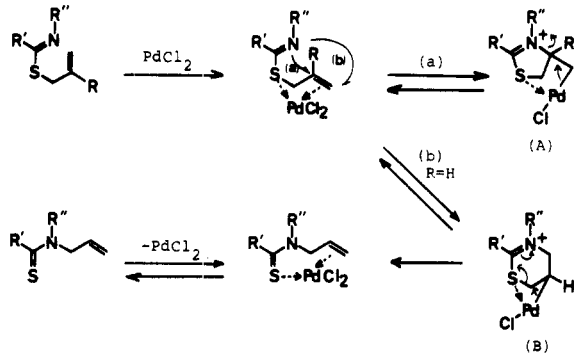
Scheme II



while in the presence of 1 mol% $PdCl_2(PhCN)_2$ the rearrangement attains completion by refluxing in THF for 24 h. With 1 equiv of $PdCl_2(PhCN)_2$ the rearrangement is complete within 1 h at room temperature and gives a precipitate of a 1:1 complex of $PdCl_2$ and **13**. Compound **13** can be isolated by treatment of the complex with excess pyridine. The technique of stabilization of the product by complex formation is successfully applied to the thermodynamically unfavorable rearrangement[11] of *S*-allyl-2-mercaptopyridine (**14**) to 1-allyl-2-thiopyridone (**15**).[12,13]

The following example is illustrative of the simplicity and utility of this catalytic reaction (entry 1). A THF (5 mL) solution of *S*-allyl-*N*-methylthiobenzimidate (1 mmol) and $PdCl_2(PhCN)_2$ (0.01 mmol) is refluxed under argon for 8 h. After evaporation of THF, the residue is subjected directly to a Kugelrohr distillation to give *N*-allyl-*N*-methylthiobenzamide in 81% yield [bp 150 °C (1.5 mmHg)].[14]

Acknowledgment. We are grateful for the partial support for this research from the Ministry of Education, the Japanese Government (Grant-in-Aid for Environmental Science No. 403022 and Grant-in-Aid for Scientific Research No. 475663).

Registry No. (*E*)-**1**, 75311-48-7; (*Z*)-**1**, 75311-49-8; **2**, 75311-50-1; **3**, 75311-51-2; (*E*)-**4**, 75311-52-3; (*Z*)-**4**, 75311-53-4; **5**, 75311-54-5; (*E*)-**6**, 75311-55-6; (*Z*)-**6**, 75311-56-7; **7**, 75311-57-8; **8**, 1558-77-6; **9**, 1558-74-3; **10**, 1558-78-7; **11**, 1558-76-5; **12**, 61076-81-1; **13**, 62139-89-3; **14**, 65063-38-9; **15**, 75332-11-5; **16**, 75311-58-9; $PdCl_2(PhCN)_2$, 14220-64-5; $PdCl_2(PPh_3)_2$, 13965-03-2.

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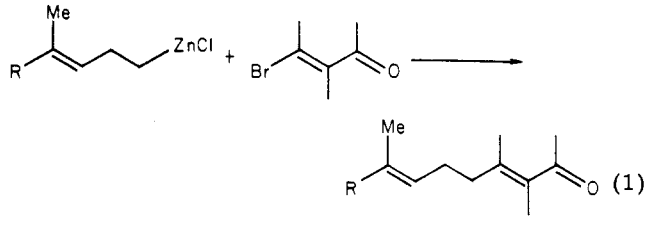
Received June 24, 1980

(11) Makisumi, Y.; Sasatani, T. *Tetrahedron Lett.* **1969**, 1975.
(12) For the Pt(II)-catalyzed rearrangement of 2-(allyloxy)pyridine to 1-allyl-2-pyridone, see: Stewart, A. F.; Seibert, R. P. *J. Org. Chem.* **1968**, *33*, 4560.
(13) 1-Allyl-2-thiopyridone (**16**) was freed from $PdCl_2$ by exposure to an excess pyridine and purified by column chromatography (50% yield). Application of heat to **16** (Kugelrohr distillation, 130 °C (6 mmHg)) caused complete isomerization to **14**.
(14) For entries 1–8, the products could be purified by a Kugelrohr distillation because the starting thioimidates showed much lower boiling points. The product **13** was purified by column chromatography on silica gel (benzene–EtOAc gradient).

