workers[12] led to *N*-(*tert*-butyloxycarbonyl)glutamic acid, which was purified and characterized via its bis(dicylohexylammonium) salt.[13] Deprotection with trifluoroacetic acid afforded free glutamic acid, which was isolated by ion-exchange chromatography and recrystallized from aqueous ethanol: $[\alpha]^{20}_D$ −30.0°, 2% in 5 N HCl, [reported[14,15] for natural L-glutamic acid: $[\alpha]^{25}_D$ +31.8°, 2% in 5 N HCl].

As summarized above, levorotatory 2-amino-4-phenylbutyric acid was converted in three steps to levorotatory glutamic acid, which corresponds to unnatural D-glutamic acid.[14,15] This result is consistent with the assignment originally made by du Vigneaud[3] and later supported by Dirkx and Sixma.[5] It is thus clearly established that the absolute configuration of levorotatory 2-amino-4-phenylbutyric acid corresponds to that of the unnatural D-amino acids and the dextrotatory isomer to the natural L series.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian XL-100A or JEOL FX-60Q spectrometer and are reported in δ units, using tetramethylsilane as standard. IR spectra were recorded on a Perkin-Elmer 621 spectrometer. Mass spectra were recorded on an AEI MS-9 mass spectrometer. Melting points were recorded on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter using a 1-dm path length. Except acetonitrile, which was distilled from calcium hydride before use, all solvents and reagents were of reagent grade and were used without further purification.

Preparation of (−)-*N*-(*tert*-Butyloxycarbonyl)-2-amino-4-phenylbutyric Acid (2). To a solution of (−)-2-amino-4-phenylbutyric acid[11] (7.9 g, 44 mmol; $[\alpha]^{20}_D$ −43°, 2% in 1 N HCl) in *tert*-butyl alcohol (40 mL) containing 5.5 M aqueous sodium hydroxide solution (8 mL) at 25 °C was added a solution of di-*tert*-butyl dicarbonate (9.6 g, 44 mmol) in *tert*-butyl alcohol (10 mL) over a period of 10 min. The resulting mixture was stirred at 25 °C for 24 h, after which water and pentane were added, and the mixture was filtered. The aqueous layer was separated, washed with pentane, and acidified with 5% aqueous potassium hydrogen sulfate. The solution was extracted four times with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate, and concentrated to give **2** as a viscous oil (6.4 g, 52%): ^{13}C NMR ($CDCl_3$) δ 176.6, 157, 140.6, 128.3, 126.0, 80, 55, 33.9, 31.5, 28.1; ^{1}H NMR ($CDCl_3$) δ 7.1–7.3 (5 H, m, aromatic H), 5.1 (1 H, NH), 4.3 (1 H, m, CH), 2.7 (2 H, t, $PhCH_2$), 2.1 (2 H, m, $CHCH_2CH_2$), 1.45 (9 H, s, $C(CH_3)_3$); IR ($CHCl_3$) 1715 cm^{-1}; mass spectrum, *m/e* 279; $[\alpha]^{20}_D$ −5.6° (*c* 2, ethanol). A salt was prepared from **2** (490 mg) and dicyclohexylamine (350 μL) in ether: mp 153.5–154.5 °C after recrystallization from acetonitrile. Anal. Calcd for $C_{27}H_{44}N_2O_4 \cdot 0.25H_2O$: C, 69.71; H, 9.64; N, 6.02. Found: C, 69.63; H, 9.44; N, 5.99.

Preparation of (−)-*N*-(*tert*-Butyloxycarbonyl)glutamic Acid (3). To a mixture of **2** (5.2 g, 18.6 mmol), sodium metaperiodate (70 g, 0.33 mol), carbon tetrachloride (80 mL), acetonitrile (80 mL), and water (120 mL) was added ruthenium trichloride hydrate (130 mg, 0.5 mmol). The resulting mixture was stirred at 25 °C for 21 h, after which it was diluted with water (500 mL) and ethyl acetate (500 mL) and filtered. The filtrate was separated and the aqueous layer was extracted four more times with ethyl acetate. The organic layers were combined and extracted three times with 10% aqueous sodium bicarbonate solution. The aqueous extracts were then acidified with 5% potassium hydrogen sulfate solution and extracted three times with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and concentrated to give a foamy solid (2.0 g), which was chromatographed on Silicar CC4 (Mallinckrodt, chloroform to ethyl acetate elution gradient) to give **3** as a clear, viscous oil (900 mg, 19%). A salt was prepared from dicyclohexylamine and recrystallized twice from ethanol/ether (900 mg, 8%): mp 172–173 °C; $[\alpha]^{20}_D$ −7° (*c* 1, CH_3OH) [lit. for the naturally occurring L isomer:[13] mp 171–172 °C; $[\alpha]_D$ + 9.1° (*c* 1, CH_3OH)]. Anal. Calcd for $C_{38}H_{63}N_3O_6 \cdot 0.5H_2O$: C, 65.98; H, 10.42; N, 6.79. Found: C, 66.10; H, 10.27; N, 6.77.

