64332-79-2; **4b**, 27163-65-1; **4c**, 20758-60-5; **5** (X = *m*-Cl), 64332-78-1; **5** (X = *p*-OCH_3), 64332-77-0; **6** (X = *m*-Cl), 64332-76-9; **6** (X = *p*-OCH_3), 64332-75-8; xenon difluoride, 13709-36-9.

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Chemistry of Carbanions. 31. Cyclization of the Metal Enolates from ω-Bromo Ketones[1]

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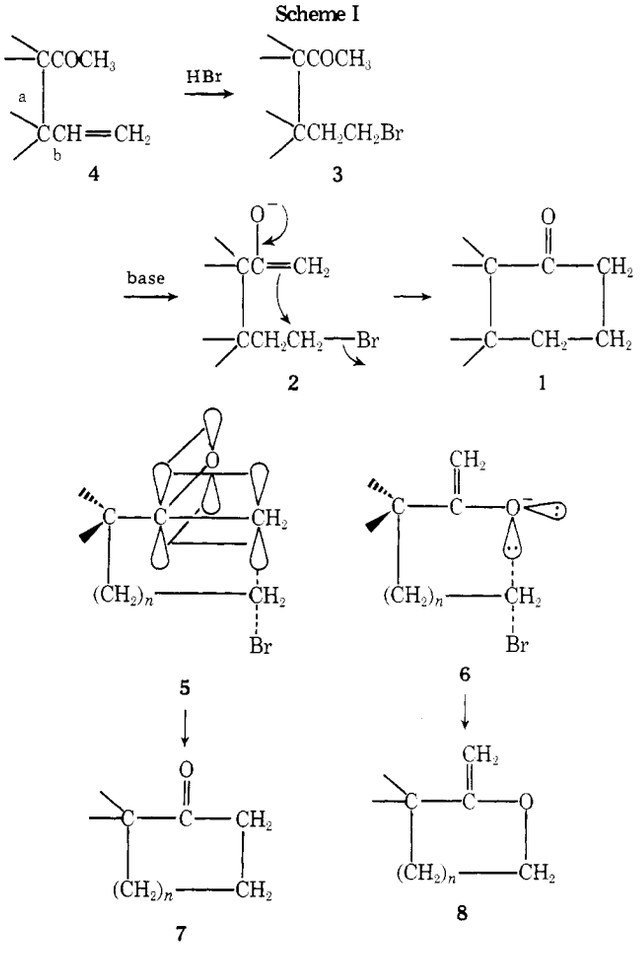
Utilizing *stable solutions* of *i*-Pr_2NLi in hexane, a convenient procedure is described for the conversion of methyl ω-bromoalkyl ketones **9–12**, **32**, **42**, **50**, and **67** to mixtures of Li^+ enolates containing predominantly the terminal enolates. Although solutions of these Li^+ enolates in Et_2O–hexane mixtures are stable at 0 °C, when activating ligands such as 4 molar equiv of HMP [$(Me_2N)_3PO$], 1 molar equiv of triglyme (**15**) or the 14-crown-4 ether **16**, or excess DME are added these Li^+ enolates undergo intramolecular cyclization reactions. In the absence of serious geometrical constraints (cf. bromo ketone **32**), the enolates of bromo ketones **9–12** underwent intramolecular C-alkylation to form the corresponding cyclohexanone derivatives in 60–80% yield. Similar intramolecular cyclization by bromo ketone **67** produced a mixture of five-membered and seven-membered C-alkylated products, but intramolecular cyclization of the bromo ketone **42** yielded only the five-membered O-alkylated product **43**. The Li^+ enolate of bromo ketone **50** underwent a very slow intramolecular cyclization to produce a mixture of O-alkylated and C-alkylated four-membered ring products. Thus, the method described constitutes a useful synthetic route to cyclohexanone derivatives and, with limitations, is also applicable to the synthesis of cycloheptanone derivatives.

The most common synthetic routes to cyclohexane derivatives involve the reduction of benzene derivatives, use of the Diels–Alder reaction to form intermediate cyclohexenes, or use of the Robinson annulation technique (or related procedures) to form intermediate cyclohexenones. It seemed to us that another rather general synthetic route to cyclohexanone derivatives **1** (Scheme I) could be based on the cyclization of a regiospecifically generated metal enolate **2** derived from an ω-bromo ketone **3**. We have noted elsewhere[2] that the requisite ω-bromo ketones **3** can readily be obtained by addition of HBr to the vinyl ketones **4** in a free-radical chain process. The vinyl ketone precursors **4** can generally be assembled either by addition of a $(vinyl)_2CuLi$ reagent to an enone to form bond b in **4** or by allylation of a regiospecifically generated metal enolate to form bond a in **4**.

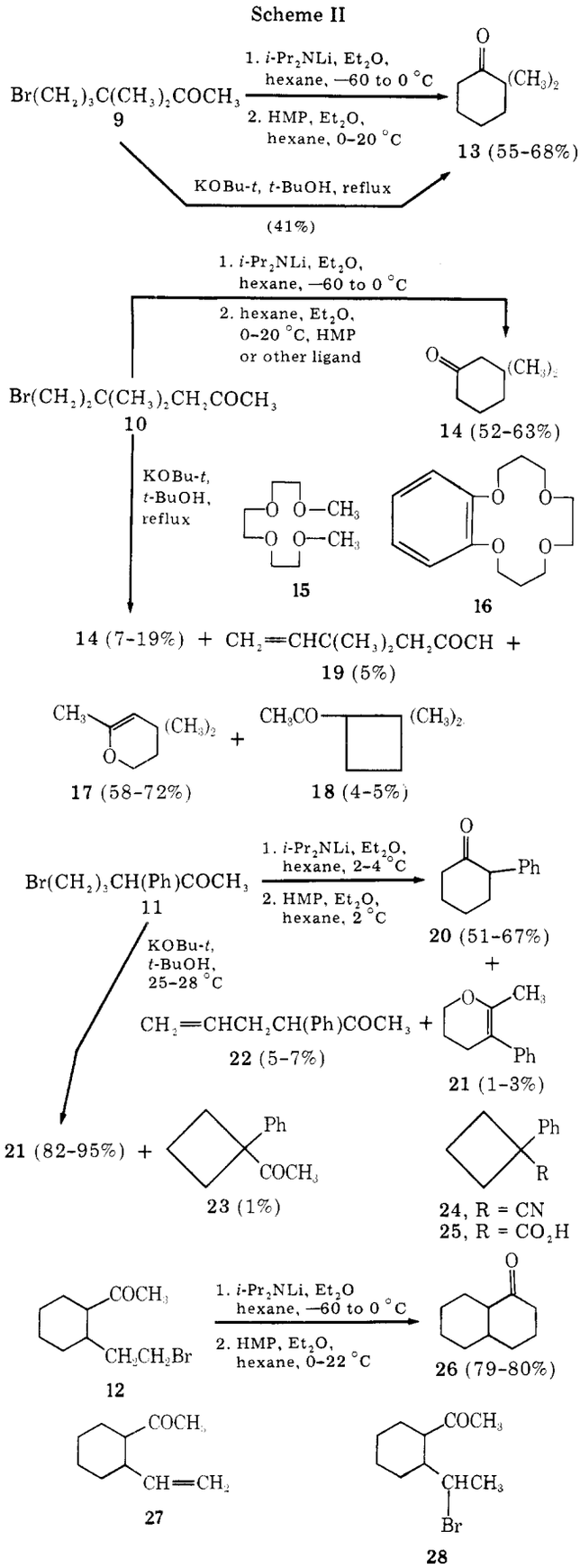
Superficially the intramolecular C-alkylation reaction (arrows in structure **2**) would appear to be straightforward. However, when one imposes the geometrical constraints that the nucleophile (the enolate α-carbon atom) attack along a path collinear with the C–Br bond[3] and that the electron density at the α carbon of the enolate is concentrated in orbitals perpendicular to the plane of the enolate anion, then the transition state required for this intramolecular C-alkylation is represented by structure **5**. In this transition state **5** three of the carbon atoms lie in a plane perpendicular to the forming C–C bond. Study of molecular models indicates that this transition state **5** can be attained without excessive distortion of normal carbon bond angles when *n* has values of two or larger to form cyclic ketones **7** with six or more ring members. However, substantial distortion of normal carbon bond angles is required to attain the transition state **5** when *n* has values one or zero. In such cases an alternative transition state **6** in which the forming C–O bond lies in the plane of the enolate anion with a nonbonded electron pair on the oxygen atom

Scheme I



0022-3263/78/1943-0700$01.00/0

Scheme II



serving as the nucleophile seems much more attractive. In short, these geometrical considerations suggest that these intramolecular alkylation reactions **5** → **7** should be favorable (or at least feasible) when ketones with six or more ring members (**7**, n = 2, 3, etc.) are being formed, but should be unfavorable for the formation of four- and five-membered ketones (**7**, n = 0, 1). In these latter cases either intramolecular O-alkylation **6** → **8** or intermolecular reactions might be expected.

Generation of Enolates and the Formation of Six-Membered Rings. To explore these considerations experimentally, we have examined the behavior of various metal enolates derived from the previously described[2] bromo ketones. Scheme II summarizes our study of bromo ketones **9**–**12** that could be converted to six-membered cyclic ketones. The bromo ketones **3** were converted to the intermediate terminal enolates **2** by the slow addition of the ketones to a slight excess of the strong, sterically hindered base, i-Pr_2NLi, dissolved in a cold (−60 to 0 °C) mixture of Et_2O and hexane (typically 9:1 v/v). This kinetically controlled deprotonation procedure is known[4] to convert methyl n-alkyl ketones to mixtures of lithium enolates in which the terminal enolate predominates (typically 85% of the enolate mixture) and the proportion of the terminal enolate is even larger (typically 95%) when branching is present at the α-carbon atom of the alkyl group. The regiospecificity of this enolate generation procedure is illustrated by the conversion of the ketone **11** to its terminal enolate (and subsequently to the ketone **20**) in spite of the fact that the internal enolate, stabilized by a phenyl substituent, is substantially more stable at equilibrium. Note that conversion of ketone **11** to its enolates under equilibrating conditions (KOBu-t in t-BuOH) yielded only products **21** and **23** derived from the more stable internal enolate.

Since i-Pr_2NLi is a sufficiently strong base to deprotonate and cleave solvents such as Et_2O, THF, and especially DME and HMP [$(Me_2N)_3PO$] at temperatures above 0 °C, it is not practical to prepare stock solutions of i-Pr_2NLi in these solvents. However, we have found that if commercial solutions of n-BuLi in hexane are diluted with additional hexane or pentane and then treated with 1 molar equiv of i-Pr_2NH, *stable solutions* of i-Pr_2NLi (0.5–0.6 M) in hexane or hexane–pentane mixtures are formed. Provided that these hexane solutions are not cooled or concentrated to induce the irreversible separation of solid i-Pr_2NLi, they may be standardized (titration with 2,2′-bipyridyl indicator) and stored at 25 °C without deterioration for weeks. Thus, it is especially convenient to prepare solutions of i-Pr_2NLi for reactions by adding a known volume of the stable hexane solution to the desired volume of cold (<0 °C) ethereal solvent such as Et_2O or THF.

Utilizing the above procedures, we were able to generate 0.05 M solutions (dilute solutions were used to disfavor intermolecular reactions) of the lithium bromoenolates **2** from each of the various bromo ketones studied. At 0 °C in Et_2O–hexane solution these lithium bromoenolates (which are presumably aggregated as dimers, trimers, tetramers, etc.) were stable to further change for at least 1 h, allowing us first to prepare solutions of the lithium bromoenolates **2** and then to activate these bromoenolates for further reactions by adding ligands such as HMP (4 molar equiv/Li^+), DME (excess), triglyme (**15**, 1 molar equiv/Li^+), or the 14-crown-4 ether **16** (1 mol equiv/Li^+).[5] Among these activating ligands, stoichiometric amounts of HMP appeared to be most effective with stoichiometric amounts of either triglyme (**15**) or the crown **16**, affording slightly lower yields in the conversion of bromo ketone **10** to ketone **14**. In reactions where the polyethers **15** or **16** were used, as the reaction proceeded the LiBr produced formed Et_2O-insoluble complexes with these polyethers, facilitating the separation of these materials from the remaining reaction products.

