precipitate obtained was dried and recrystallized (chloroform/ethyl acetate). (3,3-Trimethylenedithiobutyl)triphenylphosphonium nitrate (**4a**) showed the following: mp 219 °C; ^{1}H NMR δ 4.13–3.26 (m, 2 H, $^+PCH_2$), 3.00–1.72 (m, 8 H), 1.62 (s, 3 H, CH_3); ^{31}P NMR δ 25.52.

Electrochemical Deprotection of γ-Thioacetalated Phosphonium Nitrates (4). In method A (compounds **4a–e**), the electrolysis cell was charged with 2 mmol of the phosphonium nitrate and 90 mL of a 90:10 mixture of CH_3CN/H_2O containing 0.1 M $LiClO_4$. The mixture was oxidized at the potential of the peak recorded on CV until the current had decayed to 10% of its initial value. The amount of current passed was 2 ± 0.2 F mol^{-1}. The mixture was filtered, concentrated in vacuo to about 30 mL, and then diluted with chloroform to 200 mL. The organic phase was washed with water (30 mL, three times), dried (Na_2SO_4), concentrated in vacuo to about 50 mL, and added dropwise to 500 mL of ether. The precipitate was dried (P_2O_5, room temperature, 24 h), and a part of it (about 500 mg) was recrystallized from acetone/ethyl acetate for analytical purposes.

The procedure followed **in method B** (compounds **4f,g**) was identical with that of A with the exception that the electrolysis solvent was a mixture of $CH_3CN/H_2O/Me_2SO$ (80:10:10) and electrolyses were terminated after 2.5 F mol^{-1} had passed. (3-oxobutyl)triphenylphosphonium perchlorate (**5a**) showed the following: mp 212 °C dec; IR 1716 cm^{-1}; ^{1}H NMR δ 3.80–2.57 (m, 4 H, $^+PCH_2CH_2$), 2.12 (s, 3 H, CH_3); ^{31}P NMR δ 24.70.

Synthesis of β-Branched α,β-Ethylenic Ketones and Aldehydes (6). The dried chloroformic phase resulting from the electrochemical hydrolysis of 5 mmol of compounds 4 was concentrated in vacuo to 100 mL and diluted with 100 mL of methanol. Triethylamine (10 mmol) was added and the reaction allowed to stirr at room temperature until the complete disappearance of the phosphonium salt (monitored by TLC on silica). The reaction mixture was then concentrated in vacuo to about 50 mL and diluted with chloroform to about 200 mL. The organic phase was washed (30 mL, three times), dried (Na_2SO_4), concentrated in vacuo to about 50 mL, passed through a short plug of silica (elimination of perchlorates), and concentrated in vacuo to an oily crude mixture. Purification by column chromatography (silica gel, hexane/dichloromethane (10:90)) afforded the pure β-branched α,β-ethylenic ketone or aldehyde **6**. The compounds were identified by coinjection on GC and by comparison of their IR and NMR spectra with those of authentic samples.

Acknowledgment. We are grateful to the Carbone-Lorraine and Du Pont companies for gifts of vitreous carbon and Nafion membrane.

Registry No. **4a**, 85066-89-3; **4b**, 85066-91-7; **4c**, 85066-93-9; **4d**, 85066-95-1; **4e**, 85082-15-1; **4f**, 85066-97-3; **4g**, 85066-99-5; **5a**, 43101-01-5; **5b**, 85067-01-2; **5c**, 85067-03-4; **5d**, 43100-94-3; **5e**, 85067-05-6; **5f**, 85067-07-8; **5g**, 85067-09-0; **6a**, 78-94-4; (*E*)-**6b**, 3102-33-8; (*E*)-**6c**, 18402-82-9; (*E*)-**6d**, 1896-62-4; **6e**, 930-68-7; (*E*)-**6f**, 123-73-9; (*E*)-**6g**, 14371-10-9.

Supplementary Material Available: Physical properties of phosphonium salts 4 and 5 (3 pages). Ordering information is given on any current masthead page.