The free acid was liberated from the salt by dissolution in 5% aqueous potassium hydrogen sulfate and extraction with ethyl acetate: ^{13}C NMR (CD_3OD) δ 176.4, 175.6, 157.8, 80.6, 55, 31.1, 28.7, 28.1; $[\alpha]^{20}_D$ +13.2° (*c* 1, CH_3OH) [lit.[13] $[\alpha]_D$ −16.1° (*c* 1, CH_3OH) for the naturally occurring L isomer].

Preparation of (−)-Glutamic Acid (4). A solution of **3** (free acid, derived from 900 mg of the bis(dicyclohexylammonium) salt as described above) in trifluoroacetic acid was stirred at 25 °C for 1 h, after which it was concentrated by rotary evaporation. The residue was dissolved in water and applied to a column of excess AG50W × 2 ion-exchange resin (proton form). The column was eluted with water to remove trifluoroacetic acid and then with 5% aqueous pyridine. Fractions were monitored with ninhydrin spray reagent; those giving a positive stain were combined and concentrated. The residue was recrystallized to give (−)-glutamic acid (109 mg, 50%): $[\alpha]^{20}_D$ −30.0° (*c* 2, 5 N HCl) [lit.[14,15] $[\alpha]^{25}_D$ +31.8° (*c* 2, 5 N HCl) for the naturally occurring L isomer]. The synthetic material was identical with an authentic sample: ^{1}H NMR, IR, TLC, melting point.

Acknowledgment. We thank Dr. Jollie D. Godfrey for helpful discussions during the course of this work. Spectra and microanalyses were determined through the courtesy of the Department of Analytical Chemistry of the Squibb Institute.

Registry No. 1, 82795-51-5; 2, 82732-07-8; 3, 34404-28-9; 4, 6893-26-1; $(Boc)_2O$, 24424-99-5; 3·2$(C_6H_{11})_2NH$, 82732-08-9.

(12) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(13) Schroder, E.; Klieger, E. *Chem. Ber.* **1964**, *673*, 196.
(14) Greenstein, J. P.; Winitz, M. "Chemistry of the Amino Acids"; Wiley: New York, 1961; Vol. 3, p 1929.
(15) The specific rotation of D-glutamic acid has been reported as $[\alpha]^{20}_D$ −31.7° in 1.7 N HCl: Camien, M. N.; McClure, L. E.; Dunn, M. S. *Arch. Biochem.* **1950**, *28*, 220.

Palladium-Catalyzed Reactions of Allylic Electrophiles with Organometallic Reagents. A Regioselective 1,4-Elimination and a Regio- and Stereoselective Reduction of Allylic Derivatives[1]

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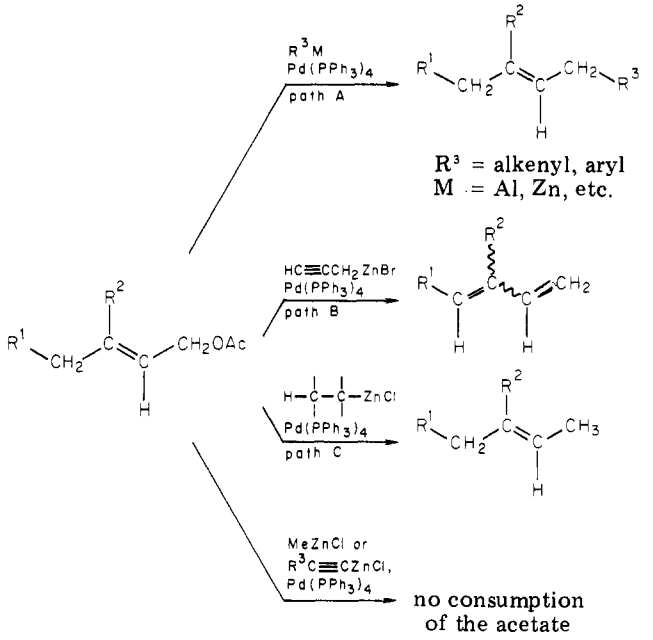
Palladium complexes have been shown to be effective catalysts in the cross-coupling reaction[3] of allylic electrophiles with alkenyl- or arylmetals containing Al,[4] B,[5] Hg,[6] Mg,[7] Si,[8] Sn,[4] and Zr,[4,9] as well as allylmetals containing Na[10] and Sn.[11] In addition, a few Pd-promoted stoi-

