thio)propanoate, 777-80-0; *cis*-dihydro-5-methyl-4-(phenylthio)-2-(3*H*)-furanone, 75717-32-7; *trans*-dihydro-5-methyl-4-(phenylthio)-2(3*H*)-furanone, 75717-33-8; 3-(phenylthio)cyclopentanone, 75717-34-9; 3-(phenylthio)cyclohexanone, 35155-84-1; (*E*)-3-(phenylthio)-2-propenenitrile, 2974-75-6; (*Z*)-3-(phenylthio)-2-propenenitrile, 2974-76-7; ethyl (*E*)-3-(phenylthio)-2-propenoate, 75717-35-0; ethyl (*Z*)-3-(phenylthio)-2-propenoate, 75717-36-1; methyl (*E*)-2-methyl-3-(phenylthio)-2-propenoate, 71847-74-0; methyl (*Z*)-2-methyl-3-(phenylthio)-2-propenoate, 66349-63-1; 5-methyl-4-(phenylthio)-2-(5*H*)-furanone, 75717-37-2; 3-(phenylthio)-2-cyclopenten-1-one, 75717-38-3; 3-(phenylthio)-2-cyclohexen-1-one, 75717-39-4; thiophenol, 108-98-5; ethyl bromide, 74-96-4; (phenylthio)ethane, 622-38-8; (phenylthio)ethene, 1822-73-7; 1-(phenylthio)octane, 13910-16-2; (*E*)-1-(phenylthio)-1-octene, 75717-40-7; (*Z*)-1-(phenylthio)-1-octene, 75717-41-8; (phenylthio)cyclohexane, 7570-92-5; (phenylthio)cyclohexene, 4922-47-8.

Selective γ Alkylation of Copper Enolates Derived from α,β-Unsaturated Acids: Factors Affecting Scope and Regio- and Stereoselectivity

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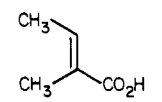
Copper dienolates derived from α,β-unsaturated acids undergo alkylation at the γ-carbon with high regioselectivity. A systematic investigation has been made of several factors that affect the γ-alkylation process of the dienolate derived tiglic acid (1): alterations in the nature of the counterion, in the stoichiometry of cuprous ion, and in the nature of the electrophile. Compared to allylic electrophiles, nonallylic electrophiles react with copper dienolates sluggishly and with little selectivity for the γ-carbon; vinylic epoxides, however, are particularly good alkylating agents. They undergo allylic transposition and react at the γ-carbon of the dienolate with high selectivity (70–90%), generating an allylic unit that forms part of a 1,5-diene skeleton oxygenated at both ends. Tiglic (1) and crotonic (3) acids react with vinylic epoxides to form a 1,5-diene with entirely *E* stereochemistry at the 2,3 double bond, while senecioic acid (2) forms a 1,5-diene with mostly *Z* stereochemistry at the 2,3 double bond. Geometry at the 6,7 double bond depends both on the α,β-unsaturated acid used and on the structure of the epoxide. With allylic electrophiles under direct (S_N2) attack, stereochemical analysis showed that some isomerization occurs around the 6,7 double bond (derived from the electrophile). Addition of cuprous ion to the lithium dianion of 2-hexenoic acid (17) was found to enhance the regioselectivity of γ alkylation, but a subsequent Michael addition reaction limits the potential of γ alkylation in this system.

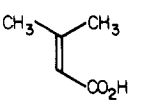
One approach to the synthesis of isoprenoid 1,5-polyolefins is the coupling of two allylic units containing the appropriate olefinic stereochemistry; this is, in fact, the basis of linear terpenoid biosynthesis. Complications develop in the chemical adaptation of this approach that involves the displacement of an allylic electrophile by an allylic nucleophile: allylic electrophiles can undergo S_N2 or S_N2' attack, and their geometrical integrity is not assured;[1] the nucelophile is an ambident anion and its olefinic stereochemistry is subject to ready isomer equilibration.[2]