Optically Active Nicotine Analogues. Synthesis of (*S*)-(−)-2,5-Dihydro-1-methyl-2-(3-pyridyl)pyrrole ((*S*)-(−)-3′,4′-Dehydronicotine)

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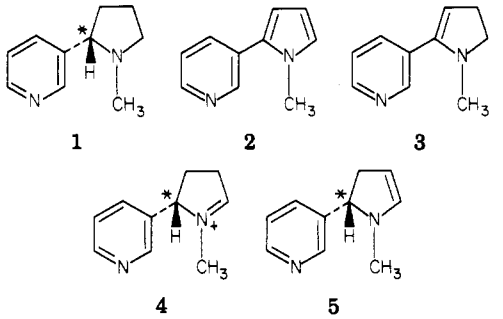
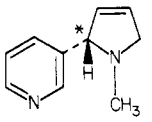
For some time, we have been engaged in the preparation of analogues of nicotine (**1**) for chemical and pharmacological studies.[2] One area of interest concerns the family



1 **2** **3** **4** **5**

of compounds possessing unsaturation in the pyrrolidine ring. The tobacco alkaloid nicotyrine **2**[3] is the most well-known example. *N*-Methylmyosmine (**3**) has been implicated as an intermediate in the degradation of nicotine in tobacco.[4] Recently, **3**, which is highly unstable, was synthesized and fully characterized.[4] There is strong evidence for the formation and intermediacy of the nicotine $\Delta^{1'(5')}$-iminium ion (**4**) in the mammalian metabolic transformation of nicotine to cotinine.[5] The diperchlorate salt of **4** has also recently been prepared.[6] In addition, 4′,5′-dehydronicotine (**5**) has also been proposed as a possible metabolic intermediate.[5,6] Enamine **5**, which would be expected to be rather unstable, has not, as yet, been synthesized.

Of the various dihydropyrrole derivatives, (*S*)-(−)-2,5-dihydro-1-methyl-2-(3-pyridyl)pyrrole (**6**; (*S*)-(−)-3′,4′-dehydronicotine) may most closely mimic **1** in its pharmacological characteristics. Compound **6** has been pre-



6

pared previously, but strictly as a racemic mixture.[7] Racemic **6** has been shown to be significantly more potent than **1** in several insecticidal studies.[8] Due to the significant potency of racemic **6** and the enhanced biological activity of (*S*)-nicotine over (*R,S*)-nicotine, we required a means of obtaining optically active **6**, i.e., the *S* enantiomer. A reported attempt to resolve racemic **6** by fractional crystallization was unsuccessful.[9] We now report an op-

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(2) (a) Seeman, J. I.; Secor, H. V.; Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L.; Whidby, J. F. *J. Org. Chem.* **1981**, *46*, 3040. (b) Secor, H. V.; Chavdarian, C. G.; Seeman, J. I. *Tetrahedron Lett.* **1981**, 3151. (c) Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L. *J. Org. Chem.* **1982**, *47*, 1069. (d) Chavdarian, C. G.; Seeman, J. I.; Wooten, J. B. *Ibid.* **1983**, *48*, 492.

(3) Frank, R. L.; Holley, R. W.; Wikholm, D. M. *J. Am. Chem. Soc.* **1942**, *64*, 2835.

(4) Maeda, S.; Matsushita, H.; Mikami, Y.; Kisaki, T. *Agric. Biol. Chem.* **1978**, *42*, 2177.

(5) Brandänge, S.; Lindblom, L. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 991.

(6) Brandänge, S.; Lindblom, L. *Acta Chem. Scand., Ser. B* **1979**, *B33*, 187.

(7) (a) Swain, M. L.; Eisner, A.; Woodward, C. F.; Brice, B. A. *J. Am. Chem. Soc.* **1949**, *71*, 1341. (b) Haines, P. G.; Eisner, A. *Ibid.* **1950**, *72*, 1719. In our hands, this preparation (Zn/HCl) resulted in some overreduction of nicotyrine to nicotine (ratio of racemic dehydronicotine to nicotine, 86:14). (c) Acheson, R. M.; Ferris, M. J.; Sinclair, N. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 579. (d) Mechoulam, R; Gaoni, Y. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 1159.

(8) (a) Yamamoto, I.; Kammura, H.; Yamamoto, R.; Sakai, S.; Goda, M. *Agric. Biol. Chem.* **1962**, *26*, 709. (b) Yamamoto, I.; Soeda, Y.; Kamimura, H.; Yamamoto, R. *Ibid.* **1968**, *32*, 1341.