(1) Some preliminary results were presented in the 1st IUPAC Symposium on Organometallic Chemistry Directed toward Organic Synthesis, Fort Collins, CO, Aug 2–6, 1981.
(2) On leave from the Japan Tobacco & Salt Public Corp.
(3) For reviews of the Pd-catalyzed cross coupling, see: (a) Negishi, E. In "Aspects of Mechanism and Organometallic Chemistry"; Brewster, J. H., Ed.; Plenum: New York, 1978; p 285. (b) Negishi, E., submitted for publication in *Acc. Chem. Res.*
(4) (a) Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882. (b) Negishi, E.; Chatterjee, S.; Matsushita, H. *Tetrahedron Lett.* **1981**, *22*, 3737. (c) Matsushita, H.; Negishi, E., *J. Chem. Soc., Chem. Commun.* **1982**, 160.
(5) Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865.
(6) (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531. (b) Larock, R. C.; Bernhardt, J. C.; Driggs, R. J. *J. Organomet. Chem.* **1978**, *156*, 45.
(7) Okamura, H.; Takei, H. *Tetrahedron Lett.* **1979**, 3425.
(8) Yoshida, J.; Tamao, K.; Takahashi, M.; Kumada, M. *Tetrahedron Lett.* **1978**, 2161.
(9) Hayashi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* **1981**, *22*, 2629.

0022-3263/82/1947-4161$01.25/0

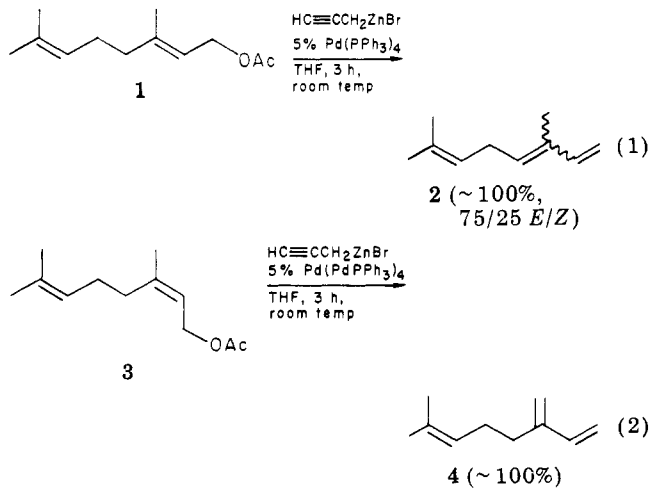
Scheme I



chiometric reactions involving Mg,[12] Cd,[12] and Zr[13] have also been reported within the past few years. Prompted by our own favorable results[4] obtained with alkenyl and aryl derivatives containing Al, Zn, and Zr, we examined the Pd-catalyzed reaction of allylic electrophiles with other types of organometallics containing these metals.

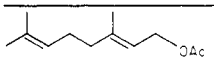
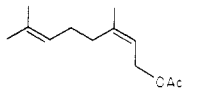
We now report that, in addition to the cross coupling (path A) observed with alkenyl-, aryl-, or allylmetals,[4-11] the Pd-catalyzed reaction of allylic electrophiles with organometallics can selectively follow at least the following three distinct paths: (i) a regioselective 1,4-elimination (path B), (ii) a regio- and stereoselective reduction (path C), and (iii) inhibition of the 1,4-elimination (Scheme I).

Most noteworthy from the synthetic viewpoint is the essentially 100% regioselective 1,4-elimination reaction of allylic acetates with propargylzinc bromide catalyzed by $Pd(PPh_3)_4$. Specifically, geranyl acetate (1) is converted into ocimene (2) in essentially quantitative yield to the exclusion of myrcene (<1%) (eq 1), while neryl acetate (3)



gives only myrcene in quantitative yield (eq 2). No products are formed in the absence of $Pd(PPh_3)_4$, indicating that these reactions are indeed catalyzed by the Pd complex. Although the conversion of allylic acetates into conjugated dienes under the influence of Pd complexes is a known reaction,[14,15] it is nonregioselective under the reported reaction conditions.

Table I. Palladium-Catalyzed 1,4-Elimination of Allylic Acetates[a]

allylic acetate	basic reagent added	time, h	product yield,[b] % 2	4
	none	48	74	26
	none[c]	1	40	60
	$HC{\equiv}CCH_2ZnBr$	3	100[d]	0
	NEt_3	48	33	41
	Dabco[e]	48	44	56
	$NaNH_2$	48	28	63
	none[c]	1	26	74
	$HC{\equiv}CCH_2ZnBr$	3	0	100

[a] Unless otherwise mentioned, the reaction was run at room temperature in THF in the presence of 5 mol % of $Pd(PPh_3)_4$. [b] By GLC. [c] These results were reported in ref 14 and are included for comparison. The reaction was run in refluxing dioxane in the presence of 1% of $Pd(OAc)_2$ and 10% of PPh_3. [d] E/Z ratio of 75/25. [e] Dabco = 1,4-diazabicyclo[2.2.2]octane.

