Alkylation of Enolate Ions Generated Regiospecifically *via* Organocopper Reactions. Synthesis of Decalin Sesquiterpene Valerane and of Prostaglandin Model Systems[1]

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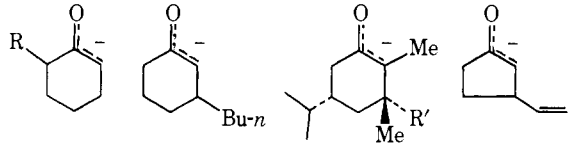
Abstract: Results are reported on alkylation reactions of four different structural types of cycloalkanone enolate ions (**1**–**4**) each of which is generated regiospecifically *via* an organocopper reaction with an α,α'-dibromo ketone or with a 2-cycloalkenone. These results provide information on the relative rates of enolate alkylation *vs.* equilibration in these systems, and they have led to a new total synthesis of the decalin sesquiterpene valerane and to an efficient method for construction of model systems for the E series of 11-deoxyprostaglandins.

Regiospecific generation and alkylation of one enolate structural isomer of an unsymmetrical ketone under non-equilibrating conditions are often difficult and yet highly desirable.[3] Copper-catalyzed conjugate addition of Grignard reagents to cyclohexenones and subsequent alkylation by reactive (*e.g.*, benzylic) halides have been used in synthesis of lycopodine alkaloids[4] and of substituted hydroazulenes.[5] Stoichiometric organocopper conjugate addition reactions followed by alkylation[6] or followed by Michael addition[7] have recently been studied and have been applied to synthesis of steroids.[8] We have been examining alkylation reactions of four different structural types of cycloalkanone enolate ions (**1**–**4**) which are generated regiospecifically *via* an organocopper reaction with an α,α'-dibromo ketone[9] or with a 2-cycloalkenone.[10] The results presented here provide information on the relative rates of enolate alkylation *vs.* enolate equilibration in these systems; these reactions have led to a new total synthesis of the decalin sesquiterpene valerane (itself not a natural product) and to a highly efficient method for direct conversion of 2-cyclopentenone to *trans*-2,3-dialkylcyclopentanones, which are models for the E series of 11-deoxyprostaglandins.



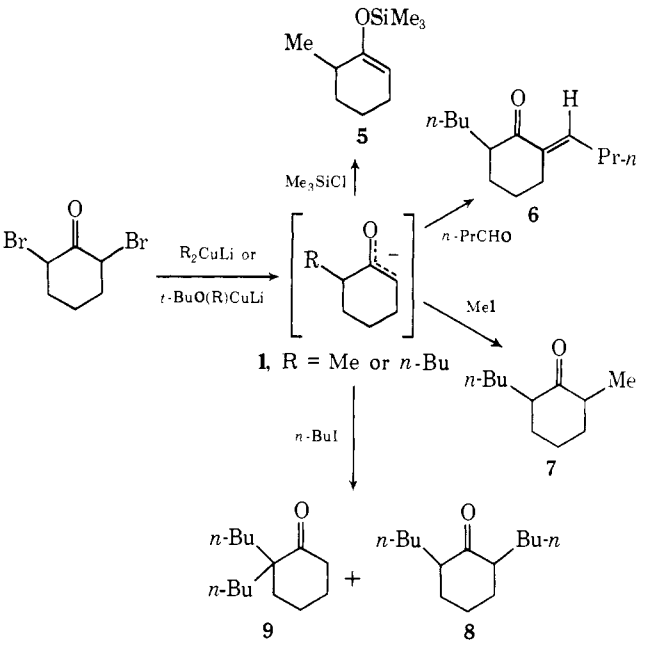
1a. R = Bu-*n* 2 3 4
b. R = Me

Results and Discussion

Enolate Ions Derived from 2,6-Dibromocyclohexanone. 2,6-Dibromocyclohexanone[11] is transformed by organocopper reagents, possibly *via* the intermediacy of a cyclopropanone,[9b,12] into enolate ion **1**. This specific enolate structural isomer reacts with trimethylsilyl chloride in the presence of triethylamine to give enol silyl ether **5** (Scheme I) as the only volatile product in 50% isolated yield after *non* aqueous work-up. Thus cyclohexanone can be converted *via* 2,6-dibromocyclohexanone directly into silyl ether **5**, in the complete absence of the more highly substituted isomeric silyl ether.[13] Reaction of silyl ether **5** with bromine,[14] ozone,[15] diborane,[16] methyl orthoformate,[17] or methylene iodide and zinc[18] would provide easy access to diverse types of synthetic intermediates.

Aldol condensation of enolate ion **1** with *n*-butyraldehyde followed by dehydration produces 2-alkylidenecyclohexanone **6** in 43% yield. This reaction is the first reported aldol condensation of organocopper generated enolate ions and offers the possibility of further functionalization at the α,β-ethylenic center (*e.g.*, organocopper conjugate addition to form a 2-*n*-butyl-6-*sec*-alkylcyclohexanone).[19] That the double bond in enone **6** has the *E* configuration is established by nmr spectroscopy, which shows an absorption for the vinyl proton at δ 6.5 as a triplet of triplets with coupling constants of 7 and 2 Hz.[20]

Scheme I



Treating enolate ion **1a** at −78° with excess methyl iodide affords 2-*n*-butyl-6-methylcyclohexanone (**7**) in only low yield. Many different reaction conditions were tried including variation of time, temperature, solvent, and cosolvent; some of these experiments are summarized in Table I. Optimal methylation results could be achieved in three ways: (1) by allowing intermediate enolate ion **1** to warm to 0° *before* adding methyl iodide; (2) by adding methyllithium to enolate ion **1** at −78°; or (3) by adding tetramethylethylenediamine (TMED) to enolate ion **1** at −78°. Although the *detailed* effect of these procedures on the nature of enolate ion **1** is not clear, it should be noted (fifth entry, Table I) that when methyllithium is added to enolate ion **1**, but methyl iodide is *not* added, some methylcyclohexanone **7** is still produced. This result suggests the intermediacy of

Table I. Methylation of Enolate 1 Generated from 2,6-Dibromocyclohexanone and R(*n*-Bu)CuLi

R	Equiv of MeI/ equiv of R(*n*-Bu)CuLi	Additive	Conditions	Cyclohexanone products, %[a] 2-*n*-Bu-	7	2-*n*-Bu-*x*, 6-Me$_2$-
t-BuO	1		0°, 1 hr	22	35	1
t-BuO	2		0°, 1 hr	8	37	9
t-BuO	12	MeLi	−78 → 0°, 1 hr		41	0
t-BuO	3	MeLi, HMPA	−78 → 0°, 1 hr		21	5
t-BuO	0	MeLi	−78 → 0°, 1 hr	32	12	
t-BuO	12	MeCu,[b] TMED	0°, 1 hr	2	70	2
n-Bu	6	TMED	−78 → 0°, 0.5 hr	3	50	0

[a] Yields were determined by glpc using calibrated internal standards. [b] Prepared from methyllithium and cuprous iodide and therefore containing lithium iodide.

an organocopper cluster complex which contains *both* enolate and methyl groups and which decomposes *via* coupling of some of the organic groups *within* the aggregate.[21] Long reaction times and very large excesses of methyl iodide tend to produce substantial amounts of dimethylated cyclohexanones.

In all cases, *cis*-2-*n*-butyl-6-methylcyclohexanone (*cis*-**7**) is formed in amounts equal to or greater than *trans*-**7**; the equilibrium ratio, under basic conditions starting from either pure *cis*-**7** or pure *trans*-**7**, is 86:14 cis:trans. In no case was 2-*n*-butyl-2-methylcyclohexanone formed in more than 1% yield (see Table II).

None of the conditions listed in Table I was satisfactory for *n*-butylation of enolate ion **1**. Addition of hexamethylphosphoramide (HMPA, 20% by volume) to the solution of enolate ion **1** along with excess *n*-butyl iodide, however, gave the optimal yields of di-*n*-butylcyclohexanones **8** and **9**; lithium di-*n*-butylcuprate and HMPA or lithium *tert*-butoxy(*n*-butyl)cuprate and HMPA produce a mixture of dibutylcyclohexanones **8** and **9** in 35 and 53% yields, respectively; the ratio of **8** to **9** in both cases is about 3:2. Thus, under these conditions the rate of equilibration of enolate ion **1** to the isomeric more highly substituted enolate ion is *roughly* comparable to the rate of *n*-butylation. Enolate structural isomers of type **1** derived from 2-alkylcyclohexanones are known to be less stable than the isomeric more highly substituted enolates,[3] and it has been shown previously that equilibration is slower than benzylation[22] but faster than *n*-butylation[23] of *lithium* enolate **1b**. Thus, formation of 2,6-di-*n*-butylcyclohexanone (**8**) in substantial amounts directly from enolate ion **1** may be of synthetic use.[24] In all cases, *cis*-dibutylcyclohexanone **8** is formed in much larger amounts than *trans*-**8**; equilibration of *cis*-**8** or *trans*-**8** under basic conditions produces a 90:10 cis:trans mixture.

That some proton transfer (and enolate equilibration) is occurring during *n*-butylation of enolate ion **1** is further indicated by performing this *n*-butylation reaction in the presence of 5-nonanone; a small amount of 4-*n*-butyl-5-nonanone is isolated. The enolate ion of 5-nonanone may be formed *via* interaction of 5-nonanone with enolate ion **1** or directly with a dialkylcuprate reagent.[25]

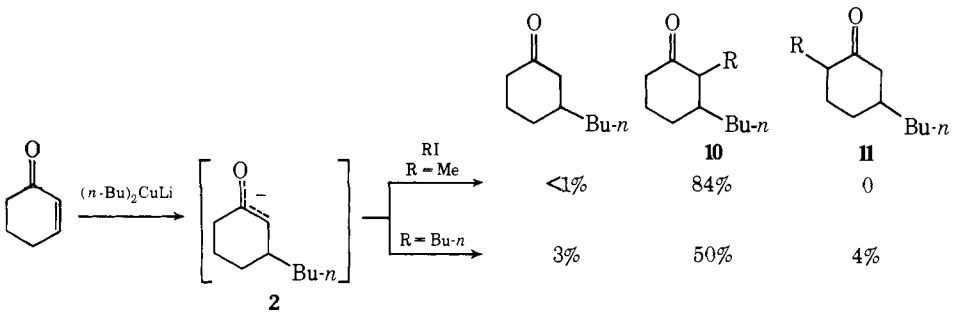
Treatment of enolate ion **1** with allyl bromide, alkyl tosylates,[26] and cyclohexene oxide[27] causes relatively little (<25%) alkylation. Likewise lithium *tert*-butoxy(*tert*-butyl)cuprate reacts under various conditions with 2,6-dibromocyclohexanone and then with methyl iodide to form 2-*tert*-butyl-6-methylcyclohexanone in low yield. In all reactions of enolate ion **1** with electrophiles, varying amounts of nonvolatile polymeric material are formed, which account for the remainder of the mass balance in most cases.[9a]

The transformation shown in Scheme I represent a new and effective process for forming carbon–carbon bonds at *both* positions adjacent (*i.e.*, α,α') to the carbonyl group of cyclohexanone. We have shown previously that similar α,α'-dialkylations can be achieved in acyclic and in 12-membered cyclic ketones.[9b]

Enolate Ions Derived from 2-Cyclohexenones. Conjugate addition of organocopper reagents to 2-cycloalkenones leads to specific enolate structural isomers some of which have been alkylated directly by reactive (*e.g.*, methyl, allyl, and benzyl) halides,[6] and such conjugate additions have been used to prepare specific enol acetates,[22] enol silyl ethers,[13] and enol phosphorylated species.[23,28] 2-Cyclohexenone reacts with excess lithium di-*n*-butylcuprate in THF at −78° for 0.5 hr to produce enolate ion **2**; addition of excess methyl iodide in HMPA at −78°, warming to between −40 and −30° (but no higher), and reaction at that temperature for 2 hr give *trans*- and *cis*-3-*n*-butyl-2-methylcyclohexanones (**10**, R = Me) in 7:1 ratio in 84% yield (Scheme II). No 5-*n*-butyl-2-methylcyclohexanone (**11**, R = Me) is formed, which indicates that methylation is much faster than equilibration of enolate ion **2** under these conditions even in the presence of HMPA. Interestingly, enolate ion **2** generated *via* reaction of 2-cyclohexenone with lithium *tert*-butoxy(*n*-butyl)cuprate reacts with methyl iodide even in the absence of HMPA to form 2,3-dialkylcyclohexanone **10** (R = Me) and 2,5-dialkylcyclohexanone **11** (R = Me), *in roughly equal amounts;* thus, use of the mixed hetero(alkyl)cuprate to generate enolate ion **2** apparently causes substantial enolate ion equilibration in this system. *n*-Butylation (HMPA present) of enolate ion **2** generated using lithium di-*n*-butylcuprate produces *trans*- and *cis*-2,3-di-*n*-butylcyclohexanones (**10**, R = Bu-*n*) in 4.5:1 ratio as the major products (50% yield), along with a small amount of 2,5-di-*n*-butylcyclohexanone (**11**, R = Bu-*n*). This is one of the first examples of direct high-yield normal-alkylation of an enolate generated by organocopper conjugate addition;[6a] that *n*-alkylation proceeds appreciably faster than equilibration of enolate ion **2** is especially noteworthy, because 3-alkylcyclohexanones normally undergo alkylation to form only 2,5-dialkylcyclohexanones and not 2,3-dialkylcyclohexanones.[3c,29] Equilibration of *cis*- or *trans*-cyclohexanones **10** under basic conditions produces a mixture in which the trans isomer predominates: 80:20 trans:cis for **10**, R = Me, and 56:44 trans:cis for **10**, R = Bu-*n*.

