Hz, 1 H), 3.13 (d, J = 15 Hz, 1 H), 3.08 (m, 2 H), 2.09 (s, CH_3), 1.72 (s, CH_3); IR (neat) cm^{-1} 3600–2800 (mb), 2950 (s), 2250 (m), 1740 (s), 1400 (m), 1260 (s), 1100–1000 (s).

(*R*)-(−)-Mevalolactone. A solution of BH_3·THF (1.2 mL, 1 M) was added to the acid **6** (225 mg, 1.2 mmol) dissolved in THF (12 mL) under N_2 at −50 °C. The solution was allowed to warm to room temperature and stirred for 20 h. Next H_2O (5 mL) and K_2CO_3 were added, the mixture stirred for a few minutes, the layers were separated, and the aqueous layer was extracted with ether (5 × 10 mL). The combined extracts were then washed with saturated NH_4Cl (20 mL), dried ($MgSO_4$), and concentrated to give 210 mg of a mixture of the desired **7** (63% by ^1H NMR) and other compounds. [The optically active material was carried on to mevalolactone without purification at this stage; however, racemic **7**, prepared from racemic **5**, was purified (flash chromatography 50% EtOAc/hexanes) to allow estimation of the yield in the optically active compound by ^1H NMR analysis of the mixture obtained. Purified racemic **7**: ^1H NMR ($CDCl_3$) δ 4.29 (t, J = 6 Hz, 2 H), 2.62 (s, 3 H), 2.09 (s, CH_3), 2.00 (dt, J = 4 Hz, 7 Hz, 2 H), 1.42 (s, CH_3); IR (neat) cm^{-1} 3500 (s), 2950 (m), 2250 (m), 1740 (s), 1400 (m), 1250 (s).] The impure optically active **7** (ca. 0.75 mmol) was hydrolized with a mixture of 3 N NaOH (5 mL) and 30% H_2O_2 (1.7 mL) by heating at 70 °C for 6 h. The solution was then cooled to 0 °C, acidified to pH 3 with 6 N HCl, let stir 0.5 h, and continously extracted with $CHCl_3$ for 16 h. The $CHCl_3$ extract was dried ($MgSO_4$), concentrated, and flash chromatographed (100% EtOAc) to give 90 mg (58% from acid **7**) of pure (*R*)-(−)-mevalolactone: $[\alpha]^{20}_D$ −21.6° (*c* 1.565, 95% EtOH) [lit. $[\alpha]^{20}_D$ −23.0° (*c* 6, EtOH)[3]]. The ^1H NMR of this compound was identical with that of a sample of racemate purchased from the US Biological Corporation. A chiral shift experiment following the method of Wilson, Scallen, and Morrow[15] revealed no *S* isomer in the material. Addition of 7% of the racemate and integration of the upfield wing of the AB pattern from the CH_2 α to the carbonyl following Lorentzian to Gaussian line-shape transformation indicated ≥98% ee.

(*R*)-(+)-3-Hydroxy-3-methyl-4-phenylbutanoic Acid (8). A mixture of 3 N NaOH (12 mL) and 30% H_2O_2 (4.5 mL) was added to hydroxy nitrile **5** (330 mg, 1.9 mmol), and the mixture was heated at 65 °C for 1 h and then at 100 °C for 1 h and allowed to cool to room temperature over 1 h. Next the solution was cooled to 0 °C, 6 N HCl was added until the material was acidic, the resulting aqueous suspension was extracted with ether (4 × 20 mL), and the ether was dried ($MgSO_4$) and concentrated to give 350 mg (95%) of **8**, a strong smelling oil, pure by TLC: $[\alpha]^{20}_D$ +1.89° (*c* 1.214, 95; EtOH); ^1H NMR ($CDCl_3$) δ 7.80 (s, 2 H), 7.23 (m, 5 H), 2.88 (s, 2 H), 2.56 (d, J = 15 Hz, 1 H), 2.48 (d, J = 15 Hz), 1.28 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 177.0, 136.6, 130.5, 128.2, 126.7, 71.7, 47.9, 44.2, 26.8; IR (neat) cm^{-1} 3600–2900 (sb), 1710 (s), 1600 (w).