Interestingly, the above 1,4-elimination reaction, that can also proceed slowly even in the absence of an organometallic reagent, is totally inhibited at room temperature by using 1 equiv of either MeZnCl or (1-octynyl)zinc chloride in place of propargylzinc bromide. Under these conditions no consumption of geranyl acetate occurs within 24 h. Neither the role of propargylzinc bromide in the regioselective 1,4-elimination nor the mechanism of its inhibition by MeZnCl or (1-octynyl)zinc chloride is clear at the present time.[16] To further delineate the scope of the regioselective 1,4-elimination as well as to search for more obvious reagents for the 1,4-elimination, we have tested a few representative amine bases, i.e., NEt_3, Dabco, and $NaNH_2$, and other types of organozinc derivatives. However, the remarkably high regioselectivity observed with propargylzinc bromide has not so far been matched by any other basic reagents (Table I). The reaction of benzylzinc bromide with geranyl acetate in THF in the presence of 5 mol % of $Pd(PPh_3)_4$ is sluggish at room temperature and gives, after 48 h, only an unidentified product, presumably the cross-coupled product, in low yield without producing 2 and/or 4. Somewhat surprisingly, the corresponding reaction of benzylzinc bromide with 2-cyclohexenyl acetate is much faster and cleanly produces 3-benzyl-1-cyclohexene in 88% yield within 3 h at room temperature. The Pd-catalyzed reaction of allylzinc halides with geranyl acetate does not produce, after 24 h at room temperature, 2 and/or 4 in any significant yields (<5%).

The Pd-catalyzed reaction of allylic acetates with alkylzinc derivatives containing β-hydrogens takes an entirely different reaction path (path C). Thus, the reaction of geranyl acetate with *n*-butylzinc chloride in the presence of 5 mol % of $Pd(PPh_3)_4$ gives a 94:6 mixture of the *E* and *Z* isomers of 2,6-dimethyl-2,6-octadiene (5) in 96% yield

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(11) (a) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595. (b) Stille, J. K.; Goldschalx, J. *Ibid.* **1980**, *21*, 2599.
(12) Castanet, Y.; Petit, F. *Tetrahedron Lett.* **1979**, 3221.
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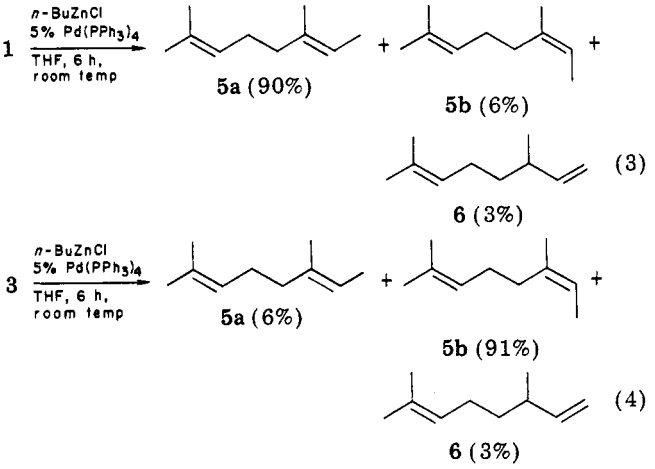
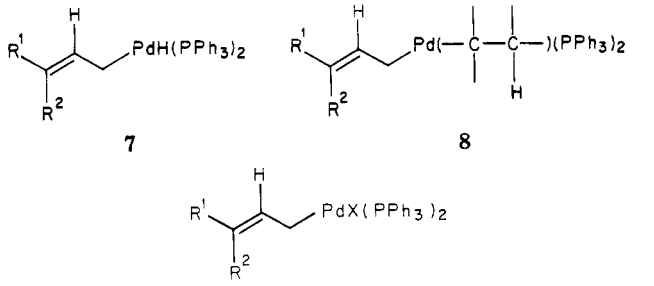
(16) A study directed toward clarification of these aspects of the reaction is underway.

along with its regioisomer, 3,7-dimethyl-1,6-octadiene (6, 3%). In an analogous manner, neryl acetate is reduced to 5 (E/Z ratio of 6/94) and 6 in 97% and 3% yields, respectively (eq 3 and 4). Although Pd-catalyzed reductions of 1 and 3 have been recently reported,[17,18] these reactions are nonspecific.



Interestingly, the regiospecificity of the reduction is very much dependent on the nature of the alkyl group of an organometallic reagent. As the results summarized in Table II indicate, the specificity decreases in the following order: n-BuZnCl > i-BuZnCl > sec-BuZnCl > t-BuZnCl. These results appear to be inconsistent with the intermediacy of palladium hydride species such as 7. However, the reaction may well proceed via 8 and/or 9.



The Pd-catalyzed reduction of geranyl derivatives containing Cl and OTs groups with n-BuZnCl also proceeds well, producing 5 in 96–97% yields with 94–95% stereospecificity along with 2–3% of 6. Very similar results are observed in the reduction of geranyl chloride with $LiBEt_3H$ in the absence of a Pd catalyst. However, $LiBEt_3H$ fails to reduce cleanly either the acetate or the tosylate even in the presence of $Pd(PPh_3)_4$. While the scope of the Pd-catalyzed reduction with n-BuZnCl is yet to be explored, the high regio- and stereospecificity observed with geranyl and neryl derivatives is highly encouraging.