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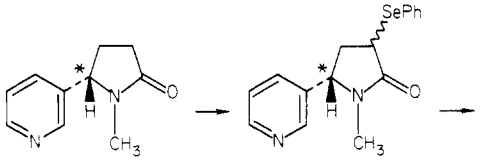
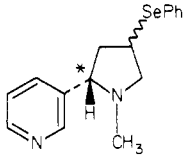
tically active synthesis of **6**. The key feature of our approach involves the preparation of an appropriately substituted organoselenium intermediate for conversion to the $\Delta^{3'(4')}$ system.

Treatment of (*S*)-(−)-cotinine (**7**)[10] with 2 equiv of lithium diisopropylamide in THF at −70 °C followed by the addition of one equivalent of phenylselenenyl chloride[11] provided the desired α-phenylselenocotinine **8**, as a diastereomeric mixture, in 51% distilled yield ($[\alpha]^{20}_D$ +63°, methanol). With 1 equiv of lithium diisopropylamide, **8**



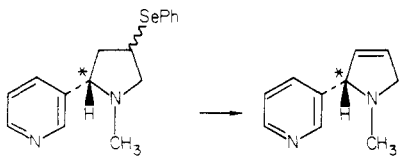
7 **8**



9

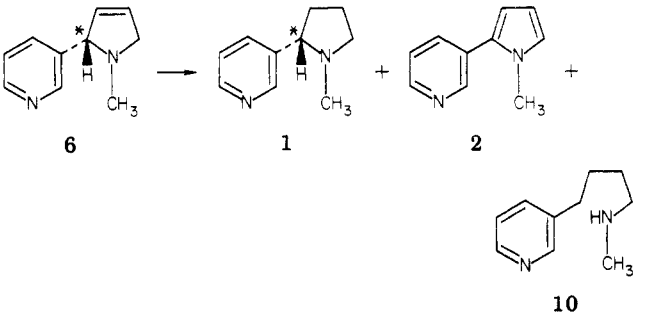
was obtained in very low yield along with a sizable recovery of **7**. This is consistent with the results of Zoretic[12] in a study of the sulfenylation and selenenylation of *N*-methylpyrrolidinone. Reduction of **8** with diborane in refluxing THF afforded 4′-phenylselenonicotine (**9**), also as a mixture of diastereomers, in 59% distilled yield ($[\alpha]^{20}_D$ −113°, methanol).

The final step required oxidation of the selenide to the selenoxide followed by in situ selenoxide elimination to the olefin. Reich[13] has shown that selenoxides substituted β to an amine functionality undergo eliminations primarily away from the amine rather than toward it to form an enamine. Depending on the system, enamine formation can be significant, although still less so than formation of the β,γ-olefin. Oxidation of **9** with hydrogen peroxide in THF at 0 °C to room temperature resulted in the isolation of *only* (*S*)-(−)-3′,4′-dehydronicotine (**6**) in a distilled yield of 45% ($[\alpha]^{20}_D$ −364°, methylene chloride). ^{1}H NMR and capillary gas chromatographic analyses did not detect the presence of **5**, the alternate elimination product. The ^{1}H NMR spectrum and double-resonance experiments confirmed the structure shown for **6**. The ^{1}H NMR spectrum of **6** was identical with that of racemic **6** prepared by the literature procedure.[7a,b,d] It is conceivable that **5** may have been produced but simply did not survive the workup conditions.



9 **6**

Dehydronicotine **6**, although possessing a high specific rotation, was reduced to (−)-nicotine (**1**) in order to determine its degree of optical purity. Hydrogenation at 50 psi with 10% Pt/C in ethanol proved to be extremely sluggish. Although nicotine was produced, the lengthy reaction time (20 h) lead to some aromatization of **6** to **2**[14] along with the formation of a sizable quantity of dihydrometanicotine (**10**) side product (ratio of **1/2/10**, 60:10:30). Apparently, reductive conversion of nicotine (**1**) to dihydrometanicotine (**10**) in the presence of platinum catalyst[15] is competitive with nicotine formation from **6**. The isolated nicotine ($[\alpha]^{20}_D$ −154°, methylene chloride) was obtained in 91% enantiomeric excess. Hydrogenation of **6** with 5% Pd/C (presaturated with hydrogen[16]) in ethanol at 15 psi was complete after 2 h and provided a high yield of nicotine (**1**) with only a small percent of **2** and a trace of **10** (ratio of **1/2/10**, 96.5:3.0:0.5). In this case, the nicotine ($[\alpha]^{20}_D$ −146°, methylene chloride) was obtained in 86% enantiomeric excess. These results confirm the high optical purity of **6**. Indeed, **6** may be essentially optically pure. The fact that the hydrogenation of **6** provides nicotine in less than 100% enantiomeric excess may simply be due to the well-known propensity of palladium and platinum catalysts to effect double-bond migration.[17] This would result in some racemization of the chiral center of **6**. Note that the use of palladium afforded (−)-nicotine (**1**) in even lower optical purity than did the use of platinum. This is consistent with the fact that palladium has a greater tendency to promote olefinic migration than platinum.[17]



