A Biogenetic-Type Synthesis of the Cyclohexyl Constituents of the Boll Weevil Pheromone[1]

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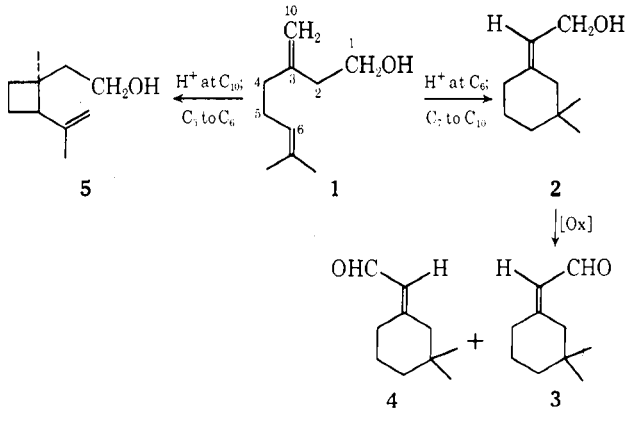
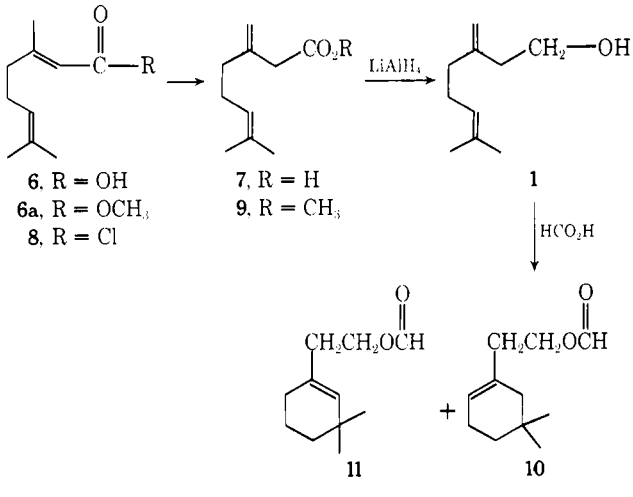
Treatment of the acid chloride of geranic acid (**6**) with triethylamine and methanol affords methyl γ-geranate (**9**) contaminated by ca. 10% of methyl geranate. Acid-catalyzed cyclization of methyl γ-geranate affords, in high yield, a mixture composed primarily of methyl 3,3-dimethylcyclohexenylacetates (**12** and **13**). The endocyclic unsaturated isomers **12** and **13** were converted to the desired conjugated, exocyclic isomers **15** and **16** by addition of hydrogen bromide followed by dehydrobromination with triethylamine. Lithium aluminum hydride reduction of **15** and **16** gave (*Z*)- and (*E*)-3,3-dimethyl-$\Delta^{1,8}$-cyclohexaneethanol (**2** and **2a**), which, in turn, were converted into the corresponding aldehydes by oxidation with manganese dioxide.

7-Methyl-3-methylene-6-octen-1-ol (**1**), henceforth referred to as γ-geraniol, has been postulated as the biosynthetic precursor for the four components, **2, 3, 4,** and **5,** of the boll weevil sex pheromone.[2,3,4] We have examined the acid-catalyzed cyclization of γ-geraniol and its derivatives and wish to report procedures which afford alcohol **2** and aldehydes **3** and **4** from readily available starting materials such as citral or geranic acid (**6**).[5]



5 1 2 4 3

γ-Geraniol (**1**)[7] is not commercially available, and γ-geranic acid (**7**) was not known prior to this work. These compounds are readily prepared from geranic acid (**6**) using a procedure to deconjugate a double bond suggested by Iwakura.[8] The acid chloride **8**, prepared from the sodium salt of geranic acid (**6**),[9,10] was treated with 1 equiv of triethylamine and methanol in benzene to give methyl γ-geranate (**9**),[11] contaminated by ca. 10% of methyl geranate (**6a**), in up to 83% isolated yield.[12] Essentially pure **9** can be obtained by distillation using a spinning band column. Lithium aluminum hydride reduction of **9** affords γ-geraniol (**1**).