Experimental Section

All palladium-catalyzed reactions were run under an atmosphere of nitrogen. Tetrakis(triphenylphosphine)palladium was prepared as described in the literature.[19] Geranyl acetate [bp 128–130 °C (20 mm), lit.[20a] bp 128–130 °C (21 mm)], neryl acetate [bp 105–106 °C (10 mm), lit.[20b] bp 93–94 °C (3 mm)], and 2-cyclohexenyl acetate [bp 68–70 °C (12 mm), lit.[21] bp 68–71 °C (12 mm)] were prepared by treating the corresponding alcohols with acetic anhydride in pyridine. Geranyl chloride was prepared as described in the literature.[22] Geranyl tosylate was generated in situ by treating at −78 °C geraniol with 1 equiv of n-butyllithium followed by addition of 1 equiv of p-toluenesulfonyl chloride in THF. The resultant mixture was used without further purification. Geraniol and nerol were obtained from Aldrich Chemicals and Albany International Chemicals, respectively. Their stereo- and regioisomeric purities were ≥99% by ^{13}C NMR.

Myrcene (4). Reaction of Neryl Acetate with Propargyl Bromide under the Influence of Tetrakis(triphenylphosphine)palladium. The following procedure is representative of the 1,4-elimination reaction of allylic acetates catalyzed by $Pd(PPh_3)_4$. To 0.587 g (0.50 mmol) of $Pd(PPh_3)_4$ and 1.96 g (10 mmol) of neryl acetate in 10 mL of THF is added propargylzinc bromide[23] prepared from 0.784 g (12 mmol) of zinc powder and 1.43 g (12 mmol) of propargyl bromide in 20 mL of THF. The reaction mixture was stirred for 3 h at room temperature and was then sequentially treated with pentane, 3 N HCl, water, aqueous $NaHCO_3$, and water. After drying the organic layer over $MgSO_4$, distillative workup gives 1.23 g (90% yield) of myrcene (4): bp 75–76 °C (32 mm) [lit.[24] 93 °C (70 mm)]; n^{24}_D 1.4691 (lit.[24] n^{20}_D 1.4692); IR (neat) 3090 (m), 1595 (s), 1375 (m), 1108 (w), 990 (m), 903 (sh), 889 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.61 (d, J = 1.5 Hz, 3 H), 1.70 (s, 3 H), 2.22 (br s, 4 H), 4.9–5.4 (m with peaks at 5.02, 5.14, and 5.34, 5 H), 6.42 (dd, J = 10, 17 Hz, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 17.67, 25.69, 27.05, 31.75, 112.85, 115.57, 124.48, 131.50, 139.25, 146.33.

The GLC yield determined in a separate run using a hydrocarbon internal standard was 100%. The amount of ocimene determined by GLC was <1%.

Ocimene (2). Conversion of geranyl acetate into a 75:25 mixture of (E)- and (Z)-ocimene was carried out in a manner similar to that described above for the preparation of myrcene. The product yielded the following data: yield by isolation 77%; bp 75–76 °C (28 mm) [lit.[25] bp 63 °C (10 mm)]; IR (neat) 1640 (m), 1375 (m), 1108 (m), 985 (s), 898 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.55–1.9 (m with peaks at 1.62, 1.67, 1.75, and 1.80, 9 H), 2.84 (t, J = 7 Hz, 2 H), 4.8–5.5 (m, 2 H), 6.35 (dd for the Z isomer, J = 11, 18 Hz, 0.25 H), 6.80 (dd for the E isomer, J = 11, 18 Hz, 0.75 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 11.64, 17.70, 19.75, 25.66, 26.59, 27.46, 110.48, 113.44, 122.44, 122.78, 129.67, 131.76, 131.86, 132.05, 133.78, 141.67.

In a separate run, the GLC yield was found to be 100%. Formation of myrcene was not detected by GLC.

Reaction of Geranyl Acetate with Tetrakis(triphenylphosphine)palladium. This reaction was carried out in THF by using 5 mol % of $Pd(PPh_3)_4$ at room temperature in the absence of any basic reagent. The reaction mixture was analyzed by GLC (SE-30), and the reaction was essentially complete after 48 h. The results are summarized in Table I.

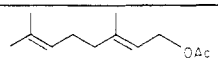
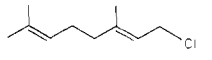
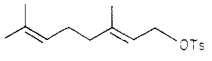
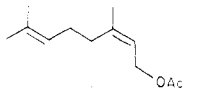
Reactions of Geranyl Acetate with Basic Reagents under the Influence of Tetrakis(triphenylphosphine)palladium. These reactions were carried out in a manner similar to that described for the preparation of myrcene, and the results are summarized in Table I and briefly described below.