A number of successful strategies to 1,5-diene synthesis by allylic–allylic coupling involve the alkylation of a charge-stabilized allylic organometallic reagent with an allylic electrophile. Groups such as sulfone,[3-5] sulfoxide,[6] sulfide,[7,8] carbonyl,[9] or alkylphosphonium bromide[10] have been used to stabilize allylic anions and direct alkylation α to themselves. The stabilizing group can be reductively cleaved with double bond transposition[4,6,8] or without[3,10] to yield a 1,5-diene. One problem encountered with this approach is that product mixtures are often obtained in the reductive cleavage step. In some cases (allylic ethers and thioethers) alkylation occurs at the site γ to the stabilizing group.[11-14]

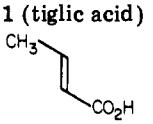
Chart I. Structures of α,β-Unsaturated Acids



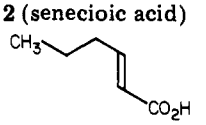
1 (tiglic acid)



2 (senecioic acid)



3 (crotonic acid)



4 (2-hexenoic acid)

Theoretically, carbonyl-stabilized allylic anions (i.e., dienolates derived from α,β-unsaturated carbonyl compounds) are capable of this type of γ alkylation. A major advantage of the use of such carbonyl-stabilized precursors is that a natural oxygenation pattern (at the chain terminus) is maintained, whether elongation of the isoprene chain proceeds from tail to head or vice versa. Unfortunately, the anions derived from most α,β-unsaturated ketones,[15] aldehydes,[16] and aldimines[17] have been found to alkylate predominantly at the α-carbon, although certain

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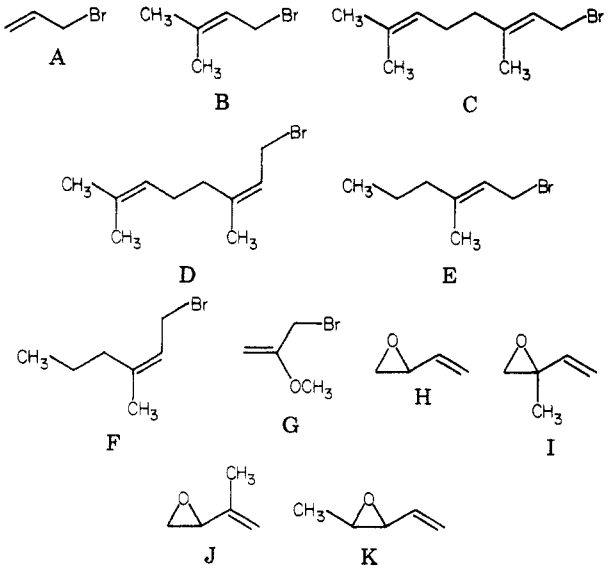
Chart II. Structures of Allylic Electrophiles



dienolates of α,β-unsaturated carbonyl compounds with a heteroatom substituent at the β position have been found to undergo alkylation predominantly at the γ site.[18-22] The alkali metal dienolates of α,β-unsaturated esters also alkylate predominantly at the α-carbon (although there have been a few reports of selective γ addition to carbonyl compounds[23-25]). In contrast, the copper dienolates of esters will in some cases undergo selective γ alkylation with allylic halides.[26,27]

Dianionic species derived from α,β-unsaturated amides show a higher percentage of γ products when alkylated than do the esters,[28-30] and there are numerous reports of the dianionic species of α,β-unsaturated acids undergoing alkylation with increased γ selectivity.[31-34] Previously, we described studies on the alkylation of dienolate dianions derived from α,β-unsaturated acids.[35] The copper salts of these dianions show a much greater tendency for selective γ alkylation than those derived from the esters. Selective γ alkylation could, in certain cases, be achieved without or with complete transposition of the allylic halide.