6 **1** **2**

10

The organoselenium procedure should also be applicable to the preparation of other compounds of interest, e.g., the tobacco alkaloid *N*-methylanatabine.

Experimental Section

Melting points and boiling points are uncorrected. The ^{1}H NMR spectra were determined on a Bruker WP-80 spectrometer. IR spectra were determined on a Perkin-Elmer 735B infrared spectrophotometer. Low-resolution mass spectra were obtained on a Finnigan 3300 mass spectrometer. Optical rotations were obtained with a Perkin-Elmer 241 MC polarimeter. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

(3*RS*,5*S*)-1-Methyl-3-(phenylseleno)-5-(3-pyridyl)-2-pyrrolidinone (8). To a solution of 1.32 g (13.06 mmol) of diisopropylamine in 25 mL of dry THF under nitrogen at −20 °C was added 7.63 mL (12.21 mmol) of 1.6 M *n*-butyllithium in hexane such that the temperature did not rise above −10 °C. After stirring the solution below −20 °C for 15 min, the solution was cooled to −70 °C. To the solution was added a solution of 1.0 g (5.68 mmol) of (−)-cotinine[10] in 5 mL of THF over 10 min. The resultant yellow solution was stirred at −70 °C for 20 min followed

(9) Oosterhuis, A. G.; Wibaut, J. P. *Recl. Trav. Chim. Pays-Bas* **1936**, *55*, 727.
(10) Bowman, E. R.; McKennis, H., Jr. *Biochem. Prep.* **1963**, *10*, 36.
(11) Available from the Aldrich Chemical Company.
(12) Zoretic, P. A.; Soja, P.; Sinha, N. D. *J. Org. Chem.* **1978**, *43*, 1379.
(13) Reich, H. J.; Renga, J. M. *J. Org. Chem.* **1975**, *40*, 3313.
(14) Nicotine (**1**) undergoes dehydrogenation to nicotyrine (**2**) in the presence of either platinum or palladium catalyst; see ref 3.
(15) For the preparation of dihydrometanicotine by treatment of nicotine with H_2–10% Pt/C, see: Erdtman, H.; Haglid, F.; Wellings, I. *Acta Chem. Scand.* **1963**, *17*, 1717.
(16) We have found that saturation of the palladium catalyst with hydrogen prior to hydrogenation of **6** is necessary in order to minimize dehydrogenation of dehydronicotine **6** to nicotyrine (**2**).[14] Without presaturation, dehydrogenation is substantial. In addition, presaturation with hydrogen should also help to minimize double-bond isomerization.
(17) For a discussion of catalysts and olefinic migration, see: Rylander, P. N. "Catalytic Hydrogenation in Organic Syntheses"; Academic Press: New York, 1979; Chapter 3.

by the addition of a solution of 1.14 g (5.96 mmol) of phenylselenenyl chloride[11] in 5 mL of THF over 2 min. The light yellow solution was stirred at −70 °C for 30 min and at 0 °C for 30 min. The solution was then quenched with 20 mL of 10% aqueous HCl. The mixture was washed with ether (2 × 25 mL), and the aqueous layer was basified with aqueous NaOH and extracted with ether (2 × 25 mL). The ethereal layer was dried ($MgSO_4$) and evaporated to a viscous, yellow oil. Bulb-to-bulb distillation [oven temperature 170–190 °C (0.15 torr)] afforded 0.954 g (51%) of **8**, a very viscous oil: $[\alpha]^{20}_D$ +63° (*c* 1.289, methanol); ^1H NMR ($CDCl_3$) δ 8.48–8.68 (m, 1), 8.18–8.43 (m, 1), 6.88–7.83 (m, 7), 4.48 (t, *J* = 8 Hz, 1), 3.85–4.18 (m, 1), 1.73–3.25 (m, 2), 2.55 and 2.63 (diastereomeric methyl s's, 3); EI mass spectrum, *m/z* 330, 332 (M^+ consisting of the two major selenium isotopes).