(a) With Methylzinc Chloride or 1-Octynylzinc Chloride. After 24 h at room temperature, essentially 100% of geranyl acetate was recovered unchanged in either case. Methylzinc chloride and 1-octynylzinc chloride were generated in situ by treating methyllithium and 1-octynyllithium, respectively, with 1 equiv of freshly dried zinc chloride and were used without purification.

(b) With Triethylamine, Dabco, or Sodium Amide. Geranyl acetate was treated with 1 equiv of a base in the presence of 5 mol % of tetrakis(triphenylphosphine)palladium. The results are summarized in Table I.

(17) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613.
(18) Hutchins, R. O.; Learn, K.; Fulton, R. P. *Tetrahedron Lett.* **1980**, *21*, 27. In a private communication, Professor Hutchins has informed us of some of their more recent results displaying a much higher degree of regio- and stereospecificity.
(19) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
(20) (a) Knights, J.; Waight, E. S. *J. Chem. Soc.* **1955**, 2830. (b) Sornet, R. *Rev. Quim. Ind. (Rio de* Janeiro) **1930**, *204*, 98.
(21) Bedos, P.; Ruyer, A. *C. R. Hebd. Seances Acad. Sci.* **1937**, *204*, 1350.
(22) Calzada, J. G.; Hooz, J. *Org. Synth.* **1974**, *54*, 63.
(23) Gaudemar, M. *C. R. Hebd. Seances Acad. Sci.* **1957**, *245*, 2054.
(24) Ohloff, G.; Seible, J.; Kovats, E. *Justus Liebigs Ann. Chem.* **1964**, *675*, 83.
(25) Sutherland, M. D. *J. Am. Chem. Soc.* **1952**, *74*, 2688.

Table II. Palladium-Catalyzed Allylic Deoxygenation and Dehalogenation[a]

allylic derivative	hydride source	% $Pd(PPh_3)_4$	time, h	product yield,[b] % 5	6
	*n*-BuZnCl	5	6	96[c] (78)	3
	i-BuZnCl	5	6	95	5
	sec-BuZnCl	5	6	45	55
	t-BuZnCl	5	6	26	36[d]
	$LiBEt_3H$	5	3	33	trace[d]
	$LiBEt_3H$	0	3	trace	[e]
	*n*-BuZnCl	5	3	96[c] (79)	3
	$LiBEt_3H$	0	3	98	2
	i-Bu_2AlH	5	1	60	38
	*n*-BuZnCl	5	3	97	2
	$LiBEt_3H$	5	3	90	4
	$LiBEt_3H$	0	3	64	2[f]
	*n*-BuZnCl	5	6	97[g] (87)	3

[a] All reactions were run at room temperature in THF. [b] By GLC. The numbers in parentheses are isolated yields. [c] *E*/*Z* ratio of 94/6. [d] Other unidentified products were detected by GLC. [e] The amount of geranyl acetate remaining unreacted was 50%. No other major GLC peaks were discernible. [f] Geraniol was formed in 32% yield. [g] *E*/*Z* ratio of 6/94.

Reaction of 2-Cyclohexenyl Acetate with Benzylzinc Bromide under the Influence of Tetrakis(triphenylphosphine)palladium. 3-Benzyl-1-cyclohexene. To a 100-mL flask equipped with a septum inlet, a magnetic stirring bar, and an outlet connected to a mercury bubbler were introduced 0.578 g (0.5 mmol) of tetrakis(triphenylphosphine)palladium and 1.40 g (10 mmol) of 2-cyclohexenyl acetate in 10 mL of dry THF. To this was added benzylzinc bromide[26] prepared by treating 1.88 g (11 mmol) of benzyl bromide with 0.72 g (11 mmol) of zinc powder. After the mixture had been stirred for 3 h at room temperature, it was sequentially treated with pentane, 3 *N* HCl, water, aqueous $NaHCO_3$, water, and $MgSO_4$. Distillative workup gave 1.52 g (88% yield) of 3-benzyl-1-cyclohexene: bp 69–70 °C (0.18 mm) [lit.[27] bp 130–135 °C (20 mm)]; n^{25}_D 1.5279; IR (neat) 1610 (w), 1495 (m), 1455 (m), 910 (m), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.1–2.7 (m, 9 H), 5.4–5.8 (m with a peak at 5.60, 2 H)8 7.0–7.4 (m with peaks at 7.18 and 7.20, 5 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.30, 25.40, 28.93, 37.21, 42.75, 125.78, 127.35, 128.16, 129.16, 131.35, 140.92.

Reaction of Geranyl Acetate with Benzylzinc Bromide under the Influence of Tetrakis(triphenylphosphine)palladium. This reaction was carried out in a manner similar to that described above for the preparation of 3-benzyl-1-cyclohexene. Somewhat unexpectedly, the reaction was complete after 48 h only to the extent of 25%, as judged by the amount of geranyl acetate remaining unreacted. One unidentified product, presumably 2,6-dimethly-9-phenyl-2,6-nonadiene, was detected by GLC.