A Palladium-Catalyzed Stereospecific Substitution Reaction of Homoallylzincs with β-Bromo-Substituted α,β-Unsaturated Carbonyl Derivatives. A Highly Selective Synthesis of Mokupalide[1]

Summary: Stereodefined homoallylzinc halides readily participate in a Pd-catalyzed stereospecific (≥98%) substitution reaction with β-bromo-substituted α,β-unsaturated carbonyl derivatives, thereby providing a highly stereoselective and efficient route to butenolides and furans of terpenoid origin, such as mokupalide (**1**) and dendrolasin (**2**).

Sir: We report that the Pd-catalyzed reaction of alkylzinc derivatives with alkenyl halides reported recently by us[2] can readily be adapted to effect the "conjugate substitution" reaction[3-5] of stereodefined homoallylzinc derivatives with β-halo-α,β-unsaturated carbonyl derivatives (eq 1). We further report that the reaction is well



suited for the selective synthesis of butenolides and furans of terpenoid origin, such as mokupalide[6] (**1**) and dendrolasin[7] (**2**).

(1) Selective Carbon–Carbon Bond Formation via Transition Metal Catalysis. 16. Controlled Carbometalation. 7. Part 6: M. Kobayashi, L. F. Valente, E. Negishi, W. Patterson, and A. Silveira, Jr., *Synthesis*, in press.
(2) (a) E. Negishi, L. F. Valente, and M. Kobayashi, *J. Am. Chem. Soc.*, **102**, 3298 (1980). For earlier publications on related reactions, see also the following: (b) S. Baba and E. Negishi, *J. Am. Chem. Soc.*, **98**, 6729 (1976); (c) N. Okukado, D. E. Van Horn, W. L. Klima, and E. Negishi, *Tetrahedron Lett.*, 1027 (1978); (d) E. Negishi, N. Okukado, A. O. King, D. E. Van Horn, and B. I. Spiegel, *J. Am. Chem. Soc.*, **100**, 2254 (1978); (e) A. O. King, N. Okukado, E. Negishi, *J. Chem. Soc., Chem. Commun.*, 683 (1977).
(3) In contrast to the conjugate addition reaction its substitution counterpart, i.e., substitution on the β carbon atom of α,β-unsaturated carbonyl and related derivatives ("conjugate substitution"), has not been well developed for widespread use as a method of carbon–carbon bond formation. The Cu-catalyzed or -promoted cross-coupling reaction of α,β-unsaturated carbonyl derivatives that are β-substituted with O,[4a-c] S,[4d,e] and halogen[4f-i] groups is promising.[5] Its current scope is, however, essentially limited to those cases where the groups displacing the β substituents are simple alkyl groups such as methyl and *n*-butyl.
(4) (a) C. P. Casey, D. F. Martin, and R. A. Boggs, *Tetrahedron Lett.*, 2071 (1973); (b) C. P. Casey and D. F. Martin, *Synth. Commun.*, **3**, 321 (1973); (c) S. Caechi, A. Caputo, and D. Misiti, *Indian J. Chem.*, **12**, 325 (1974); (d) G. H. Posner and D. J. Brunelle, *J. Chem. Soc., Chem. Commun.*, 907 (1973); (e) S. Kobayashi, H. Takei, and T. Mukaiyama, *Chem. Lett.*, 1097 (1973); (f) L. Decaux and R. Vessiere, *C. R., Hebd. Seances Acad. Sci.*, **267**, 738 (1968); (g) E. Piers and I. Nagakura, *J. Org. Chem.*, **40**, 2694 (1975); (h) E. Piers, I. Nagakura, and H. E. Morton, *ibid.*, **43**, 3630 (1978); (i) K. E. Harding and C. Tseng, *ibid.*, **43**, 3974 (1978).
(5) In addition to the organocopper reactions in ref 4 the following "conjugate substitution" reactions should also be noted. (a) Pd: for a review, see R. F. Heck, *Acc. Chem. Res.*, **12**, 146 (1979). (b) Mg: see, for example, R. Ramage and A. Satter, *J. Chem. Soc. D.*, 173 (1970). (c) B: G. A. Molander and H. C. Brown, *J. Org. Chem.*, **42**, 3106 (1977).
(6) (a) M. B. Yunker and P. J. Scheuer, *J. Am. Chem. Soc.*, **100**, 307 (1978); (b) F. W. Sum and L. Weiler, *ibid.*, **101**, 4401 (1979).
(7) (a) R. Bernardi, C. Cardani, D. Ghiringhelli, A. Selva, A. Baggini, and M. Pavan, *Tetrahedron Lett.*, 3893 (1967); (b) K. A. Parker and W. S. Johnson, *ibid.*, 1329 (1969); (c) A. F. Thomas and M. Ozainne, *J. Chem. Soc. C*, 220 (1970); (d) M. E. Garst and T. A. Spencer, *J. Am. Chem. Soc.*, **95**, 250 (1973); (e) K. Kondo and M. Matsumoto, *Tetrahedron Lett.*, 391 (1976); (f) S. Takahashi, *Synth. Commun.*, **6**, 331 (1976); (g) Y. Kojima, S. Wakita, and N. Kato, *Tetrahedron Lett.*, 4577 (1979).