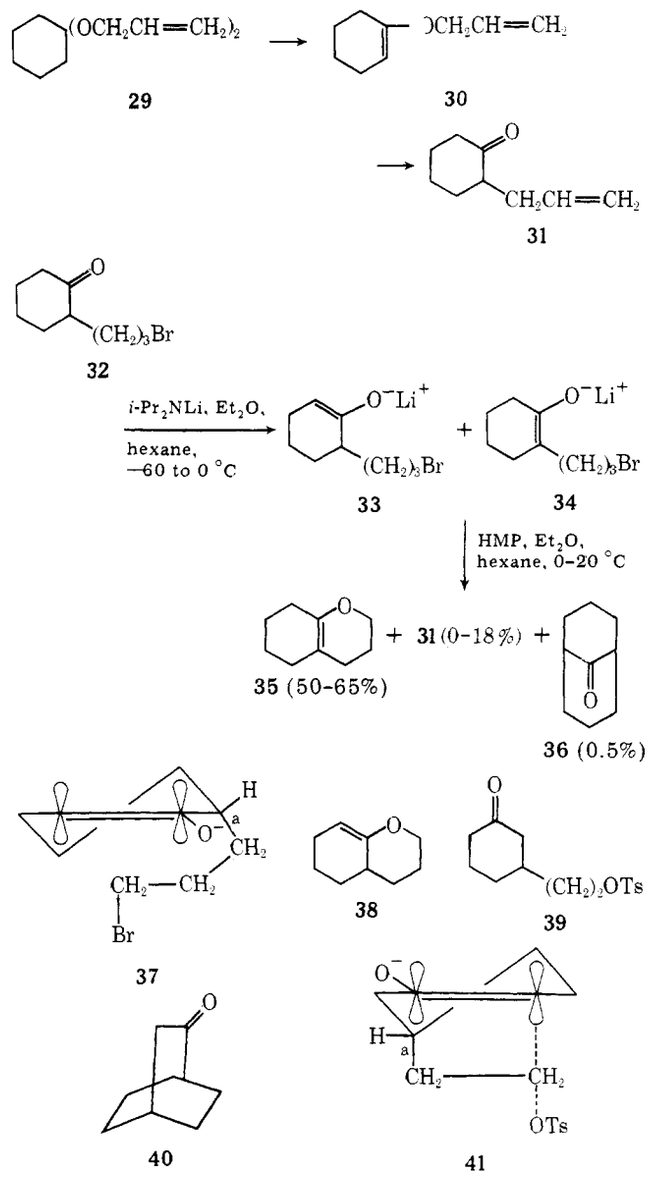
Utilizing the above procedures to generate and activate the lithium bromoenolates **2**, each of the acyclic bromo ketones **9**,[6] **10**, and **11** could be converted to the corresponding six-membered cyclic ketone **13**, **14**, or **20** in 60–70% by reaction at 0–20 °C for 1 h. Even with bromo ketones **10** and **11**, where

two structurally isomeric enolates could be formed, by-products derived from the internal enolate (e.g., **21**) were minor. In each of these cyclizations (**9–11**), the main by-product was a complex mixture of higher molecular weight compounds that was apparently derived from intermolecular reaction of the bromoenolate **2** either with itself or with the reaction product. When the bromo ketones **10** and **11** were converted to their enolates with KOBu-*t* in *t*-BuOH (conditions that allow enolate equilibration), the major products **17**, **18**, **21**, and **23** were derived from the internal enolates and the typical preference for forming a six-membered ring by O-alkylation (**17** and **21**) rather than a four-membered ring by C-alkylation (**18** and **23**) was observed. When one considers the relative rates of ring closure of the enolates derived from KOBu-*t* and the malonates $(Cl)Br(CH_2)_nCH(CO_2Et)_2$ [3-ring > 5-ring > 6-ring > 4-ring],[7] where incorporation of the entire planar enolate system into the cyclic transition state (i.e., structure **5**) is not required, the fact that we observe relatively little 6-ring C-alkylation with bromo ketones **10** and **11** under equilibrating conditions suggests that the transition state **5** (n = 2), although attainable, must still possess significant strain. The formation of appreciable quantities of by-product from intermolecular reaction, even at relatively low enolate concentrations, is also in keeping with this idea.

When we turned our attention to the cyclization of the bromo ketone **12**, a compound in which the derived terminal enolate and the C–Br bond are held in positions favorable for attaining the transition state **5** (n = 2), the yield of intramolecularly cyclized product **26** was significantly improved. We have observed this phenomenon with other cyclizations of bromo ketones to form bicyclic products that will be reported elsewhere.

The foregoing results demonstrate that the projected cyclization **3** → **2** → **1** can be a viable synthetic route to six-membered cyclic ketones, although there is an indication of strain in the six-membered transition state **5** (n = 2) leading to products. One can then anticipate that adding other structural features that would be unfavorable to attaining this transition state **5** (n = 2) would prevent formation of a cyclohexanone derivative. This idea is illustrated by the behavior of the bromo ketone **32** (Scheme III). In an earlier study,[8] reaction of this ketone **32** with KOBu-*t* (equilibrating conditions) in PhH was found to yield the O-alkylated product **35** that would be derived from the *more stable* enolate **34**. We have now treated this bromo ketone **32** with *i*-Pr_2NLi under conditions that will clearly favor formation of the less stable, but kinetically favored, enolate **33**.[4] After activation with HMP, this mixture of enolates **33** and **34** underwent a relatively slow reaction (accompanied by enolate equilibration) to form the same enol ether **35** observed earlier with only a very minor product corresponding to the cyclohexanone derivative **36**. Although we found no indication of the presence of the isomeric enol ether **38**, we cannot exclude the possibility that this substance **38** was destroyed or isomerized during our isolation procedure. We attribute the failure of enolate **33** to form the cyclohexanone **36** to the geometrical problem illustrated in structure **37**. Since the enolate **33** can at best only adopt a conformation with the bromoalkyl side chain on a pseudoaxial bond (bond a in structure **37**) which is not perpendicular to the plane of the enolate, considerable distortion would be required to obtain the collinear arrangement C···C···Br needed in the transition state **5** for C-alkylation. In contrast, reaction of the related keto tosylate **39** with NaH in DME produced the bicyclic ketone **40** in good yield.[8] As indicated in structure **41**, the enolate derived from ketone **39** can adopt a conformation with the tosyloxyalkyl side chain on a normal axial bond (bond a in structure **41**) allowing the collinear arrangement needed for C-alkylation. Further support for this explanation is found in the successful C-alkylations performed with enolates similar to enolate **33**, but possessing four-carbon ω-haloalkyl side chains.[9]

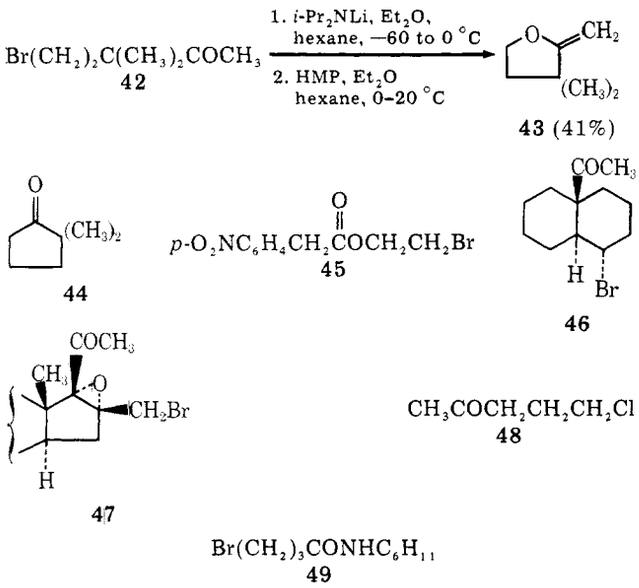
Scheme III



The Formation of Five- and Four-Membered Rings. Application of the previously discussed procedure for the formation and activation of the enolate to the bromo ketone **42**[6] (Scheme IV) resulted in the formation of the enol ether **43** and a complex mixture of higher molecular weight products (presumably formed by intermolecular reactions). However, none of the C-alkylated product **44** was detected, supporting the earlier hypothesis that it would be very difficult to attain the geometry required for the transition state **5** (n = 1). Earlier examples of bromocarbonyl compounds that have reacted with bases to form enol ethers (O-alkylation) rather than five-membered carbonyl compounds (C-alkylation) include the bromo ester **45**[10] and bromo ketones **46**[11] and **47**.[12] Related phenomena include the reaction of the chloro ketone **48** with base to form only methyl cyclopropyl ketone and no cyclopentanone[13] and the cyclization of the bromo amide **49** to form an O-alkylated imino ether rather than an N-alkylated lactam.[14] All of these examples support the general idea that the synthetic sequence **5** → **7** is unlikely to be a satisfactory route to cyclopentanone derivatives **7** (n = 1).

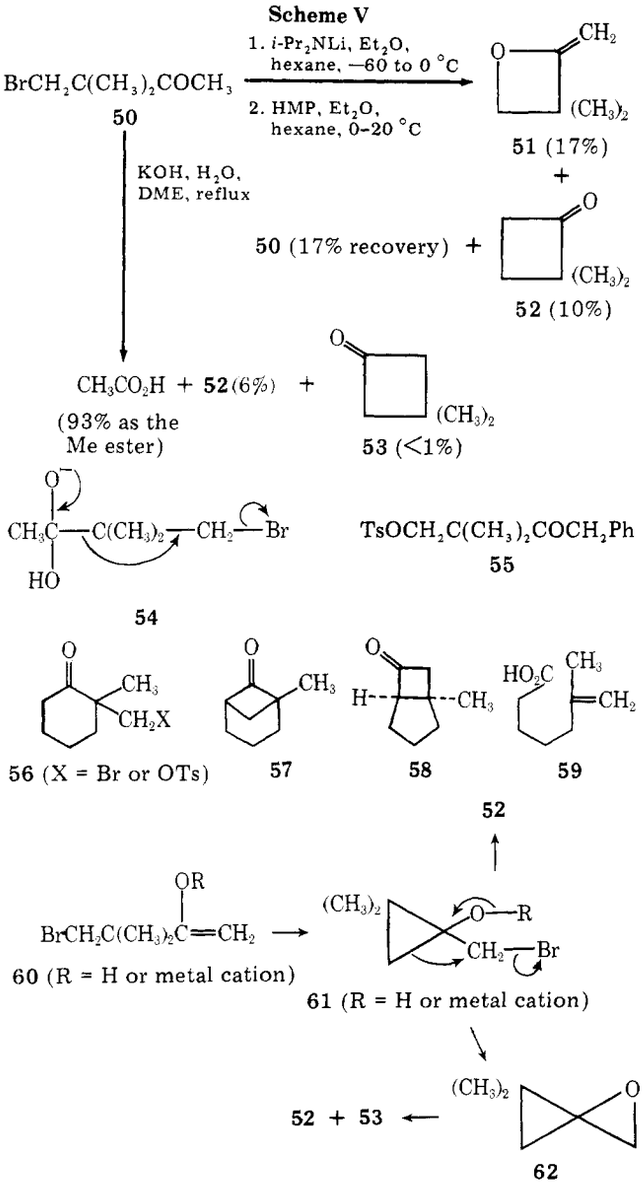
Conversion of the bromo ketone **50** (Scheme V) to its Li^+ enolate followed by activation with HMP resulted in a very slow reaction (part of the bromo ketone **50** was recovered after

Scheme IV



reaction for 2.5 h) to form a mixture of comparable amounts of the enol ether **51** and the cyclobutanone **52** as well as a mixture of higher molecular weight materials. A similar mixture of O-alkylated and C-alkylated products was reported[15] from the reaction of the tosyloxy ketone **55** with NaH or KH in THF. Although the formation of O-alkylated products such as **51** by way of a transition state of the type **6** (n = 0) is reasonable, the formation of the cyclobutanone products (e.g., **52**) by a normal S_N2 displacement (structure **5**, n = 0) seems most improbable. A further indication that a different pathway may be involved in cyclobutanone formation is provided by earlier studies of the reactions of the related bromo (or tosyloxy) ketones **56**.[16] The reaction of this ketone **56** with KOH or NaOH in a polar, partially aqueous solvent (H_2O–dioxane, H_2O–MeOH) produced a mixture of the "expected" cyclobutanone **57**, the rearranged cyclobutanone **58** (frequently the major product), and the acid **59** resulting from fragmentation. When we subjected the bromo ketone **50** to similar reaction conditions (KOH in refluxing H_2O–DME), the major product was NaOAc from fragmentation (see structure **54**) accompanied by lesser amounts of the "expected" cyclobutanone **52** and the rearranged cyclobutanone **53**.