(*R*)-(+)-3-Methyl-4-phenyl-1,3-butanediol (9). Acid **8** (150 mg, 0.78 mmol) was dissolved in absolute THF (10 mL) under N_2, $LiAlH_4$ (ca. 200 mg) was added via a powder addition tube, and the mixture refluxed for 2.5 h. The material was then cooled to 0 °C and quenched with saturated NH_4Cl, the salts were dissolved with concentrated HCl, the layers were separated, and the aqueous layer was extracted with ether (4 × 20 mL). The combined organic solution was washed with saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$), concentrated, and flash chromatographed (50% EtOAc/hexanes) to give 118 mg (92%) of **9**, a clear oil; $[\alpha]^{20}_D$ +1.77° (*c* 1.811, 95% EtOH); ^1H NMR ($CDCl_3$) (as the bis-trifluoroacetate) δ 7.26 (m, 5 H), 4.48 (t, J = 6 Hz, 2 H), 3.28 (d, J = 14 Hz, 1 H), 3.16 (d, J = 14 Hz, 1 H), 2.42 (m, 1 H), 2.27 (m, 1 H), 1.58 (s, CH_3).

(*S*)-(+)-Mevalolactone. The diacetate of diol **9** (360 mg, 1.4 mmol) was formed in the same fashion as the acetate derivative of **6** and was dissolved in a mixture of CH_3CN (6 mL), CCl_4 (6 mL), and H_2O (15 mL) and then $NaIO_4$ (5.7 g, 27 mmol) and $RuCl_3$ (50 mg, 15 mol %) were added sequentially to this mixture. The material was stirred at 70 °C for 14 h, cooled to room temperature, and worked up as before to give 317 mg of crude material (95% pure by ^1H NMR). [Racemic material was purified at this stage: ^1H NMR ($CDCl_3$) δ 9.82 (s, 1 H), 4.18 (m, 2 H), 3.06 (d, J = 15 Hz, 1 H), 2.94 (d, J = 15 Hz, 1 H), 2.37 (m, 1 H), 2.16 (m, 1 H), 2.04 (s, CH_3), 2.01 (s, CH_3), 1.58 (s, CH_3).] The crude diacetate of mevalonic acid (ca. 1.3 mmol) obtained above was dissolved in 90% MeOH (20 mL), K_2CO_3 (1 g, 7 mmol) was added, and the mixture was stirred overnight at 70 °C. Next the MeOH was removed, H_2O (10 mL) was added, and the solution was cooled to 0 °C, acidified to pH 3 with 6 N HCl, and continuously extracted with $CHCl_3$. The $CHCl_3$ was dried ($MgSO_4$), concentrated, and flash chromatographed (100% EtOAc) to give 105 mg (60% from diol **9**) of pure (*S*)-(+)-mevalolactone: $[\alpha]^{26}_D$ +21.7° (*c* 0.751, 95% EtoH) [lit. $[\alpha]^{20}_D$ +22.8° (*c* 10, EtOH)[3]]; ^1H NMR identical with racemate. A chiral shift experiment (vide supra) indicated ≥98% ee.

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Registry No. **1**, 79563-75-0; **1** (carbinol), 79563-69-2; **2**, 96948-91-3; **3**, 96948-92-4; (±)-**3**, 96998-28-6; **3** (aldehyde), 96949-05-2; **4**, 96948-93-5; **5**, 96948-94-6; (±)-**5**, 96998-29-7; **5** (acetate), 96948-95-7; (±)-**5** (acetate), 96998-30-0; **6**, 96948-96-8; (±)-**6**, 96998-31-1; **7**, 96948-97-9; (±)-**7**, 96998-32-2; **8**, 96948-98-0; (±)-**8**, 96998-33-3; **9**, 96948-99-1; (±)-**9**, 96998-34-4; **9** (bis-trifluoroacetate), 96949-00-7; **9** (diacetate), 96949-01-8; (±)-**9** (diacetate), 96998-35-5; $HOCH_2COCH_3$, 116-09-6; $LiCH_2CN$, 55440-71-6; $PhCH_2COCH_3$, 103-79-7; (*S*)-mevalonic acid diacetate, 96949-02-9; (±)-mevalonic acid diacetate, 96998-36-6; sodium (*R*)-mevalonate, 96949-03-0; potassium (*S*)-mevalonate, 96949-04-1; (*R*)-(−)-mevalolactone, 19115-49-2; (*S*)-(+)-mevalolactone, 19022-60-7; (4a*S*,7*R*,8a*R*)-4,4,7-trimethyl-4a,5,6,7,8,8a-hexahydro-1,3-benzoxathiane, 79618-03-4.