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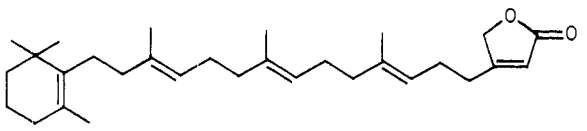

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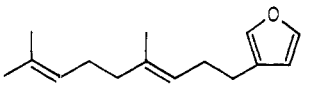
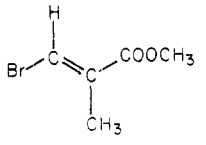
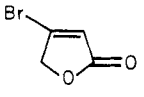


2

Development of this procedure required clarification of the following two points: (1) Can the Pd-catalyzed alkenyl–homoallyl coupling procedure be applied to those cases where the alkenyl halides are β-carbonyl substituted? (2) Can stereodefined homoallylzinc halides be used without undesirable stereochemical scrambling that can in principle occur via homoallyl–cyclopropylcarbinyl rearrangement? As indicated by entries 1 and 2 in Table I, no difficulty is encountered in coupling 3-butenylzinc chloride with either methyl (*E*)-3-bromo-2-methylpropenoate (**3**) or 4-bromo-2(5*H*)-furanone[8] (**4**). The stereospecificity observed



3



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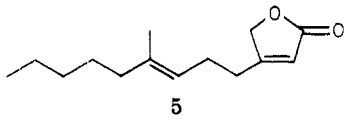


5

in the reaction with **3**, which is ≥98% *E*, is ≥97%. On the other hand, the use of stereodefined homoallylic derivatives requires careful control of the reaction conditions. After comparing several reaction conditions we have found that homoallylic bromides can be stereospecifically (≥98%) converted into the corresponding zinc derivatives by treating them first with magnesium turning in THF at 0–25 °C over 2–4 h and then with $ZnCl_2$ or $ZnBr_2$ at room temperature, although this procedure produces a minor amount (ca. 5%) of the homocoupled dimers of the homoallylic halides. This side reaction can be almost totally suppressed by treating the homoallylic halides with a mixture of magnesium and $ZnCl_2$ or $ZnBr_2$ in THF, as previously described.[2a] Unfortunately, the maximum stereospecificity observed under these conditions is 94% (at 0 °C to room temperature).

