation strategy based on the thermal combination of heterosubstituted acetylenes and cyclobutenones has been applied in an efficient total synthesis of the antitumor antibiotic mycophenolic acid. The key annulation components **3** and **4** are rapidly assembled by straightforward routes and then heated in benzene at 120 °C for 14 h. This annulation reaction generates the pentasubstituted aromatic intermediate **2** in 73% yield. Ortho bromination of this phenol and carboxylation of the aryllithium derivative then furnishes the carboxylic acid **10**, which is converted to mycophenolic acid (**1**) by acid hydrolysis followed by Jones oxidation. This convergent approach delivers mycophenolic acid in nine steps in an overall yield of 17-19%.

The *Penicillium* metabolite mycophenolic acid was first isolated in 1896[2] and is one of the oldest known antibiotics.[3] Recently, the compound has been identified as a potent inhibitor of IMP dehydrogenase and GMP synthetase[4] and in addition has been found to possess significant antiviral and antitumor activity.[5] The application of mycophenolic acid in the treatment of psoriasis[6] and leishmaniasis[7] is also currently the subject of active investigation.

The chemical structure of mycophenolic acid incorporates as a key feature a highly functionalized, hexasubstituted aromatic ring. The regiocontrolled synthesis of such highly substituted aromatic systems presents a formidable synthetic challenge, which is often best met by the application of annulation strategies that assemble the requisite aromatic unit in a single step with all (or most) substituents already in place.[8] Recently, we described a regiocontrolled annulation approach to aromatic compounds based on the *one-step* thermal combination of heterosubstituted alkynes with cyclobutenones (Scheme I).[9] In this article, we now report the application of this method in a convergent and highly efficient synthetic route to mycophenolic acid.[10]

Scheme II summarizes our synthetic strategy. The pivotal step in this approach is the construction of the pentasubstituted resorcinol derivative **2** via thermal addition of the alkynyl ether **3** to the cyclobutenone **4**. The indicated regiochemical outcome of this key transformation follows from the results of our earlier investigation,[9] which established that these aromatic annulations proceed via a cascade of four pericyclic reactions to regiospecifically generate products of general structure f as formulated in Scheme I. With the key pentasubstituted aromatic intermediate **2** in hand, completion of the synthesis of mycophenolic acid would simply require the introduction of a carboxyl function at C-6 of the aromatic nucleus and conversion of the resulting acid to the target antibiotic via hydrolysis and oxidation.

The following synthetic routes provided convenient access to the key annulation components **3** and **4**. Reduction of the known

(1) Fellow of the Alfred P. Sloan Foundation, 1981-1985.

(2) *Isolation*: Gosio, B. *Riv. Igiene Sanita publica Ann.* **1896**, *7*, 825. Structure determination: (a) Birkinshaw, J. H.; Raistrick, H.; Ross, D. J. *Biochem. J.* **1952**, *50*, 630. (b) Logan, W. R.; Newbold, G. T. *J. Chem. Soc.* **1957**, 1946.

(3) (a) Abraham, E. P. *Biochem. J.* **1945**, *39*, 398. (b) Florey, H. W.; Gilliver, K.; Jennings, M. A.; Sanders, A. G. *Lancet* **1946**, *250*, 46. (c) Gilliver, K. *Ann. Bot. (London)* **1946**, *10*, 271. (d) Brian, P. W. *Ibid.* **1949**, *13*, 59.

(4) (a) Franklin, T. J.; Cook, J. M. *Biochem. J.* **1969**, *113*, 515. (b) Sweeney, M. J.; Hoffman, D. H.; Esterman, M. A. *Cancer Res.* **1972**, *32*, 1803.

(5) (a) Ando, K.; Suzuki, S.; Tamura, G.; Arima, K. *J. Antibiot.* **1968**, *21*, 649. (b) Carter, S. B.; Franklin, T. J.; Jones, D. F.; Leonard, B. J.; Mills, S. D.; Turner, R. W.; Turner, W. B. *Nature (London)* **1969**, *223*, 848. (c) Sweeney, M. J.; Gerzon, K.; Harris, P. N.; Holmes, R. E.; Poore, G. A.; Williams, R. H. *Cancer Res.* **1972**, *32*, 1795.

(6) (a) Marianarai, R.; Fleischmajer, R.; Schragger, A. H.; Rosenthal, A. L. *Arch. Dermatol.* **1977**, *113*, 930. (b) Lynch, W. S.; Roenigk, H. H. *Ibid.* **1977**, *113*, 1203. (c) Gomez, E. C.; Menendez, L.; Frost, P. *J. Am. Acad. Dermatol.* **1979**, *1*, 531.

(7) Berman, J. D.; Webster, H. K. *Antimicrob. Agents Chemother.* **1982**, *21*, 887.

(8) For a recent review, see: Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441.

(9) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672.

(10) For earlier syntheses of mycophenolic acid, see: (a) Birch, A. J.; Wright, J. J. *Aust. J. Chem.* **1969**, *22*, 2635. (b) Canonica, L.; Rindone, B.; Santaniello, E.; Scolastico, C. *Tetrahedron* **1972**, *28*, 4395.