Reactions of Geranyl Acetate with Alkylzinc Chlorides in the Presence of Tetrakis(triphenylphosphine)palladium. The following procedure involving the use of *n*-butylzinc chloride is representative of the reaction of geranyl acetate with an alkylzinc chloride.

To a 100-mL flask equipped with a septum inlet, a magnetic stirring bar, and an outlet connected to a mercury bubbler was placed 2.73 g (20 mmol) of zinc chloride. After thoroughly drying zinc chloride at reduced pressure at 50–60 °C, the reaction system was filled with nitrogen. To this were added sequentially at 0 °C THF (10 mL), a 2.4 *M* solution of *n*-butyllithium (8.34 mL, 20 mmol) in hexane, and a freshly prepared mixture of geranyl acetate (3.93 g, 20 mmol) and tetrakis(triphenylphosphine)palladium (1.16 g, 1 mmol) in 10 mL of THF. The reaction mixture was allowed to warm to room temperature and was stirred for 6 h, at which time GLC examination of a small aliquot (<0.2 mmol) indicated that the reaction was essentially complete. The reaction mixture was treated with 3 *N* HCl and extracted with ethyl ether. The organic layer was separated, washed with water, aqueous $NaHCO_3$, and water and dried over $MgSO_4$. After evaporation of volatile substances at reduced pressure, the concentrated mixture was passed through a short (8–10 in.) silica gel column to remove traces of palladium-containing compounds, if any. Distillation yielded 2.15 g (78%) of 2,6-dimethyl-2,6-octadiene (**5**) contaminated with 3% of 3,7-dimethyl-1,6-octadiene (**6**). The ^{13}C NMR spectrum indicates that the *E*/*Z* ratio is 94/6. This sample yielded the following data: bp 74–75 °C (32 mm) [lit.[28] bp 75 °C (30 mm)]; IR (neat) 1665 (w), 1445 (s), 1380 (s), 820 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.5–1.75 (m with peaks at 1.55, 1.60, and 1.68, 12 H), 2.02 (br s, 4 H), 4.95–5.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.33, 15.67, 17.62, 25.70, 27.05, 40.03, 118.45, 124.75, 131.09, 135.74. In addition to these peaks, those assignable to the *Z* isomer and **6** were also discernible. In a separate run, the GLC yields of **5** and **6** were found to be 96% and 3%, respectively.

The corresponding reactions with alkylzinc chlorides containing isobutyl, *sec*-butyl, and *tert*-butyl groups were run in a similar manner, and the results of GLC examinations were summarized in Table II.

Reaction of Neryl Acetate with *n*-Butylzinc Chloride in the Presence of Tetrakis(triphenylphosphine)palladium. This reaction was carried out in a manner similar to that described above for the corresponding reaction of geranyl accetate. The results of GLC examination are summarized in Table II, and a mixture consisting of **5a**, **5b**, and **6** in a 6:91:3 ratio was isolated in a combined yield of 87%. This mixture yielded the following data: bp 72–73 °C (32 mm); IR (neat) 1675 (w), 1445 (s), 1375 (s), 1105 (w), 815 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.5–1.8 (m with peaks at 1.54, 1.62, 1.70, 12 H), 1.95–2.15 (m, 4 H), 5.0–5.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.23, 17.58, 23.44, 25.73, 26.70, 31.86, 119.23, 124.76, 131.25, 135.92. In addition to these peaks, those assignable to the *E* isomer and **6** were also discernible.

Reactions of Geranyl Chloride or Geranyl Tosylate with *n*-Butylzinc Chloride, Lithium Triethylborohydride, or Diisobutylaluminum Hydride. These reactions were carried out in THF at room temperature either in the presence of 5 mol % of tetrakis(triphenylphosphine)palladium or in its absence. The results are summarized in Table II.

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Registry No. **1**, 105-87-3; (*E*)-**2**, 27400-72-2; (*Z*)-**2**, 3338-55-4; **3**, 141-12-8; **4**, 123-35-3; (*E*)-**5**, 2609-23-6; **6**, 2436-90-0; $Pd(PPh_3)_4$,

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14221-01-3; propargylzinc bromide, 106-96-7; triethylamine, 121-44-8; 1,4-diazabicyclo[2.2.2]octane, 280-57-9; sodium amide, 7782-92-5; methylzinc chloride, 5158-46-3; 1-octynylzinc chloride, 68113-72-4; 2-cyclohexenyl acetate, 14447-34-8; benzylzinc bromide, 62673-31-8; 3-benzyl-1-cyclohexene, 4714-10-7; geranyl chloride, 5389-87-7; geranyl tosylate, 33169-56-1; *n*-BuZnCl, 42930-39-2; *i*-BuZnCl, 82510-93-8; *s*-BuZnCl, 74133-06-5; *t*-BuZnCl, 62987-33-1; $LiBEt_3H$, 22560-16-3; *i*-Bu_2AlH, 1191-15-7.