Synthesis of Natural (−)-Combretastatin[1]

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In 1982 we reported the isolation and crystal structure determination of (−)-combretastatin (**1**).[1b] Isolation of this substance from the South African tree *Combretum caffrum* (Eckl. Zeyh.) Kuntze was based upon its activity in reversing the differentiation of AC glioma cells into astrocytes; this represented the first isolation of a natural product guided by bioassay using the U.S. National Cancer Institute's (NCI) astrocyte reversal system (9ASK).[2] Subsequently, combretastatin was found to inhibit growth (in vitro) of the NCI P388 lymphocytic leukemia, cause a significant rise in the mitotic index of L1210 cells (evidence for an effective antimitotic agent), inhibit tubulin polymerization, stimulate tubulin-dependent GTP hydrolysis, and competitively inhibit the binding of colchicine (**2**) to tubulin.[3] The obvious need to obtain larger quantities of combretastatin for evaluation against key NCI in vivo antineoplastic systems led us to devise a convenient synthesis[4] of this interesting isovanillin derivative.

One of the most attractive synthetic routes to combretastatin involves coupling 3,4,5-trimethoxybenzaldehyde with a suitably substituted benzylic bromide using a

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(4) During the course of this investigation an eight-step synthesis (13% overall yield) was reported: Annapurna, G. S.; Deshpande, V. H. *Synth. Commun.* **1983**, *13*, 1075. We thank Dr. Deshpande for thoughtfully informing us of his interesting synthesis prior to publication.

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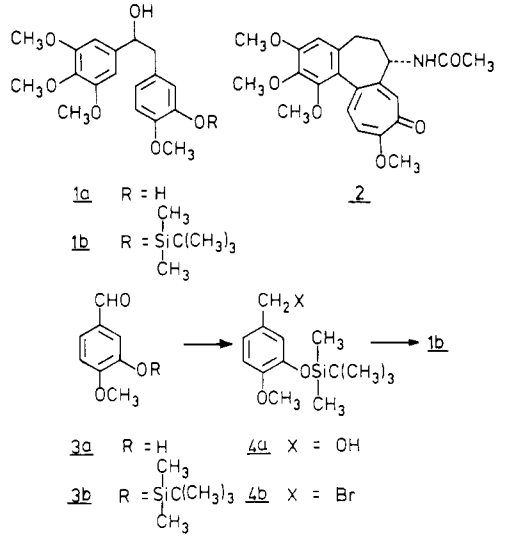
Barbier reaction.[5] Use of lithium in place of magnesium in the Barbier reaction usually leads to significantly improved yields except with benzyl halides where Wurtz coupling normally predominates.[6] We did not succeed in overcoming this difficulty with benzyl halides derived from *O*-methoxymethyl[7]-protected isovanillin (**3a**) or the lithium derivative prepared from the analogously blocked benzyl ether. Annapurna and Deshpande[4] were nicely able to circumvent these problems by coupling the lithium derivative of 3,4,5-trimethoxybenzaldehyde ethylene dithioacetal with the benzyl bromide from 3-(benzyloxy)-isovanillin. Eventually we were able to prepare the requisite benzyllithium intermediate using a very effective ultrasound procedure.[8] Once this problem was solved a very convenient synthesis of racemic combretastatin (**1**) in 29% overall yield was readily developed as follows.

After conversion of isovanillin **3a** to *tert*-butyldimethylsilyl ether[9] **3b** the aldehyde was reduced to benzyl alcohol **4a** by employing sodium borohydride. The most satisfactory means found for preparing benzyl bromide **4b** involved reaction with trimethylsilyl chloride and lithium bromide in dry acetonitrile[10] (52% yield from isovanillin). Lithium sand was allowed to react with benzyl bromide **4b** by using ultrasound[8] and the product was coupled with 3,4,5-trimethoxybenzaldehyde in 60% yield. Conversion of the product (**1b**) to (±)-combretastatin (**1a**) in 93% yield



(29.3% overall for the five steps) was achieved by utilizing tetrabutylammonium fluoride for cleaving the silyl ether. Isolation of (−)-combretastatin, identical with the natural product, was realized by resolution of the racemic silyl derivative **1b** on a column of covalently bonded *N*-(3,5-dinitrobenzoyl)-D-phenylglycine[11] followed by cleavage of the silyl ether.

The simple and efficient synthesis of natural (−)-combretastatin has now provided a good source for further biological studies, and comparisons of both enantiomers should provide a valuable insight into the importance of the chiral center. Present availability of both enantiomers should also allow the absolute configuration of combretastatin to be determined and this study is in progress. The ultrasound Barbier reaction is presently being applied to synthesis of combretastatin modifications to evaluate structure–activity relationships.