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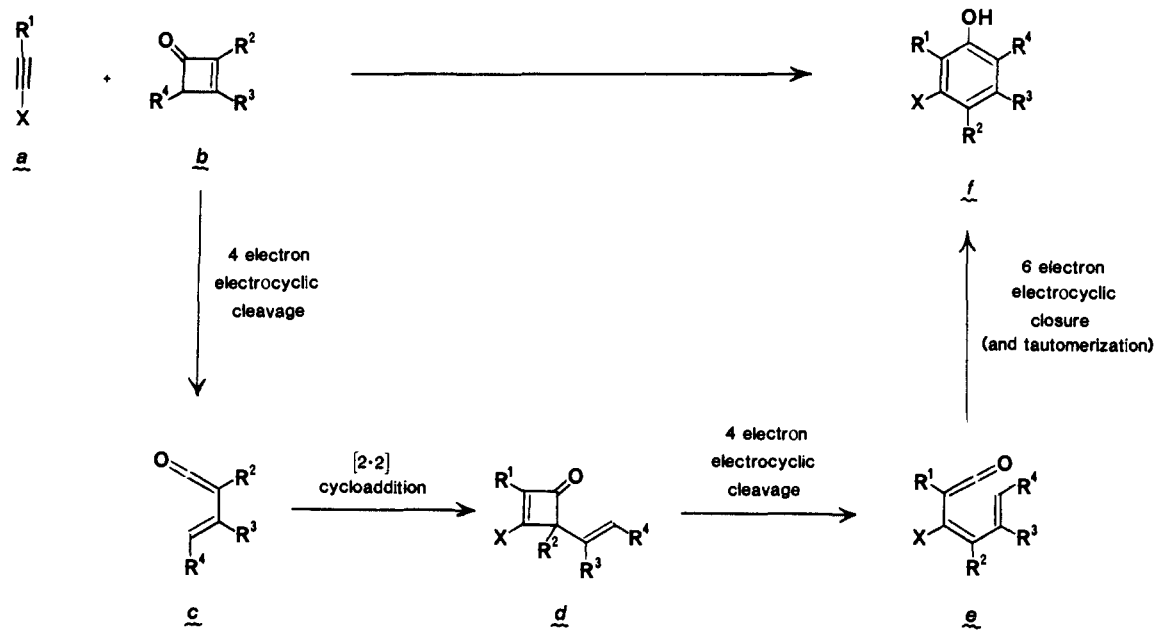
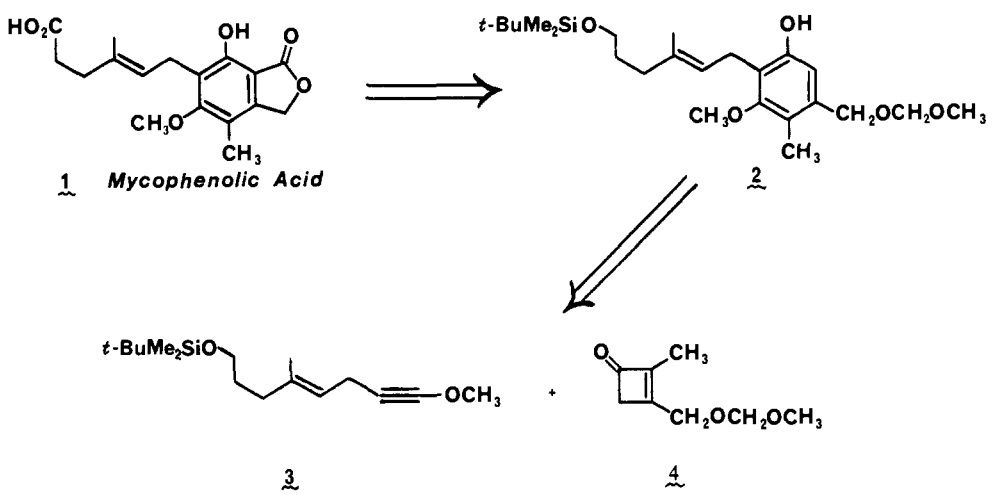
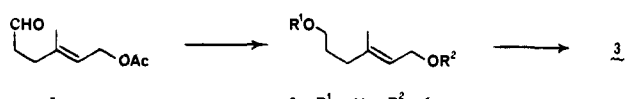
Scheme I



Scheme II



aldehyde **5**[11] with $NaBH_4$ in ethanol (25 °C, 25 min) produced the expected alcohol **6**, which was converted to the *tert*-butyldimethylsilyl ether **7** by exposure to 1.1 equiv of *t*-$BuMe_2SiCl$ and 1.2 equiv of Et_3N in the presence of a catalytic amount of 4-(dimethylamino)pyridine[12] (CH_2Cl_2, 25 °C, 20 h). Saponification



6 R^1 = H, R^2 = Ac
7 R^1 = Si*t*-BuMe$_2$, R^2 = Ac
8 R^1 = Si*t*-BuMe$_2$, R^2 = H

of **7** using K_2CO_3 in methanol (25 °C, 24 h) then furnished the allylic alcohol **8** in 70–75% overall yield from **5**. Conversion of **8** to the desired alkynyl ether was achieved in one flask via the coupling procedure previously employed for a related transformation in our synthesis of the antibiotic grifolin.[9] Thus, sequential treatment of a solution of **8** in THF with 1.1 equiv of *n*-BuLi (−78 °C, 35 min), 1.1 equiv of MsCl (−78 °C, 2 h), and finally 2.4 equiv of MeOC≡CMgBr and 0.04 equiv of Li_2CuCl_4[13] (−78 → 25 °C, 5.5 h) afforded the acetylene **3** (bp 75–80 °C, 0.005 mmHg) in 85–93% yield. The second annulation component, the cyclobutenone **4**, was efficiently prepared in 81% yield via the addition of $LiCH_2OCH_2OCH_3$[14] to 3-ethoxy-2-methylcyclobutenone[15] (THF, −78 °C, 2 h, and then workup at 0 °C with 5% HCl).