Scheme V

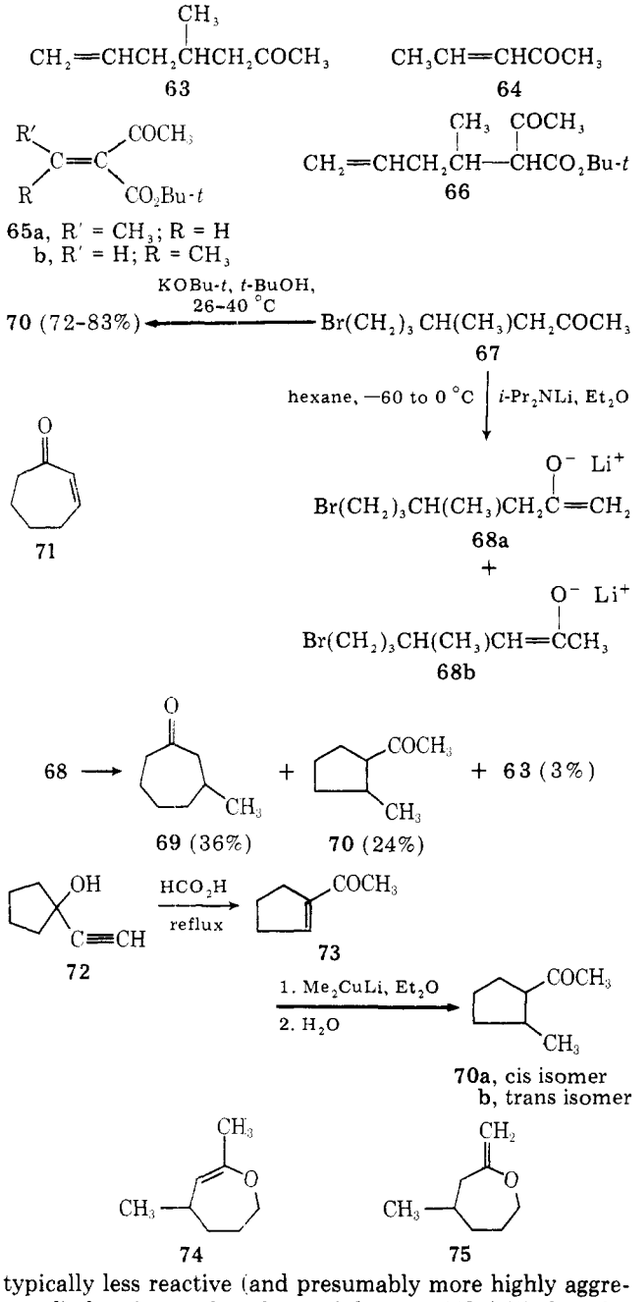


A possible interpretation of these results would involve the initial solvolytic rearrangement of the bromoenol (or enolate) **60** to the cyclopropanol derivative **61** (or the related cyclopropylcarbinyl cation, cf. ref 16d). This rearrangement **60** → **61** is, of course, an example of the homoallyl → cyclopropylcarbinyl rearrangement. Further base-catalyzed rearrangement of this intermediate (arrows in **61**) or conversion to the oxaspiropentane **62** followed by rearrangement would provide pathways to the cyclobutanones **52** and **53**. Since the oxaspiropentane **62** is known[17] to rearrange to a mixture of ketones **52** (minor) and **53** (major) when treated with various Lewis acids including Li^+ salts, the fact that the rearranged cyclobutanone **53** was, at most, the minor product in our reaction indicates that the oxaspiropentane **62** is not an important intermediate in the reactions we have studied.

The Formation of a Seven-Membered Ring. We had previously obtained the olefinic precursor **63** (Scheme VI) for the bromo ketone **67** by a rather inefficient oxy-Cope rearrangement.[2] Although this precursor **63** can also be obtained by the reaction of the enone **64** with $(CH_2{=}CHCH_2)_2CuLi$,[18] use of the more readily accessible organometallic reagent, $CH_2{=}CHCH_2MgBr$, with the enone **64** gave primarily the 1,2-addition product even in the presence of added Me_2SCuBr catalyst. To explore the possibility that Cu-catalyzed conjugate addition of $CH_2{=}CHCH_2MgBr$ would be more efficient with a substrate having a less negative reduction potential than enone **64** (E_{red} = −2.08 V vs. SCE), we prepared the enones **65** (E_{red} = −1.80 and −1.79 V vs. SCE). The Cu-catalyzed addition of $CH_2{=}CHCH_2MgBr$ to the enone **65** produced cleanly the conjugate adduct **66** that could be cleaved and decarboxylated to form the unsaturated ketone **63**.

The usual reaction of the bromo ketone **67** with i-Pr_2NLi followed by activation of the resulting enolate with HMP resulted in a slow reaction (about 2 h at 0 °C was required for complete reaction) to form a mixture of comparable amounts of the five- and seven-membered ring products **70** and **69**. Authentic samples of these products were obtained by addition of Me_2CuLi to the enones **71** and **73**. Conversion of the bromo ketone **67** to its enolates under equilibrating conditions (KOBu-t in t-BuOH or KH in DME) resulted in the formation of only the five-membered ring C-alkylated product **70** accompanied by minor amounts of two by-products that may be the enol ethers **74** and **75**. This result indicates that cyclization of the enolate **68b** to **70** is more rapid than cyclization of enolate **68a** to **69**. The formation of comparable amounts of five-membered (**70**) and seven-membered (**69**) C-alkylated products from cyclization of the kinetically generated mixture of Li^+ enolates **68** (mainly **68a**) is thus attributable to a combination of three factors: (1) cyclization **68b** → **70** is faster than cyclization **68a** → **69**; (2) terminal enolates such as **68a** are

Scheme VI



typically less reactive (and presumably more highly aggregated) than internal enolates of the type **68b**;[4] (3) the relatively slow cyclization **68a** → **70** allows time for enolate equilibration (**68a** ⇌ **68b**) to compete with the desired cyclization process. By varying the temperature used for this cyclization from the usual range 0–20 °C to 25 °C we were able to shorten the time required for the cyclization from 2 h to 1 h and to increase the ratio of seven-membered (**69**) to five-membered (**70**) products from 44:56 to 60:40. However, it appears that the best way to increase substantially the proportion of seven-member cyclization product is to utilize systems with an alkyl substituent at the α carbon of the ω-bromoalkyl methyl ketone (which will diminish both the equilibrium concentration and the reactivity of the internal enolate)[4] and to use more rigid bromo ketone substrates analogous to **12** in order to increase the rate of the desired cyclization to a seven-membered ring product. Bromo ketone substrates incorporating these features are being prepared and the study of their cyclization will be reported subsequently.

Experimental Section[19]

Preparation of *i*-Pr_2NLi. After 22.8 mL of a hexane solution containing[20] 34.2 mmol of *n*-BuLi (Foote Mineral Co.) had been diluted with 30 mL of anhydrous pentane, 4.15 g (41.5 mmol) of *i*-Pr_2NH was added dropwise and with stirring during 45 min. Titration[20] of the resulting colorless solution of *i*-Pr_2NLi with a 2,2′-bipyridyl indicator indicated the concentration of the amide to be 0.53 M; at the end point of this titration the color of the solution changed from dark brown to pale yellow green. Such solutions of *i*-Pr_2NLi in pentane–hexane mixtures were stable for weeks at 25 °C provided that they were not cooled or concentrated to induce the irreversible separation of solid *i*-Pr_2NLi.

Preparation of Starting Materials. A. Known Bromo Ketones. Previously described procedures[2] were used to obtain samples of bromo ketones **9**, **10**, **11**, **42**, and **50**.

B. Bromo Ketone 12. The previously described[2] light-catalyzed addition of HBr to 1.500 g (9.87 mmol) of the vinyl ketone **27** in 300 mL of anhydrous pentane yielded 2.22 g (96.5%) of the crude bromo ketone **12** as a pale yellow liquid. Low-pressure liquid chromatography on silica gel (Woelm 0.032–0.064 mm) with an EtOAc–hexane eluent (7:93 v/v) separated 101 mg (4.5%) of early liquid fractions containing (NMR analysis) mainly the secondary bromo ketone **28** accompanied by ~33% of the primary bromo ketone **12**: IR (CCl_4) 1712 cm^{-1} (C=O); NMR (CCl_4) δ 4.23 (q, J = 7 Hz, additional splitting not resolved, CHBr of **28**), 3.38 (m, CH_2Br of **12**), and a multiplet in the region 0.9–2.8 upon which were superimposed singlets at 2.13 (CH_3CO of **28**) and 2.08 (CH_3CO of **12**) and a doublet (J = 7 Hz) at 1.67 (CH_3 of **28**). Later chromatographic fractions contained (NMR analysis) 1.802 g of the primary bromide **12** not contaminated with the isomer **28**. Distillation afforded 1.398 g (60.8%) of the pure bromide **12** as a colorless liquid, bp 76.5–77 °C (0.02 mm), $n^{25}D$ 1.4988–1.4992, as well as 166 mg of less pure bromide in the forerun, bp 76–77 °C (0.02 mm), $n^{25}D$ 1.4990. The spectral properties of the pure bromo ketone **12** were: IR (CCl_4) 1708 cm^{-1} (C=O); NMR (CCl_4) δ 3.2–3.6 (2 H, m, CH_2Br) and 0.9–2.4 (15 H, m, aliphatic CH including a CH_3 singlet at 2.08); mass spectrum m/e (rel intensity) 234 (M^+, <1), 232 (M^+, <1), 153 (20), 109 (21), 81 (11), 67 (19), 55 (13), 43 (100), and 41 (17).

Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.52; H, 7.36; Br, 34.27. Found: C, 51.59; H, 7.37; Br, 34.30.

C. Bromo Ketone 32. Use of a previously described procedure[21a] formed the acetal **29**, bp 96–98 °C (10 mm), $n^{25}D$ 1.4597 [lit.[21a] bp 98 °C (10 mm), $n^{25}D$ 1.4600], in 67% yield. Conversion of the acetal **29** to the enol ether **30** accompanied by rearrangement[21b] formed the ketone **31** in 90% yield: bp 86–88 °C (15 mm); $n^{25}D$ 1.4672 [lit.[21b] bp 86–88 °C (15 mm); $n^{25}D$ 1.4670]; IR (CCl_4) 1715 (C=O), 1640 (C=C), and 920 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.7–6.0 (3 H, m, vinyl CH) and 1.2–2.7 (11 H, m, aliphatic CH). The previously described[2] light-catalyzed addition of HBr to 1.38 g (10 mmol) of the unsaturated ketone **31** in 300 mL of anhydrous pentane yielded 2.02 g (92%) of the crude bromo ketone **32** as a pink liquid. Distillation afforded 1.87 g (85%) of the pure bromo ketone **32** as a colorless liquid: bp 99–100 °C (0.3 mm); $n^{25}D$ 1.5035 [lit.[22] bp 74–76 °C (0.05 mm)]; IR (CCl_4) 1712 cm^{-1} (C=O); NMR (CCl_4) δ 3.37 (2 H, t, J = 7 Hz, CH_2Br) and 1.1–2.6 (13 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 220 (M^+, <1), 218 (M^+, <1), 139 (100), 138 (28), 111 (20), 110 (34), 109 (20), 98 (24), 95 (44), 81 (31), 69 (34), 67 (28), 55 (56), 41 (41), and 39 (23).

Anal. Calcd for $C_9H_{15}BrO$: C, 49.32; H, 6.85; Br, 36.53. Found: C, 49.35; H, 6.91; Br, 36.39.