Experimental Section

The 3,4,5-trimethoxybenzaldehyde[12] was provided by OTSUKA Chemical Co., Ltd. Ether refers to diethyl ether, and all solvents were distilled. Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate. Column chromatographic separations were performed with 70–200-mesh silica gel supplied by E. Merck, Darmstadt. Thin layer chromatography was performed with silica gel GHLF and Alumina GF precoated (250 μm) plates, obtained from Analtech, Inc. The plates were visualized by ultraviolet light or developed with an anisaldehyde–sulfuric acid spray reagent.

All melting points are uncorrected and were observed by utilizing a Koefler-type melting point apparatus. Each new substance was colorless. Optical rotations were determined in chloroform solution with a Perkin-Elmer Model 241 polarimeter. Infrared spectra were recorded with a Nicolet MX-1 FT-IR spectrophotometer. The ^{1}H NMR spectra were measured on a Bruker WH-90 spectrophotometer by Dr. R. Nieman. All NMR spectra were recorded in deuteriochloroform solution, using tetramethylsilane as internal reference, and δ values are reported. Mass spectra were obtained on a MAT 312 spectrometer.

3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxybenzaldehyde (3b). Diisopropylethylamine (1.7 mL, 9.75 mmol) was added to a stirred solution of isovanillin (**3a**, 1.0 g, 6.5 mmol) in dimethylformamide (10 mL, under argon) followed by addition of *tert*-butyldimethylsilyl chloride (1.17 g, 7.8 mmol).[9] Before water (2 mL) was added, the reaction mixture was stirred at room temperature for 1 h. The mixture was stirred for 10 min, ether (30 mL) was added followed by saturated sodium bicarbonate solution, and stirring was continued for 15 min. The ether phase was separated, and the aqueous solution was again extracted with ether (20 mL). The combined ether extract was washed with brine (20 mL) followed by water (20 mL). Solvents were removed (reduced pressure) to afford silyl ether **3b** as a chromatographically homogeneous viscous oil (1.71 g, 95%): bp 170–175 °C (3 mm); IR (neat) ν_{max} 2956, 2931, 1693, 1596, 1509, 1442, 1434, 1281, 1133, 852 cm^{-1}; ^{1}H NMR 0.18 (s, 6 H, 2 × CH_3), 1.00 (s, 9 H, 3 × CH_3), 3.90 (s, 3 H, OCH_3), 6.96 (d, 1 H, J = 8 Hz, 5-H), 7.38 (d, 1 H, J = 2 Hz, 2-H), 7.50 (dd, 1 H, J = 8, 2 Hz, 6-H) ppm; EI mass spectrum, m/e 266 (M^+), 251, 209, 193 (base), 165, 137.

Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.12; H, 8.32. Found: C, 63.16; H, 8.43.

3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxybenzyl Alcohol (4a). To a solution of aldehyde **3b** (1.67 g, 6.3 mmol) in ethanol (20 mL) was added sodium borohydride (0.266 g, 7.0 mmol), and the mixture was stirred for 30 min. After completion of the reaction, water (5 mL) was added, and the solution was concentrated under reduced pressure. The concentrate was extracted with 2 N sodium hydroxide (5 mL) and the organic phase was extracted with ether (3 × 10 mL). The ether solution was washed with water (2 × 10 mL). Evaporation of the ethereal solution at reduced pressure furnished alcohol **4a** as a homogeneous (TLC) viscous oil (1.43 g, 85%): bp 180–90 °C (1.5 mm); IR (neat) ν_{max} 3350, 2955, 2930, 2858, 1512, 1287, 1271, 1256, 848, 840, 783, cm^{-1}; ^{1}H NMR 0.16 (s, 6 H, 2 × CH_3), 1.00 (s, 9 H, 3 × CH_3), 1.90 (br s, 1 H, OH, D_2O exchange), 3.80 (s, 3 H, OCH_3), 4.56 (s, 2 H, CH_2OH), 6.86 (br s, 3 H, Ar H) ppm; EI mass spectrum, m/e 268 (M^+), 253, 211, 196 (base), 167, 149, 114, 98.

Anal. Calcd for $C_{14}H_{24}O_3Si$: C, 62.64; H, 9.01. Found: C, 62.61; H, 9.21.