The stage was now set for us to examine the feasibility of the pivotal aromatic annulation step. The target compound **2** constituted the most densely functionalized system we had yet attempted to synthesize employing our annulation strategy. In the event, this key reaction proceeded smoothly, and in 73% yield, when a degassed benzene solution of the alkynyl ether **3** and 1.1 equiv of the cyclobutenone **4** was heated in a sealed tube at 120 °C for 14 h. The resulting pentasubstituted annulation product incorporates the complete carbon skeleton of mycophenolic acid with the exception of the C-6 carboxyl group. Introduction of this last carbon atom and the completion of the synthesis was accomplished by employing the following four-step sequence (Scheme III).

(11) Readily available via ozonolytic cleavage of geranyl acetate: (a) Stork, G.; Gregson, M.; Grieco, P. A. *Tetrahedron Lett.* **1969**, 1391. (b) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318. (c) Watanabe, M.; Imada, I.; Morimoto, H. *Biochemistry* **1970**, *9*, 2879.

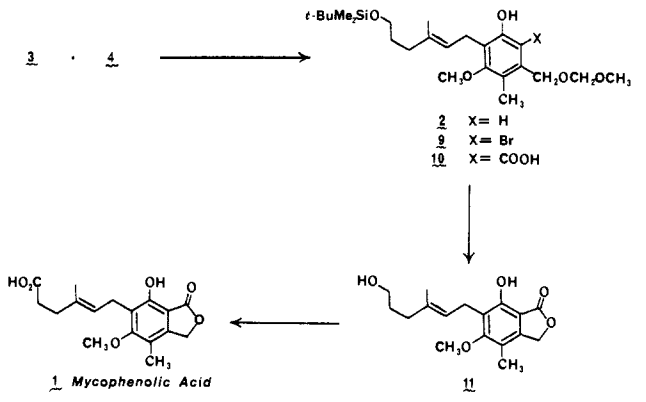
(12) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

(13) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.

(14) This organolithium compound was generated in situ from *n*-$Bu_3SnCH_2OCH_2OCH_3$ (**12**) by treatment with 1.0 equiv of *n*-BuLi in THF at −78 °C for 30 min.

(15) Prepared by the addition of ketene to 1-ethoxypropyne: (a) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670. (b) Ficini, J.; Genet, J. P. *Tetrahedron Lett.* **1975**, 2633.

Scheme III



First, chemoselective bromination at C-6 of the aromatic ring was achieved by treating the annulation product **2** with Br_2/t-$BuNH_2$[16] in toluene at −78 °C to 5 °C for 4 h. The desired *o*-bromophenol **9** was obtained in 85% yield in this fashion; the formation of byproducts resulting from benzylic bromination or addition to the side-chain double bond was not observed to take place under these conditions. Conversion of **9** to the desired carboxylic acid **10** was then accomplished by sequential treatment of the bromophenol in THF (−78 °C) with 2 equiv of CH_3Li (generation of the phenolate salt), 2 equiv of *t*-BuLi (halogen–metal exchange), and excess anhydrous CO_2 (−78 → 0 °C, 30 min). The resulting carboxylic acid (**10**) was next transformed without purification to the phthalide **11** by heating a solution of **10** and a catalytic amount of concentrated HCl in methanol at reflux for 4.5 h. The desired phthalide derivative **11** (mp 104–106 °C [lit.[17] mp 105–107 °C]) was obtained in 70% overall yield from **9** in this manner. Jones oxidation of **11** (−30 °C, 5 h, 61% yield) then furnished mycophenolic acid (**1**) as colorless crystals, mp 139–141 °C [lit.[2a] mp 141 °C], with spectral properties indistinguishable from those of an authentic sample.[18]

In conclusion, the total synthesis reported in this article serves to demonstrate the utility of our aromatic annulation method as an efficient strategy for the rapid assembly of complex aromatic compounds. This highly convergent route delivers mycophenolic acid in nine steps (17–19% overall yield) and is capable of supporting the preparation of multigram quantities of the natural product, as well as biologically interesting analogues.

Experimental Section

Instrumentation. Infrared spectra were obtained by using Perkin-Elmer 283B and 1320 grating spectrophotometers. ^1H NMR spectra were measured with a Perkin-Elmer R-24B (60 MHz), Bruker WM-250 (250 MHz), or WM-270 (270 MHz) spectrometer. ^{13}C NMR spectra were determined on a Bruker WM-270 (67.9 MHz) spectrometer. Chemical shifts are expressed in parts per million (ppm) (δ) downfield from tetramethylsilane. UV spectra were measured on a Varian Cary Model 118 UV–vis spectrophotometer. Low-resolution mass spectra (MS) were determined on Varian MAT 44 or Finnegan MAT 8200 instruments; high-resolution mass spectra (HRMS) were measured with a Du Pont CEC-110B or Finnegan MAT 8200 spectrometer. Elemental analyses were performed by Robertson Laboratory, Inc., in Florham Park, NJ. Melting points and boiling points are uncorrected.