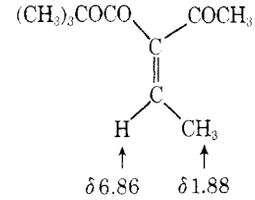
D. Enone 65. To a cold (−6 °C) mixture of 79.0 g (500 mmol) of the keto ester $CH_3COCH_2CO_2Bu$-*t* and 26.4 g (600 mmol) of CH_3CHO was added, dropwise with stirring and cooling (−6 to −1 °C) during 10 min, a solution of 2.2 g (26 mmol) of piperidine in 10 mL of EtOH. After the resulting mixture had been stirred at −6 to −1 °C for 30 min, it was allowed to stand at −22 °C for 45 h and then partitioned between Et_2O and aqueous NH_4Cl. The ethereal layer was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried, concentrated, and distilled to separate 66.23 g (70%) of the enone **65**, bp 83–105 °C (4.3 mm), $n^{25}D$ 1.4415–1.4434 [lit.[23] bp 95–96 °C (9 mm), $n^{20}D$ 1.4457]. This product contained (TLC, silica gel coating with an Et_2O–pentane eluent, 1:1 v/v) a mixture of isomer **65a** (R_f 0.58) and isomer **65b** (R_f 0.43). A 1.132-g aliquot was subjected to low-pressure liquid chromatography on silica gel with an Et_2O–hexane eluent (2:3 v/v) to separate early fractions containing 244 mg of isomer **65a**, $n^{25}D$ 1.4408, 542 mg of intermediate fractions containing (TLC) mixtures, and finally fractions containing 80 mg of isomer **65b**, $n^{25}D$ 1.4466. The spectral properties of isomer **65a** follow: IR (CCl_4) 1722 (ester C=O), 1708 (C=O), and 1640 cm^{-1} (weak, C=C); UV (95% EtOH) end absorption with ϵ 6900 at 210 nm; NMR (CCl_4) δ 6.86 (1 H, q, J = 7 Hz, vinyl CH), 2.28 (3 H, s, $COCH_3$), 1.88 (3 H, d, J = 7 Hz, CH_3), and 1.52 (9 H, s, *t*-Bu); mass spectrum m/e (rel intensity) 169 (1), 128 (32), 111 (44), 69 (45), 57 (100), 43 (56), and 41 (59).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.92; H, 8.81.

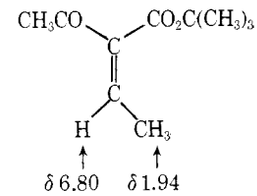
The spectral properties of isomer **65b** follow: IR (CCl_4) 1725 (ester C=O), 1700, 1682 (C=O), 1645, and 1628 cm^{-1} (C=C); UV max (95% EtOH) 217 nm (ε 8400); NMR (CCl_4) δ 6.80 (1 H, q, J = 7 Hz, vinyl CH), 2.21 (3 H, s, CH_3CO), 1.94 (3 H, d, J = 7 Hz, CH_3), and 1.54 (9 H, s, t-Bu); mass spectrum m/e (rel intensity), 169 (2), 129 (60), 128 (43), 113 (23), 111 (94), 74 (43), 69 (73), 57 (100), 43 (80), 41 (56), and 39 (40).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.22; H, 8.78.

We have tentatively assigned the stereochemistry indicated in structures **65a** and **65b** to these two geometrical isomers based upon

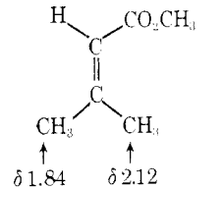


65a [UV end absorption with ε 6900 at 210 nm]



65b [UV max 217 nm (ε 8400)]

the differences in their ^1H NMR (CCl_4) and UV (95% EtOH) spectra. It has been noted that a carboalkoxy group (see structure **76**) will normally cause a larger downfield shift than an acetyl group (see structure **77**) on the NMR signal of a *cis*-methyl group.[24] This cor-



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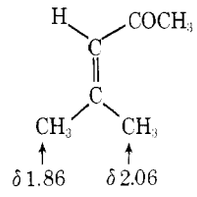

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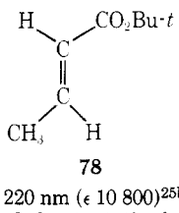
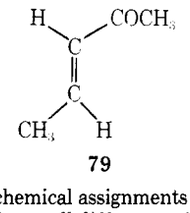
relation would argue that the isomer with the lower field allylic CH_3 group should be assigned structure **65b**. Also based on the expectation that the group cis to the methyl group is more likely to be twisted away from coplanarity with the remainder of the π system, it is reasonable to assume that the UV spectrum of isomer **65a** will resemble the spectrum of ester **78** [UV max (95% EtOH) 205 nm (ε 11 600)[25a]] while the spectrum of isomer **65b** should resemble enone **79** [UV max (95%



78



79

EtOH) 220 nm (ε 10 800)[25b]]. These stereochemical assignments must be regarded as tentative both because of the small differences in the spectra and because of uncertainty about the predominant conformations of the two carbonyl functions in each isomer.

Polarographic measurments[26] of the enones **65** employed a custom-made polarographic module utilizing solid-state amplifiers that followed the typical three-electrode design. Descriptions of the cell, working electrodes, reference electrode, reagent purification, and measurement procedures have been published previously.[27] Solutions in anhydrous DMF containing 0.5 M n-Bu_4NBF_4 and 1.2–2.3 × 10^{-3} M enone **65a** exhibited a polarographic $E_{1/2}$ value of −1.80 V vs. SCE (n = 1.4, i_d = 6–18 μA). A comparable measurement of solutions in anhydrous DMF containing 0.5 M n-Bu_4NBF_4 and 1.9–2.1 × 10^{-3} M enone **65b** gave a polarographic $E_{1/2}$ value of −1.79 V vs. SCE (n = 1.3, i_d = 12–13 μA).

E. Keto Ester 66. To a cold (−74 °C) solution of 8.40 g (40.8 mmol) of Me_2SCuBr[28] and 25.00 g (136 mmol) of the enone **65** (a mixture of stereoisomers) in 35 mL of Me_2S and 450 mL of Et_2O was added, dropwise with stirring and cooling (−73 to −74 °C) during 130 min, 170 mL of an ethereal solution containing 151 mmol of CH_2=$CHCH_2MgBr$. The reaction mixture, a pale yellow suspension that became brownish red in color as the last of the Grignard reagent was added, was stirred at −73 to −74 °C for 30 min and then allowed to warm to 20 °C with stirring during 135 min. The reaction solution was siphoned into a stirred aqueous solution of aqueous NH_3 and NH_4Cl and then extracted with Et_2O. After the ethereal solution had been washed successively with aqueous NH_4Cl and with aqueous NaCl, it was dried and concentrated to leave 36.6 g of crude yellow liquid product. Distillation separated 1.13 g of forerun, bp 84–87 °C (1.6 mm), n^{25}_D 1.4379, and 23.16 g (75%) of the keto ester **66**, bp 88–89 °C (1.6 mm), n^{25}_D 1.4396–1.4402, that contained (TLC, silica gel coating with an Et_2O–hexane eluent, 3:7 v/v) the keto ester **66** (R_f 0.38) and several very minor impurities. A portion of this product was chromatographed on silica gel with Et_2O–hexane mixtures as the eluent to separate the pure (TLC) keto ester **66** as a colorless liquid: n^{25}_D 1.4400; IR (CCl_4) 1750 (shoulder, ester C=O), 1716 (C=O), 1642 (C=C), and 922 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.8–6.0 (3 H, m, vinyl CH), 3.0–3.2 (1 H, m, COCHCO of two diastereoisomers), 1.5–2.6 (6 H, m, aliphatic CH including a CH_3CO singlet at 2.11), 1.42 (9 H, s, t-Bu), and 0.8–1.1 (3 H, m, CH_3 of two diastereoisomers); mass spectrum m/e (rel intensity) 170 (7), 153 (7), 111 (22), 69 (48), 68 (100), 59 (20), 57 (71), 43 (88), and 41 (48).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.02; H, 9.84.

Although the same keto ester **66** was formed by the reaction of the enone **65** with CH_2=$CHCH_2MgBr$ in the absence of Me_2SCuBr, the crude reaction product contained (TLC) additional products not present in the copper-catalyzed reactions.

F. Unsaturated Ketone 63 and Bromo Ketone 67. To a warm (72 °C) solution of 4.70 g (24.8 mmol) of p-TsOH in 275 mL of PhH was added rapidly a solution of 13.6 g (60.2 mmol) of the keto ester **66** in 50 mL of PhH. The resulting solution, from which gas evolution was vigorous at temperatures above 70 °C, was heated to 72–74 °C[29] for 45 min and then cooled rapidly, diluted with Et_2O, and washed successively with aqueous $NaHCO_3$ and with aqueous NaCl. After the organic solution had been dried and concentrated, fractional distillation separated 5.09 g (65%) of the pure (GLC, IR, and NMR analyses) ketone **63**: bp 79 °C (43 mm), n^{25}_D 1.4272–1.4277 [lit.[2] bp 85 °C (56 mm), n^{25}_D 1.4251–1.4254]. The unsaturated ketone **63** was converted to the bromo ketone **67** by the previously described procedure.[2]

Cyclization Studies. A. General Procedure for Bromo Ketone 9 with *i*-Pr_2NLi. To a cold (−60 °C) solution of 10.5 mmol of *i*-Pr_2NLi, 19.8 mL of a pentane–hexane mixture, and several milligrams of 2,2′-bipyridyl (an indicator) in 155 mL of Et_2O was added, dropwise and with stirring at −60 °C during 30 min, a solution of 2.07 g (10.0 mmol) of the bromo ketone **9** in 20 mL of Et_2O. The resulting pale yellow (excess *i*-Pr_2NLi) solution of the lithium enolate (~0.05 M) was warmed to 0 °C, treated with 7.53 g (42 mmol, 4 equiv/Li^+) of HMP [bp 70–71 °C (1.5 mm), freshly distilled from a blue solution of Na], and then stirred at 0 °C for 30 min and at 0–20 °C for 30 min. A white precipitate separated from the pale yellow solution during the reaction period. After the reaction mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic phase was dried and concentrated to leave 1.221 g of yellow liquid product. After an aliquot of this crude product had been mixed with a known amount of internal standard (n-$C_{12}H_{26}$), GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of n-$C_{12}H_{26}$ (retention time 21.1 min), the ketone **13** (28.8 min, 68% yield), and several minor, rapidly eluted impurities; none of the unchanged bromo ketone **9** was detected by NMR or GLC analysis. A 960-mg aliquot of the crude product was chromatographed on silica gel (Et_2O–hexane eluent, 1:9 v/v) to separate in the early fractions 2.0 mg of liquid believed to be the enol ether [IR (CCl_4) 1680 cm^{-1} (enol ether C=C)] and 5.0 mg of the crude known[2] unsaturated ketone CH_2=$CHCH_2C(CH_3)_2COCH_3$. Subsequent fractions contained 557 mg (58%) of the ketone **13**; distillation gave 524 mg (55%) of the ketone **13** as a colorless liquid, bp 89.5–90 °C (55 mm), n^{25}_D 1.4458 [lit.[30b] bp 170–170.5 °C (761 mm)], that was identified with an authentic sample[30a] by comparison of IR, NMR, and mass spectra.

Subsequent chromatographic fractions, eluted with Et_2O–hexane mixtures, contained a total of 186 mg of viscous colorless to yellow liquids. The fractions were complex mixtures exhibiting IR absorption (CCl_4) attributable to both OH (3600, 3420 cm^{-1}) and C=O functions (1710 cm^{-1}). Thus, these by-products are apparently higher molecular weight products formed from the bromo ketone **9** and/or ketone product **13**. When a comparable cyclization was performed employing a higher concentration of enolate (ca. 0.12 M) from bromo ketone **9**, the yield of the ketone **13** (62%, GLC analysis) was lower.

B. General Procedure for Bromo Ketone 9 with KOBu-*t*.[31] To a solution of 5.0 mmol of KOBu-t in 10 mL of t-BuOH was added, dropwise and with stirring at 25 °C during 10 min, a solution of 1.012 g (4.9 mmol) of the bromo ketone **9** in 10 mL of pentane. During this addition the solution changed from colorless to yellow to dark tan in color with separation of a white precipitate. After the resulting mixture had been stirred at 25–28 °C for 15 min, it was refluxed for 45 min

and then partitioned between H_2O and pentane. The organic phase was dried and concentrated to leave 611 mg of crude product as a red liquid. After an aliquot of the crude product had been mixed with an internal standard (n-$C_{12}H_{26}$), GLC analysis indicated that all of the bromo ketone **9** was gone and the yield of ketone **13** was 41%. A collected (GLC) sample of product **13** was identified with an authentic sample[30a] by comparison of IR, NMR, and mass spectra. When an analogous reaction was performed employing a total reaction time of 40 min at 25–28 °C, the reaction was incomplete and the crude product contained (GLC analysis) both ketones **9** and **13**.