The ability to introduce a nucleophilic alkyl group and an electrophilic normal alkyl group at the 3 and 2 positions, respectively, of 2-cyclohexenone prompted us to explore extension of this procedure to *intra*molecular enolate alkylation with the aim of developing a conjugate addition–*cyclo*alkylation method applicable to synthesis of decalin sesquiterpenes. Indeed, lithium dimethylcuprate does react with 3,5-dialkyl-2-cyclohexenone **14** in benzene to form enolate ion **3′**; addition of HMPA (50% by volume) promotes cycloalkylation as expected to form *cis*-1-decalone **15** stereoselectively in 25–30% isolated yield (Scheme II). Reduction of decalone **15** produces *dl*-valerane (**16**). Several features of this conjugate addition–cycloalkylation process de-

Scheme II

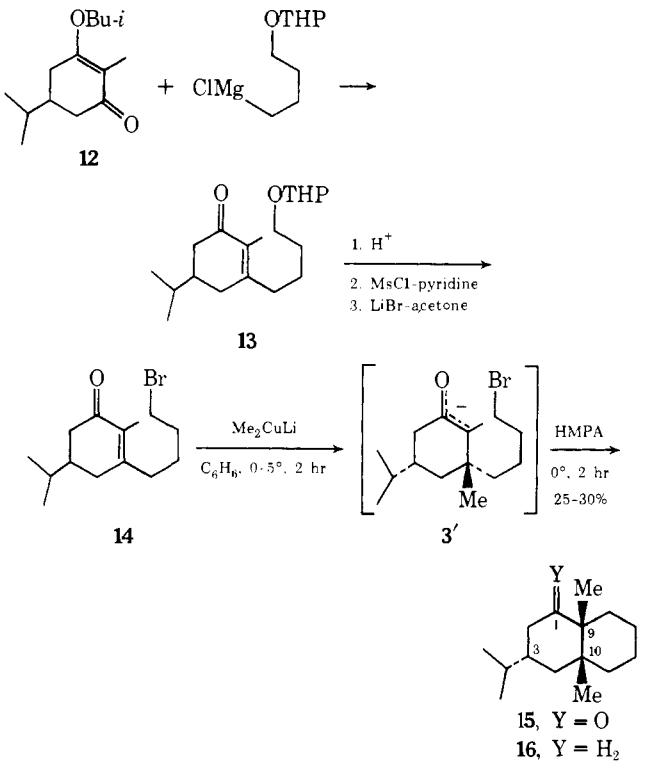


serve comment.

Bromoenone **14** is prepared conveniently in 35% overall yield from readily available enol ether **12** *via* tetrahydropyranyl ether **13** (Scheme II).[30] Attempts to perform lithium dimethylcopper selective conjugate addition to an analog of bromoenone **14** with a mesylate group in place of bromine were unsuccessful; direct displacement of this mesylate leaving group competed effectively with conjugate addition.[31] As expected, organocopper conjugate addition to sterically congested β,β-dialkyl-α,β-ethylenic ketone **14** is relatively slow.[10] Study of the effect of solvent on the rate of lithium dimethylcuprate 1,4 addition to enone **14** shows that the reaction is slower in tetrahydrofuran than in ether and faster in benzene than in ether. The methyl conjugate addition proceeds stereoselectively with axial introduction of the methyl group, trans to the isopropyl group; this is the first reported example of organocopper conjugate addition to a 3,5-dialkyl-2-cyclohexenone in which the stereochemistry of addition has been studied.[32,33] Likewise, the stereoelectronic requirements of the cycloalkylation step strongly favor a high degree of stereoselectivity in formation of a *cis*-1-decalone system,[30] as is actually observed. Addition of HMPA cosolvent is required for effective cycloalkylation of enolate ion **3′**.

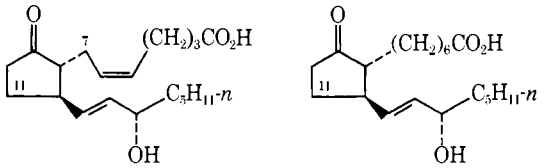
The spectral and glpc properties of *dl*-valerane (**16**) prepared *via* Scheme III[34] are identical with those of an authentic sample of *dl*-valerane and are different from those of *dl*-isovalerane, in which the angular methyl groups and the isopropyl group are all cis.[35] The overall yield of *cis*-1-decalone **15** from readily available enol ether **12** is 9% *via* Scheme III.

Scheme III



This two-step, one-pot reaction of organocopper conjugate addition–cycloalkylation represents a novel, highly stereoselective entry into the valerane class of sesquiterpenes characterized by the synthetically challenging angular *cis*-dimethyl substitution pattern.[36] Application of this method to efficient construction of other decalin and hydroazulenic sesquiterpenes is in progress.

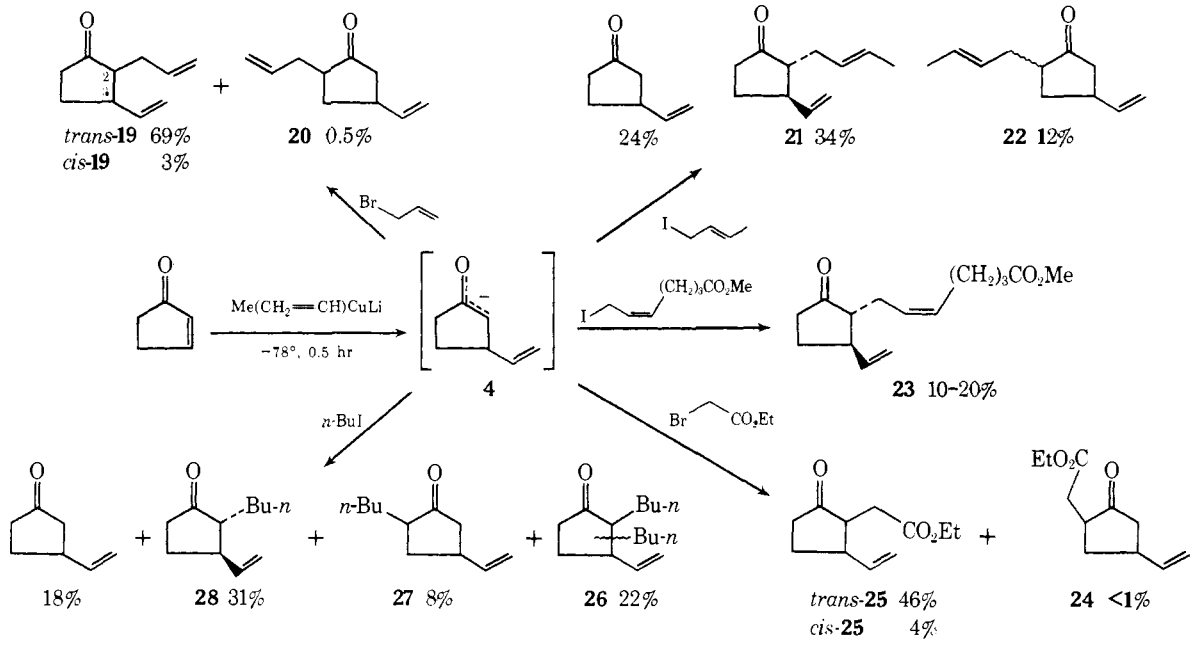
Enolate Ions Derived from 2-Cyclopentenones. Regiospecific generation and alkylation of one enolate structural isomer of an unsymmetrical cyclo*pen*tanone under nonequilibrating conditions is even more difficult than position-specific alkylation of unsymmetrical cyclo*hex*anones; cyclopentanones tend to self-condense in basic media, and cyclopentanone enolate ions are known to undergo relatively rapid equilibration.[3b,c,37] Our success, however, in converting 2-cyclohexenones directly into 2,3-dialkylcyclohexanones prompted us to explore extension of this method to 2-cyclopentenones with the ultimate goal of developing a nucleophilic β-alkylation–electrophilic α alkylation procedure applicable to efficient construction of various 2,3-dialkylcyclopentanones, such as the E series of prostaglandins (*e.g.*, **17** and **18**).[38] Toward this end, we have prepared specific enolate structural isomer **4** by a vinylcuprate conjugate addition reaction to 2-cyclopentenone; reaction of anion **4** with a variety of electrophiles has been studied, and some results are summarized in Scheme IV.



17 (11-deoxy-PGE$_2$) **18** (11-deoxy-PGE$_1$)

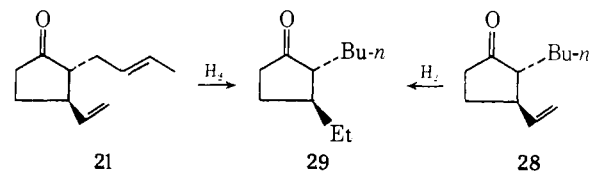
Cyclopentanone enolate ion **4** in THF solution reacts with 2 equiv of allyl bromide at −78° for 1 hr to afford *trans*-2-allyl-3-vinylcyclopentanone (*trans*-**19**) in 69% isolated yield after purification by preparative glpc. Although the trans relationship of the allyl and vinyl groups could not be determined by nmr spectroscopy *directly* on *trans*-**19**, hydrogenation of *trans*-**19** produced *trans*-3-ethyl-2-*n*-propylcyclopentanone, the trans stereochemistry of which was unambiguously determined by nmr decoupling experiments using a europium shift reagent to separate α-methylene from α-methine absorptions; the C_2H–C_3H coupling constant is 11 Hz, which is in the region characteristic of *trans*-2,3-dialkylcyclopentanones but too large for a *cis*-2,3-dialkylcyclopentanone.[39] *cis*-**19** was formed in small amount along with *trans*-**19**; *cis*-**19** was isolated by preparative glpc and was found to equilibrate under basic condi-

Scheme IV



tions to 98:2 *trans:cis*-**19**. 2-Allyl-4-vinylcyclopentanone (**20**), formed *via* allylation of the enolate ion structurally isomeric with enolate ion **4**, is produced in 0.5% yield; 2,4-isomer **20** was isolated by preparative glpc and was found not to equilibrate to either *cis*-**19** or *trans*-**19**. Thus allylation of cyclopentanone enolate ion **4** under these conditions is substantially faster than enolate ion equilibration. Similar results are obtained even when methyl valerate is added along with allyl bromide to enolate ion **4**; recovery of methyl valerate in 75% indicated that ester groups survive these allylation conditions and suggested, therefore, that the C_1–C_7 side chain of PGE_2 **17** might be introduced directly *via* attachment of a suitable allylic group containing a terminal ester functionality. Because allylic rearrangements have been observed in coupling reactions of allylic halides with enolate ions[40] and with organocopper reagents,[41] however, it became important to explore the course of interaction between enolate ion **4** and various allylic electrophiles.