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Boron trifluoride etherate was distilled with excess diethyl ether from calcium hydride under reduced pressure. Dimethoxymethane and ethanol were distilled from sodium. Benzene, toluene, triethylamine, *tert*-butylamine, dichloromethane, and methoxyacetylene were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium benzophenone dianion. Alkyllithium reagents were titrated with diphenylacetic acid[19] or 1,3-diphenylacetone *p*-tosylhydrazone.[20]

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated by using a Büchi rotary evaporator at 15–25 mmHg. Column chromatography was performed by using Baker or E. Merck silica gel (230–400 mesh) or Woelm neutral alumina (60–200 mesh, deactivated as indicated). Radial preparative thin-layer chromatography was carried out by using a Harrison Research, Inc., Chromatotron on plates coated with E. Merck PF-254 silica gel.

(*E*)-1-Acetoxy-3-methyl-2-hexen-6-ol (6). A 250-mL, three-necked, round-bottomed flask equipped with a 25-mL addition funnel, nitrogen inlet adapter, and polyethylene stopper was charged with sodium borohydride (1.85 g, 50.0 mmol) and 80 mL of absolute ethanol and was then cooled at 0 °C while a solution of the aldehyde **5** (5.55 g, 32.6 mmol) in 10 mL of ethanol was added dropwise over 5 min. The ice–water bath was then removed, and after 25 min, the reaction mixture was again cooled to 0 °C and acidified to pH 2 with 5% aqueous HCl solution. The aqueous phase of the resulting mixture was separated and extracted with three 70-mL portions of dichloromethane, and the combined organic phases were washed with two 50-mL portions of H_2O and 100 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 4.97 g of a colorless liquid. Kugelrohr distillation (oven temperature 95–100 °C, 0.005 mmHg) provided 4.74 g (84%) of **6** as a colorless oil: IR (film) 3650–3100, 2925, 2860, 1730, 1660, 1440, 1380, 1360, 1240, 1045, 1020, 950, 920, and 730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.38 (br dt, 1 H, J = 1.1, 7.1 Hz), 4.59 (d, 2 H, J = 7.1 Hz), 3.64 (t, 2 H, J = 6.5 Hz), 2.13 (br t, 2 H, J = 7.7 Hz), 2.06 (s, 3 H), 1.89 (br, s, 1 H), 1.72 (s, 3 H), and 1.64–1.76 (m, 2 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 171.1, 141.8, 118.5, 62.2, 61.2, 35.7, 30.4, 20.9, and 16.3; MS, m/e 129 (M^+ − 43), 113, 112, 97, 95, 85, 84, 81, 79, 71, 69, 68, 67, 55, 53, 43, 41, and 37; HRMS, m/e calcd for $C_7H_{13}O_2$ ($M^+ - CH_3CO$) 129.0916, found 129.0907.

(*E*)-1-Acetoxy-6-(*tert*-butyldimethylsiloxy)-3-methyl-2-hexene (7). A 250-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and polyethylene stopper was charged with the alcohol **6** (4.69 g, 26.6 mmol), triethylamine (3.22 g, 31.9 mmol), *tert*-butyldimethylsilyl chloride (4.40 g, 29.3 mmol), 4-(dimethylamino)pyridine (0.002 g, 0.02 mmol), and 50 mL of dichloromethane. The resulting solution was then stirred at room temperature for 20 h, diluted with 60 mL of dichloromethane, washed with 100 mL of H_2O, 50 mL of 2% aqueous HCl solution, and two 100-mL portions of H_2O, dried over Na_2SO_4, filtered, and concentrated to give 8.16 g of **7** as an oil, used in the next step without purification: IR (film), 2930, 2860, 1740, 1450, 1380, 1360, 1240, 1020, 960, 840, and 780 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 5.20–5.60 (m, 1 H), 4.60 (d, 2 H, J = 7 Hz), 3.60 (t, 2 H, J = 7 Hz), 2.00 (s, 3 H), 1.70 (br, s, 3 H), 1.40–1.80 (m, 2 H), 0.85 (s, 9 H), and 0.00 (s, 6 H).

(*E*)-6-(*tert*-Butyldimethylsiloxy)-3-methyl-2-hexen-1-ol (8). A 250-mL, one-necked, round-bottomed flask equipped with an argon inlet adapter was charged with the unpurified ester **7** (8.16 g) prepared in the preceding reaction, potassium carbonate (0.010 g, 0.07 mmol), and 100 mL of methanol. The reaction mixture was stirred at room temperature for 24 h and then concentrated. Distillation of the residual oil afforded 5.46 g (70% overall yield from **5**) of **8** as a colorless oil: bp 85–87 °C, 0.005 mmHg; IR (film) 3550–3050, 2925, 2875, 2850, 1660, 1470, 1450, 1380, 1360, 1250, 1090, 1000, 950, 830, 810, and 770 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.35 (br t, 1 H, J = 6.8 Hz), 4.07 (d, 2 H, J = 6.8 Hz), 3.55 (t, 2 H, J = 6.5 Hz), 2.03–2.35 (br s, 1 H), 2.00 (br t, 2 H, J = 7.7 Hz), 1.61 (s, 3 H), 1.56–1.64 (m, 2 H), 0.85 (s, 9 H), and 0.00 (s, 6 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 138.8, 123.5, 62.7, 59.0, 35.7, 30.8, 25.9, 18.2, 16.1, and −5.4; MS, m/e 169 (M^+ − 75), 147, 105, 101, 97, 95, 93, 79, 77, 75, 69, 68, 67, 59, 57, 55, 45, 43, 41, and 39; HRMS, m/e calcd for $C_9H_{19}O_2Si$ ($M^+ - C_4H_9$) 187.1154, found 187.1155.