C. Bromo Ketone 10 with i-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 10.5 mmol of i-Pr_2NLi in 19.8 mL of a hexane–pentane mixture and 155 mL of Et_2O and 2.07 g (10.0 mmol) of the bromo ketone **10** in 20 mL of Et_2O, was warmed to 0 °C and treated with 7.53 g (42 mmol, 4 equiv/Li^+) of HMP. After the resulting colorless solution had been stirred at 0 °C for 30 min and at 20 °C for 30 min (during which time a precipitate separated), the previously described isolation procedure separated 1.286 g of crude product as a pale yellow liquid. An aliquot of the crude product was mixed with a known weight of n-$C_{12}H_{26}$ (internal standard) and analyzed by GLC (silicone XE-30 on Chromosorb P, apparatus calibrated with known mixtures): the crude product contained n-$C_{12}H_{26}$ (retention time 13.8 min), ketone **14** (27.4 min, 63% yield), and several minor unidentified rapidly eluted components (1.8, 3.7, and 4.5 min), but no unchanged bromo ketone **10** was observed (GLC and NMR analysis). An 834-mg aliquot of the crude product was chromatographed on silica gel with an Et_2O–hexane eluent (1:9 v/v) to separate 511 mg (61%) of the ketone **14**; distillation afforded 492 mg of the pure ketone **14**, bp 61–61.5 °C (10 mm), $n^{25}D$ 1.4454 [lit. bp 47–49 °C (5 mm),[32a] 74–74.5 °C (16 mm),[32b] $n^{25}D$ 1.4454,[32a] 1.4458[32b]], that was identified with an authentic sample[32] by comparison of IR, NMR, and mass spectra and GLC retention times.

Later fractions from the chromatography column (eluted with Et_2O) amounted to 212 mg of viscous yellow liquid containing a complex mixture of higher molecular weight components with IR absorption (CCl_4) at 3580, 3420, 1705, 1675, and 1610 cm^{-1}, suggesting the presence of OH, C=O, and C=C groups. The mass spectrum of the material exhibited relatively abundant high-mass peaks at m/e 252, 234, and 219.

Several additional experiments were performed to examine the effect on the Li^+ enolate of activating ligands other than HMP. Following the previously described procedure, a series of cold (0 °C) solutions of the Li^+ enolate (0.05 M) were prepared from 1.03 g (5.0 mmol) of the bromo ketone **10** and 5.25 mmol of i-Pr_2NLi in 88 mL of Et_2O and 10 mL of a pentane–hexane mixture. To one of these enolate solutions was added, dropwise and with stirring during 1 min, a solution of 1.30 g (5.2 mmol) of the crown ether **16**[5] in 10 mL of Et_2O. The resulting pink solution, from which a heavy white precipitate (the complex of LiBr with the crown ether **16**) rapidly separated, was stirred and allowed to warm from 0 to 20 °C during 30 min. After the resulting mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic layer was dried and concentrated. A solution of the residual yellow liquid in 20 mL of anhydrous ether was treated, dropwise and with stirring, with a solution of 1.00 g (11.5 mmol) of anhydrous LiBr in 20 mL of anhydrous DME until no further precipitate (LiBr–crown ether **16** complex) separated and then filtered to remove the crown ether **16**. The filtrate was concentrated and a portion of the residual yellow liquid (1.46 g, NMR analysis indicated residual DME but no crown ether **16**) was mixed with a known weight of n-$C_{12}H_{26}$. The calculated (GLC analysis) yield of ketone **14** was 56% and no other monomeric product was detected. A collected (GLC) sample of the ketone **14** was identified with an authentic sample by comparison of GLC retention times and IR and mass spectra. The crude product was distilled to separate 312 mg (50%) of the ketone **14**, bp 61–61.5 °C (10 mm), leaving 262 mg of viscous pot residue containing a complex mixture of higher molecular weight materials.

A second cold (0 °C) solution of the Li^+ enolate was treated, dropwise and with stirring during 2 min, with 50 mL of cold (0 °C) DME and the resulting solution was stirred, allowed to warm from 0 to 20 °C during 30 min, and then partitioned between Et_2O and aqueous $NaHCO_3$. After the organic solution had been dried and concentrated, analysis (GLC with added internal standard) of the crude liquid product (2.09 g) indicated a 52% yield of the ketone **14** with no other monomeric product being detected. Distillation separated 272 mg (43%) of the ketone **14**, bp 61–61.5 °C (10 mm), leaving 322 mg of a viscous higher molecular weight pot residue.

A third cold (0 °C) solution of the Li^+ enolate was treated, dropwise and with stirring during 1 min, with 986 mg (5.53 mmol) of triglyme [**15**, freshly distilled from $LiAlH_4$, bp 74–74.5 °C (1.2 mm)]. The resulting mixture, from which a white precipitate began to separate, was stirred at 0 °C for 30 min and then allowed to warm to 20 °C during 30 min. After the mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic layer was dried and concentrated to leave 1.505 g of crude product as a yellow liquid containing (GLC analysis with added internal standard) the ketone **14** (54% yield) with no other monomeric products being detected. A 1.416-g aliquot of the crude product was distilled to separate 305 mg (48%) of the ketone **14**, bp 63–64.5 °C (12 mm), that was identified with an authentic sample by comparison of GLC retention times and IR spectra. A subsequent distillation fraction, bp 102–103.5 °C (12 mm), contained 695 mg of triglyme and the residual brown viscous pot residue amounted to 230 mg.

D. Bromo Ketone 10 with KOBu-t. After mixing 1.66 g (8.0 mmol) of the bromo ketone **10** in 20 mL of pentane with a solution of KOBu-t from 312 mg (8.0 mg-atom) of K and 18 mL of t-BuOH, the resulting pale yellow solution, from which a precipitate gradually separated, was stirred at 25 °C for 30 min and at reflux for 45 min. After a portion of the crude liquid product (1.582 g, isolated in the usual way) had been mixed with a known weight of 1,3,5-(i-Pr)$_3C_6H_3$ (an internal standard), analysis (GLC, silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enol ether **17** (retention time 3.1 min, 69% yield), the unsaturated ketone **19** (7.1 min, 4.6% yield), the ketone **18** (9.0 min, 3.5% yield), the ketone **14** (18.3 min, 11% yield), and 1,3,5-(i-Pr)$_3C_6H_3$ (25.9 min). In a second comparable reaction the calculated product yields (GLC analysis) were: **17**, 72%; **19**, 5.4%; **18**, 4.8%; and **14**, 19%. The crude product was chromatographed on basic alumina with pentane and ether–pentane mixtures as eluents. The early fractions, eluted with pentane, contained 610 mg (60%) of the enol ether **17**. Distillation afforded 580 mg (58%) of the pure (GLC) enol ether **17** as a colorless liquid: bp 108–109 °C; $n^{25}D$ 1.4415; IR (CCl_4) 1680 (shoulder) and 1668 cm^{-1} (enol ether C=C); NMR (CCl_4) δ 4.08 (1 H, br, vinyl CH), 3.6–3.9 (2 H, m, CH_2O), 1.57 (3 H, d, J = 1 Hz, allylic CH_3), 1.3–1.6 (2 H, m, CH_2), and 0.93 (6 H, s, CH_3); mass spectrum, m/e (rel intensity) 126 (M^+, 45), 111 (100), 83 (23), 55 (25), and 43 (42).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.10; H, 11.19.

Continued elution from the chromatography column separated 69 mg (7%) of the ketone **14**. This sample and a sample collected by GLC were identified with an authentic sample of ketone **14** by comparison of GLC retention times and IR and mass spectra. A collected (GLC) sample of the unsaturated ketone **19** was identified with an authentic sample[2] by comparison of GLC retention times and IR and mass spectra. A collected (GLC) sample of the ketone **18** was obtained as a colorless liquid that was tentatively identified from the following spectral properties: IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 2.91 (1 H, t, J = 7 Hz, CHCO), 1.95 (3 H, s, CH_3CO), 1.4–1.9 (4 H, m, CH_2), 1.30 (3 H, s, CH_3), and 1.00 (3 H, s, CH_3); mass spectrum m/e (rel intensity) 126 (M^+, 14), 111 (48), 83 (73), 71 (100), 56 (48), 55 (53), 43 (51), and 41 (28). Anal. Calcd for $C_8H_{14}O$: 126.1045. Found, 126.1022.

E. Bromo Ketone 11 with i-Pr_2NLi. A cold (3 °C) solution of the enolate from 15.5 mmol of i-Pr_2NLi in 32.5 mL of hexane and 90 mL of Et_2O and 3.031 g (11.9 mmol) of the bromo ketone **11** in 30 mL of Et_2O was treated with 11.1 g (61.8 mmol or 4 equiv) of HMP. The solution was stirred at 2 °C for 30 min, during which time a precipitate separated, and then was subjected to the usual isolation procedure. After an aliquot of the crude product (1.956 g of liquid) had been mixed with a known amount of phenanthrene (an internal standard), analysis (GLC, silicone QF_1 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enol ether **21** (retention time, 4.2 min, 3% yield), the unsaturated ketone **22** (5.4 min, 5% yield), and the ketone **20** (19.5 min, 67% yield); none of the cyclobutyl ketone **23** (6.9 min) was detected. Also none of the starting bromo ketone **11** was detected in the crude product (NMR analysis). The crude product was chromatographed on silica gel with a hexane–Et_2O mixture as the eluent. The first fraction eluted (64 mg) was further purified by preparative TLC (silica gel, Et_2O–hexane eluent 3:7 v/v) to separate 22 mg (1%) of the enol ether **21**. The next fraction (201 mg) was also subjected to preparative TLC to separate 139 mg (7%) of the unsaturated ketone **22**. Subsequent chromatographic fractions contained 1.219 g (59%) of the crude ketone **20**; recrystallization from hexane separated 1.052 g (51%) of the pure ketone **20**, mp 56.5–58.5 °C. Each of the components **21**, **22**, and **20** was identified with an authentic sample by comparison of IR and NMR spectra. The final fractions eluted from the chromatography column (347 mg) contained a complex mixture of materials with IR absorption attributable to OH and C=O functions.

F. Bromo Ketone 11 with KOBu-t. The bromo ketone **11**, pre-

pared as previously described,[2] was purified by chromatography and subsequent distillation to separate the bromo ketone **11** as a colorless liquid, bp 95–96 °C (0.006 mm), n^{25}_D 1.5384–1.5386 [lit. bp 123–125 °C (0.5 mm),[33] n^{20}_D 1.5412,[33] n^{25}_D 1.5392[2]]. A solution of *t*-BuOK, from 0.84 g (21.5 mg-atom) of K and 75 mL of *t*-BuOH, and 2.64 g (10.4 mmol) of the bromo ketone **11** in 15 mL of *t*-BuOH was stirred at 25–28 °C for 2 h and then subjected to the usual isolation procedure to give 1.69 g of crude product as a pale yellow liquid containing (IR and NMR analysis) mainly the enol ether **21**. After an aliquot of the crude product had been mixed with a known amount of phenanthrene (an internal standard), GLC analysis (silicone QF_1 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enol ether **21** (retention time 4.2 min, 95% yield), the ketone **23** 7.1 min, 1% yield), and phenanthrene (27.7 min). A collected (GLC) sample of the ketone **23** was identified with an authentic sample by comparison of GLC retention times and IR and mass spectra. The remainder of the crude product (1.665 g) was distilled to separate 1.472 g (82%) of the enol ether **21** as a colorless liquid, bp 71–72 °C (0.7 mm), n^{25}_D 1.5483–1.5522, containing (GLC) 99% of the enol ether **21** and 1% of the ketone **23**. A collected (GLC) sample of the enol ether **21**, n^{25}_D 1.5532, was identified with an authentic sample by comparison of GLC retention times and IR, NMR, and mass spectra.