6, R = OH
6a, R = OCH_3
8, R = Cl

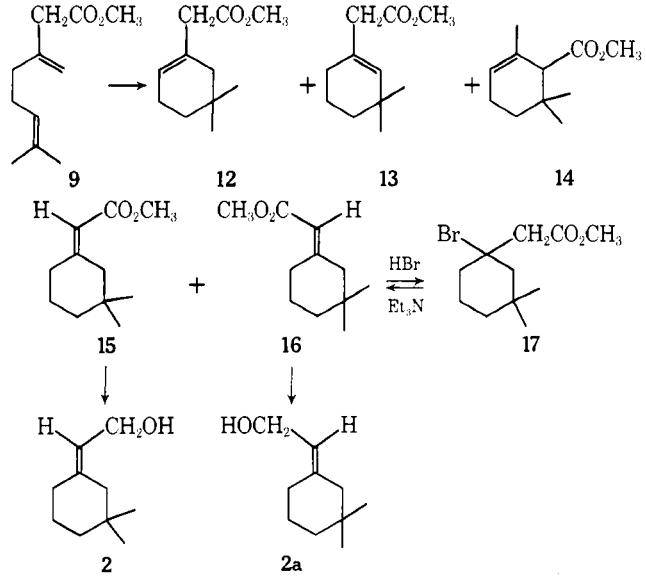
7, R = H
9, R = CH_3

1

11 10

Formic acid catalyzed cyclization of **1** gave the more thermodynamically stable endocyclic isomers **10** and **11,** and only a trace of the formates of (*Z*)-**2** and (*E*)-**2a.** Lacking a convenient handle to effect double bond isomerization to the desired alcohols **2** and **2a,** we turned our attention to the cyclization of ester **9.**

Heating ester **9** with polyphosphoric acid gave, in 90% yield, a mixture of cyclized esters **12, 13, 14, 15,** and **16.**[13] In order to shift the double bond into the less stable conjugated position,[14] the ester mixture was treated with hydrogen bromide and the resulting bromide **17** was then dehydrobrominated with triethylamine to afford a mixture containing 80% of the exocyclic isomers **15** and **16.** If desired, the exocyclic isomers can be partially separated at this stage by distillation using a spinning band column.



9 12 13 14

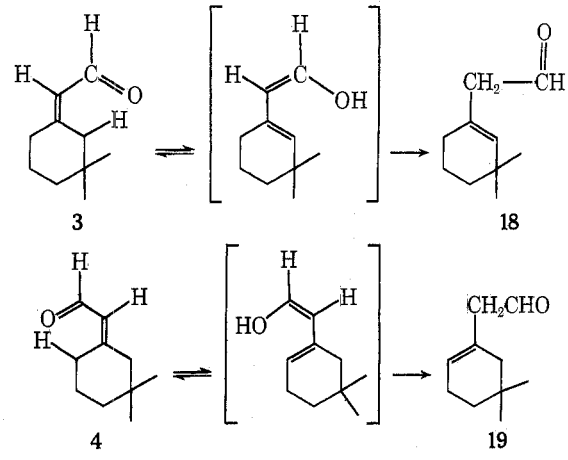
15 16 17

2 2a

The *Z* and *E* esters **15** and **16** were converted to the *Z* and *E* alcohols **2** and **2a** by reduction with lithium aluminum hydride. Oxidation of the alcohols using manganese dioxide affords the aldehydes **3** and **4** in high yield.

NMR analysis of **3** and **4** failed to indicate the presence of endocyclic isomers **18** and **19.** However, gas chromatographic analysis invariably showed the presence of these isomers. Samples of **3** and **4** collected by preparative GLC and determined to be pure by NMR were reanalyzed by GLC and once more showed the presence of **18** and **19.** We

conclude that **3** and **4** undergo 1,5-hydrogen transfer[15] in the gas chromatograph. Heating aldehydes **3** and **4** at 145° for 12 hr under a nitrogen atmosphere also gave a mixture containing ca. 20% of the endocyclic isomers **18** and **19**.



3 **18**

4 **19**

In conclusion, it is instructive to point out that two contrathermodynamic isomerizations permit the facile synthesis of the cyclohexyl constituents of the boll weevil pheromone. The failure to observe cyclobutane derivatives in the cyclization of **1** and **9** is undoubtedly related to the kinetically favored protonation of the Δ^6 double bond and the higher transition energy required to form a cyclobutane ring in the event that protonation at C-10 and subsequent C-3 to C-6 interaction does take place.