Resolution of (±)-5-Bromonornicotine. Synthesis of (*R*)- and (*S*)-Nornicotine of High Enantiomeric Purity

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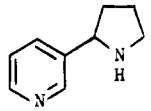
Nornicotine (1) is an alkaloid occurring in tobacco[2] and



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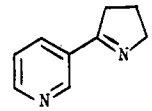

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Duboisia hopwoodii.[3] The alkaloid present in tobacco is levorotatory[2] and has been shown to be a mixture of *R* and *S* enantiomers, with the *S* enantiomer predominating,[4,5] whereas nornicotine from *Duboisia* is the partially racemized *R* isomer.[3] Although racemic nornicotine is readily synthesized on a large scale,[6,7] the enantiomers have been obtained only with difficulty.[8] Both (*R*)- and (*S*)-nornicotine may be obtained from natural sources,[2,3] but the isolation is complicated by the presence of other alkaloids. The synthesis of (*S*)-nornicotine by demethylation of nicotine has been reported; however, the yields were low, and partial racemization occurred.[9] Partially resolved (*S*)-nornicotine has been obtained from the racemate with optically active 6,6′-dinitro-2,2′-diphenic acid as a resolving agent.[10] Unfortunately, the acid is not commercially available and is tedious to synthesize.[11,12] A recent report described an unsuccessful attempt to prepare chiral nornicotine by asymmetric reduction of myosmine (**2**), as well as unsuccessful attempts to resolve racemic nornicotine using a variety of chiral acids.[13] This paper describes an efficient process for the resolution of 5-bromonornicotine. Both isomers are obtained in a high state of enantiomeric purity and may be catalytically debrominated to the corresponding enantiomers of nornicotine without loss of optical purity.

The synthetic route employed is outlined in Scheme I. Preparation of 5-bromomyosmine (**4**) was carried out by base-catalyzed condensation of ethyl 5-bromonicotinate (**3**) with *N*-vinylpyrrolidinone, followed by acid-catalyzed hydrolysis, decarboxylation, and cyclization to **4** during basic workup.[14] Reduction of **4** to 5-bromonornicotine (**5**) was accomplished with sodium borohydride in acetic acid–methanol by a modification of the method of Castonguay and Van Vunakis.[15] Resolution of racemic **5** was attempted with 12 chiral organic acids. Nine produced salts that failed to crystallize or were hygroscopic. Mandelic acid and *O,O′*-dibenzoyltartaric acid gave crystalline salts, but no enantiomeric enrichment was observed on recrystallization. However, the addition of 0.5 equiv of (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(−)-MTPA] to a solution of racemic 5-bromonornicotine in ethyl acetate gave a crystalline salt subsequently shown (see below) to be a 60:40 mixture of *R*/*S* enantiomers. Three recrystallizations from acetonitrile yielded a product that was ≥95% (*R*)-5-bromonornicotine (**5b**). The course of the resolution was readily monitored by GC using the chiral derivatizing agent *N*-(trifluoroacetyl)-(*S*)-prolyl chloride.[16,17] Base-line separation of the resulting diastereomeric amides was obtained on a 2-m SP-2250 column at 260 °C. The mother liquors from the original crystallization of the (−)-MTPA salt, enriched in the *S* enantiomer of 5-bromonornicotine, were converted to the free base and treated with (+)-MTPA to give the crystalline salt, which was ~70% (*S*)-5-bromonornicotine. Three recrystallizations from acetonitrile provided material that was ≥95% *S* enantiomer by GC analysis. Since preparations of the derivatizing agent *N*-(trifluoroacetyl)-(*S*)-prolyl chloride generally contain ~5% of the *R* enantiomer,[18] it is likely that the enantiomeric purity of the resolved 5-bromonornicotine was greater than 95%.

Conversion of the enantiomers of 5-bromonornicotine to the corresponding enantiomers of nornicotine was achieved by reductive debromination with hydrogen and a palladium catalyst. The enantiomer obtained from the (+)-MTPA salt had a specific rotation of −35.2° in methanol, which is in good agreement with the published value of −38.3° for (−)-nornicotine.[4] GC analysis indicated an optical purity of ≥95%. Similarly, the enantiomer obtained from the (−)-MTPA salt was converted into (+)-nornicotine of ≥95% enantiomeric purity. Since (−)-nornicotine has the *S* configuration, it may be inferred that the enantiomers of 5-bromonornicotine obtained from the (+)- and (−)-MTPA salts have the *S* and *R* configurations, respectively.

Nornicotine and 5-bromonornicotine are intermediates in the synthesis of a variety of tobacco alkaloid derivatives of biological interest.[13,15,19] Catalytic reduction of the bromo substituent using deuterium or tritium would provide a simple means for the incorporation of a deuterium or tritium label[20] into a chemically and metaboli-

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