Table I. Effect of the Addition of Various Transition-Metal Salts to the Dianion Derived from Tiglic Acid (1) in the Alkylation of Allyl Bromide (A)[a]

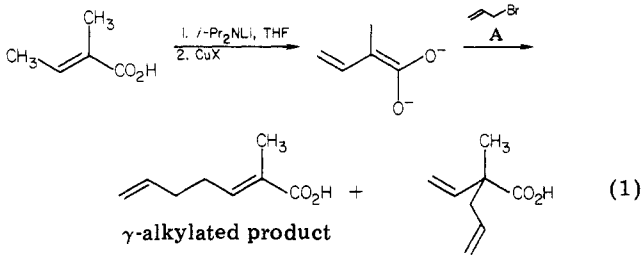
metal salt	ratio of alkylation products[b] (α:γ)	yield,[c] %
CuI	10:90	80
$CoBr_2$	60:40	59
$MgCl_2$	62:38	49
$MnCl_2$	65:35	89
$AgBF_4$	69:31	39
$FeCl_2$	70:30	81
$ZnCl_2$	72:28	49
$NiBr_2$	78:22	15
CdI_2	80:20	62
$HgCl_2$	81:19	99
Li	100:0	85

[a] Reaction was conducted as described for the general method for the copper dienolate of tiglic acid in the Experimental Section by using 2 equiv of the metal salt in place of CuI. [b] Determined by GLC on the corresponding methyl esters. [c] Isolated yield was based on yield of acidic products. They were shown to consist only of the alkylated products by ^1H NMR and GLC of the corresponding methyl esters.

In this report, we describe further studies on the alkylation of copper dienolates derived from α,β-unsaturated acids. We have examined the effects of varying the metal ion and altering stoichiometries; we have investigated isomerization that occurs in the electrophile-derived portion and also have investigated electrophiles other than allylic halides and methane sulfonates, in particular, vinylic epoxides. Charts I and II show the structures of the α,β-unsaturated acids and electrophiles that have been studied in this report.

Results

(A) Alkylation of Tiglic Acid with Allyl Bromide. Previously, we had reported[35] that when the dilithium dianion of tiglic acid (1) was treated with 2 equiv of cuprous iodide and subsequently alkylated with allyl bromide (A, eq 1), the distribution of α- vs. γ-substituted products



(1)

was 4:96, the ratio of E to Z isomers in the γ-alkylated products was 100:0, and the mode of attack on the electrophile was transposed (S_N2'). Further work has shown that this reaction proceeds at −78 °C and is complete within 15 min after the addition of the bromide. There have been reports of copper enolates[36] or organocuprates formed from Grignard reagents[37] undergoing reactions with high regioselectivity with only catalytic amounts of cuprous ion present. We have found that very small amounts of cuprous iodide make a dramatic difference in the percentage of γ alkylation in this reaction. In going from 0 to 0.1 equiv of cuprous iodide, the percentage of γ alkyl-

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Table II. Isomerization of the Double Bond in the Electrophile-Derived Portion during the Alkylation of Tiglic (1) and Senecioic (2) Acids with Allylic Halides[a]

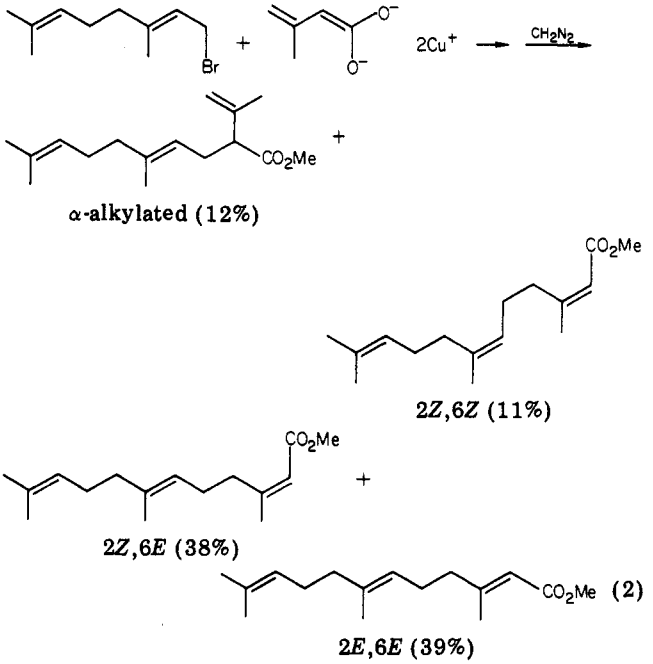
acid	geometry of Δ² of bromide	R	product ratios, % 2Z,6Z	2E,6Z	2E,6E	% isomerization
1	E (C)	$(CH_3)_2C=CHCH_2$		15	68	18
1	Z (D)	$(CH_3)_2C=CHCH_2$		81	10	11
1	E (E)	Et		6	75	8
1	Z (F)	Et		71	14	17
2[b]	E (C)	$(CH_3)_2C=CHCH_2$	11	(38)[c]	39	13[d]