Experimental Section[16]

Methyl γ-Geranate (9). Ether (600 ml) was added in small portions to the gummy mixture resulting from the combination of 200 g (1.19 mol) of geranic acid (**6**) with 49 g (1.19 mol) of sodium hydroxide in 100 ml of water. The resulting white precipitate was removed by filtration through course filter paper and washed several times with ether. The salt was first dried on a steam plate and then in a vacuum oven at 70° for 24 hr.

To a suspension of 194 g (1.02 mol) of sodium geranate in 450 ml of benzene at 0° was added dropwise 130 g (1.06 mol) of thionyl chloride. After stirring for 2 hr at ambient temperature, the solvent and unreacted thionyl chloride were removed in vacuo. Benzene (300 ml) was added to the residue and the mixture was added at 0° over a 1-hr period to 200 ml of benzene containing 115 g (1.14 mol) of triethylamine and 37 g (1.16 mol) of methanol. The mixture was filtered and the solvents were removed. Vacuum distillation afforded 168 g of liquid containing 83% of **9** and 8% of methyl geranate (**6a**) according to GLC and NMR analysis. Pure methyl γ-geranate (**9**) was obtained by distillation using a spinning band column: bp 40° (0.15 mm); ir 3.4, 5.75, 6.08, 8.65, 9.9, and 11.2 μm; NMR ($CDCl_3$) 1.61 and 1.69 [s, 6, $C{=}C(CH_3)_2$], 2.11 (d, 4), 3.03 (s, 2, $-CH_2CO_2-$), 3.68 (s, 3, $-OCH_3$), 4.91 (s, 2, $-C{=}CH_2$), and 5.10 ppm (m, 1, $-CH{=}C-$); mass spectrum *m/e* (rel intensity) 182 (9), 139 (20), 123 (12), 109 (22), 108 (32), 107 (13), 69 (100), 68 (13), 67 (13), 41 (51), and 39 (11).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.39; H, 10.15.

γ-Geraniol (1). To a solution of 13.0 g (71 mmol) of **9** in 130 ml of dry ether was added 3.0 g (79 mmol) of lithium aluminum hydride. The mixture was stirred for 30 min and aqueous sodium hydroxide solution was slowly added. The mixture was filtered, and the filtrate was dried ($MgSO_4$) and distilled to yield 11.0 g of pure **1**: bp 51° (0.10 mm); $n^{20}D$ 1.4721 [lit.[7a] bp 83–86° (2–3 mm), $n^{20}D$ 1.4717]; ir 3.0, 6.08, 9.6, and 11.25 μm; NMR ($CDCl_3$) 1.63 and 1.70 [s, 6, $C{=}C(CH_3)_2$], 1.8–2.2 (m, 4), 2.30 (t, 2, J = 6 Hz, $-CH_2CH_2O$), 3.72 (t, 2, J = 6 Hz, $-CH_2CH_2O$), 4.88 (s, 2, $-C{=}CH_2$), and 5.10 ppm (m, 1, $CH{=}C-$).

Cyclization of γ-Geraniol (1). A solution of 0.50 g (3.2 mmol) of **1** and 1 ml of 90% formic acid was refluxed for 2 hr. Pentane was added, the solution was washed with water and dried ($MgSO_4$), and the solvent was evaporated, leaving 0.59 g of a mixture of formate esters **10** and **11** in 3:1 ratio as determined by GLC (DC-200 column) and NMR analysis: peaks at 0.90 (s, CH_3CCH_3), and 5.5 ppm ($-C{=}CH-$) were assigned to **10**; those at 0.93 (s, CH_3CCH_3) and 5.2 ppm (s, $-C{=}CH-$) to compound **11**; while those at 1.2–1.4 (m), 4.23 (t, 2, $-CH_2OCOH$), and 8.05 ppm (s, 1, $-OCHO$) were common to both isomers.