G. Bromo Ketone 12 with *i*-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.053 M), from 5.94 mmol of *i*-Pr_2NLi in 11.9 mL of a hexane–pentane mixture and 87.5 mL of Et_2O and 1.318 g (5.66 mmol) of the bromo ketone **12** in 7.5 mL of Et_2O, was warmed to 0 °C, treated with 4.25 g (23.7 mmol) of HMP, stirred at 0–3 °C for 20 min, and then allowed to warm to 22 °C during 20 min. The usual isolation procedure separated 1.257 g of yellow liquid product (contained some HMP). After an aliquot of the crude product had been mixed with a known amount of 2-methylnaphthalene (an internal standard), GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of 2-methylnaphthalene (retention time 15.0 min), decalone **26** (80% yield, 19.1 min, cis and trans isomers not resolved), and three minor unidentified impurities (5.2, 10, and 43.3 min). A 1.018-g aliquot of the crude product was chromatographed on silica gel with an EtOAc–hexane eluent to separate 586 mg (84%) of decalone **26**; distillation of this material gave 550 mg (79%) of decalone **26**, bp 68–69 °C (1.0 mm), n^{25}_D 1.4844, that was identified with an authentic sample (an equilibrium mixture of cis and trans isomers) by comparison of GLC retention times and IR, NMR, and mass spectra. The later fractions from the liquid chromatograph contained 62 mg of a crude mixture of higher molecular weight products with IR absorption at 3400 and 1710 cm^{-1}.

H. Bromo Ketone 32 with *i*-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 10.5 mmol of *i*-Pr_2NLi in 22 mL of a hexane–pentane mixture and 155 mL of Et_2O and 2.20 g (10.0 mmol) of the bromo ketone **32** in 20 mL of Et_2O, was warmed to 0 °C, treated with 7.53 g (42 mmol, 4 equiv/Li^+) of HMP, and stirred at 0 °C for 30 min and at 20 °C for 30 min. The usual isolation procedure separated 2.67 g of crude product as a yellow liquid. An aliquot of crude product was mixed with a known weight of 1,3,5-triisopropylbenzene for GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures). The mixture contained the enol ether **35** (retention time 8.8 min, 59% yield), 1,3,5-triisopropylbenzene (13.2 min), the unsaturated ketone **31** (17.4 min, 18% yield), and a very small peak corresponding in retention time to the bicyclic ketone **36** (36.6 min, area corresponds to a 0.5% yield). From a second comparable reaction, GLC analysis indicated the yield of the enol ether **35** to be 65% and none of the unsaturated ketone **31** was observed. The remaining crude reaction product (2.467 g) was chromatographed on Merck basic alumina with pentane as an eluent to separate 721 mg (52%) of early fractions containing the enol ether **35**. Distillation gave 681 mg (50%) of the pure enol ether **35** as a colorless liquid: bp 104–104.5 °C (45 mm); n^{25}_D 1.4861 [lit.[22] bp 80–90 °C (14 mm)]; IR (CCl_4) 1691 cm^{-1} (enol ether C=C); NMR (CCl_4) δ 3.7–4.0 (2 H, m, CH_2O) and 1.3–2.4 (12 H, m, CH_2); mass spectrum *m/e* (relative intensity) 138 (M^+, 41), 110 (63), 109 (36), and 67 (39).

We did not find evidence for the presence of the isomeric enol ether **38** in either fractions collected by GLC or fractions collected from chromatography on basic alumina. Consequently, any of this isomeric enol ether **38** formed in the alkylation reaction must have been either isomerized or destroyed during the isolation procedures.

Fractions eluted from the chromatography column with Et_2O–pentane (1:9 v/v) contained 210 mg (15%) of the unsaturated ketone **31** that was identified with an authentic sample by comparison of GLC retention times and IR spectra. The final fractions eluted from the column with Et_2O amounted to 1.496 g of yellow liquid containing (IR and NMR analysis) a mixture of HMP and higher molecular weight material.

An authentic sample of the ketone **36** (Aldrich Chemical Co.) was recrystallized from hexane to separate the pure ketone **36** as colorless needles: mp 155–157 °C (sealed capillary) [lit.[34] mp 151–152 °C]; IR (CCl_4) 1722 cm^{-1} (C=O); NMR (CCl_4) δ 1.3–2.6 (m, aliphatic CH); mass spectrum *m/e* (rel intensity) 138 (M^+, 100), 82 (65), 81 (41), 68 (46), 67 (94), 54 (46), and 41 (46).

I. Bromo Ketone 42 with *i*-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 10.5 mmol of *i*-Pr_2NLi in 20.2 mL of a hexane–pentane mixture and 155 mL of Et_2O and 1.93 g (10 mmol) of the bromo ketone **42** in 20 mL of Et_2O, was warmed to 0 °C, treated with 7.53 g (42 mmol, 4 equiv/Li^+) of HMP, and stirred at 0 °C for 30 min and at 20 °C for 30 min. After the usual isolation procedure, the crude product (1.26 g of yellow liquid) exhibited one major GLC peak (silicone XE-60 on Chromosorb P) corresponding to the enol ether **43** (retention time 5.8 min), but no peak corresponding to the ketone **44** (12.2 min). The crude product was chromatographed on basic alumina to separate 521 mg (46%) of the enol ether **43** in early fractions eluted with pentane. Distillation afforded 462 mg (41%) of the enol ether **43** as a colorless liquid: bp 125–125.5 °C; n^{25}_D 1.4375; IR (CCl_4) 1672 (enol ether C=C) and 895 cm^{-1} (C=CH_2); NMR (CCl_4) δ 3.8–4.2 [3 H, m, overlapping triplet (J = 7 Hz) at 4.00 (CH_2O) and a partially obscured doublet (vinyl CH)], 3.61 (1 H, d, J = 1.7 Hz, vinyl CH), 1.81 (2 H, t, J = 7 Hz, CH_2), and 1.18 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 112 (M^+, 42), 97 (100), 69 (37), 67 (27), 57 (28), 55 (42), 43 (73), 42 (32), 41 (97), and 39 (34).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.91; H, 10.80.

Later fractions from the chromatography column, eluted with Et_2O, contained 732 mg of viscous red liquid with IR absorption (CCl_4) at 3670, 3460 (OH), and 1709 cm^{-1} (weak, C=O). The mass spectrum of this crude mixture exhibited abundant fragment peaks at *m/e* 179, 135, 45, and 44.

J. Bromo Ketone 50 with *i*-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 5.25 mmol of *i*-Pr_2NLi in 78 mL of Et_2O and 10 mL of a pentane–hexane mixture and 895 mg (5.0 mmol) of the bromo ketone **50** in 10 mL of Et_2O, was warmed to 0 °C, treated with 3.77 g (21 mmol, 4 equiv/Li^+) of HMP, and stirred at 0 °C for 30 min and then at 20 °C for 2 h. The usual isolation procedure separated 1.67 g of crude yellow liquid product. After an aliquot of this crude product had been mixed with an internal standard (n-$C_{11}H_{24}$), GLC analysis (silicone XE-60 on Chromosorb P at 100 °C, apparatus calibrated with known mixtures) indicated the presence of the enol ether **51** (retention time 8.8 min, 17% yield), the ketone **52** (15.8 min, 10% yield), and n-$C_{11}H_{24}$ (26.2 min). When the temperature of the GLC column was raised to 120 °C, peaks corresponding to the unchanged bromo ketone **50** (retention time 19.2 min, 17% recovery) and the internal standard n-$C_{11}H_{24}$ (6.6 min) were observed. A 923-mg aliquot of the crude product was chromatographed on Merck basic alumina with an Et_2O–pentane eluent to separate successive fractions containing 41 mg (8% yield) of the cyclobutanone **52** (IR analysis), 62 mg (13% recovery) of the bromo ketone **50** (IR analysis), and 732 mg of final fractions of yellow viscous liquid containing mixtures of HMP and components with IR absorption at 3320 (br), 1775, and 1685 cm^{-1} attributable to OH and C=O functions.

The crude product from a second comparable reaction was used to collect (GLC) samples of the monomeric products. The enol ether **51** was obtained as a very volatile colorless liquid: IR (CCl_4) 1689 (C=C), 1375, 1392 (geminal CH_3 groups), 1212, 1158 (COC), and 895 cm^{-1} (C=CH_2); NMR (CCl_4) δ 4.31 (2 H, s, CH_2O), 3.90 (1 H, d, J = 4 Hz, vinyl CH), 3.60 (1 H, d, J = 4 Hz, vinyl CH), and 1.33 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 98 (M^+, 73), 68 (100), 67 (86), 56 (34), 53 (45), 43 (22), 41 (62), 40 (25), and 39 (34). Anal. Calcd for $C_6H_{10}O$: 98.0731. Found: 98.0729.

The ketone **52** was obtained as a colorless liquid: n^{25}_D 1.4130 (lit. bp 113.5–114 °C,[35] n^{20}_D 1.4150[36b]); IR (CCl_4) 1781 cm^{-1} (C=O); NMR (CCl_4), δ 3.02 (2 H, t, J = 8.5 Hz, further partially resolved splitting apparent, CH_2CO), 1.80 (2 H, t, J = 8.5 Hz, further partially resolved splitting apparent, CH_2), and 1.18 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 98 (M^+, 13), 70 (63), 56 (88), 55 (50), 42 (59), 41 (100), and 39 (35). These spectral features correspond to those previously reported[36] for the ketone **52** and the NMR spectrum of our product clearly excludes the presence of any appreciable amount of the isomeric ketone **53**.[36b]

K. Bromo Ketone 50 with KOH in H_2O–DME. To a refluxing solution of 323 mg (5.8 mmol) of KOH in 10 mL of H_2O and 10 mL of DME was added, dropwise and with stirring during 2 h, a solution of 301 mg (1.68 mmol) of the bromo ketone **50** in 5 mL of DME. The resulting colorless solution was refluxed for an additional 2 h and then cooled and partitioned between H_2O and Et_2O. After the Et_2O solution had been dried and concentrated to leave 128 mg of crude liquid

product, an aliquot of the crude product was mixed with an internal standard (n-$C_{11}H_{24}$) and subjected to the previously described GLC analysis. Although neither the enol ether **51** nor the unchanged bromo ketone **50** were detected, the crude product contained the ketone **52** (16.8 min, 5.5% yield), n-$C_{11}H_{24}$ (27.5 min), and a minor component (19.9 min, yield <1%) believed to be the isomeric cyclobutanone **53**. A collected (GLC) sample of the ketone **52** was identified with the previously described sample by comparison of IR, NMR, and mass spectra and a collected (GLC) sample of the minor product **53** exhibited IR absorption (CCl_4) at 1780 and 1788 cm^{-1} (cyclobutanone C=O): mass spectrum m/e (relative intensity) 98 (M^+, 10), 70 (61), 56 (99), 55 (41), 42 (46), 41 (100), and 39 (23). These spectral properties correspond to those reported[36b] for the ketone **53**.

The basic aqueous phase from the above reaction was acidified, saturated with NaCl, and extracted with Et_2O. After the Et_2O solution had been concentrated, the crude acidic product (212 mg) was esterfied with excess ethereal CH_2N_2. The resulting solution contained (GLC, silicone XE-60 on Chromosorb P) Et_2O (retention time 3.0 min), $CH_3CO_2CH_3$ (5.0 min), and DME (8.4 min), but none of the ester $(CH_3)_3CCH_2CO_2CH_3$ (17.4 min, the product that could be obtanied by cleavage of ketone **53**) was detected. After an aliquot of this solution had been mixed with an internal standard (n-$C_{11}H_{24}$), GLC analysis indicated the yield of $CH_3CO_2CH_3$ to be 93% (based on the starting bromo ketone **50**). An authentic sample of the ester $(CH_3)_3CCH_2CO_2CH_3$ was obtained by esterification of the acid $(CH_3)_3CCH_2CO_2H$[37] with ethereal CH_2N_2. The product was distilled to separate the ester $(CH_3)_3CCH_2CO_2CH_3$ as a colorless liquid: bp 127–127.5 °C; $n^{25}D$ 1.4001 [lit.[38] bp 123.5 °C (739 mm); $n^{20}D$ 1.3981]; IR (CCl_4) 1740 cm^{-1} (ester C=O); NMR (CCl_4), δ 3.60 (3 H, s, OCH_3), 2.15 (2 H, s, CH_2), and 1.02 (9 H, s, t-Bu); mass spectrum m/e (rel intensity) 115 (5), 99 (40), 74 (100), 73 (95), 59 (37), 57 (95), 55 (58), 43 (54), 41 (78), and 39 (43).