(*E*)-8-(*tert*-Butyldimethylsiloxy)-1-methoxy-5-methyl-4-octen-1-yne (3). A 25-mL, two-necked, pear-shaped flask was equipped with an argon inlet adapter and a rubber septum. The flask was charged with methoxyacetylene[21] (0.350 g, 6.25 mmol) and 10 mL of THF and then cooled with an ice–water bath while 2.07 mL of a 2.9 M solution of ethylmagnesium bromide in diethyl ether (6.00 mmol) was added dropwise over 10 min. The resulting light-brown suspension was stirred at 0 °C for 30 min and then was cooled to −78 °C.

A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and polyethylene stopper was charged

(16) Pearson, D. E.; Wyson, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358.
(17) Jones, D. F.; Mills, S. D. *J. Med. Chem.* **1971**, *14*, 305.
(18) Obtained from CALBIOCHEM Biochemicals, San Diego, CA.
(19) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
(20) Lipton, M. F.; Sorenson, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.
(21) Prepared using the general method of: Newman, M. S.; Geib, J. R.; Stalick, W. M. *Org. Prep. Proced. Int.* **1972**, *4*, 89. See also: Jones, E. R. H.; Eglinton, G.; Whiting, M. C.; Shaw, B. L. In "Organic Syntheses"; Rabjohn, N., Ed.; Wiley: New York, 1963; Collect. Vol. IV, p 404.

with a solution of the alcohol **8** (0.610 g, 2.50 mmol) in 15 mL of THF and then cooled to −78 °C with a dry ice–acetone bath, while 1.06 mL of a 2.60 M solution of *n*-butyllithium in hexane (2.75 mmol) was added dropwise over 7 min. After 35 min, methanesulfonyl chloride (0.313 g, 2.75 mmol) was added in one portion, and the resulting mixture was stirred at −78 °C for 2 h. The solution of the Grignard derivative of methoxyacetylene prepared above was next transferred rapidly via cannula into the reaction mixture, to which was then added 1.0 mL of a 0.1 M solution of dilithium tetrachlorocuprate[13] in THF (0.1 mmol). The resulting solution was allowed to slowly warm to room temperature over 2.5 h, stirred at 25 °C for 3 h further, and then poured into 30 mL of saturated aqueous NH_4Cl solution buffered to pH 8 with NH_4OH. The resulting mixture was extracted with two 40-mL portions of ethyl acetate, and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a turbid brown oil. Polar impurities were removed by filtration through 2 g of activity 5 neutral alumina (elution with ethyl acetate–hexane), and the resulting yellow oil was further purified by Kugelrohr distillation (oven temperature 75–80 °C, 0.005 mmHg) to afford 0.645 g (91%) of **3** as a colorless oil: IR (film) 3030, 2940, 2900, 2865, 2285, 1460, 1385, 1365, 1300, 1245, 1175, 1100, 1005, 965, 835, and 815 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.00–5.16 (br dt, 1 H, J = 1.1, 6.6 Hz), 3.75 (s, 3 H), 3.54 (t, 2 H, J = 6.5 Hz), 2.76 (d, 2 H, J = 6.6 Hz), 1.98 (br t, 2 H, J = 7.6 Hz), 1.56 (br s, 3 H), 1.54–1.63 (m, 2 H), 0.85 (s, 9 H), and 0.00 (s, 6 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 140.7, 124.3, 91.5, 64.2, 61.6, 32.2, 31.9, 27.2, 21.8, 13.5, 11.0, 10.9, and −12.0; MS, *m/e* 226 (M^+ − 56), 225, 169, 165, 151, 149, 147, 119, 113, 109, 107, 105, 101, 96, 95, 91, 89, 79, 75, 73, 67, and 59; HRMS, *m/e* calcd for $C_{12}H_{21}O_2Si$ ($M^+ - C_4H_9$) 225.1311, found 225.1316.

(Methoxymethoxymethyl)tri-*n*-butylstannane (12). A 1-L, three-necked, round-bottomed flask was equipped with a nitrogen inlet adapter, rubber septum, and polyethylene stopper. The flask was charged with (hydroxymethyl)tri-*n*-butylstannane[22] (20.6 g, 65.6 mmol), dimethoxymethane (342 mL, 294 g, 3900 mmol), 40.0 g of powdered 4-Å molecular sieves, and 350 mL of dichloromethane and then boron trifluoride etherate (14.3 g, 100 mmol) was added in one portion. After 18 h, the resulting suspension was filtered through a sintered glass funnel with the aid of three 50-mL portions of dichloromethane, and the filtrate was then extracted with 100 mL of saturated $NaHCO_3$ solution and 100 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 20.0 g of a colorless liquid. Distillation provided 19.2 g (80%) of **12** as a colorless oil: bp 98–103 °C, 0.01 mmHg; IR (film) 2950, 2920, 2865, 2850, 1460, 1415, 1390, 1375, 1335, 1290, 1240, 1195, 1140, 1090, 1035, 955, 920, 870, 860, and 720 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.52 (s, 2 H), 3.74 (s, 2 H), 3.32 (s, 3 H), 1.46–1.57 (m, 6 H), 1.24–1.37 (m, 6 H), and 0.86–0.95 (m, 15 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 99.3, 57.4, 54.7, 29.0, 27.3, 13.6, and 8.8; MS, *m/e* 308 (M^+ − 57), 306, 234, 179, 178, 177, 176, 175, 121, 69, 46, 45, 44, 41, 40, and 39; Anal. Calcd for $C_{15}H_{34}O_2Sn$: C, 49.34; H, 9.39. Found: C, 49.32; H, 9.38.