(2′*S*,4′*RS*)-4′-Phenylselenonicotine (9). To a solution of 6.51 g (0.0197 mol) of **8** in 150 mL of THF under nitrogen at room temperature was added 111 mL of 1.06 M borane in THF. The mixture was refluxed for 17 h. After cooling in an ice bath, the mixture was very carefully and slowly quenched with 145 mL of 6 N aqueous HCl. The solution was refluxed for 3 h, cooled, and washed with ether (2 × 100 mL). The aqueous layer was basified with aqueous NaOH and extracted with ether (3 × 50 mL). The combined ethereal layer was dried ($MgSO_4$) and evaporated to a yellow oil. Bulb-to-bulb distillation [oven temperature 140–150 °C (0.15 torr)] provided 3.68 g (59%) of **9**, an oil: $[\alpha]^{20}_D$ −113° (*c* 0.402, methanol); ^1H NMR ($CDCl_3$) δ 8.43–8.60 (m, 2), 7.13–7.88 (m, 7), 1.58–4.03 (m, 6), 2.18 (s, 3); EI mass spectrum, *m/z* 316, 318 (M^+ consisting of the two major selenium isotopes).

(*S*)-(−)-2,5-Dihydro-1-methyl-2-(3-pyridyl)pyrrole (6). To a solution of 1.0 g (3.15 mmol) of **9** in 20 mL of THF at 0 °C was gradually added 484 μL (4.73 mmol) of 30% H_2O_2. The solution was stirred at 0 °C for 30 min and room temperature for 1.5 h. To the solution was added 5 mL of 10% aqueous sodium sulfite followed by 10 mL of 10% aqueous Na_2CO_3. The mixture was extracted wtih ether (3 × 15 mL), and the combined ethereal layer was dried ($MgSO_4$) and evaporated to a reddish oil. Bulb-to-bulb distillation [oven temperature 60–70 °C (0.15 torr)] afforded 0.227 g (45%) of **6**, a colorless, mobile oil: dipicrate mp 182–186 °C; $[\alpha]^{20}_D$ −364° (*c* 0.313, methylene chloride); ^1H NMR ($CDCl_3$) δ 8.51 (m, 2), 7.69 (dt, *J* = 8, 2 Hz, 1), 7.25 (dd, *J* = 8, 5 Hz, 1), 5.85–6.03 (m, 1), 5.58–5.75 (m, 1), 4.20–4.43 (m, 1), 3.68 (AB q with extensive fine coupling, 2; each multiplet located at 3.98–4.10, 3.80–3.94, 3.38–3.53, and 3.21–3.36), 2.41 (s, 3); EI mass spectrum, *m/z* 160 (M^+), 82 (*N*-methylpyrrolinyl).

Anal. Calcd for $C_{22}H_{18}N_8O_{14}$ (dipicrate): C, 42.72; H, 2.91; N, 18.12. Found: C, 42.91; H, 3.09; N, 18.10.

Acknowledgment. We thank Henry V. Secor and Dr. Jeffrey I. Seeman for helpful discussions and Anne Donathan for secretarial assistance.

Registry No. **1**, 54-11-5; **2**, 487-19-4; **6**, 85026-74-0; **6** dipicrate, 85026-75-1; **7**, 486-56-6; **8** (isomer 1), 84960-83-8; **8** (isomer 2), 84960-84-9; **9** (isomer 1), 84960-85-0; **9** (isomer 2), 84960-86-1; **10**, 3000-74-6; phenylselenenyl chloride, 5707-04-0.