L. Bromo Ketone 67 with i-Pr_2NLi. A cold (−60 °C) solution of the enolate (0.05 M), from 12.6 mmol of i-Pr_2NLi in 188 mL of Et_2O and 24 mL of a hexane–pentane mixture and 2.48 g (12.0 mmol) of the bromo ketone **67** in 10 mL of Et_2O, was warmed to 25 °C and 9.03 g (50.4 mmol, 4 equiv) of HMP was added. The solution, from which a fine precipitate slowly separated, was stirred at 25 °C for 75 min and subjected to the usual isolation procedure to separate 2.75 g of crude product as a yellow liquid. An aliquot of this crude product was mixed with a known weight of n-$C_{14}H_{30}$ (an internal standard) for GLC analysis (UCON 50HB280X on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained (GLC) the unsaturated ketone **63** (2.9% yield, retention time 5.0 min), the ketone **70** [24% yield, mainly **70b** (6.4 min) plus **70a** (7.4 min)], the ketone **69** (36% yield, 13.8 min), and n-$C_{14}H_{30}$ (29.2 min). A 2.654-g aliquot of the crude product was distilled in a short-path still to separate 1.190 g of a volatile fraction, bp 60–110 °C (25 mm), containing (GLC) a mixture of ketones **63, 69,** and **70.** The pot residue from the distillation contained a mixture of HMP and higher molecular weight products. The distillate (1.190 g) was chromatographed on silica gel with an Et_2O–hexane eluent (1:9 v/v) to separate 398 mg (26%) of early fractions containing (GLC) a mixture of ketones **63** and **70** followed by 536 mg (35%) of fractions containing (GLC) the ketone **69**. Distillation of these later fractions afforded 510 mg (34%) of the ketone **69**: bp 70–71 °C (13 mm); $n^{25}D$ 1.4558. The early chromatographic fractions (398 mg) were rechromatographed on silica gel coated with 5% $AgNO_3$ and eluted with Et_2O–hexane (1:9 v/v). The fractions eluted first (310 mg or 21%) contained the ketone **70**; these fractions were distilled to separate 300 mg (20%) of the ketone **70** (mainly **70b**): bp 70–71 °C (23 mm); $n^{25}D$ 1.4410. The final fraction from the second chromatography contained 31 mg (2%) of the unsaturated ketone **63** (GLC analyses). The isolated samples of ketones **63, 69,** and **70** were identified with authentic samples by comparisons of IR spectra and GLC retention times.

A series of comparable small-scale experiments were performed in which 2.5 mmol of the bromo ketone **67** was added to a cold (−60 °C) solution of 2.65 mmol of i-Pr_2NLi and the resulting enolate solution (0.05 M) was activated with 10.5 mmol of HMP and allowed to react at various temperatures. The product yields after various times and temperatures were: 2 h at 0 °C, 3.9% of **63**, 28% of **70**, and 22% of **69**; 1.75 h at 25 °C, 3.5% of **63**, 21% of **70**, and 31% of **69**; 2 h at 35 °C, 2.6% of **63**, 35% of **70**, and 26% of **69**. When excess i-Pr_2NLi (5.0 mmol) was used with 2.5 mmol of bromo ketone **67** and 10.5 mmol of HMP at 25 °C for 2 h dehydrohalogenation became the major reaction with the yields being 33% of **63**, 2% of **70**, and 10% of **69**. Activation of the enolate with excess DME rather than with HMP followed by reaction at 40 °C for 2 h gave the following yields: 40% of **70** and 10% of **69**. Activation of the enolate **68** with 1 molar equiv of triglyme (**15**) followed by reaction at 0 °C for 2 h resulted in recovery of most of the starting bromo ketone **67**. Thus, the most favorable ratio of seven-membered (**69**) to five-membered (**70**) product (60:40) was obtained when a solution of the enolate at 25 °C was activated with HMP and allowed to react at 25 °C for 1–2 h.

M. Bromo Ketone 67 with KOBu-t. A solution of KOBu-t, from 0.33 g (10.3 mg atom) of K and 18 mL of t-BuOH, and 2.05 g (9.9 mmol) of the bromo ketone **67** in 20 mL of pentane was stirred at 26 °C for 30 min and at 40 °C for 45 min. The usual isolation procedure separated 6.21 g (contains t-BuOH) of crude product as a yellow liquid. After an aliquot of the crude product had been mixed with a known weight of n-$C_{14}H_{30}$ (an internal standard), GLC analysis (UCON 50 HB280X on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the isomeric cyclopentyl ketones **70** (83% yield, retention times 7.3 min for **70b** and 9.0 min for **70a**), n-$C_{14}H_{30}$ (34.7 min), and two minor by-products (2.9 and 5.2 min), but no peak corresponding to the cycloheptanone **69** (15.6 min). A 5.57-g aliquot of the crude reaction product was distilled to separate low-boiling materials (mainly t-BuOH) from 789 mg (72%) of fractions, bp 78 °C (40 mm), $n^{25}D$ 1.4376–1.4392, containing (GLC) the stereoisomeric ketones **70**. A collected (GLC) sample of the ketone **70** (mainly **70b**), $n^{25}D$ 1.4392, was identified with an authentic sample by comparison of IR and NMR spectra and GLC retention times. Collected (GLC) samples of the minor, more rapidly eluted by-products (2.9 and 5.2 min) had IR and mass spectral peaks suggesting that they may be the structurally isomeric enol ethers **74** and **75**. The spectral properties of the more rapidly eluted component (2.9 min) were: IR (CCl_4) 1715, 1380, 1100, and 900 cm^{-1}; mass spectrum m/e (rel intensity) 126 (M^+, 17), 111 (36), 69 (34), 58 (27), 55 (25), 43 (100), and 41 (28). Anal. Calcd for $C_8H_{14}O$: 126.1045. Found: 126.1022. The corresponding properties for the less rapidly eluted component (5.2 min) were: IR (CCl_4) 1695, 1380, 1182, and 1170 cm^{-1}; mass spectrum m/e (rel intensity) 126 (M^+, 6), 111 (32), 55 (40), 43 (100), and 41 (29). Anal. Calcd for $C_8H_{14}O$: 126.1045. Found: 126.1051.

In a similar experiment, a cold (4 °C) mixture of 460 mg (11.5 mmol) of KH (prewashed with pentane) and 140 mg (1.4 mmol) of i-Pr_2NH in 10 mL of DME was treated, dropwise and with stirring during 8 min, with a solution of 61.1 mg (0.295 mmol) of the bromo ketone **67** and 33.3 mg of n-$C_{14}H_{30}$ in 3 mL of DME. After the mixture, from which a precipitate began to separate immediately, had been stirred at 25 °C for 1 h, the previously described isolation and analysis procedures indicated the yield of ketone **70** to be 52%.

Preparation of Authentic Samples of Products. A. Ketone 44. A previously described procedure[39] was used to obtain a sample of the ketone **44**: bp 143 °C; $n^{25}D$ 1.4320; IR (CCl_4) 1740 cm^{-1} (C=O); NMR (CCl_4) δ 1.2–2.4 (6 H, m, CH_2) and 1.02 (6 H, s, CH_3); mass spectrum m/e (rel intensity) 112 (M^+, 19), 69 (14), 56 (100), 55 (14), 41 (34), and 39 (13).

B. Enol Ether 21. To a solution of NaOEt, from 1.5 g (67 mg-atom) of Na and 40 mL of EtOH, was added, dropwise and with stirring, a solution of 8.48 g (33.3 mmol) of the bromo ketone **11** in 7 mL of EtOH. The resulting mixture was stirred at 27–33 °C for 45 min and then partitioned between hexane and aqueous $NaHCO_3$. The organic solution was washed with H_2O, dried, and concentrated to leave 5.61 g of yellow liquid that contained (TLC, silica gel, eluent 3:7 v/v Et_2O–hexane) the enol ether **21** (R_f 0.50) accompanied by several minor unidentified components (R_f 0.13, 0.27, and 0.34). The crude product was chromatographed on silica gel to separate 1.47 g (26%) of fractions (1:10 to 1:6 v/v Et_2O–hexane eluent) containing (GLC, TLC) the pure enol ether **21** as well as 1.38 g of earlier fractions containing **21** with unidentified impurities and 2.59 g of later fractions containing various mixtures of **21** and the bromo ketone **11**. The pure enol ether **21** was obtained as a colorless liquid: $n^{25}D$ 1.5533 [lit. bp 128–133 °C (18 mm);[33] $n^{25}D$ 1.5530[40]]; IR (CCl_4) 1660 cm^{-1} (enol ether C=C); UV max (95% EtOH) 256 nm (ϵ 5760); NMR (CCl_4) δ 6.9–7.3 (5 H, m, aryl CH), 3.8–4.1 (2 H, m, CH_2O), 1.8–2.5 (4 H, m, CH_2), and 1.67 (3 H, t, J = 1.8 Hz, allylic CH_3); mass spectrum m/e (rel intensity) 174 (M^+, 59), 131 (46), 104 (23), 103 (100), 77 (32), 51 (20), and 43 (94).

C. Ketone 20. A commercial sample of the ketone **20** (Pfaltz and Bauer, Inc.) was recrystallized from EtOH and then from hexane to separate the pure ketone **20** as colorless prisms: mp 57–59 °C [lit. mp 62 °C,[41] 51.5–54 °C,[42] bp 148–152 °C (15 mm)[42]]; IR (CCl_4) 1720 cm^{-1} (C=O); UV (95% EtOH) series of weak maxima (ϵ 280–618) in the region 242–264 nm with a maximum at 288 nm (ϵ 131); NMR (CCl_4) δ 6.9–7.4 (5 H, m, aryl CH), 3.2–3.7 (1 H, m, benzylic CH), and 1.4–2.6 (8 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 174 (M^+, 39), 130 (100), 117 (55), 104 (43), 91 (37), 77 (19), and 39 (17).

D. Ketone 23. To obtain an authentic sample of ketone **23**, a previously described procedure[43] was used to alkylate 50.0 g (426 mmol) of $PhCH_2CN$ by adding a solution of this nitrile and 94.74 g (469

mmol) of $Br(CH_2)_3Br$ in 165 mL of Et_2O to the base from 22.5 g (938 mmol) of NaH(washed with pentane) and 330 mL of Me_2SO. After the reaction solution was stirred at 25 °C for 1.5 h and then subjected to the previously described isolation procedure,[43] the nitrile **24** was collected as 28.29 g (42%) of colorless liquid, bp 90–91 °C (0.56 mm), n^{25}_D 1.5290 [lit. bp 120–122 °C (7 mm),[43] n^{20}_D 1.5351[44]], that exhibited one major GLC peak (silicone SE-30 on Chromosorb P) at 7.5 min: IR (CCl_4) 2240 cm^{-1} (C≡N); UV max (95% EtOH) 259 nm (ε 130); NMR (CCl_4) δ 7.1–7.5 (5 H, m, aryl CH) and 1.8–3.0 (6 H, m, CH_2); mass spectrum *m/e* (rel intensity) 157 (M^+, 10), 130 (15), 129 (100), 120 (11), 77 (7), 51 (11), and 39 (6).

A mixture of 5.00 g (31.8 mmol) of the nitrile **24**, 5 mL of concentrated H_2SO_4, 5 mL of H_2O, and 5 mL of HOAc was refluxed for 1.5 h and then partitioned between Et_2O and H_2O. After the organic layer was extracted with aqueous 5% NaOH, acidification of the alkaline aqueous extract precipitated 4.65 g (83%) of the acid **25** as a white solid, mp 104–106 °C. Recrystallization from hexane afforded the pure acid **25** as white plates: mp 106.5–108 °C (lit.[45] mp 106–107 °C); IR (CCl_4) 3300–2500 (carboxyl OH) and 1698 cm^{-1} (carboxyl C=O); UV max (95% EtOH) 256 (ε 144) and 218 nm (shoulder, ε 4620); NMR (CCl_4) δ 12.14 (1 H, s, OH), 7.0–7.4 (5 H, m, aryl CH), and 1.6–3.1 (6 H, m, CH_2); mass spectrum *m/e* (rel intensity) 176 (M^+, 16), 148 (100), 131 (15), 103 (82), 91 (15), 77 (24), and 51 (17).