3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxybenzyl Bromide (4b). Trimethylsilyl chloride (1.17 mL, 9.2 mmol) was added to a vigorously stirred solution of lithium bromide (0.64 g, 7.4 mmol) in acetonitrile (15 mL) under argon.[10] After benzyl alcohol **4a** (1.0 g, 3.7 mmol) was added, the reaction mixture was stirred

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for 1 h. Progress of the reaction was monitored by TLC using hexane–ethyl acetate (1:1) as mobile phase. A solution of the reaction mixture in ether (40 mL) was washed successively with water (2 × 10 mL), saturated sodium bicarbonate (2 × 20 mL), 2 N sodium hydroxide (2 × 20 mL), and water (2 × 20 mL). Evaporation (reduced pressure) of the ether afforded benzyl bromide **4b** as a thermally unstable viscous oil, homogeneous by TLC, (0.8 g, 65%) [attempted purification by high vacuum distillation (160 °C; 10^{-4} mmHg) failed due to thermal decomposition]: IR (neat) ν_{max} 2956, 2931, 1512, 1291, 1272, 1256, 1140, 989, 848, 783 cm^{-1}; ^1H NMR 0.16 (s, 6 H, 2 × CH_3), 1.00 (s, 9 H, 3 × CH_3), 3.80 (s, 3 H, OCH_3), 4.44 (s, 2 H, CH_2), 6.7–7.0 (3 H, Ar H) ppm; EI mass spectrum, *m/e* 332, 330 (M^+), 315, 313, 275, 273, 251, 229, 214, 179, 149, 73 (base).

5-[(*tert*-Butyldimethylsilyl)oxy]-(±)-combretastatin (1b). Lithium sand (96.6 mg) in anhydrous tetrahydrofuran (10 mL) was treated under argon with ultrasound (bath, 150 W).[8] A mixture of benzyl bromide **4b** (0.76 g, 2.3 mmol) and 3,4,5-trimethoxybenzaldehyde (0.29 g, 1.5 mmol in 20 mL of tetrahydrofuran) was added (dropwise) followed by a small piece of sodium. Treatment of the reaction mixture with ultrasound was continued for 3 h. Progress of the reaction was monitored by TLC (1:1 hexane–ethyl acetate) by following disappearance of the benzyl bromide. The aldehyde and product showed the same R_f value. Excess lithium was removed by filtration (Celite), and the filtrate solvent was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (75 g) with a gradient of hexane–ethyl acetate (9:1 → 7:3) to give protected (±)-combretastatin **5** (0.40 g, 60%) as a very viscous oil: IR (neat) ν_{max} 3500, 2954, 2934, 1593, 1511, 1463, 1422, 1272, 1230, 1128, 840 cm^{-1}; ^1H NMR 0.14 (s, 6 H, 2 × CH_3), 1.00 (s, 9 H, 3 × CH_3), 2.90 (distorted d, 2 H, J = 6 Hz, CH_2), 3.78 (s, 3 H, OCH_3), 3.84 (s, 9 H, 3 × OCH_3), 4.85 (t, 1 H, J = 7.0 Hz, C*H*OH), 6.58 (s, 2 H, Ar H), 6.66–6.86 (3 H, Ar H).

Anal. Calcd for $C_{24}H_{36}O_6Si$: C, 64.25; H, 8.09. Found: C, 64.55; H, 8.25.

Racemic Combretastatin (1a). To a solution of silyl ether **1b** (0.23 g) in dry tetrahydrofuran (5 mL, stirred under argon) was added (dropwise) a 1 M tetrahydrofuran solution of tetrabutylammonium fluoride (2 mL, 2 mmol). After addition, a yellow color appeared immediately and reaction was complete within 10 min (indicated by TLC using 35:65 hexane–ethyl acetate). The reaction mixture was extracted with ether (25 mL) and the ethereal solution washed with water (2 × 10 mL). Evaporation of the ether yielded pure (±)-combretastatin (0.16 g, 93%) as an amorphous solid: mp 103–105 °C; IR (thin film) ν_{max} 3450, 2937, 1592, 1510, 1462, 1457, 1419, 1274, 1234, 1125, 650 cm^{-1}; ^1H NMR 2.85 (distorted AB system, 2 H CH_2), 3.78 (s, 12 H, 4 × OCH_3), 4.66 (dd, 1 H, J = 9, 5 Hz, -C*H*OH), 6.45 (s, 2 H), 6.52–6.75 (3 H, Ar H).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.67; H, 6.65.