Several different butenyl electrophiles were examined, including 2-butenyl acetate, tosylate, bromide, and iodide. Of these, *trans*-1-iodo-2-butene gave the highest yields of 2-butenyl-3-vinylcyclopentanones. Variation of reaction solvent, cosolvent, time, and temperature revealed that the time and especially temperature variables were most critical; enolate ion **4** reacts with *trans*-2-butenyl iodide at −45° (Dry Ice–acetonitrile bath) during 1 hr in the presence of HMPA or *N*-methylpyrrolidone to form *trans*-2-(*trans*-2′-butenyl)-3-vinylcyclopentanone (**21**) in 34% yield, along with substantial amounts of 3-vinylcyclopentanone and 2-butenyl-4-vinylcyclopentanone **22**. Longer reaction times cause production of larger amounts of polyalkylated cyclopentanones, and lower temperatures (either with or without any cosolvent) cause formation of significant amounts of what appear to be allylically rearranged (1-buten-3-yl)vinylcyclopentanones. The stereochemistry of butenylcyclopentanone **21** was determined as follows: a strong infrared absorption at 960 cm^{-1} indicated that the 2-butenyl group has a trans-double bond;[42] hydrogenation of **21** gave *trans*-2-*n*-butyl-3-ethylcyclopentanone (**29**) identical in all respects (tlc, glpc, nmr) with the same compound formed *via* hydrogenation of *trans*-2-*n*-butyl-3-vinylcyclopentanone (**28**, see eq 1) and having a decoupled nmr spectrum consistent with its being a *trans*-2,3-dialkylcyclopentanone. Butenylcyclopentanones **21** and **22** are not epimerized by treatment with base.



(1)

Satisfactory conditions for α attachment of a butenyl group without rearrangement were applied to reaction of enolate ion **4** with methyl 7-iodo-*cis*-5-heptenoate.[43] 11-Deoxy-PGE_2 model system **23** was isolated in 20% yield by column chromatography on silica. Further repeated purification by preparative tlc on silica gel gave **23** (10% yield) having nmr and ir spectra and glpc retention time matching those of **23** prepared independently *via* vinyl conjugate addition to 2-(6-methoxycarbonyl-2-*cis*-hexenyl)-2-cyclopentenone.[44] *trans*-2-Alkyl-3-vinylcyclopentanone **23** is not epimerized by base (and therefore is not the cis isomer). It should be noted that the 10–20% yield of **23** in this 2,3 *di*-alkylation of 2-cyclopentenone compares reasonably well with the 25% yields reported for conjugate vinylation of 2-(6-methoxycarbonylhexyl)-2-cyclopentenone, *with yield based on the transferred vinyl group.*[38c]

Treatment of enolate ion **4** in THF solution with α-iodo, α-bromo-, or α-chloroacetates produces vinyl esters **24** and **25**. Best results are obtined with ethyl α-*bromo* acetate; *trans*-**25** is formed in 46% yield along with 4% of *cis*-**25** and less than 1% of 2,4-disubstituted cyclopentanone **24**. *cis*-**25** equilibrates under basic conditions to mainly *trans*-**25**, but 2,4 isomer **24** does not equilibrate to 2,3 isomers *trans*- or *cis*-**25**. Thus, enolate ion **4** reacts with reactive electrophiles such as allyl bromide and ethyl α-bromoacetate substantially faster than it undergoes equilibration to a structurally isomeric enolate ion. Transformations (*e.g.*, intramolecular cyclizations)[45] of olefinic esters such as **25** may lead to useful, new synthetic intermediates.

In contrast to allylation and (ethoxycarbonyl)methylation of enolate ion **4** in THF, *n*-butylation in THF is so slow that HMPA is required as a cosolvent to cause the reaction to proceed at an appreciable rate. HMPA, however, increases not only the rate of the *n*-butylation but also the rate of enolate ion equilibration.[46] A series of experiments under various reaction conditions, including use of

1,2-dimethoxyethane as solvent or cosolvent as recently described,[6a] shows that addition of 50% by volume of HMPA to enolate ion **4** in THF at 0° and then product isolation after only 10 min are the best conditions for selective formation of 2-*n*-butyl-3-vinylcyclopentanone (**28**). Even under these optimal conditions, however, glpc analysis indicates formation of substantial amounts of 3-vinylcyclopentanone and of di-*n*-butylated cyclopentanones **26** (2,2-dibutyl or 2,5-dibutyl), as well as 9% of 2-*n*-butyl-4-vinylcyclopentanone (**27**, which had not been detected earlier).[1] 2,4-Isomer **27** does not equilibrate to 2,3-isomer **28**, and therefore **27** is not *cis*-**28**. Basic equilibration of *trans*-**28** gives no detectable amount of *cis*-**28** by glpc analysis, and hydrogenation of *trans*-**28** produces *trans*-2-*n*-butyl-3-ethylcyclopentanone (**29**, eq 1).

It should be noted that *n*-butylation of cyclo*pent*anone enolate ion **4** is accompanied by much more enolate ion equilibration than is *n*-butylation of cyclo*hex*anone enolate ion **2**; this result is not unexpected (see ref 3). More important is the tendency of cyclopentanone enolate ion **4** to undergo allylation and (alkoxycarbonyl)methylation under carefully controlled conditions *without significant enolate ion equilibration.*

A new mixed cuprate(I) reagent, lithium methyl(vinyl)cuprate(I), was developed for conjugate vinylation of 2-cyclopentenone, as shown in Scheme III. This reagent in THF solution selectively transfers the vinyl group to C-3 of 2-cyclopentenone; the degree of transfer selectivity in THF is about 25:1 vinyl:methyl, and only 1.1 equiv of this mixed cuprate reagents is needed for complete conversion of 2-cyclopentenone to enolate ion **4**. This near-ideal stoichiometry in vinyl group transfer will be of utmost importance if this approach is to be applied to attachment of the valuable ω side chain common to the natural prostaglandins (*cf.* **17**, **18**).[38] Although several mixed acetylenic (vinyl)cuprate reagents also transfer vinyl groups selectively in conjugate addition reactions,[21b,47] preparation of these reagents is more difficult than preparation of lithium methyl(vinyl)cuprate, which is prepared conveniently and rapidly *in situ* by adding 1 equiv of vinyllithium and then 1 equiv of methyllithium to 1.1 equiv of cuprous iodide in THF at −35°. Furthermore, enolate ion **4** generated from 2-cyclopentenone and an acetylenic (vinyl)cuprate is not so easily allylated as enolate ion **4** generated from 2-cyclopentenone and lithium methyl(vinyl)cuprate. Interestingly, lithium methyl(vinyl)cuprate in THF undergoes preferential transfer of the *methyl* group in coupling reactions with acid chlorides and epoxides, and, when *diethyl ether* is used as solvent instead of THF, the methyl and the vinyl groups are both transferred to C-3 of 2-cyclopentenone. The factors which govern transfer of one or the other group from a mixed cuprate are not presently well understood.[48]

Conclusions

The three different enolate ions **1**, **2**, and **4** couple with reactive electrophiles (*e.g.*, methyl iodide, allyl bromide, ethyl α-bromoacetate) faster than they equilibrate to structurally isomeric enolate ions, but only enolate ion **2** couples with *n*-alkyl iodides much faster than it equilibrates (even in the presence of HMPA); cyclohexanone enolate ion **1** and especially cyclopentanone enolate ion **4** equilibrate during *n*-alkylation in the presence of HMPA. The results reported herein represent a useful new procedure for introduction of two different alkyl substituents either α,α' or α,β to cyclohexanone and cyclopentanone carbonyl groups. This work extends our previously reported α,α'-dialkylation of acyclic and of cyclic 12-membered ring ketones[9] and complements our research on α-tertiary alkylation of ketones[9,49] and on preparation of hindered ketones from carboxylic acid chlorides.[9a,25a]

Experimental Section

General. Infrared spectra were obtained with Perkin-Elmer 337 and 457 infrared spectrophotometers, as liquid films, KBr pellets, or in $CHCl_3$ or CCl_4 solution. Nmr spectra were obtained with a Varian A-60 or a Jeol MH-100 spectrometer in CCl_4 or $CDCl_3$ solutions, with TMS as internal standard. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6 mass spectrometer. Melting points, determined with a Mel-Temp melting point apparatus, and boiling points are uncorrected. Analytical glpc were performed on a Varian Aerograph series 1200 gas chromatograph, using the following columns: (A) 10 ft × 0.25 in. FFAP on Chrom W (60–80); (B) 10 ft × 0.25 in. Carbowax 20-M on Chrom W (60–80); (C) 9 ft × ⅛ in. 5% SE-30 on Chrom G (100–140); (D) 18 ft × ⅛ in. 20% Reoplex on Anachrom AS (80–90). Yields were determined by analytical glpc using internal standards whose response factors relative to those of authentic product samples had been calibrated. Preparative glpc was performed on a Varian Aerograph Model 90-P gas chromatograph, using the following columns: (E) 20 ft × ⅜ in. 20% QF-1 on Chrom W (45–60); (F) 10 ft × 0.25 in. 20% SE-30 on Chrom W (45–60); (G) 20 ft × ⅜ in. 20% SE-30 on Chrom W (45–60); (H) 20 ft × 0.25 in. 20% FFAP on Chrom W (45–60); analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Chemalytics, Inc., Tempe, Ariz.

All reactions involving organometallic compounds were performed in three-necked round-bottom flasks equipped with serum stoppers and a nitrogen-filled balloon. Prior to the introduction of reactants, the apparatus was dried with a Bunsen burner flame while being purged with N_2.

Reagents and Solvents. The following materials were obtained from commercial sources and were used without further purification: cyclopentenone, methyl iodide, methyl valerate, isobutyl alcohol, *p*-toluenesulfonic acid monohydrate, acetyl chloride, methanesulfonyl chloride, lithium bromide, 1,2-ethanedithiol, boron trifluoride etherate, Raney nickel activated to W-2, and 10% palladium on charcoal.

The following reagents were obtained from commercial sources and were purified by distillation from CaH_2: allyl bromide, 1-bromo-2-butene, *n*-butyl iodide, *tert*-butyl alcohol, *n*-butyraldehyde, hexamethylphosphoric triamide, tetramethylethylenediamine, triethylamine, trimethylchlorosilane, ethyl α-bromoacetate, and *N*-methylpyrrolidone. Cyclohexenone was distilled at 68° (22 mm).

Commercial solvents were used from freshly opened bottles without further treatment except that tetrahydrofuran was distilled from lithium aluminum hydride and stored under N_2.

Cuprous iodide (Fisher Chemical Co.) was continuously extracted with tetrahydrofuran in a Soxhlet extractor for 12 hr and dried *in vacuo* at 25°; the cuprous iodide thus purified remained pure on standing for several months, and aliquots were used for reaction with organolithium reagents to generate cuprates(I).