Cyclization of Methyl γ-Geranate (9). A mixture of 40 g (0.22 mol) of **9** (containing ca. 10% of methyl geranate) and 1.0 g of polyphosphoric acid was stirred at 130° for 2 hr. The products were distilled directly from the reaction vessel, yielding 36 g (90%) of liquid, bp 40–45° (0.1 mm). Preparative GLC using a 12 ft × 0.375 in. 15% Carbowax 20M column at 175° yielded five fractions. Compound **12** (53%, retention time 8.0 min): ir 5.73 μm; NMR ($CDCl_3$) 0.91 [s, 6, $-C(CH_3)_2$], 1.30 (t, 2), 1.5–2.2 (m, 4), 2.95 (s, 2, $-CH_2CO_2-$), 3.68 (s, 3, $-OCH_3$), and 5.55 ppm (s, 1, $-C{=}CH-$). Compound **13** (25%, retention time 6.3 min): ir 5.73 μm; NMR ($CDCl_3$) 0.96 [s, 6, $-C(CH_3)_2$], 1.2–2.6 (m, 6), 2.93 (s, 2, $-CH_2CO_2-$), 3.68 (s, 3, $-OCH_3$), and 5.30 ppm (s, 1, $-C{=}CH-$). Compound **14** (12%, retention time 5.1 min): ir 5.76 μm, NMR ($CDCl_3$) 0.92 [s, 6, $-C(CH_3)_2$], 1.65 (s, 3, $-C{=}CCH_3$), 1.7–2.5 (m, 4), 2.61 (s, 1, $-CHCO_2-$), 3.68 (s, 3, $-OCH_3$) and 5.60 ppm (s, 1, $-C{=}CH-$). Compound **15** (5%, retention time 8.8 min): ir 5.81 μm; NMR ($CDCl_3$) 0.91 [s, 6, $-C(CH_3)_2$], 1.2–1.9 (m, 4), 2.17 (t, 2, $-CH_2-$ trans to $-CO_2Me$), 2.68 (s, 2, $-CH_2-$ cis to $-CO_2Me$), 3.68 (s, 3, $-OCH_3$), and 5.68 ppm (s, 1, $-C{=}CH-$). Compound **16** (5%, retention time 9.6 min): ir 5.81 μm; NMR ($CDCl_3$) 0.90 [s, 6, $-C(CH_3)_2$], 1.3–1.9 (m, 4), 1.97 (s, 2, $-CH_2-$ trans to $-CO_2Me$), 2.78 (t, 2, $-CH_2-$ cis to $-CO_2Me$), 3.68 (s, 3, $-OCH_3$), and 5.58 ppm (s, 1, $-C{=}CH-$).

Isomerization of Esters 12 and 13 to 15 and 16. Hydrogen bromide was bubbled into a solution of 36 g of the mixture of **12, 13, 14, 15,** and **16** described above in 400 ml of methylene chloride at room temperature. The addition was complete (by NMR analysis) after 10 hr. The solvent and excess hydrogen bromide were removed in vacuo. The residue was taken up in benzene and 85 g of dry triethylamine and more benzene was added to bring the volume to 500 ml. The solution was refluxed for 36 hr, filtered, and washed twice with water, and the solvent was removed, leaving 35 g (97%) of liquid containing 75% of **15** and **16** as determined by GLC analysis. A portion of this material was distilled using a spinning band column and fractions boiling in the range of 47–48° (0.2 mm) collected. The initial fractions were enriched in **15** and the later ones in **16.**

(*Z*)-3,3-Dimethyl-$\Delta^{1,8}$-cyclohexaneethanol (*2*). To a solution of 9.0 g (49 mmol) of **15** (containing 25% of **16**) in 110 ml of dry ether was added 1.86 g (49 mmol) of lithium aluminum hydride. The mixture was stirred for 1 hr at ambient temperature, aqueous sodium hydroxide was added, the mixture was filtered and dried ($MgSO_4$), and the solvent was removed, affording 6.7 g of liquid which was purified by distillation using a spinning band column. Pure *Z* alcohol showed bp 44° (0.2 mm); ir 3.05, 6.0, 9.3, 9.7, and 10.0 μm; NMR ($CDCl_3$) 0.90 [s, 6, $-C(CH_3)_2$], 1.30–2.20 (m, 6), 1.98 (s, 2, $-CH_2-$ cis to $-CH_2OH$), 4.12 (d, 2, J = 7 Hz, $-CH_2OH$), and 5.50 ppm (t, 1, J = 7 Hz).

(*E*)-3,3-Dimethyl-$\Delta^{1,8}$-cyclohexaneethanol (2a). The *E* ester **16** (containing 14% of **15**) was reduced in the same manner to yield 90% of alcohol **2a** (containing 14% of **2**): bp 40° (0.15 mm); ir 3.05, 6.0, 9.3, and 10.0 μm; NMR ($CDCl_3$) 0.87 [s, 6, $-C(CH_3)_2$], 1.2–2.2 (m, 6), 1.90 (s, 2, $-CH_2-$ trans to $-CH_2OH$), 4.15 (d, 2, J = 7 Hz, $-CH_2OH$), and 5.32 ppm (t, 1, J = 7 Hz, $-C{=}CH-$).