To a solution of CH_3MgI, prepared from 1.858 g (76.4 mg-atom) of Mg, 10.84 g (76.4 mmol) of CH_3I, and 100 mL of Et_2O, was added a solution of 10.00 g (63.7 mmol) of the nitrile **24**. The reaction solution, from which a white precipitate separated after 1 h, was stirred overnight at 23–25 °C and then partitioned between Et_2O and aqueous 5% H_2SO_4. The Et_2O extracts were washed successively with aqueous $NaHCO_3$ and with H_2O and then dried and concentrated. Distillation of the residual yellow liquid (10.3 g) separated 8.03 g (73%) of the ketone **23** as a colorless liquid: bp 81 °C (0.4 mm); n^{25}_D 1.5274 [lit.[46] bp 56–57 °C (0.2 mm)]; IR (CCl_4) 1708 cm^{-1} (C=O); UV max (95% EtOH) 218 (shoulder, ε 5900), 266 (ε 210), and 291 nm (ε 250); NMR (CCl_4) δ 7.0–7.4 (5 H, m, aryl CH) and 1.7–3.0 (9 H, m, aliphatic CH including an CH_3CO singlet at 1.79); mass spectrum *m/e* (rel intensity) 174 (M^+, 16), 131 (100), 103 (57), 91 (19), 77 (13), and 43 (18).

E. Ketone 69. To a cold (4 °C) solution of $LiCuMe_2$, prepared from 2.81 g (13.6 mmol) of Me_2S–CuBr,[28] 27.3 mmol of MeLi, and 26.5 mL of Et_2O, was added, dropwise with stirring at 4–13 °C during 7 min, a solution of 1.00 g (9.09 mmol) of the enone **71** in 5 mL of Et_2O. The reaction mixture, from which a yellow precipitate of $(MeCu)_n$ began to precipitate almost immediately, was stirred at 10 °C for 10 min and at 25 °C for 3 h and then partitioned between Et_2O and an aqueous solution of NH_3 and NH_4Cl. The organic layer was washed with aqueous NaCl, dried over molecular sieves, no. 4A, and concentrated to leave 1.00 g (88%) of the crude ketone **69** (GLC analyses) as a pale yellow liquid. Distillation afforded 718 mg (63%) of the pure ketone **69** as a colorless liquid: bp 68–72 °C (13 mm); n^{25}_D 1.4557–1.4559 [lit.[47] bp 104–105 °C (60 mm); $n^{26.5}_D$ 1.4540]; IR (CCl_4) 1701 cm^{-1} (C=O); NMR (CCl_4) δ 2.2–2.6 (4 H, m, CH_2CO), 1.2–2.2 (7 H, m, aliphatic CH), and 1.01 (3 H, d, J = 5.5 Hz, CH_3); mass spectrum *m/e* (rel intensity) 126 (M^+, 11), 82 (65), 69 (100), 56 (44), 55 (57), 42 (26), 41 (56), and 39 (19).

F. Ketone 70. A THF solution containing (by total base titration) 0.88 M HC≡CMgBr was prepared from HC≡CH and a THF solution of EtMgBr as previously described.[48] A solution of 28.0 g (333 mmol) of cyclopentanone in 75 mL of THF was added, dropwise and with stirring during 50 min, to 450 mL of a cold (3–4 °C) THF solution containing 395 mmol of HC≡CMgBr. The resulting pale green mixture was stirred at 25 °C for 20 h and partitioned between Et_2O and aqueous $NaHCO_3$, and the organic layer was washed with aqueous NaCl, dried, and concentrated. Distillation of the residual yellow liquid (41.4 g) separated 25.34 g (69%) of the pure (GLC) alcohol **72** as a colorless liquid: bp 68–75 °C (18–25 mm); n^{25}_D 1.4716–1.4717 [lit. bp 65–65.5 °C (16 mm);[49] n^{20}_D 1.4741;[49] mp 24 °C[50]]; IR (CCl_4) 3600, 3470 (OH), 3305 (acetylenic CH), and 2115 cm^{-1} (weak, C≡C); NMR (CCl_4) δ 2.83 (1 H, s, OH, exchanged with D_2O), 2.37 (1 H, s, C≡CH), and 1.4–2.2 (8 H, m, CH_2); mass spectrum *m/e* (rel intensity) 110 (M^+, 5), 109 (50), 95 (73), 82 (65), 81 (100), 68 (78), 67 (67), 55 (70), 54 (38), 53 (61), 41 (54), and 39 (55).

A solution of 5.00 g (45.5 mmol) of the alcohol **72** in 50 mL of 92% HCO_2H was refluxed for 80 min and then cooled and partitioned between H_2O and pentane. The organic layer was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried, concentrated, and distilled to separate 1.71 g of the crude enone **73**: bp 69 °C (18 mm); n^{25}_D 1.4748–1.4786. The aqueous phase was neutralized with solid $NaHCO_3$ and again extracted with pentane to separate, after drying and distillation, an additional 0.88 g of crude enone **73**: bp 70 °C (20 mm); n^{25}_D 1.4788–1.4792 (total yield 2.59 g or 52%). This crude product contained (GLC, UCON 50HB280 X on Chromosorb P) the enone **73** (6.1 min) accompanied by two minor, unidentified impurities (3.1 and 4.0 min). A collected (GLC) sample of the pure enone **73** was obtained as a colorless liquid: n^{25}_D 1.4792 [lit.[50] bp 67 °C (16 mm); n^{23}_D 1.4776]; IR (CCl_4) 1670 (C=O) and 1615 cm^{-1} (C=C); UV max (95% EtOH) 238.5 (ε 10 000) and 305 nm (ε 46); NMR (CCl_4) δ 6.5–6.7 (1 H, m, vinyl CH) and 1.5–3.1 (9 H, m, aliphatic CH including a CH_3CO singlet at 2.23); mass spectrum *m/e* (rel intensity) 110 (M^+, 57), 95 (100), 67 (90), 65 (24), 43 (71), 41 (47), and 39 (27).

To a cold (3 °C) solution of Me_2CuLi, from 3.08 g (14.9 mmol) of Me_2SCuBr[28] and 29.9 mmol of MeLi in 36 mL of Et_2O, was added, dropwise with stirring and cooling (3–9 °C) during 10 min, a solution of 1.006 g (9.14 mmol) of the enone **73**. After the resulting mixture had been stirred at 3 °C for 15 min, the cooling bath was removed and the mixture was allowed to warm to 25 °C with stirring during 80 min. After the reaction mixture had been partitioned between Et_2O and an aqueous solution of NH_3 and NH_4Cl, the organic layer was washed with aqueous NaCl, dried, concentrated, and distilled to separate 0.87 g (76%) of the ketone **70** as a colorless liquid: bp 70 °C (23 mm); n^{25}_D 1.4410–1.4423 [lit.[51] cis-isomer **70a**, bp 53–53.5 °C (14 mm), n^{25}_D 1.4418; trans-isomer **70b**, bp 53.5–54 °C (14 mm), n^{25}_D 1.4383]. This product contained (GLC, UCON 50HB280 X on Chromosorb P) a mixture of trans-isomer **70b** (retention time 4.1 min, ~65%) and the cis-isomer **70a** (4.8 min, ~35%); IR (CCl_4) 1712 cm^{-1} (C=O); NMR (CCl_4) δ 1.4–2.8 (11 H, m, aliphatic CH including a CH_3CO singlet at 2.08) and two doublets (total 3H) at 1.02 (J = 6 Hz, CH_3 of trans-isomer **70b**[52]) and 0.92 (J = 7 Hz, CH_3 of cis-isomer **70a**[52]); mass spectrum *m/e* (rel intensity) 126 (M^+, 68), 111 (68), 85 (56), 84 (34), 83 (100), 71 (75), 67 (50), 55 (80), 43 (75), 41 (52), and 39 (31). A solution of 545 mg (4.3 mmol) of this mixture of ketones **70** and 0.30 g (2.7 mmol) of *t*-BuOK in 25 mL of *t*-BuOH was stirred at 28 °C for 30 min and then partitioned between pentane and aqueous NaCl. The pentane layer was dried, concentrated, and distilled in a short-path still to separate 254 mg (47% recovery) of the ketone **70**, n^{25}_D 1.4388, containing (NMR and GLC analyses) about 94% of the trans-ketone **70b** and about 6% of the cis-ketone **70a**.

Registry No.—**9,** 61675-00-1; **10,** 61675-01-2; **11,** 36307-12-7; **12,** 64507-82-0; **13,** 1193-47-1; **14,** 2979-19-3; **17,** 64507-83-1; **18,** 64507-84-2; **20,** 1444-65-1; **21,** 25252-74-8; **23,** 3972-67-6; **24,** 14377-68-5; **25,** 37828-19-6; **28,** 61675-08-9; **31,** 94-66-6; **32,** 10468-37-8; **35,** 7106-07-2; **36,** 17931-55-4; **42,** 61689-48-3; **43,** 63820-00-8; **44,** 4541-32-6; **50,** 19961-40-1; **51,** 64507-85-3; **52,** 1192-14-9; **53,** 1192-33-2; **63,** 35194-34-4; **65a,** 64507-86-4; **65b,** 64507-87-5; **66** (*R*R**), 64507-88-6; **66** (*R*S**), 64507-89-7; **67,** 61675-02-3; **69,** 933-17-5; **70a,** 3664-69-5; **70b,** 3664-70-8; **71,** 1121-66-0; **72,** 17356-19-3; **73,** 16112-10-0; **74,** 64507-66-0; **75,** 64507-65-9; *i*-Pr_2NLi, 4111-54-0; *n*-BuLi, 109-72-8; *tert*-butyl acetoacetate, 1694-31-1; acetaldehyde, 75-07-0; allyl bromide, 106-95-6; KOBu-*t*, 865-47-4; KOH, 1310-58-3; 3,3-dimethylbutanoic acid methyl ester, 10250-48-3; CH_3I, 74-88-4; $LiCuMe_2$, 15681-48-8; cyclopentanone, 120-92-3; ethynyl bromide, 593-61-3.

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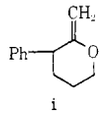

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Mercury in Organic Chemistry. 13.[1] Stereospecific Synthesis of α,β-Unsaturated Ketones via Acylation of Vinylmercurials[2]

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Treatment of vinylmercuric chlorides with acid chlorides and aluminum trichloride for 5 min at room temperature in methylene chloride solvent provides a very mild, convenient method for the synthesis of α,β-unsaturated ketones in excellent yields and high stereochemical purity. The reaction is applicable to the synthesis of functionally substituted enones as well as dienones. Rhodium(I) and palladium(0) reagents also promote the reaction, but in lower yield. The use of titanium tetrachloride instead of aluminum trichloride leads to enones of inverted stereochemistry in some cases, but the reaction is not synthetically useful due to its irreproducibility. Both the aluminum trichloride and titanium tetrachloride reactions appear to proceed through addition of the complexed acid chloride to the carbon–carbon double bond of the vinylmercurial, followed by mercuric chloride elimination. However, direct substitution at the carbon–mercury bond cannot be ruled out in the aluminum trichloride reactions.

A variety of methods presently exist for the synthesis of α,β-unsaturated ketones. The aldol condensation is one important approach to the synthesis of α,β-unsaturated ketones.[6] Another important method employs the Friedel–Crafts reaction of acid chlorides, acids, or anhydrides with olefins.[7] Recently a new procedure involving the hydrozirconation of acetylenes and subsequent aluminum chloride promoted acylation of the resulting vinylzirconium compounds has been added to the list of important methods of preparing α,β-unsaturated ketones.[8] The acylation of vinylmercurials appeared to be an equally promising route to enones since vinylmercurials are readily available directly from acetylenes.[9,10] We wish now to report in detail our studies on the successful development of just such a procedure.

Although a number of reactions of organomercurials which lead to ketones have been reported previously, there are only isolated examples of the direct reaction of acid chlorides with organomercuric chlorides to give ketones.[11] Most of the ex-

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