Alkyllithium reagents were obtained from Foote Mineral Co. and Alfa Inorganics and were used directly from the bottle. Methyllithium was about 2.0 *M* in diethyl ether solution and was stored at ambient temperature. *n*-Butyllithium was about 2.0 *M* in hexane solution, and vinyllithium was about 2.0 *M* in tetrahydrofuran solution. These were stored at 0°. Molarity was determined by a double titration procedure.[50] The preparation of lithium *tert*-butoxide has been described previously.[9]

Trimethylsilyl (6-Methyl-1-cyclohexen-1-ol) Ether (5). To a stirred suspension of 970 mg (5.1 mmol) of cuprous iodide in 12 ml of diethyl ether at 0° was added 5.7 ml of 1.76 *M* (10.0 mmol) methyllithium. After stirring for 3 min, the solution was cooled to −78°, and 256 mg (1.0 mmol) of 2,6-dibromocyclohexanone in 1 ml of ether was added, followed in 0.5 hr by a freshly filtered solution of 2.7 ml (25 mmol) of chlorotrimethylsilane and 3.5 ml (25 mmol) of triethylamine. The reaction mixture was allowed to warm to ambient temperature for 1 hr at which time the solvent and other volatiles were removed at aspirator pressure without heating. Silyl ether **5** was isolated by short path distillation directly from the reaction vessel yielding 85 mg (46%) of **5** pure by glpc (column C, 120°, 5 min) with spectral data fully consistent with the literature values.[51]

Table II. Experimental Data on Dialkylcyclohexanones and Dialkylcyclopentanones

Compd	Glpc column	Retention time, min	Combustion analysis	Mass spectrometry, *m/e* of parent ion	Miscellaneous
			Dialkylcyclohexanones		
cis-**7**	D[a]	36		168	Spectra and glpc retention time match those of authentic sample[b]
trans-**7**	D[a]	39		168	Equilibrates to mainly *cis*-**7**
2-*n*-Bu-2-Me	D[a]	41		168	Spectra and glpc retention time match those of authentic sample[b]
cis-**8**	D[c]	32.5		210.1983[d]	Equilibrates to 9:1 *cis*:*trans*-**8**
trans-**8**	D[c]	34.0		210	Equilibrates to 9:1 *cis*:*trans*-**8**
9	D[c]	35.0	C, 80.17; H, 12.77[e]		
2-Me-5-*n*-Bu	C[a]	9.5		168	
trans-**10**[o]	C[a]	10.5	C, 78.67; H, 12.34[f]	168	Equilibrates to 80:20 trans:cis
cis-**10**[o]	C[a]	10.8		168	Equilibrates to 80:20 trans:cis
trans-**10**[p]	C[g]	9.5	C, 79.64; H, 12.26[e]		Equilibrates to 56:44 *trans*:*cis*-**10**
cis-**10**[p]	C[g]	10.3			Equilibrates to 56:44 *trans*:*cis*-**10**
11	C[g]	11.0		210.1993[d]	Does not equilibrate to **10**
			Dialkylcyclopentanones		
trans-**19**	A[h]	6.5	C, 79.92; H, 9.44[i]	150	
cis-**19**	A[h]	7.0		150	Equilibrates to mainly *trans*-**19**
20	A[h]	8.2		150	Does not equilibrate to *trans*- or *cis*-**19**
21	A[j]	7.0	C, 80.86; H, 9.83[k]	164	Does not epimerize in base
22	A[j]	8.0	C, 80.31; H, 9.68[k]		Does not equilibrate to **21**
trans-**25**	C[h]	7.8	C, 66.98; H, 8.45[l]		Does not epimerize in base
cis-**25**	C[h]	9.0			Equilibrates to mainly *trans*-**25**
24	C[h]	9.8		196	Does not equilibrate to *trans*- or *cis*-**25**
28	A[m]	10.6	C, 79.07; H, 10.76[n]	166	Stereochemical assignment based on nmr
27	A[m]	13.0	C, 79.24; H, 10.99[n]		Does not equilibrate to **28**

[a] 130°, flow rate 35 ml/min. [b] See ref 9 for preparation of authentic sample. [c] 160°, flow rate 35 ml/min. [d] Calcd for $C_{14}H_{26}O$: *m/* 210.1983. [e] Calcd for $C_{14}H_{26}O$: C, 79.93; H, 12.46. [f] Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. [g] 180°, flow rate 35 ml/min. [h] 160°, flow rate 60 ml/min. [i] Calcd for $C_{10}H_{14}O$: C, 79.95: H, 9.39. [j] 170°, flow rate 60 ml/min. [k] Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. [l] Calcd for $C_{11}H_{16}O_3$: C, 67.20; H, 8.32. [m] 150°, flow rate 35 ml/min. [n] Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. [o] 2-Methyl. [p] 2-*n*-Butyl.

Reaction of 2,6-Dibromocyclohexanone with *n*-Butylcuprate Reagents. A. *n*-Butyraldehyde Quench. To a stirred suspension of 485 mg (2.55 mmol) of cuprous iodide in 6 ml of tetrahydrofuran at 0° was added 2.5 ml of 1.0 *M* (2.5 mmol) lithium *tert*-butoxide.[9] After stirring for 3 min the green mixture was cooled to −78°, and 1.3 ml of 1.91 *M* (2.5 mmol) *n*-butyllithium was added, followed by 128 mg (0.5 mmol) of 2,6-dibromocyclohexanone in 1 ml of THF. After 30 min, the reaction mixture was allowed to warm to room temperature for 15 min; then 0.44 ml (5.0 mmol) of *n*-butyraldehyde in 5 ml of THF was added dropwise over 10 min, followed in 5 min by 1 ml of absolute methanol. The reaction mixture was then poured into saturated aqueous ammonium chloride, diluted with diethyl ether, and stirred for 1 hr, and the layers were separated. The aqueous phase was extracted once with ether, and the combined organic layers were washed with 2% aqueous sodium thiosulfate and dried over magnesium sulfate. Three products were observed *via* glpc (column C, 180°, valerophenone internal standard): A (2.5 min), B (5.5 min), and C (10.5 min).

A is 2-*n*-butylcyclohexanone (3 mg, 4%) identified by comparing its retention time with that of authentic material.[9]

B was shown not to be a cyclohexanone derivative and was not further characterized.

C is 2-(*n*-butylidene)-6-*n*-butylcyclohexanone (**6**, 45 mg, 43%) isolated *via* preparative glpc (column F, 185°, 26 min, 32 mg, 31%): nmr (CCl_4) δ 6.5 (t of t, 1 H, J = 7 and 2 Hz), 1.0–2.6 (m, 17 H), 0.6–1.0 (m, 6 H); ir (CCl_4) 1690 (C=O) and 1618 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (relative intensity) 208 (10, molecular ion), 165 (30), 153 (50), 152 (100); high resolution mass spectrum 208.1832 (calcd for $C_{14}H_{24}O$, 208.1827).

2-(*n*-Butylidene)-6-*n*-butylcyclohexanone (**6**, 65 mg, 0.31 mmol) was hydrogenated on 10 mg of 10% palladium on carbon in 2 ml of absolute ethanol at 1 atm pressure of hydrogen for 12 hr.[51] The major product was 95% pure by glpc (column C, 180°, 6.5 min). It was isolated *via* preparative glpc (column F, 180°, 20 min) and was identified as 2,6-di-*n*-butylcyclohexanone (**8**, 55 mg, 85%): nmr (CCl_4) δ 0.7–2.5 (broad multiplet); ir (CCl_4) 1710 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 210 (15, molecular ion), 154 (100), 111 (50), 98 (80); high resolution mass spectrum 210.1983 (calcd for $C_{14}H_{26}O$, 210.1983).

This product could be further resolved *via* glpc (column D, 160°) into two equally sized heavily overlapping peaks with retention times of 32.5 and 34 min. They could not be resolved preparatively; however, treatment with ethanolic sodium ethoxide changed the ratio to *ca.* 9:1. Thus the first peak is assigned the structure *cis*-2,6-di-*n*-butylcyclohexanone, and the second trans in analogy with the relative retention times and equilibrium composition of the corresponding 2-*n*-butyl-6-methylcyclohexanones (*vide infra*).

B. Methyl Iodide Quench. To a stirred suspension of 970 mg (5.1 mmol) of cuprous iodide in 12 ml of THF at −50° was added 5.2 ml of 1.91 *M* (10.0 mmol) *n*-butyllithium. The black mixture was immediately cooled to −78°, and 256 mg (1.0 mmol) of 2,6-dibromocyclohexanone in 1 ml of THF was added. After 30 min, 1.3 ml (10.0 mmol) of neat tetramethylethylenediamine was added, followed after 30 min by 1.9 ml (30.0 mmol) of neat methyl iodide. The reaction mixture was allowed to warm to room temperature for 30 min at which time it was poured into saturated aqueous ammonium chloride. After 1 hr of stirring, the mixture was filtered, and the separated organic layer was washed with 10% hydrochloric acid followed by saturated aqueous sodium bicarbonate and then 2% sodium thiosulfate. Glpc analysis (column C, 130°, cyclooctanone internal standard) indicated three major products: A (1.9 min), B (2.2 min), and C (9.5 min). Peak C was further resolved on column D (130°) to D (36 min) and E (39 min).[53]

A is cyclohexanone (3 mg, 3%) identified by comparing its retention time to that of an authentic sample.

B is 2-methylcyclohexanone (3 mg, 3%) identified by comparing its retention time to that of an authentic sample.

D is *cis*-2-*n*-butyl-6-methylcyclohexanone (*cis*-**7**, 67 mg, 40%) isolated *via* preparative glpc (column E, 170°. 43 min); nmr (CCl_4) methyl doublet at δ 0.95 (J = 6.5 Hz); ir (CCl_4) 1709 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 168 (20, molecular ion), 126 (20), 112 (100), 97 (50); bp 242° (760 mm).

E is *trans*-2-*n*-butyl-6-methylcyclohexanone (*trans*-**7**, 17 mg, 10%) isolated *via* preparative glpc (column E, 170°, 52 min): nmr (CCl_4) methyl doublet at δ 1.0 (J = 7.0 Hz); ir (CCl_4) C=O 1709 cm^{-1}; mass spectrum (70 eV) *m/e* 168 (5, molecular ion), 126 (10), 112 (10), 88 (10), 87 (100). The total yield of *n*-butylmethylcyclohexanones **7** is 84 mg (50%).

Stereochemical assignment is based on the fact that D and E separately both equilibrate to an 86:14 mixture of D:E in ethanolic sodium ethoxide. As both alkyl groups can be equatorial in the cis isomer, this is presumably the more stable one. Assignment of cis stereochemistry to D is based on analogy with *cis*- and *trans*-4-*tert*-butyl-2-methylcyclohexanones in which the axial methyl absorption in the nmr spectrum is further downfield than the equatorial methyl absorption.[54]

Enolate ion **1a** was also prepared by reacting 256 mg (1.0 mmol) of 2,6-dibromocyclohexanone with 5.0 mmol of lithium *tert*-butoxy(*n*-butyl)cuprate in 19 ml of THF at −78° for 30 min as described above, and then allowed to warm to 0° during 15 min at which time 0.32 ml (5.0 mmol) of neat methyl iodide was added *via* syringe. After stirring for 1 hr, the reaction mixture was poured into saturated aqueous ammonium chloride, diluted with diethyl ether, and stirred for 1 hr at which time the layers were separated, and the aqueous phase was extracted once with ether. The combined organic layers were washed with a 2% solution of sodium thiosulfate and dried over magnesium sulfate. Under these conditions, the three products observed on glpc (column C, 130°, cyclooctanone internal standard) were: A (8.5 min), B (9.5 min), and C (10.5 min). Peak B was further resolved (column D, 130°) to D (36 min), E (39 min), and F (41 min).

A is 2-*n*-butylcyclohexanone (12 mg, 8%) by comparing retention time with that of authentic material.[9]

D is *cis*-**7** (30 mg, 18%).

E is *trans*-**7** (30 mg, 18%).

F is 2-*n*-butyl-2-methylcyclohexanone (2 mg, 1%) isolated *via* preparative glpc (column E, 170°, 55 min) and identified by spectra and glpc comparison with authentic material.[9]

C appears to be a mixture of 6-*n*-butyl-2,2-dimethylcyclohexanone and 2-*n*-butyl-2,6-dimethylcyclohexanone (16 mg, 9%) isolated *via* preparative glpc (column G, 180°, 58 min): nmr (CCl_4) δ 0.7–2.7 (m); ir (CCl_4) 1710 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 182 (20, molecular ion), 126 (90), 111 (60), 82 (100). *Anal.* Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.12. Found: C, 78.79; H, 11.90.