Aldehydes 3 and 4. A mixture of 2.4 g (19.5 mmol) of alcohols **2** and **2a** in 100 ml of pentane and 10 g (115 mmol) of manganese dioxide was stirred at ambient temperature for 10 hr and filtered, and the solvent was removed, leaving 2.0 g (83%) of essentially pure aldehydes **3** and **4** showing properties consistent with those reported by Tumlinson:[3] ir 5.95 and 6.12 μ; NMR ($CDCl_3$) peaks at 0.97 (s), 2.24 (t, $-CH_2-$ trans to CHO), 2.49 (s, $-CH_2-$ cis to CHO), and 5.95 ppm (d, J = 8 Hz, $-C{=}CH-$) were assigned to **3,** while those at 0.92 (s), 2.10 (s, $-CH_2-$ trans to CHO), 2.68 (t, $-CH_2-$ cis to CHO), and 5.80 ppm (d, J = 8 Hz) were assigned to **4.** NMR peaks at 1.2–1.9 and 10.01 ppm (d, CHO) were common to both isomers.

A GLC-collected sample of a mixture of aldehydes **3** and **4** (shown to be pure by NMR), when injected again into a 12-ft DC-200 column employing an injector temperature of 235°, gave 15% of a broad peak with a lower retention time. This peak was collected and identified as a mixture of endocyclic aldehydes **18** and **19** on the basis of its ir and NMR spectra: peaks at 0.99 (s) and 5.35 ppm (s, $-C{=}CH-$) assigned to **18,** peaks at 0.91 (s) and 5.60 ppm (s, $-C{=}CH-$) assigned to **19,** and those at 1.2–2.4 and 2.98 ppm ($-CH_2CHO$) were common to both isomers.

Registry No.—**1**, 13066-51-8; **2**, 26532-23-0; **2a**, 30346-27-1; **3**, 26532-24-1; **4**, 26532-25-2; (*E*)-**6**, 4698-08-2; (*Z*)-**6**, 4613-38-1; (*E*)-**6a**, 1189-09-9; (*Z*)-**6a**, 1862-61-9; **9**, 55298-92-5; **10**, 55298-93-6; **11**, 55298-94-7; **12**, 55298-95-8; **13**, 55298-96-9; **14**, 28043-10-9; **15**, 30346-23-7; **16**, 30346-25-9; **18**, 36866-77-0; **19**, 55298-72-1.

References and Notes

(1) Presented in part at the VI International Congress of Essential Oils, San Francisco, Calif., Sept 1974.
(2) J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard, "Chemicals Controlling Insect Behavior", M. Beroza, Ed., Academic Press, New York, N.Y., 1970.
(3) For the isolation, identification, and synthesis of **2**, **3**, **4**, and **5** see J. H. Tumlinson, D. D. Hardee, R. C. Gueldner, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *Science*, **166**, 1010 (1969); J. H. Tumlinson et al., *J. Org. Chem.*, **36**, 2616 (1971).
(4) For syntheses of grandisol (**5**) see (a) R. C. Gueldner, A. C. Thompson, and P. A. Hedin, *J. Org. Chem.*, **37**, 1854 (1972); (b) R. Zurflüh, L. L. Dunham, V. L. Spain, and J. B. Siddal, *J. Am. Chem. Soc.*, **92**, 425 (1970); (c) W. E. Billups, J. H. Cross, and C. V. Smith, *ibid.*, **95**, 3438 (1973); (d) G. Stork and J. F. Cohen, *ibid.*, **96**, 5270 (1974).
(5) Geranic acid is available from Fritzsche D & O, or can be synthesized by silver oxide oxidation of citral.[6]
(6) K. Bernhauer and R. Forster, *J. Prakt. Chem.*, **147**, 199 (1936).
(7) For earlier syntheses of γ-geraniol, see (a) H. C. Brown, K. Singh, and B. J. Garner, *J. Organomet. Chem.*, **1**, 2 (1963); (b) S. Watanabe and K. Suga, *Bull. Chem. Soc. Jpn.*, **36**, 1495 (1963); (c) A. I. Lebedeva and L. V. Kukhareva, *Zh. Obshch. Khim.*, **28**, 2782 (1958).
(8) Y. Iwakura, F. Toda, R. Iwata, and Y. Torii, *Bull. Chem. Soc. Jpn.*, **42**, 841 (1969).
(9) Geranic acid is a mixture of *E* and *Z* isomers.
(10) The reaction of geranic acid with thionyl chloride resulted in the addition of the by-product HCl to the $\Delta^{6,7}$ double bond.
(11) The nonconjugated ester **9** most likely forms by way of a vinyl ketene intermediate, as suggested by Iwakura.[8]
(12) Typical runs on a small scale yield 65% **9**.
(13) Compound **14** arises by cyclization of methyl geranate (**6a**), which was present in the sample of **9**.
(14) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); G. A. R. Kon and R. P. Linstead, *J. Chem. Soc.*, 1269 (1929).
(15) For examples of analogous 1,5-hydrogen transfers involving β,γ-unsaturated aldehydes, ketones, and esters see (a) G. Ohloff, *Tetrahedron Lett.*, **11**, 10 (1960); (b) G. Ohloff, J. Osiecki, and C. Djerassi, *Chem. Ber.*, **95**, 1400 (1962); (c) D. E. McGreer and N. W. K. Chiu, *Can. J. Chem.*, **46**, 2225 (1968).
(16) All boiling points are uncorrected. GLC analyses were performed using a 12 ft × 0.375 in. Carbowax 20M column at 175° except as otherwise noted. NMR spectra were determined with a Varian Associates A-60 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. Mass spectra were determined at 70 eV with a Hitachi RMU-6A mass spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.