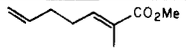
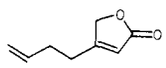
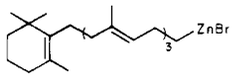
The following procedure for the preparation of 4-[(*E*)-4-methyl-3-nonenyl]-2(5*H*)-furanone (**5**) from [(*E*)-4-methyl-3-nonenyl]zinc bromide and **4** is representative. [(*E*)-4-Methyl-3-nonenyl]zinc bromide was prepared as follows. 1-Heptyne was first converted into (*E*)-4-methyl-3-nonen-1-ol in 78% yield via the Zr-catalyzed carboalumination–ate complexation–hydroxyethylation sequence reported by us recently.[1] The above-obtained alcohol was tosylated in pyridine at 0 °C and then treated with LiBr (acetone, room temperature) to produce (*E*)-1-bromo-4-methyl-3-nonene in 73% yield, based on the starting alcohol. To magnesium turnings (0.24 g, 10 mmol) and a small piece of iodine covered with 3 mL of THF were added at room temperature under nitrogen a few drops of methyl iodide and a small portion ($<^1/_{10}$) of the homoallylic bromide (1.10 g, 5 mmol) in 7 mL of THF. The remainder of the bromide was added dropwise over 1 h. After the reaction mixture was stirred at room temperature for a few additional hours, examination of an aliquot by iodine titration indicated that the desired Grignard reagent was formed in ca. 80% yield. The supernatant solution of the Grignard reagent was added at 0 °C to anhydrous $ZnBr_2$ (1.13 g, 5 mmol) dissolved in 5 mL of THF by using a double-tipped needle. After the reaction mixture was stirred for 30 min at 0 °C it was warmed to room temperature. To a Pd catalyst prepared by treating $Cl_2Pd(PPh_3)_2$ (105 mg, 0.15 mmol) suspended in 3 mL of THF with 0.30 mL (0.3 mmol) of 1.0 M *i*-Bu_2AlH in hexane[2] were added sequentially at 0 °C the organozinc reagent prepared from 2 mmol of the homoallylic bromide as described above and 489 mg (3 mmol) of **4** in 3 mL of THF. After the reaction mixture was stirred first at 0 °C (1 h) and then at room temperature (overnight) it was quenched with saturated aqueous NH_4Cl, extracted with *n*-hexane, washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Filtration and evaporation of volatile compounds produced **5** (~70% yield) which was ≥95% pure by GLC and ^1H NMR. The *E*/*Z* ratio as judged by the area ratio of the allylic methyl proton peaks at δ 1.50 and 1.62 in C_6D_6, respectively, was ≥98%. This conclusion was further supported by comparing the area ratio of the ^{13}C NMR signals at 121.67 and 122.35 ppm which have tentatively been assigned to the C-6 carbons of the *E* and *Z* isomers. A ≥98%-pure sample of **5** was readily obtained by merely passing the crude product through a short-path neutral alumina column (*n*-hexane/EtOAc, 9:1): exact mass calcd for $C_{14}H_{22}O_2$ 222.162, found 222.163; n^{23}_D 1.4852; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.87 (t, *J* = 7 Hz, 3 H), 1.0–1.5 (m, 6 H), 1.59 (s, 3 H), 1.8–2.1 (m, 2 H), 2.1–2.6 (m, 4 H), 4.71 (d, *J* = 1.8 Hz, 2 H), 4.95–5.2 (m, 1 H), 5.7–5.85 (m, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.05, 16.05, 22.57, 25.72, 27.58, 28.79, 31.53, 39.59, 73.18, 115.56, 121.67, 137.83, 170.44, 174.06; IR (neat) 1780 (s), 1750 (s), 1630 (m) cm^{-1}.