If the reaction is allowed to run for extended periods of time (4–5 hr) under these conditions, methylation continues, and a new product predominates (column C, 130°, 11.5 min) which was isolated *via* preparative glpc (column G, 180°, 62 min) and identified as 2-*n*-butyl-2,6,6-trimethylcyclohexanone: nmr (CCl_4) 0.7–1.9 (broad multiplet); ir (CCl_4) 1694 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 196 (molecular ion), 140 (100), 126 (40), 115 (50). *Anal.* Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.68; H, 12.21.

C. ***n*-Butyl Iodide Quench.** Enolate ion **1a** was prepared by reacting 768 mg (3.0 mmol) of 2,6-dibromocyclohexanone with 12.0 mmol of lithium *tert*-butoxy(*n*-butyl)cuprate in 29 ml of tetrahydrofuran at −78° for 30 min as described above. After allowing the reaction mixture to warm to room temperature during 15 min, 3.24 ml (30.0 mmol) of *n*-butyl iodide in 12 ml of hexamethylphosphoric triamide was added *via* syringe. Two hours later the reaction mixture was poured into saturated aqueous ammonium chloride, diluted with diethyl ether, and stirred for 1 hr at which time the layers were separated, and the aqueous phase was extracted once with diethyl ether. The combined organic layers were washed once with a 2% solution of sodium thiosulfate and five times with water, dried over magnesium sulfate, and concentrated by solvent removal under reduced pressure.[55] Analytical glpc (column C, 180°) indicated three major products: A (5 min), B (7.5 min), and C (19 min). Isolation was achieved by column chromatography on 30 g of silica. Hexane first eluted a 1:1 mixture of A and B (100 mg) followed by pure B (290 mg).

A was shown not to be a cyclohexanone derivative and was not further characterized.

B was further resolved *via* glpc (column D, 160°) into three overlapping peaks: D (32.5 min), E (34 min), and F (34.5 min).

D and E were isolated together *via* preparative glpc (column E, 200°, 29 min) and identified as an equilibrium mixture of *cis*- and *trans*-2,6-di-*n*-butylcyclohexanone (**8**, 174 mg, 28%) spectrally and chromatographically identical with an authentic sample (*vide supra*).

F is 2,2-di-*n*-butylcyclohexanone (**9**, 116 mg, 17%) isolated *via* preparative glpc (column E, 200°, 34 min): nmr (CCl_4) δ 2.1–2.4 (m, 2 H, α methylene protons, could be coalesced into a singlet by spin–spin decoupling at δ 1.80), 0.8–2.0 (m, 24 H); ir (CCl_4) 1706 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 210 (10, molecular ion), 154 (100), 111 (80), 98 (80). See Table II for analysis.

C is 2,2,6-tributylcyclohexanone (105 mg, 13%) isolated *via* preparative glpc (column F, 180°, 64 min): nmr (CCl_4) 0.6–2.6 (broad multiplet); ir (CCl_4) 1703 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 266 (molecular ion), 210 (100), 167 (30), 154 (50). *Anal.* Calcd for $C_{18}H_{34}O$: C, 81.13; H, 12.86. Found: C, 81.04; H, 13.29.

Enolate **1a** may also be prepared by treating 256 mg (1.0 mmol) of 2,6-dibromocyclohexanone with 5.0 mmol of lithium di-*n*-butylcuprate at −78° for 30 min. When this enolate is treated with 1.14 ml (10.0 mmol) of *n*-butyl iodide in 4 ml of hexamethylphosphoric triamide, allowed to warm to room temperature for 2 hr, and worked up as described above, the ratio of 2,6-di-*n*-butylcyclohexanones (**8**) to 2,2-di-*n*-butylcyclohexanone (9) is very similar to the ratio observed using the mixed cuprate. However, using the dibutylcuprate instead of the *tert*-butoxy(butyl)cuprate gives di-*n*-butylcyclohexanones **8** and **9**, formed in only 31% yield (column C, 180°, cyclododecanone internal standard) as compared with 45% yield with the mixed cuprate.

Reaction of 2-Cyclohexenone with *n*-Butylcuprate Reagents. A. Methyl Iodide Quenches. To a stirred suspension of 295 mg (1.55 mmol) of cuprous iodide in 4 ml of THF at −50° was added 1.2 ml of 2.47 *M* (3.0 mmol) of *n*-butyllithium. The dark mixture was cooled to −78°, and 96 mg (1.0 mmol) of 2-cyclohexenone in 1 ml of THF was added. After the mixture was stirred for 30 min, 0.16 ml (2.0 mmol) of methyl iodide in 2 ml of HMPA was added, and the reaction mixture was allowed to warm to −30°. The temperature was maintained between −30 and −40° for 2 hr after which time 1 ml of absolute methanol was added, and the reaction mixture was allowed to warm to room temperature and poured into saturated aqueous ammonium chloride, diluted with diethyl ether, and stirred for 1 hr at which time the layers were separated and the aqueous phase was extracted once with ether. The combined organic layers were washed with a 2% solution of sodium thiosulfate and dried over magnesium sulfate.[55] Analysis *via* glpc (column C, 130°, cyclooctanone internal standard) indicated three products: A (9.5 min), B (10.0 min), and C (10.8 min).

A is 3-*n*-butylcyclohexanone (1 mg, 1%) identified by comparing retention times with that of an authentic sample.[9]

B is *trans*-3-*n*-butyl-2-methylcyclohexanone (*trans*-**10**, R = Me, 124 mg, 74%) which was isolated *via* preparative glpc (column F, 150°, 25 min): nmr (CCl_4) δ 1.1–2.4 (m, 14 H), 0.8–1.4 (distorted t with d at 0.97, J = 7 Hz, 6 H); ir (CCl_4) 1712 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 168 (molecular ion), 125, 111, 97, 55; bp 238° (760 mm). See Table II for analyses.

C is *cis*-3-*n*-butyl-2-methylcyclohexanone (*cis*-**10**, R = Me, 15 mg, 10%) which could only be isolated in small quantities using column D, 160°, as a preparative column: mass spectrum (70 eV) *m/e* 168 (10, molecular ion), 125 (50), 111 (100), 97 (80).

Both B and C could be equilibrated to a 80:20 mixture of B:C. Trans stereochemistry is assigned to B as this is undoubtedly the more thermodynamically stable isomer with both alkyl groups equatorial.

No 5-*n*-butyl-2-methylcyclohexanone (see below) or polymethylated products are observed under these conditions, although a small amount of the latter are formed at slightly higher temperatures. However, enolate ion **2** was also prepared by treating 96 mg (1.0 mmol) of 2-cyclohexenone with 1.5 mmol of lithium *tert*-butoxy(*n*-butyl)cuprate at −50° for 1 hr at which time the reaction mixture was allowed to warm to −40°, and 0.16 ml (2.0 mmol) of methyl iodide in 2 ml of HMPA was added. The mixture was stirred at −30 to −40° for 2 hr at which time 1 ml of absolute methanol was added. The reaction mixture was allowed to warm to room temperature, poured into saturated aqueous ammonium chloride, and diluted with diethyl ether. After the reaction mixture was stirred for 1 hr, the separated aqueous phase was extracted once with ether, and the combined organic layers were dried over magnesium sulfate.[55] Under these reaction conditions there were seven products observed on analytical glpc (column C, 130°): A (6 min), B (9.5 min), overlapping C (10 min), D (10.8 min), E (12 min), F (13 min), and G (13.5 min).

A is 3-*n*-butylcyclohexanone (3% of mixture) identified by comparing glpc retention times with authentic material.[9]

B (23% of mixture) could not be easily resolved from C *via* preparative glpc; however, a B-enriched sample (column F, 150°, 22

min) indicated it to be 5-*n*-butyl-2-methylcyclohexanone: nmr (CCl_4) δ 1.1–2.5 (m, 14 H), 0.7–1.1 (m, 6 H); ir (CCl_4) 1712 cm^{-1} (C=O); a small pure sample was collected for a mass spectrum (70 eV) *m/e* 168 (20, molecular ion), 111 (100), 97 (50).

C is *trans*-**10**, R = Me (35% of mixture), identified by comparing spectra and glpc retention times with those of authentic material (see above).

D is *cis*-**10**, R = Me (4% of mixture), identified by comparing glpc retention times with that of authentic material (see above).

E, F, and G each had ir, nmr, and mass spectral data consistent with three dimethylated isomers: 3-*n*-butyl-2,2-dimethyl and two stereoisomers of 3-*n*-butyl-2,6-dimethylcyclohexanone.

B. *n*-Butyl Iodide Quench. Enolate ion **2** was prepared by treating 392 mg (4.0 mmol) of 2-cyclohexenone with 6 mmol of lithium di-*n*-butylcuprate at −78° for 30 min. At that time 4.56 ml (40 mmol) of *n*-butyl iodide in 16 ml of HMPA was added, and the reaction mixture was allowed to warm to room temperature for 30 min at which time it was poured into saturated aqueous ammonium chloride, diluted with diethyl ether, and stirred for 1 hr. The layers were separated, and the aqueous phase was extracted once with ether, and the combined organic layers were washed with 2% sodium thiosulfate and were dried over magnesium sulfate. Five products were observed on glpc (column C, 180°, dimethyl sebacate internal standard): A (2.5 min), B (5 min), C (9.5 min), D (10.3 min), and E (11.0 min).

A is 3-*n*-butylcyclohexanone (20 mg, 3%) by comparing glpc retention time with that of an authentic sample.[9]

B was shown not to be a cyclohexanone derivative and was not further characterized.

C is *trans*-2,3-di-*n*-butylcyclohexanone (*trans*-**10**, R = Bu-*n*, 375 mg, 45%) isolated *via* preparative glpc (column E, 210°, 47 min): nmr (CCl_4) δ 0.7–2.4 (broad m); ir (CCl_4) 1712 cm^{-1} (C=O); bp 293° (760 mm). See Table II for analysis.

The trans-2,3-disubstitution pattern is assigned by utilizing a combination of nmr lanthanide shift reagent[58] and spin–spin decoupling. To 50 mg of *trans*-**10**, R = Bu-*n*, in 0.5 ml of CCl_4 was added 100 mg of Eu(fod)$_3$ ("Resolve-Al") resulting in the following nmr: δ 0.5 (s, shift reagent) 1.0 (t, 6 H, 2 methyl groups), 1.2–2.8 (m, chain and ring protons), 3.0–3.2 (m, 1 H, α methine), 3.2–3.9 (m, 2 H, α methylene). Irradiating at δ 2.17 resolved the α methine proton at δ 3.08 into a doublet, J = 6.0 Hz.[59] The shorter retention time of C than D suggests also that C is *trans*- rather than *cis*-**10**, R = *n*-Bu.

D is *cis*-2,3-di-*n*-butylcyclohexanone (*cis*-**10**, R = Bu-*n*, 35 mg, 4%) isolated *via* preparative glpc (column E, 210°, 57 min); nmr (CCl_4) δ 0.7–2.4 (broad m); ir (CCl_4) 1712 cm^{-1} (C=O). Both C and D could be equilibrated to a 56:44 mixture of C:D in ethanolic sodium ethoxide. Unfortunately, the C_2–C_3 nmr coupling constant of D could not be determined clearly.

E is 2,5-di-*n*-butylcyclohexanone (**11**, 33 mg, 4%) isolated *via* preparative glpc (column E, 210°, 63 min): nmr (CCl_4) 0.7–2.4 (broad m); ir (CCl_4) 1712 cm^{-1} (C=O); for high resolution mass spectrum, see Table II.

E was not affected by treatment with ethanolic sodium ethoxide.

Enolate ion **2** was also prepared by treating 96 mg (1.0 mmol) of 2-cyclohexenone with 1.5 mmol of lithium *tert*-butoxy(*n*-butyl)cuprate at −50° for 1 hr. However, the enolate formed under these conditions could not be successfully butylated with *n*-butyl iodide.