3-(Methoxymethoxymethyl)-2-methylcyclobuten-1-one (4). A 100-mL, three-necked, round-bottomed flask equipped with a 10-mL addition funnel, rubber septum, and nitrogen inlet adapter was charged with (methoxymethoxymethyl)tri-*n*-butylstannane (5.77 g, 15.8 mmol) and 60 mL of THF and then cooled to −78 °C with a dry ice–acetone bath, while 6.1 mL of a 2.60 M solution of *n*-butyllithium in hexane (15.9 mmol) was added dropwise over 25 min. The resulting mixture was stirred at −78 °C for 25 min further and then a solution of 3-ethoxy-2-methylcyclobuten-1-one[15] (1.66 g, 13.2 mmol) in 5 mL of THF was added dropwise over 40 min. After 2 h, the dry ice–acetone bath was replaced with an ice–water bath, and 20 mL of 5% aqueous HCl solution was added to the reaction mixture in one portion. After 15 min, the aqueous phase was separated and extracted with two 25-mL portions of dichloromethane. The combined organic phases were washed with 20 mL of saturated $NaHCO_3$ solution and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 8.37 g of a biphasic oil. Column chromatography on silica gel (elution with ethyl acetate–hexane) gave 1.66 g (80%) of **4** as a colorless oil: IR (film) 2925, 2890, 2850, 2830, 2780, 1760, 1645, 1440, 1370, 1310, 1280, 1215, 1155, 1105, 1040, 945, and 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.71 (s, 2 H), 4.56 (q, 2 H, J = 1.2 Hz), 3.41 (s, 3 H), 3.14 (m, 2 H), and 1.74 (m, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 189.0, 166.3, 144.9, 96.1, 64.6, 55.3, 48.0, and 8.0; UV max (isooctane) 227 nm (ϵ 7660) and 307 (41); MS, *m/e* 156 (M^+), 126, 111, 95, 83, 67, 53, 45, 41, and 39; HRMS, *m/e* calcd for $C_8H_{12}O_3$ 156.0786, found 156.0791.

(*E*)-2-(6-(*tert*-Butyldimethylsiloxy)-3-methyl-2-hexenyl)-3-methoxy-5-(methoxymethoxymethyl)-4-methylphenol (2). A 10-mm-diameter Pyrex tube was charged with a solution of the cyclobutenone **4** (0.495 g, 3.17 mmol) and the alkynyl ether **3** (0.746 g, 2.65 mmol) in 1.0 mL of benzene and then freeze-thaw-degassed 5 times under a vacuum of 0.01 mmHg. The reaction tube was sealed under a static vacuum of ca. 200 mmHg and then heated in an oil bath at 120 °C for 14 h. After cooling to room temperature, the reaction mixture was transferred to a 100-mL recovery flask with the aid of 10 mL of dichloromethane and then concentrated. The residual yellow oil was dissolved in 40 mL of methanol, K_2CO_3 (0.005 g, 0.04 mmol) was added, and the resulting solution was stirred at room temperature for 5 h[23] and then concentrated to afford a yellow oil. Preparative radial thin-layer chromatography on a 4-mm silica gel plate (elution with ethyl acetate–hexane) furnished 0.794 g (73%) of **2** as a pale-yellow oil: IR (film) 3620–3140, 2940, 2900, 2870, 1595, 1465, 1455, 1415, 1380, 1320, 1255, 1215, 1150, 1085, 1040, 835, 775, and 735 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.68 (s, 1 H), 5.48 (br s, 1 H), 5.24 (dd, 1 H, J = 5.9, 6.9 Hz), 4.72 (s, 2 H) 4.52 (s, 2 H), 3.69 (s, 3 H), 3.58 (t, 2 H, J = 6.5 Hz), 3.43 (s, 3 H), 3.40–3.43 (m, 2 H), 2.20 (s, 3 H), 2.06 (br t, 2 H, J = 7.7 Hz), 1.82 (br s, 3 H), 1.57–1.69 (m, 2 H), 0.89 (s, 9 H), and 0.04 (s, 6 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 157.1, 153.3, 137.4, 135.5, 122.1, 121.2, 120.0, 112.2, 95.7, 67.3, 62.8, 60.8, 55.4, 35.8, 31.0, 25.9, 23.2, 18.2, 16.2, 11.0, and −5.4; UV max (isooctane) 281 nm (ϵ 1840); MS, *m/e* 438 (M^+), 381, 361, 321, 320, 319, 299, 263, 251, 239, 225, 221, 191, 165, 164, 149, 89, 81, 79, 77, 75, 73, 69, 67, 59, 57, 45, 43, and 41; HRMS, *m/e* calcd for $C_{24}H_{42}O_5Si$ 438.2802, found 438.2773. Anal. Calcd for $C_{24}H_{42}O_5Si$: C, 65.71; H, 9.65. Found: C, 65.75; H, 9.72.