Natural (−)-Combretastatin (1a). A semipreparative HPLC column was prepared by using the chiral adsorbent, Pirkle prep-10-DNBPG (D) [*N*-(3,5-dinitrobenzoyl)-D-phenylglycine bonded to silica, 10μm, irregular, supplied by Regis Chemical Co.], and slurry-packed (acetone–chloroform, 1:1) under high pressure (3000–6000 psi) in a stainless steel column (10 mm × 50 cm). The protected racemic combretastatin (**1b**) was found to have almost base-line resolution on a similar analytical column (4.6 mm × 25 cm, 5μm, supplied by Regis). Therefore, **1b** (700 mg) was dissolved in hexane–isopropyl alcohol (9:1, 5 mL) and applied to the semipreparative column in 0.5-mL aliquots. The resolution was performed by using hexane–isopropyl alcohol (9:1) as mobile phase at a flow rate of 2.5 mL per min. All the fractions were subjected to analytical HPLC and the enantiomerically pure early fractions from all ten aliquots were combined to yield the pure (−) enantiomer (83.1 mg, 24%): $[\alpha]^{25}_D$ −33.33°. The pure enantiomer was deprotected as with the racemic material to afford natural combretastatin (**1a**) displaying $[\alpha]^{25}_D$ −7.8 (*c* 0.51, $CHCl_3$), identical with the natural product $[\alpha]^{25}_D$ −8.5 (*c* 1.41, $CHCl_3$).[1b]

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Registry No. (−)-**1a**, 82855-09-2; (±)-**1a**, 89064-44-8; (±)-**1b**, 97315-17-8; (−)-**1b**, 97315-21-4; **3a**, 621-59-0; **3b**, 97315-18-9; **4a**, 97315-19-0; **4b**, 97315-20-3; 3,4,5-trimethoxybenzaldehyde, 86-81-7.

Palladium-Catalyzed Reaction of Organoalanes and Organozincs with α,β-Unsaturated Acetals and Ortho Esters as Conjugate Addition Equivalents[1]

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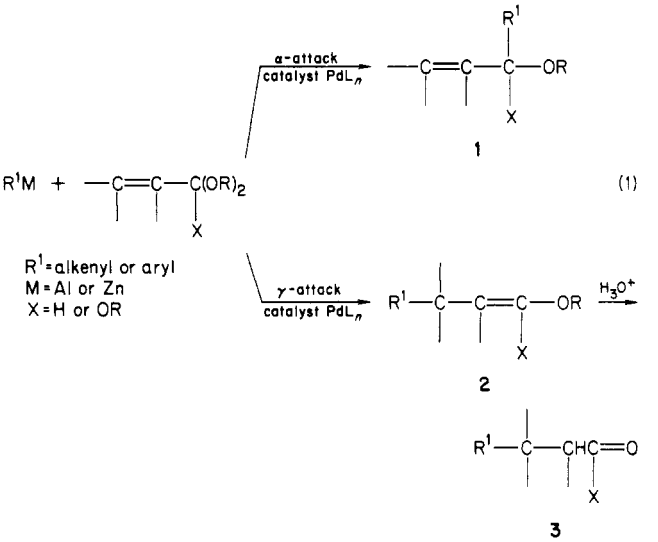
We have recently developed a Pd-catalyzed allylation of organoalanes and organozincs that proceeds with retention of regio- and stereochemistry of the allylic group.[3] Of particular interest is the fact that a wide variety of allylic electrophiles, such as those containing halogens, OAc, $OAlR_2$, $OPO(OR)_2$, and even $OSiR_3$, participate in the reaction.[3b] This finding prompted us to investigate the Pd-catalyzed reaction of organoalanes and organozincs with α,β-unsaturated acetals and ortho esters. In principle, the reaction may involve allylation in the α- and/or γ-position (eq 1). Since the products of γ-attack can be



hydrolyzed to give **3**, the overall transformation via γ-attack is equivalent to conjugate addition to α,β-unsaturated aldehydes or esters. Since conjugate addition of organometals to α,β-unsaturated aldehydes and esters, especially those that are β-unsubstituted, is prone to competitive polymerization of the α,β-unsaturated carbonyl derivatives

(1) Selective Carbon–Carbon Bond Formation via Transition Metal Catalysis. 41. Part 40: Negishi, E.; Miller, J. A.; Yoshida, T. *Tetrahedron Lett.* **1984**, *25*, 3407.

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