3-Isobutoxy-5-isopropyl-2-methyl-2-cyclohexen-1-one (12). Following Eschenmoser's procedure,[56] to a solution of 6.00 g (81.0 mmol) of isobutyl alcohol in 30 ml of benzene were added 5.00 g (29.7 mmol) of 5-isopropyl-2-methyl-1,3-cyclohexanedione[57] and 0.138 g (0.73 mmol) of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed for 18 hr with continuous separation of water *via* a Dean-Stark apparatus. The contents of the reaction vessel was cooled to room temperature and poured into 50 ml of saturated, aqueous sodium bicarbonate. The aqueous phase was extracted with three 50-ml portions of ether, and the combined ether extracts were washed with water and dried over sodium sulfate. After solvent was removed by rotary evaporation, short path distillation afforded 5.65 g (75%) of 3-isobutoxy-5-isopropyl-2-methyl-2-cyclohexen-1-one, bp 117–124° (0.2 mm). This enol ether was extremely sensitive to air and moisture, and therefore it was not further purified for combustion analysis: nmr δ 0.95 (d, J = 6 Hz, 6 H, $-CH(CH_3)_2$), 1.00 (d, J = 6 Hz, 6 H, $-CH(CH_3)_2$), 1.4–2.6 (broad m), 1.60 (distorted t), 3.78 (d of d, J_{ax} = 6, J_{bx} = 10; Hz, 1 H, $-OCHCH(CH_3)_2$).

3-(4-Tetrahydropyranyloxybutyl)-5-isopropyl-2-methyl-2-cyclohexen-1-one (13). Following the procedure of Conia and Rouessac,[30] a solution of enol ether **12** (3.0 g, 13.4 mmol) in 5.0 ml of THF was added dropwise to a refluxing solution of 13.4 mmol of 4-tetrahydropyranyloxy-*n*-butylmagnesium chloride in THF. After refluxing for 18 hr the reaction mixture was cooled and poured onto 50 g of ice. The aqueous layer was acidified to pH 5 and extracted with three 50-ml portions of ether. The combined ether extracts were dried with magnesium sulfate, and evaporation of solvent left 5.00 g of crude tetrahydropyranyl enone **13**. Attempts to characterize tetrahydropyranyl enone **13** unambiguously by mass spectrometry and by combustion analysis failed; no parent ion was found in the mass spectrum of **13** even at low voltage, and a purified sample of **13** sent for analysis decomposed in the mail. Attempted hydrolysis followed by fractional distillation to afford pure 3-(4-hydroxybutyl)-5-isopropyl-2-methyl-2-cyclohexen-1-one was unsuccessful (unhydrolyzed tetrahydropyranyl ether **13** and hydroxy enone could not be separated).

This hydroxy enone was therefore characterized as its acetate, 3-(4-acetoxybutyl)-5-isopropyl-2-methyl-2-cyclohexen-1-one. A portion of the crude tetrahydropyranyl enone **13** (2.0 g; 40%, theoretically 5.36 mmol) was dissolved in 18 ml of 1:1:1 ethanol:ether:water. A solution of 0.6 ml of sulfuric acid in 6 ml of 2:1 ethanol:water was added, and the hydrolysis mixture was stirred at 25° for 4 hr. Dilution with 50 ml of water was followed by extraction with three 50-ml portions of ether. The combined ether extracts were washed with sodium bicarbonate and dried over magnesium sulfate. Rotary evaporation of solvent left 1.54 g of crude hydroxy enone. A portion of this material (616 mg; 40%, theoretically 2.14 mmol) was added to 10 ml of acetyl chloride containing 1 ml of pyridine. After 1 hr, excess acetyl chloride was removed *in vacuo*, and the residue was taken up in ether. Washing the ether extract with 1:1 HCl and drying over $MgSO_4$ afforded crude acetoxy enone. This material was purified by column chromatography (silica gel), and 333 mg (58% based on enol ether **12**) of acetoxy enone was obtained as a yellow oil. The spectral properties of the chromatographed material were identical with those of an analytical sample obtained by preparative glpc (column B, 200°): ir (CCl_4) 2960 (s), 2880 (s), 1740 (s, ester C=O), 1670 (s, enone C=O), 1630 (m, C=C), 1470 (m), 1430 (m), 1390 (m), 1360 (s), 1350 (m), 1310 (m), 1245 (s), 1050 cm^{-1} (s); nmr (CCl_4) δ 0.95 (d, J = 6 Hz, 6 H), 1.1–2.0 (broad m), 1.70 (broad s, 3 H), 2.0 (s, 3 H), 2.35 (m), 4.07 (t, 2 H). *Anal.* Calcd for $C_{16}H_{26}O_3$: C, 71.84; H, 9.84. Found: C, 72.14; H, 10.24.

3-(4-Bromobutyl)-5-isopropyl-2-methyl-2-cyclohexen-1-one (14). Following the procedure just described for hydrolysis of tetrahydropyranyl enone **13**, 500 mg, 10%, of the crude tetrahydropyranyl enone **13** obtained above (theoretically 1.36 mmol) was hydrolyzed to the crude hydroxy enone. This alcohol was added to a cold (0°) solution of 229 mg (2.00 mmol) of methanesulfonyl chloride in 3.0 ml of pyridine, and the reaction mixture was stoppered and stored for 12 hr at 0°. The crude mesylate product was then obtained by pouring the reaction mixture onto 10 g of ice and extracting with three 25-ml portions of ether. The combined ether extracts were washed with two 25-ml portions of ice-cold 6 *N* hydrochloric acid followed by 25 ml of saturated aqueous sodium carbonate. The ether phase was dried with magnesium sulfate, and solvent was removed *in vacuo*. Column chromatography of the residue (over silica gel) afforded 192 mg (47% yield based on enol ether **12**) of 5-isopropyl-3-(4-mesyloxybutyl)-2-methyl-2-cyclohexen-1-one as a colorless oil: nmr (CCl_4) δ 0.95 (d, J = 6 Hz, 6 H), 1.2–2.0 (broad m), 1.77 (broad s, 3 H), 2.0–2.8 (broad m), 3.02 (s, 3 H), 4.12 (t, 2 H).

To a solution of 1.74 g (20 mmol) of lithium bromide in 20 ml of acetone was added 592 mg (1.96 mmol) of this mesylate. The reaction mixture was stirred for 24 hr at room temperature, and the solvent was removed by rotary evaporation. The residue was taken up in 25 ml of ether and washed with two 25-ml portions of water. The ether phase was then dried over magnesium sulfate, and solvent was removed under reduced pressure. Microdistillation of the crude product gave 416 mg (74%) of bromo enone **14**, bp 120° (bath temperature, 0.2 mm): ir (CCl_4) 2960 (m), 2930 (sh), 2870 (m), 1670 (s, enone C=O), 1630 (w, C=O), 1460 (w), 1430 (w), 1390 (w), 1380 (w), 1370 (w), 1340 (w), 1310 (w), 1285 (w), 1250

(w), 1080 cm^{-1} (w); nmr (CCl_4) δ 0.93 (d, J = 6 Hz, 6 H), 1.2–3.0 (broad m), 1.80 (broad s), 3.47 (t, 2 H); mass spectrum, parent ions m/e 288.0921 and 286.0938 (calcd for $C_{14}H_{23}BrO$, 288.0912 and 286.0932).

***dl*-3-α-Isopropyl-*cis*-9β,10β-dimethyl-1-decalone (15).** To a solution of 5.00 mmol of lithium dimethylcuprate in 20 ml of benzene at *ca.* 5° was added 283 mg (0.99 mmol) of 3-(4-bromobutyl)-5-isopropyl-2-methyl-2-cyclohexen-1-one (**14**) in 1 ml of benzene. After 2 hr, 20 ml of HMPA was added, and the reaction mixture became homogeneous. After an additional 2 hr at 0°, excess organometallic reagent was quenched by injection of 1.0 ml (*ca.* 25 mmol) of absolute methanol. Products were isolated by pouring the reaction mixture into 50 ml of saturated, aqueous ammonium chloride and extracting with three 50-ml portions of ether. The combined ether phases were washed five times with 50-ml portions of water. The ether extracts were dried over magnesium sulfate, and analytical glpc indicated one major product which was 1-decalone **15** [identified initially by comparison of retention time with that of a sample of the decalone prepared from 3-(4-bromobutyl)-2,3-dimethyl-5-isopropylcyclohexanone and sodium *tert*-amyloxide by the method of Conia and Rouessac[30]].[34] Quantitative glpc (column B, 200°) indicated 62 mg (28%) of decalone **15** to be present in the ether extracts. Column chromatography on silica gel gave 60 mg (27%) of decalone **15** which was >95% pure by glpc: ir (CCl_4) 2950 (s), 2870 (m), 1700 (s), 1465 (m), 1380 (m), 1355 (w), 1340 (w), 1240 (w), 1210 (w), 1170 (w), 1150 cm^{-1} (w); nmr (CCl_4) δ 0.78 (s, 3 H), 0.93 (d, J = 3.5 Hz, 6 H), 1.08 (s, 3 H), 1.0–2.6 (broad m); mass spectrum [m/e (relative intensity)] 208 (14, molecular ion), 193 (60), 165 (27), 151 (13), 137 (24), 123 (24), 109 (76), 95 (73), 93 (80), 69 (100), 55 (70), 41 (63). An analytical sample was isolated by preparative glpc (column F, 185°). *Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.17; H, 11.97.

The stereochemistry of ring fusion and the relationship of the methyl groups and the isopropyl group were demonstrated by conversion of decalone **15** to *dl*-valerane (**16**).

***dl*-2-α-Isopropyl-*cis*-9β,10β-dimethyldecalin (16) (*dl*-Valerane).** Following the procedure of Rao,[35] to a solution of decalone **15** (60 mg, 0.27 mmol) in 0.5 ml of ethanedithiol was added 0.5 ml of boron trifluoride etherate. The reaction mixture was stirred overnight and then warmed to 70–75° for 4 hr. The crude dithioketal was isolated by pouring the reaction mixture into 5 ml of water and extracting with three 5-ml portions of ether. The combined ether extracts were washed with saturated, aqueous ammonium chloride and dried over magnesium sulfate. Evaporation of solvent left the crude dithioketal, and the infrared spectrum indicated the absence of the carbonyl group. Desulfurization with Raney nickel catalyst (W-2, one level teaspoonful) was carried out in 50 ml of acetone. After 4 hr of refluxing, the catalyst was separated by filtration, and the solvent was evaporated to leave 52 mg of a yellow oil. Preparative glpc (column B, 170°) afforded *dl*-valerane (10 mg, 18%) having nmr spectral properties and glpc retention time identical with those of authentic *dl*-valerane and different from those of authentic *dl*-isovalerane (having the angular methyl groups and the isopropyl group all cis):[35] ir (CCl_4) 2965 (sh), 2950 (sh), 2920 (s), 2860 (s), 2840 (sh), 1465 (m), 1450 (m), 1440 (m), 1380 (m), 1370 cm^{-1} (m); nmr (CCl_4) δ 0.84 (s, 3 H), 0.85 (d, J = 6 Hz, 6 H), 0.86 (s, 3 H), δ 1.0–1.6 (broad m); mass spectrum [m/e (relative intensity)] 208 (16, molecular ion), 193 (56), 165 (30), 109 (86), 95 (83), 83 (88), 69 (100), 55 (80), 41 (58).

Reaction of 2-Cyclopentenone with Lithium Methyl(vinyl)cuprate. A. Allyl Bromide Quench. To a stirred suspension of 228 mg (1.2 mmol) of cuprous iodide in 4 ml of tetrahydrofuran at −35° was added 0.44 ml of 2.51 M (1.1 mmol) vinyllithium, followed by 0.62 ml of 1.78 M (1.1 mmol) methyllithium. The dark solution was immediately cooled to −78° and then 82 mg (1.0 mmol) of 2-cyclopentenone in 1 ml of tetrahydrofuran was added. After 30 min, 0.17 ml (2 mmol) of neat allyl bromide was added *via* syringe, followed after 1 hr by 1 ml of absolute methanol. The reaction mixture was then allowed to warm to room temperature and poured into saturated aqueous ammonium chloride, diluted with diethyl ether, and stirred for 1 hr at which time the layers were separated; the aqueous phase was extracted once with ether and the combined organic layers were washed once with a 2% solution of sodium thiosulfate and dried over magnesium sulfate. Analytical glpc (column A, 150°, cymene internal standard) indicated five products: A (3 min), B (4 min); C (6.5 min), D (7 min), and E (8.2 min).