(*E*)-2-Bromo-6-(6-(*tert*-butyldimethylsiloxy)-3-methyl-2-hexenyl)-5-methoxy-3-(methoxymethoxymethyl)-4-methylphenol (9). A 50-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, rubber septum, and polyethylene stopper was charged with a solution of *tert*-butylamine (0.198 g, 2.72 mmol) in 15 mL of toluene and then cooled to between −25 and −30 °C with a dry ice–acetone bath. Bromine (0.207 g, 1.30 mmol) was added rapidly dropwise via syringe, and the resulting pale-yellow solution was stirred at −25 °C for 20 min and then cooled to −78 °C. A precooled (−78 °C) solution of the phenol **2** (0.496 g, 1.13 mmol) in 5 mL of toluene was rapidly transferred via cannula into the reaction mixture, and the resulting mixture was allowed to slowly warm to 5 °C over 4 h. The resulting golden-yellow solution was diluted with 40 mL of ethyl acetate and washed with 40 mL of H_2O and 40 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to yield a yellow oil. Column chromatography on silica gel (elution with ethyl acetate–hexane) gave 0.494 g (85%) of **9** as a pale-yellow oil: IR (CCl_4) 3520, 2960, 2930, 2880, 2860, 1440, 1410, 1095, 1035, 945, and 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.68 (s, 1 H, D_2O exch), 5.15–5.20 (m, 1 H), 4.73 (s, 2 H), 4.70 (s, 2 H), 3.65 (s, 3 H), 3.52 (t, 2 H, J = 6.6 Hz), 3.43 (s, 3 H), 3.39 (m, 2 H), 2.30 (s, 3 H), 1.92–2.01 (m, 2 H), 1.76 (br s, 3 H), 1.52–1.68 (m, 2 H), 0.84 (s, 9 H), and −0.01 (s, 6 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 156.8, 149.3, 135.9, 133.1, 124.8, 122.8, 122.0, 110.0, 96.2, 67.0, 62.8, 60.8, 55.6, 35.9, 31.1, 25.9, 24.3, 18.3, 16.2, 12.3, and −5.3; UV max (isooctane) 288 nm (ϵ 3140); MS, *m/e* 518 (M^+), 516, 461, 459, 399, 397, 361, 331, 303, 301, 245, 243, and 237; HRMS, *m/e* calcd for $C_{20}H_{32}{}^{81}BrO_5Si$ ($M^+ - C_4H_9$) 461.1182, found 461.1180.

(*E*)-6-(1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenol (11). A 50-mL, two-necked, pear-shaped flask equipped with a rubber septum and a nitrogen inlet adapter was charged with a solution of the bromophenol **9** (0.281 g, 0.543 mmol) in 14 mL of THF and cooled to −78 °C with a dry ice–acetone bath, while 0.72 mL of a 1.51 M solution of methyllithium–lithium bromide in diethyl ether (1.09 mmol) was added dropwise over 10 min. After 50 min, 0.72 mL of a 1.53 M solution of *tert*-butyllithium in pentane (1.10 mmol) was added dropwise over 5 min, and the resulting golden-yellow solution was stirred at −78 °C for 1 h. The dry ice–acetone bath was then removed, and anhydrous carbon dioxide gas was bubbled through the reaction mixture via a stainless steel needle as the now colorless solution was allowed to warm to 0 °C over 30 min. The reaction mixture was acidified to pH 1 with 2% aqueous HCl solution and then diluted with 40 mL of dichloromethane. The organic phase was separated and washed with 40 mL of H_2O and 40 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford a yellow oil which was dissolved in 10 mL of methanol containing 3 drops of concentrated HCl solution and heated at reflux for 4.5 h. The resulting solution was concentrated to furnish a yellow oil. Column chromatography on silica gel (elution with ethyl acetate–hexane) provided 0.117 g (70%) of **11** as colorless needles, mp 104–106 °C [lit.[17] mp 105–107 °C]; IR (CCl_4) 3640, 3550, 3430, 2940, 2875, 1738, 1452, 1415, 1365, 1330, 1135, 1095,

(22) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(23) Treatment of the crude annulation product with K_2CO_3 in methanol serves to saponify the small amount of ester formed by the reaction of the phenolic product with excess vinylketene.

1075, 1025, 970, and 950 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.69 (s, 1 H), 5.20–5.25 (m, 1 H), 5.20 (s, 2 H), 3.77 (s, 3 H), 3.60 (t, 2 H, J = 6.2 Hz), 3.40 (d, 2 H, J = 6.8 Hz), 2.15 (s, 3 H), 2.07 (t, 2 H, J = 7.4 Hz), 1.81 (br s, 3 H), and 1.64–1.73 (m, 2 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 172.8, 163.6, 153.6, 143.9, 135.5, 122.3, 116.7, 106.3, 69.9, 62.7, 60.9, 36.0, 30.6, 22.6, 16.0, and 11.5; UV max (isooctane) 249 nm (ϵ 6200) and 305 (3700); MS, m/e 306 (M^+), 288, 273, 260, 247, 229, 219, 207, 159, and 85. Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.39; H, 7.30.