To demonstrate the utility of the "conjugate substitution" reaction in the natural products synthesis we chose mokupalide[6] (**1**) and butenolide **6**, which has previously been converted into dendrolasin[7f,9] (**2**), and synthesized them as follows. The synthesis of the trienyne **7** was previously described by us.[2a] Its conversion into first the tetraenol **8** (62%), then the bromotetraene **9** (80%), and finally mokupalide (**1**) (62%) was carried out in a manner similar to that described above for the synthesis of **5**. The stereoisomeric purity of **7** was ≥98%. Examination of the subsequent steps by ^1H and ^{13}C NMR indicates that each of these three steps is ≥98% stereospecific. Each product was purified merely by passage through a short-path column containing either Florisil or neutral alumina, mainly to remove any trace of metal-containing byproducts. The final product **1** was homogeneous on one- or two-dimensional TLC (R_f 0.53, benzene/EtOAc, 9:1; R_f 0.34, *n*-hexane/EtOAc, 4:1; R_f 0.24, *n*-hexane/dichloromethane, 1:4). Its spectral data summarized in Table I are in good agreement with the assigned structure as well as the data reported in the literature.[6] Based on the ^{13}C NMR spectrum we estimate that the overall stereoisomeric and regioisomeric purity of **1** obtained by us is ≥95%.

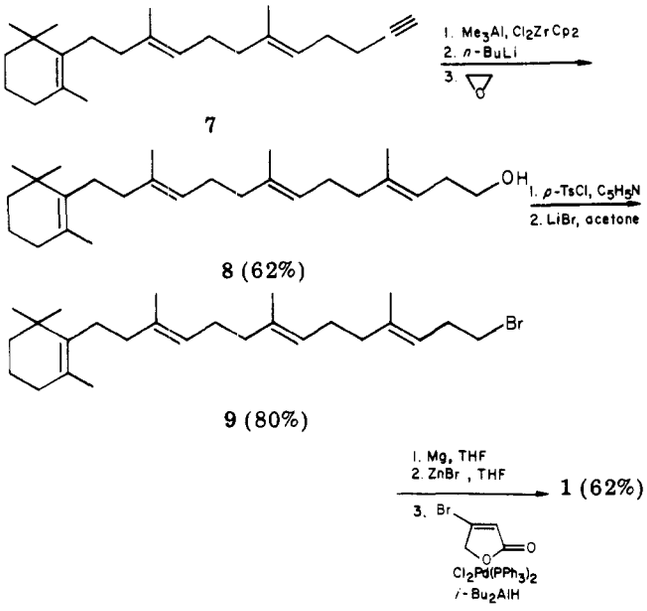
(8) The reagent **4** was prepared from propargyl alcohol via carbonation and addition of aqueous HBr: (a) R. Lespieau and P. L. Viguier, *C. R. Hebd. Seances Acad. Sci.*, 148, 419 (1909); (b) T. M. Mabry, *J. Org. Chem.*, 28, 1699 (1963).

(9) A more recent paper reports much more favorable results (85–95% yields) on the reduction of butenolides to the corresponding furans [J. E. McMurry and S. F. Donovan, *Tetrahedron Lett.*, 2869 (1977)] than those reported in ref 7f.

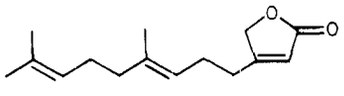
Table I. Pd-Catalyzed Reaction of Homoallylzinc Halides with β-Bromo-Substituted α,β-Unsaturated Carbonyl Derivatives

entry	homoallylzinc halide (RZnX) R	X	alkenyl halide	catalyst[a]	product[b]	% yield[c]
1	3-butenyl	Cl	3	A		62 (82)
2	3-butenyl	Cl	4	A		80 (94)
3	(*E*)-4-methyl-3-nonenyl	Br	4	B	5	69 (94)
4	(*E*)-4,8-dimethyl-3,7-nonadienyl	Cl	4	B	6[d]	55 (82)
5			4	B	1[e]	62