A is 3-vinylcyclopentanone (2 mg, 2%) identified by comparing its glpc retention time with that of authentic material.[9]

Nmr, ir, and mass spectra of B are consistent with 2-allyl-3-methylcyclopentanone (5 mg, 3%).

C is *trans*-2-allyl-3-vinylcyclopentanone (*trans*-**19**, 108 mg, 72%) isolated *via* preparative glpc (104 mg, 69%, column F, 135°, 16 min): nmr (CCl_4) δ 5.58–6.05 (m, 2 H); 4.90–5.30 (m, 4 H); 1.4–2.7 (m, 8 H); ir (CCl_4) 1744 (C=O) and 1641 cm^{-1} (C=C); mass spectrum (70 eV) m/e 150 (20, molecular ion), 96 (100), 79 (70), 67 (60); bp 199–200° (760 mm). See Table II for analysis.

To 100 mg of *trans*-**19** in 50 ml of absolute ethanol was added 20 mg of 10% palladium on charcoal. The mixture was hydrogenated under 50 lb of hydrogen pressure in a Parr hydrogenator at 70° for 12 hr. After that time, the one major product was isolated *via* preparative glpc (column F, 150°, 10 min) and identified as *trans*-3-ethyl-2-*n*-propylcyclopentanone: nmr ($CDCl_3$) 2.0–2.3 (m, 3 H), 1.1–1.9 (m, 7 H), 0.95 (t, J = 8 Hz, 6 H); ir (CCl_4) 1740 cm^{-1} (C=O); mass spectrum (70 eV) m/e 154 (4 molecular ion), 125 (4), 112 (26), 83 (100), 55 (29). *Anal.* Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.96; H, 12.02.

The trans-2,3-substitution pattern was determined utilizing a combination of nmr shift reagent[58] and spin–spin decoupling. When 75 mg of $Eu(fod)_3$ ("Resolve-Al") was added to 30 mg of 3-ethyl-2-propylcyclopentanone in 0.5 ml of $CDCl_3$, the following nmr spectrum resulted: δ 0.90 (s, shift reagent), 1.4–1.6 (pair of overlapping t, J = 7 Hz, 6 H, methyl groups), 2.3 (m, protons of *n*-propyl chain), 2.5–3.6 (m, cyclopentyl and ethyl protons), 3.9 (m, 2 H, methylene of propyl group adjacent to ring), 5.6 (m, 1 H, α-methine proton), 5.9 (m, 2 H, α-methylene protons). When the signal at δ 3.80 was irradiated, the signal for the α-methine proton was resolved into a doublet, J = 11 Hz. This indicates the substitution is 2,3, and that the groups are trans to one another.[39] Also when the signal at δ 3.17 was irradiated, the α-methylene signals resolved into two singlets.

D is *cis*-2-allyl-3-vinylcyclopentanone (*cis*-**19**, 4 mg, 3%), isolated *via* preparative glpc (column F, 135°, 19 min): nmr (CCl_4) δ 5.5–6.3 (m, 2 H), 4.8–5.3 (m, 4 H), 1.6–2.8 (m, 8 H); ir (CCl_4) 1746 (C=O) and 1643 cm^{-1} (C=C); mass spectrum (70 eV) m/e 150 (20, molecular ion), 96 (100), 79 (90), 67 (55). Both C and D could be equilibrated to a 98:2 mixture of C:D in refluxing absolute ethanol containing a catalytic amount of sodium acetate for 1 hr.

E is spectrally consistent with 2-allyl-4-vinylcyclopentanone (**20**, 1 mg, 0.5%) isolated *via* preparative glpc (column F, 135°, 21 min). When E was treated with refluxing absolute ethanol containing a catalytic amount of sodium acetate for 24 hr, no change was noted.

B. 2-Butenyl Iodide Quench. To 3.75 g (25 mmol) of sodium iodide in 50 ml of acetone was added 2.7 g (20 mmol) of 1-bromo-2-butene in 1 ml of acetone forming an immediate precipitate.[60] After 2 hr, the suspension was poured into water and extracted with diethyl ether. The organic layer was washed twice with water and once with 2% sodium thiosulfate, dried over magnesium sulfate, and concentrated to 3 g of orange oil which was distilled at 35 mm; the major fraction, collected at 48–49°, is *trans*-1-iodo-2-butene: nmr (CCl_4) δ 5.5–5.9 (m, 2 H), 3.8–4.0 (m, 2 H), 1.6–1.8 (m, 3 H), $n^{20}D$ 1.5506 (lit.[61] $n^{20}D$ 1.5500).

Enolate ion **4** was prepared by treating 82 mg (1.0 mmol) of 2-cyclopentenone with 1.2 mmol of lithium methyl(vinyl)cuprate at −78° for 30 min. At that time the reaction mixture was allowed to warm to −45°, and 0.32 ml (2.5 mmol) of neat tetramethylethylenediamine was added, followed in 10 min by 546 mg (3.0 mmol) of *trans*-1-iodo-2-butene in 4 ml of *N*-methylpyrrolidene. After the reaction mixture was stirred for 1 hr at −45 to −50°, 1 ml of absolute methanol was added, and the reaction mixture was allowed to warm to room temperature, poured into saturated aqueous ammonium chloride, and diluted with diethyl ether. After stirring for 1 hr the layers were separated, and the aqueous phase was extracted once with ether; the combined organic phases were washed with 2% sodium thiosulfate and dried over magnesium sulfate.[55] Analytical glpc (column A, 170°, valerophenone internal standard) indicated five major products: A (3.5 min), B (5.5 min), C (5.7 min), D (7 min), and E (8 min).

A is 3-vinylcyclopentanone (26 mg, 24%) identified by comparing retention times with that of authentic material.[9]

B and C are spectrally consistent with 2-(1′-buten-3′-yl)-3-vinylcyclopentanones (1.5 mg, 1%) containing the allylically rearranged side chain. B and C were incompletely resolved and thus imperfectly isolated *via* preparative glpc (column E, 160°, 28 and 30 min, respectively). Neither was affected by treatment with ethanolic sodium ethoxide. The nmr spectrum of B has a doublet (J = 6 Hz) at δ 1.1, whereas the nmr spectrum of C has a doublet (J = 7 Hz) at δ 1.0.

D is *trans*-2-(*trans*-2′-buten-1′-yl)-3-vinylcyclopropanone (**21,** 56 mg, 34%) isolated *via* preparative glpc (column E, 160°, 36 min): nmr (CCl_4) δ 4.8–5.8 (m, 5 H), 1.4–2.6 (m, 11 H); ir (CCl_4) 1745 (C=O), 1642 (C=C), 912 and 983 (terminal vinyl), and 963 cm^{-1} (trans olefin); mass spectrum (70 eV) *m/e* 164 (30, molecular ion), 110 (100), 109 (50), 95 (90); bp 229° (760 mm). See Table II for analysis.

No change in glpc (column D, 160°) was noted when **21** was treated with ethanolic sodium ethoxide. A pure sample of **21** was hydrogenated at 50 lb of hydrogen pressure on 10% palladium on charcoal catalyst in absolute ethanol on a Parr hydrogenator. Only one product was observed, *trans*-2-*n*-butyl-3-ethylcyclopentanone **29** (*vide infra*).

E is 2-(*trans*-2-buten-1-yl)-4-vinylcyclopentanone (**22,** 27 mg, 12%), isolated *via* preparative glpc (column E, 160°, 41 min): nmr (CCl_4) δ 4.8–5.8 (m, 5 H), 1.2–2.6 (m, 11 H); ir (CCl_4) 1748 (C=O), 1642 (C=C), 912 and 983 (terminal vinyl), 961 (trans olefin); mass spectrum (70 eV) *m/e* 164 (30, molecular ion), 110 (90), 109 (40), 95 (100). See Table II for analysis.

If the *trans*-1-iodo-2-butene-*N*-methylpyrrolidone is added at −78°, the yield of **21** is 74 mg (45%), but there is now 7 mg (4%) of the allylically rearranged products B and C. Likewise if HMPA is substituted for *N*-methylpyrrolidone (at −78°), 84 mg (51%) of **21** is observed, but the yields of B and C are also increased to 14 mg (8.5%). If no cosolvent is used and *trans*-1-iodo-2-butene is added neat at −78°, the rearranged products predominate (61 mg, 37%) with only 30 mg (18%) of **21**. Adding neat *trans*-1-iodo-2-butene at −20° results in 41 mg (25%) of **21** with a negligible amount of rearranged B and C. In all these cases, the yield of dibutenylcyclopentanone **22** was about one-half that of **21;** however, longer reaction times and higher temperatures favored other products with longer glpc retention times.

C. **Methyl 7-Iodo-*cis*-5-heptenoate Quench.** To 600 mg (4 mmol) of sodium iodide dissolved in 20 ml of acetone was added 663 mg (3 mmol) of methyl 7-bromo-*cis*-5-heptenoate[43] in 1 ml of acetone, forming an immediate white precipitate.[60] Two hours later the reaction mixture was poured into water and was extracted with diethyl ether. The organic layer was washed twice with water and once with 2% aqueous sodium thiosulfate, dried over magnesium sulfate, and concentrated to 730 mg (91%) of red oily methyl 7-iodo-*cis*-5-heptenoate: nmr (CCl_4) δ 5.2–6.0 (m, 2 H), 3.8–4.1 (m, 2 H), 3.65 (s, 3 H), 1.4–2.5 (m, 6 H); ir (CCl_4) 1742 (C=O) and 1656 cm^{-1} (C=C).

Enolate ion **4** was prepared by treating 41 mg (0.5 mmol) of 2-cyclopentenone with 0.6 mmol of lithium methyl(vinyl)cuprate at −78° for 30 min at which time the reaction mixture was allowed to warm to −20° for 5 min, and 536 mg (2.0 mmol) of methyl 7-iodo-*cis*-5-heptenoate was added in 0.5 ml of THF. After the mixture was stirred for 20 min at −20°, 1 ml of absolute methanol was added; the reaction mixture was allowed to warm to room temperature, poured into saturated aqueous ammonium chloride, and diluted with diethyl ether. After stirring for 1 hr, the phases were separated, and the aqueous layer was extracted once with diethyl ether; the combined organic layers were washed with sodium thiosulfate, dried over magnesium sulfate, and concentrated *in vacuo* to 485 mg of a green oil. The bulk of this material seems to be methyl 7-iodo-*cis*-5-heptenoate as well as the products resulting from methyl coupling with that species. The crude product was column chromatographed on 20 g of silica. Following extended elution with hexane, a 10% ether–90% hexane solution eluted 25 mg of material containing three components by glpc [9 ft × ⅛ in. 5% Lexan on Chrom W (80–90) column, 190°]: A (9.5 min), B (12.5 min. small shoulder on C), and C (13.5 min).

A (≪1 mg, ≪1%) has a glpc retention time identical with that of 2-(6-methoxycarbonyl-2-*cis*-hexenyl)-3-methylcyclopentanone, prepared independently *via* lithium dimethylcopper conjugate addition to 2-(6-methoxycarbonyl-2-*cis*-hexenyl)-2-cyclopentenone.[44]

B (<1 mg, <5%) could not be completely separated from C. A mixture containing B and C does not change on exposure to methanolic sodium methoxide. Likewise pure C does not change under these basic conditions; therefore B is not *cis*-**23**. B is probably 2-(6-methoxycarbonyl-2-*cis*-hexenyl)-4-vinylcyclopentanone.

C (24 mg, 20%) is *trans*-2-(6-methoxycarbonyl-2-*cis*-hexenyl)-3-vinylcyclopentanone (**23**) having a glpc retention time identical with that of authentic **23** prepared independently from vinyl conjugate addition to 2-(6-methoxycarbonyl-2-*cis*-hexenyl)-2-cyclopentenone.[44] Preparative tlc on silica gel with benzene elution gave **23** (R_F 0.4, 12 mg, 10%) having ir and nmr spectra matching those of authentic **23**: ir (CCl_4) 1744 (C=O), 1641 (C=C), 915 cm^{-1} (terminal vinyl), no trans olefinic absorption at 965 cm^{-1};[42] nmr (CCl_4) δ 4.7–5.7 (m, 5 H), 3.5 (s, 3 H), 1.0–2.7 (m, 14 H); mass spectrum (70 eV) *m/e* (relative intensity): 250 (15, molecular ion), 218 (30), 201 (25), 141 (100); high resolution mass spectrum 250.1571 (calcd for $C_{15}H_{22}O_3$, 250.1569).