(*E*)-6-(1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic Acid (1). A 50-mL recovery flask equipped with a Claisen head, rubber septum, and nitrogen inlet adapter was charged with a solution of the alcohol **11** (0.086 g, 0.28 mmol) in 25 mL of acetone and then cooled to −30 °C with a dry ice–bromobenzene bath. Jones reagent[24] (0.20 mL, 1.4 equiv) was then added dropwise by syringe over 3 min, and the resulting brown mixture was stirred at −30 °C for 5 h. Isopropyl alcohol (55 mg, 0.070 mL, 0.92 mmol) was then added, and the resulting mixture was filtered through a pad of Celite with the aid of two 5-mL portions of acetone and then concentrated to afford a brown oil. Column chromatography on silica gel (elution with dichloromethane–ethyl acetate) provided 0.056 g (61%) of mycophenolic acid (**1**) as colorless crystals: mp 139–141 °C (ethanol–water [lit.[2a] mp 141 °C]); IR (CCl_4) 3430, 3300–2900, 2935, 1740, 1710, 1410, 1130, 1075, 1025, 905 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.68 (br s, 1 H), 5.20–5.30 (m, 1 H), 5.20 (s, 2 H), 3.76 (s, 3 H), 3.39 (d, 2 H, J = 6.9 Hz), 2.41–2.48 (m, 2 H), 2.28–2.34 (m, 2 H), 2.15 (s, 3 H), and 1.90 (s, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 179.1, 172.8, 163.5, 153.5, 144.0, 133.8, 122.8, 122.0, 116.6, 106.2, 70.0, 60.9, 34.1, 32.6, 22.5, 16.0 and 11.4; UV max (ethanol) 305 nm (ϵ 5300) and 249 (10 300); MS, m/e 320 (M^+), 302, 261, 260, 247, 245, 229, 219, 207, 159, 152, and 149. Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.82; H, 6.31.

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(24) See Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547 and references cited therein.

99% Chirally Selective Syntheses via Pinanediol Boronic Esters: Insect Pheromones, Diols, and an Amino Alcohol

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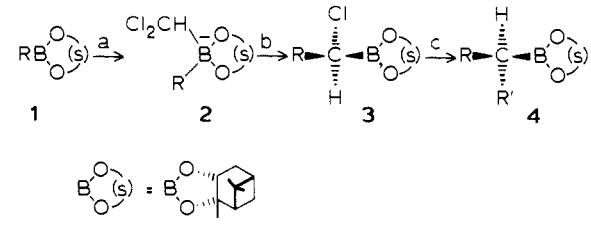
Abstract: Chiral selectivities generally exceed 99% in the homologation of (+)-pinanediol alkylboronates (**1**) to (1*S*)-(1-chloroalkyl)boronates (**3**) by reaction of **1** with (dichloromethyl)lithium at −100 °C followed by zinc chloride catalyzed rearrangement of the resulting borate complexes (**2**) at 0–25 °C. Diastereoselectivity falls to 95.7% with the methylboronate. (−)-Pinanediol leads to the 1*R* isomers. Nucleophilic displacements on (1-chloroalkyl)boronic esters yield new chiral boronic esters which can be homologated further. Compatible substituents include α- or β-benzyloxy, δ- or ϵ-ethylene ketal, β-carbo-*tert*-butoxy, α-azido, and β-hexylthio. Three insect pheromones each containing two chiral centers have been synthesized: (3*S*,4*S*)-4-methyl-3-heptanol (**5**) (elm bark beetle), *exo*-brevicomin (**12**) (western pine beetle), and eldanolide (**18**) (African sugar cane borer). Synthetic utility is further illustrated by stereocontrolled syntheses of a chiral *vic*-diol (**22**), an alcohol having three adjacent chiral centers (**24a**), a chiral α,γ-diol (**24b**), and a chiral *vic*-amino alcohol (**28b**).

Directed chiral synthesis is based on the reaction of chiral boronic esters (**1**, Scheme I) with (dichloromethyl)lithium gives the chemist absolute choice of the chirality of the carbon atom introduced and provides a unique means for systematic construction of a series of chiral centers.[1-3] The starting materials are easily obtained and the laboratory procedures are relatively simple. In the present work, we show that zinc chloride catalysis of the rearrangement of the intermediate borate complexes (**2**) results in very high diastereoselection (typically >99%) and high yields (usually 85–90%) of (1-chloroalkyl)boronic esters (**3**). Enantiomerically pure (+)- or (−)-pinanediol is used as the chiral directing group.

The present work establishes the compatibility of this process with various functional groups. Remote ketal and carboxylic ester groups do not interfere, and the utility of the process has been demonstrated with the synthesis of three insect pheromones, each of which contains two adjacent chiral centers. More crucial is the question of β-elimination of boron and nucleofugic substituents. The promise of the new process is therefore illustrated by the successful homologation of boronic esters bearing α- or β-benzyloxy, α-azido, or β-alkylthio substituents, and several subsidiary problems created by such substituents have been solved. Also illustrated are syntheses of a chiral *vic*-diol, the assembly of three adjacent chiral centers, a chiral α,γ-diol, and a chiral *vic*-amino alcohol,

Scheme I[a,b]



[a] Conditions: (a) $LiCHCl_2$, −100 °C; (b) $ZnCl_2$, 20 °C; (c) R'MgX or R'Li at −78 °C, then 20 °C. [b] **a**, R = CH_3; **b**, R = $CH_3CH_2CH_2$; **c**, R = $CH_3(CH_2)_3$; **d**, R = $(CH_3)_2CHCH_2$; **e**, R = $C_6H_5CH_2$; **f**, R = $CH_3CH_2CH_2CH(CH_3)$ (see Scheme II for configuration); **g**, R = *n*-$C_6H_{13}SCH_2CH_2$.

(1) Preliminary communication: Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077–2078; correction, 6195 (identification of tabulated compounds).

(2) (a) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. *Organometallics* **1983**, *2*, 1536–1543. (b) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591.

(3) Sadhu, K. M.; Matteson, D. S.; Hurst, G. D.; Kurosky, J. M. *Organometallics* **1984**, *3*, 804–806.

0002-7863/86/1508-0810$01.50/0