Alkylation of Allylic Derivatives. 6. Regiochemistry of Alkylation of Allylic Acetates with Dialkylcuprates

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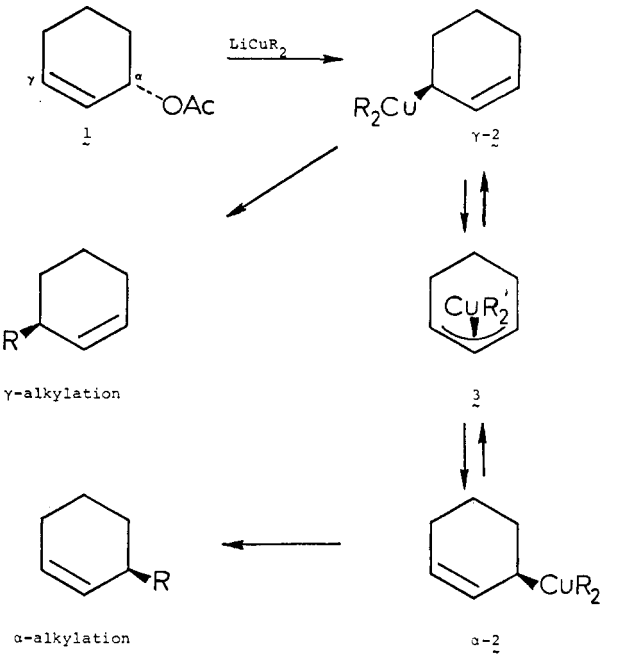
Recently we concluded that the mechanistic pathway for alkylation of allylic carboxylates with cuprates involves oxidative addition with allylic rearrangement to give a σ-allylcopper(III) complex (γ-**2**) as illustrated for the cyclohexenyl system (**1**) in Scheme I.[1a] The stereochemistry

Scheme I. Mechanistic Pathway for Alkylation of 2-Cyclohexenyl Acetate with Dialkyl Cuprates



of alkylation shows that the **1** → γ-**2** transformation is stereospecific as well as regiospecific and in unhindered systems gives the anti-σ-allyl complex (γ-**2**) as shown in the scheme.[1,2] Evidence for oxidative addition with allylic rearrangement is that excess γ-alkylation is involved in all cases where regiospecificity[3] has been observed. The reason for the S_N2' regiochemistry is thought to result from prior complexation of the cuprate with the double bond to give a cuprate–olefin π complex that is converted to γ-**2**.[1]

The initially formed copper(III) complex (γ-**2**) can (1) undergo stereospecific[4] reductive elimination to give anti-γ-alkylation or (2) isomerize to the π-allyl complex (**3**) in which case stereochemistry is preserved but regiochemistry is lost. The regiochemistry of alkylation depends on the relative rates of these two processes, and this seems to depend on the nature of the ligands on copper.[1b] With lithium dialkylcuprates little if any regiospecificity is observed in either cyclic[2,5] or acyclic[6,7] systems. This indicates that the **2** → **3** isomerization is fast relative to reductive elimination when there are two alkyl ligands on copper.

(1) (a) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1983**, *48*, 721. (b) Goering, H. L.; Kantner, S. S. *Ibid.* **1981**, *46*, 2144.
(2) Goering, H. L.; Singleton, V. D., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854.
(3) In this series the terms regiospecific and regioselective are used in the same sense as stereospecific and stereoselective as defined by Zimmerman et al. Zimmerman, H. E.; Singer, L.; Thyagarajan, B. S. *J. Am. Chem. Soc.* **1959**, *81*, 108 in footnote 16. Thus, if two isomeric allylic carboxylates related to the same allylic intermediate (e.g., anion, cation, radical, or π-allyl complex) give the same alkylation product, or mixtures with the same composition, there is no regiospecificity. If in this case one of two possible alkylation products predominates the reaction is regioselective but not regiospecific. Put another way, if there is excess α- or γ-alkylation in a system related to a symmetrical allylic intermediate (such as the cyclohexenyl system), the reaction is regiospecific. Regiospecificity can be partial (mixtures with different compositions derived from isomeric allylic carboxylates or excess γ-alkylation is an unbiased symmetrical system) as well as complete (e.g., exclusive γ-alkylation for both allylic isomers or in a symmetrical system).
(4) Whitesides, G. M.; Fischer, W. F., Jr.; San Filippo, J., Jr.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871. Johnson, C. R.; Dutra, G. A. *Ibid.* **1973**, *95*, 7777, 7783.
(5) Kreft, A. *Tetrahedron Lett.* **1977**, 1035.
(6) Goering, H. L.; Seitz, E. P., Jr.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5304.
(7) Anderson, R. J.; Henrick, C. A.; Siddall, J. B.; Zurfluh, R. *J. Am. Chem. Soc.* **1972**, *94*, 5379.

0022-3263/83/1948-1531$01.50/0