D. Ethyl α-Bromoacetate Quench. To a stirred suspension of 209 mg (1.1 mmol) of cuprous iodide in 2.5 ml of THF at −35° was added 0.44 ml of 2.50 *M* (1.1 mmol) vinyllithium immediately followed by 0.67 ml of 1.64 *M* (1.1 mmol) methyllithium. The resulting mixture was cooled to −78°, and 82 mg (1.0 mmol) of 2-cyclopentenone in 1.0 ml of THF was added. After 30 min at −78°, 0.22 ml (2.0 mmol) of ethyl α-bromoacetate was added and the mixture maintained at −78° for 1 hr with stirring. After warming to 0°, the reaction mixture was worked up by pouring it into 50 ml of saturated aqueous ammonium chloride and extracting it with three 30-ml portions of diethyl ether. The combined organic phases were washed with 30 ml of 5% sodium thiosulfate solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. [A fraction of the product solution was analyzed by glpc (column C at 160°, hexadecane internal standard), indicating formation of four products: A (3 min), B (7.8 min), C (9.0 min), and D (9.8 min).] The resulting residue was purified by bulb-to-bulb distillation and preparative glpc (column F at 160°) where products A–D were identified in the following manner.

A, identified by coinjection with an authentic sample, is 3-vinylcyclopentanone (25 mg, 13%).[9]

B is *trans*-2-(ethoxycarbonylmethyl)-3-vinylcyclopentanone (*trans*-**25,** 90 mg, 46%): nmr (CCl_4) δ 4.00 (q, 2 H, OCH_2), 1.20 (t, 3 H, CH_3), 2.19 (m, 6 H, ring protons), 5.65 (m, 1 H, —CH=), 5.10 (m, 2 H, $=CH_2$); ir (CCl_4) 1648, 920 (C=C), 1735 (C=O), 1195 (C—O—C) cm^{-1}; mass spectrum (70 eV) *m/e* 196 (15, parent ion), 151 (80), 109 (100), 55 (85). See Table II for analysis. The stereochemistry of *trans*-**25** was established as shown in Table II.

C is *cis*-2-(ethoxycarbonylmethyl)-3-vinylcyclopentanone (*cis*-**25,** 7.8 mg, 4%). This assignment is based on the equilibration of this material to *trans*-**25** upon refluxing in absolute ethanol with a catalytic amount of potassium acetate for 1 hr.

D is 2-(ethoxycarbonylmethyl)-4-vinylcyclopentanone (**24,** <2 mg, <1%); mass spectrum (70 eV) *m/e* 196 (parent ion).

E. *n*-Butyl Iodide Quench. Enolate ion **4** was prepared by reacting 1.2 mmol of lithium methyl(vinyl)cuprate in 5 ml of tetrahydrofuran at −78° with 82 mg (1.0 mmol) of 2-cyclopentenone for 30 min as described above. The reaction mixture was then allowed to warm to 0° during 15 min at which time 0.57 ml (5.0 mmol) of *n*-butyl iodide in 4 ml of hexamethylphosphoric triamide was added. Thirty minutes later, 1 ml of methanol was added, and the reaction mixture was poured into saturated aqueous ammonium chloride, diluted with diethyl ether, and stirred for 1 hr at which time the layers were separated, the aqueous phase was extracted once with ether, and the combined organic layers were washed once with a 2% solution of sodium thiosulfate and dried over magnesium sulfate.[55] Analytical glpc (column A, 150°, cymene internal standard) indicated four major products: A (3 min), B (10.6 min), C (13.0 min), and D (30 min).

A is 3-vinylcyclopentanone (20 mg, 18%) identified by comparing glpc retention times with that of authentic material.[9]

B is *trans*-2-*n*-butyl-3-vinylcyclopentanone (**28,** 52 mg, 31%) isolated *via* preparative glpc (column F, 150°, 20 min): nmr (CCl_4) δ 5.6–6.5 (m, 1 H), 4.95–5.3 (m, 2 H), 0.7–2.6 (m, 17 H); ir (CCl_4) 1745 (C=O) and 1640 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* 166 (15, molecular ion), 137 (10), 110 (100), 109 (50), 95 (30). See Table II for analysis.

To a pure sample of cyclopentanone **28** in ethanol was added 5%

palladium on charcoal. The mixture was placed in a hydrogenation bottle and reacted under 60 lb of hydrogen pressure in a Parr hydrogenator at 50° for 18 hr. After that time, the solution was filtered, and the solvent was removed by rotary evaporation to give a crude product. Analytical glpc (column C, 150°, and column A, 160°) showed this material to be the same as that derived from *trans*-**21**. Bulb-to-bulb distillation followed by isolation by preparative glpc (column E, 180°) gave pure *trans*-2-*n*-butyl-3-ethylcyclopentanone: nmr ($CDCl_3$) δ 0.92 (t, J = 7 Hz, 6 H), 1.2–1.9 (broad m, 11 H), 2.0–2.4 (m, 3 H, α protons); ir (CCl_4) 2950, 2940, 2850, 1740 (C=O), 1455 cm^{-1}; mass spectrum (70 eV) *m/e* 168.1529 (calcd for $C_{11}H_{20}O$, 168.1514). Nmr spectroscopy using $Eu(fod)_3$ and decoupling as described above for 3-ethyl-2-*n*-propylcyclopentanone showed the C_2H–C_3H coupling constant to be 9 Hz, consistent with trans stereochemistry.[39]

C is 2-*n*-butyl-4-vinylcyclopentanone (**27**, 13 mg, 8%) isolated *via* preparative glpc (column F, 150°, 26 min): nmr (CCl_4) δ 5.6–6.1 (m, 1 H), 5.0–5.3 (m, 2 H), 0.8–3.0 (m, 17 H); ir (CCl_4) 1746 (C=O) and 1641 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* 166 (30, molecular ion), 137 (20), 110 (100), 109 (50), 95 (80). See Table II for analysis.

D is 2,5- (or 2,2-) di-*n*-butyl-3-vinylcyclopentanone (**26**, 50 mg, 22%) isolated *via* preparative glpc (column E, 200°, 40 min): nmr (CCl_4) δ 5.8 (m, 1 H), 5.04 (m, 2 H), 1.1–2.9 (m, 17 H), 0.84 (m, 6 H); ir (CCl_4) 1738 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 222 (molecular ion), 179, 166, 137, 109, 55. *Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.92; H, 11.78.

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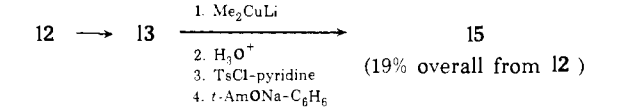

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Addition, Substitution, Rearrangement, and Elimination in Allylic Systems

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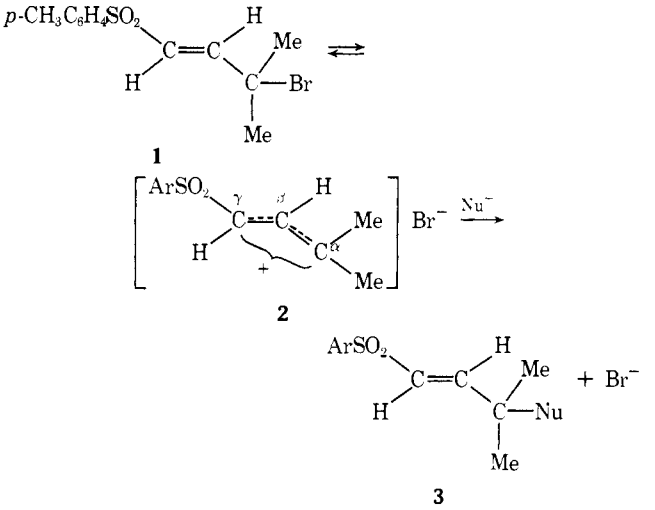
Abstract: Methanol adds to the double bond of tertiary allylic bromide **1**, $ArSO_2CH{=}CHC(CH_3)_2Br$, when **1** is treated with NaOMe–MeOH at 25°. This Michael adduct does not rearrange to the methoxide substitution product of **1** (OMe replaces Br). The SN2′–SNi′ route to SN2-type substitution products of **1** was also ruled out. Reaction of **1** with thiophenoxide salts under carefully controlled conditions did give the SN2′-type product, $ArSO_2CH(SPh)CH{=}C(CH_3)_2$, and this did undergo SNi′ rearrangement under ionizing conditions. The product formed in the SNi′-type rearrangement was, however, $PhSCH{=}CHC(CH_3)_2SO_2Ar$, an isomer of the SN2-type substitution product. Reaction of **1** with $NaNO_2$ in DMF gave a high yield of SN2-type substitution product. An analog of **1** in which the two methyl groups were replaced by a cyclohexyl group (**11**) was found to react principally by elimination under all conditions (Table I). Both sodium thiophenoxide and potassium thioacetate were found to be more effective in methanol at promoting elimination from **11** than was sodium methoxide. It is concluded that the greater reactivity of the sulfur nucleophiles is associated with their greater affinity for the cation of an ion-pair intermediate. The reactions are given the mechanistic classification ion-pair E2, $(E2)_{ip}$. The reaction of **11** with sodium methoxide was shown to be first order in methoxide concentration.

In previous papers we have shown that tertiary allylic bromide **1** displays unique properties in reacting with nucleophiles.[2] For example, **1**, unlike most tertiary bromides, gives substantial amounts of SN2-type substitution products with many weakly basic nucleophiles. Furthermore, the reactions in several instances have been shown to be first order in nucleophile.[2a] This unusual behavior has been attributed to the combined presence of the electron-withdrawing $ArSO_2$ group and the C=C bond. The $ArSO_2$ group apparently inhibits ion-pair dissociation but does not stop ion-pair formation. The allylic system in **1** allows sufficient delocalization of the positive charge in the cation of the ion pair to inhibit elimination. As a consequence, weakly basic nucleophiles are able to react at the cationic α-carbon atom in the ion-pair intermediate (**2**) to effect SN2-type substitution reactions giving **3**. The present paper presents a more detailed product study for reactions of certain nucleophiles with **1**, and reports results with an analogous tertiary allylic cyclohexyl bromide (**11**) wherein the tendency toward elimination is greatly enhanced.



Results and Discussion

Michael Addition. Since SN2-type reactions at tertiary carbon atoms are rare,[2a] one must be on the alert for other pathways leading to the observed substitution products (**3**). Several mechanisms involving Michael-type addition can be imagined which might give **3** (*e.g.*, paths a and c).

Reaction of bromide **1** with NaOMe in MeOH at 25° gives an 89% yield of Michael adduct **4** (Nu = OMe). This shows that path b is much preferred to path a. Conceivably the Nu group in adduct **4** could initiate neighboring group participation, possibly aided by simultaneous loss of a proton from the γ-carbon atom, to displace Br and give the SN2-type product **3** (Nu = OMe). Alternatively, the C–Br bond in adduct **4** might dissociate to a C^+Br^- ion pair, and Nu could migrate to the electrophilic center thus produced; simultaneous or subsequent loss of a proton from the γ-carbon atom would give **3**. In practice, neither of these c pathways was realized.[3] Instead adduct **4** underwent methanolysis on refluxing for 27 hr to form 42% of the dimethoxy compound (**5**, Nu = OCH_3) and 58% of the diene derived from **4** by loss of HBr and HOMe. These results rule out the paths a and c for the (observed) formation of **3** (Nu = OCH_3) by treatment of bromide **1** with methanol or methanol containing small amounts of sodium methoxide. They also argue against a Michael-type addition pathway as a reasonable alternative to SN2-type displacement for the formation of **3** from **1**.