[a] A = $Pd(PPh_3)_4$, B = $Cl_2Pd(PPh_3)_2$ + 2 *i*-Bu_2AlH. [b] The elemental compositions of the products have been established by high-resolution mass spectrometry. All isolated products and intermediates exhibit satisfactory spectral data. [c] The numbers in parentheses are GLC yields. [d] n^{21}_D 1.5006; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.61 (s, 6 H), 1.68 (s, 3 H), 1.95–2.2 (m, with a peak at δ 2.01, 4 H), 2.2–2.5 (m, 4 H), 4.73 (d, J = 1.8 Hz), 4.9–5.3 (m, 2 H), 5.75–5.9 (m, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 16.16, 17.70, 25.69, 25.76, 26.56, 28.76, 39.64, 73.17, 115.66, 122.01, 124.01, 131.53, 137.54, 170.26, 174.06; IR (neat) 1780 (s), 1750 (s), 1630 (m) cm^{-1}. [e] n^{24}_D 1.5159; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.97 (s, 6 H), 1.1–2.5 (m, with peaks at δ 1.58, 1.60 and 2.00, 34 H), 4.69 (d, J = 1.8 Hz, 2 H), 4.95–5.2 (m, 3 H), 5.80 (m, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 16.06, 16.20, 19.62, 19.82, 25.77, 26.56, 26.65, 28.02, 28.67, 28.79, 32.81, 35.00, 39.73, 39.94, 40.36, 73.13, 115.66, 121.86, 123.62, 123.93, 126.89, 135.29, 135.98, 137.25, 137.64, 170.12, 174.01; IR (neat) 1780 (s), 1750 (s), 1640 (w) cm^{-1}.



In a very analogous manner **6** was synthesized in three steps from 2-methyl-2-hepten-6-yne via (*E*)-1-bromo-4,8-dimethyl-3,7-nonadiene (**10**). Here again no significant



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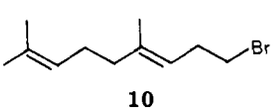

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amount (>2%) of the undesirable *Z* isomer is detectable in each step, and the overall procedure is estimated to be 97–98% stereoselective. The experimental results and the physical properties of these butenolides are summarized in Table I.

Acknowledgment is made to the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 1, 65717-88-6; 3, 40053-01-8; 4, 56634-50-5; 5, 75476-44-7; 6, 61315-76-2; 7, 74133-12-3; 8, 75476-45-8; 9, 75476-46-9; 10, 69405-35-2; 1-heptyne, 628-71-7; (*E*)-4-methyl-3-nonen-1-ol, 75476-47-0; (*E*)-4-methyl-3-nonen-1-ol tosylate, 75476-48-1; 3-butenylzinc chloride, 74133-07-6; (*E*)-4-methyl-3-nonenylzinc bromide, 75476-49-2; (*E*)-4,8-dimethyl-3,7-nonadienylzinc chloride, 75476-50-5; (*E,E,E*)-4,8,12-trimethyl-14-(2,6,6-trimethyl-1-cyclohexen-1-yl)tetradeca-3,7,11-trienylzinc bromide, 75476-51-6; methyl (*E*)-2-methylhepta-2,6-dienoate, 66052-31-1; 4-(3-butenyl)-2(5*H*)-furanone, 75476-52-7; (*E*)-1-bromo-4-methyl-3-nonene, 75476-53-8.

Supplementary Material Available: Physical and spectral data for methyl (*E*)-2-methylhepta-2,6-dienoate, 4-(3-butenyl)-2(5*H*)-furanone, (*E*)-1-bromo-4-methyl-3-nonene, (*E*)-1-bromo-4,8-dimethyl-3,7-nonadiene, (*E,E,E*)-4,8,12-trimethyl-14-(2,6,6-trimethyl-1-cyclohexen-1-yl)-tetradeca-3,7,11-trien-1-ol, and (*E,E,E*)-1-bromo-4,8,12-trimethyl-14-(2,6,6-trimethyl-1-cyclohexen-1-yl)tetradeca-3,7,11-triene (2 pages). Ordering information is given on any current masthead page.

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Synthesis of 1,3-Diazepin-2-one Nucleosides as Transition-State Inhibitors of Cytidine Deaminase. 2[1]

Summary: Syntheses of the novel seven-membered-ring (±)-5-hydroxy-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-one (**8**) and its 1-β-D-ribofuranosyl nucleosides **4a** and **4b** have been accomplished by adaptation of the transpositional allylic oxidation procedure following the electrophilic ad-

(1) Presented in part at the 179th National Meeting of the American Chemical Society, Houston, TX, March 1980, Division of Carbohydrate Chemistry, paper no. 14.