Regiospecific Alkylation of Enolate Ions in Liquid Ammonia–Tetrahydrofuran

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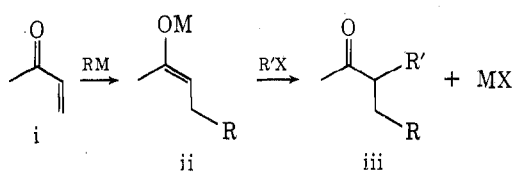
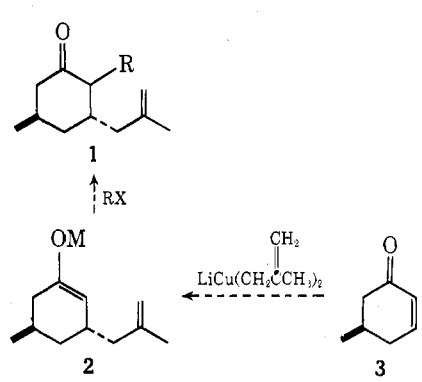
Specific cyclohexanone enolates are generated by cleaving the corresponding trimethylsilyl enol ethers with lithium amide in liquid ammonia. Butylation proceeds in high yield in this solvent, with little enolate equilibration. With corresponding sodium and potassium enolates, alkylation and enolate equilibration proceed at comparable rates.

Vicinal dialkylation of enones, by conjugate addition[1] and alkylation of the resulting specific enolate (i → ii → iii), is an important synthetic process which has received considerable recent attention.[2] The main problem is the



matter of proton exchange vs. alkylation. With very reactive electrophiles such as benzylic and allylic halides, alkylation is significantly more rapid than proton exchange, and regiospecific vicinal alkylation results.[2a,b,d] Coates found dimethoxyethane (DME) to be an effective solvent for promoting alkylation vis-à-vis proton transfer, although he still encountered substantial proton transfer in some cases.[2f]

In connection with a projected alkaloid synthesis, we required 2-alkyl-3-methallyl-5-methylcyclohexanones, in which the C-3 and C-5 substituents are trans (1). Since the conjugate addition of dialkylcuprates to 5-methylcyclohex-2-en-1-one is known to occur with good trans stereoselectivity,[3] the vicinal dialkylation process is an attractive route to **1**.



In the process of this study, we discovered that specific lithium enolates undergo alkylation in a mixture of liquid ammonia–tetrahydrofuran under conditions where proton transfer is an insignificant side reaction.[4] In this paper, we report the results of a limited study of this phenomenon.

Preparation of Alkylation Substrates. The ketone enolates which we have studied were prepared by cleavage of the appropriate silyl enol ether with methyllithium in the appropriate ether[4] or with lithium amide in liquid ammonia.[5] Silyl enol ethers **4**, **5**, and **6** were prepared by literature procedures.[6] Ether **7** was prepared in a similar manner from *cis*-3,5-dimethylcyclohexanone. This ether was contaminated with 10% of the *trans*-3,5-dimethyl isomer **9**,