[a] Determined by GLC analysis of the corresponding methyl esters; the remaining product is S_N2' type (see Scheme I). [b] Products also include 12% α-alkylated material (see text). [c] This is the 2Z,6E isomer which is poorly separated from the 2E,6Z isomer. [d] Based on 2Z,6Z isomer vs. total γ-alkylated products (see text).

ation goes from 0 to ca. 90%; beyond this, the effect levels off, the same percentage of γ alkylation being obtained whether 0.3 or 2 equiv of cuprous iodide is used.

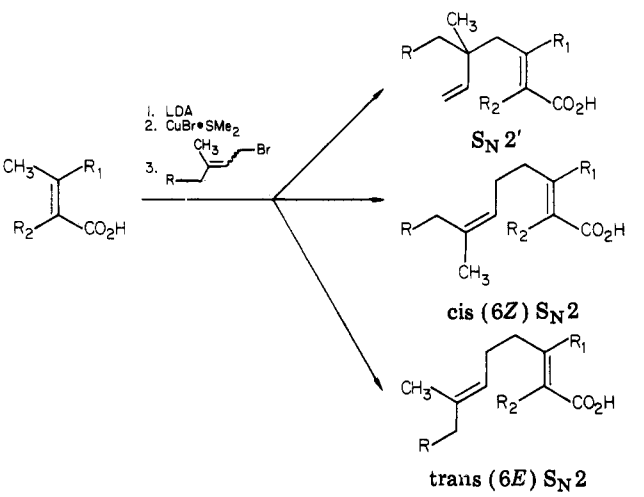
The maximum percentage of γ alkylation and the highest yields were obtained in this reaction when $CuBr_2 \cdot SMe_2$ was used to form the copper dienolate: The α:γ-substituted product ratio was 10:90 and the yield was 80% with CuI and these were 0:100 and 88% with $CuBr \cdot SMe_2$. At present it is somewhat unclear how the copper(I) counterions are able to effect such a dramatic alteration in alkylation regioselectivity, but as is illustrated in Table I, the effect is very specific for copper.

(B) Isomerization of the Electrophile-Derived Portion during Direct (S_N2) Attack. Previously, we had reported[35] that the synthesis of methyl farnesenate by alkylation of the dicopper dienolate of senecioic acid (2) with geranyl bromide followed by methylation with diazomethane gave the α-alkylated product together with the (2Z,6E)- and (2E,6E)-farnesenate isomers in a 10:36:54 ratio, respectively (eq 2). Repetition of the synthesis with



more careful GLC analysis of the crude methyl esters revealed four peaks in the ratio of 12:11:38:39 (in order of increasing retention time). Careful spinning-band distillation afforded pure samples of all four peaks, and by ^1H NMR analysis,[38] the first peak was identified as the α-alkylated material (12%), the second as the 2Z,6Z isomer (11%), the third as the 2Z,6E isomer (38%) (with possibly a small amount of the 2E,6Z isomer as a shoulder on this peak), and the fourth as the 2E,6E isomer (39%) (Scheme I). The surprising finding was that an appreciable fraction of 6Z isomers was formed (13% of the total γ-alkylated products), even though pure (E)-geranyl bromide was used.

Scheme I



This isomerization was investigated further in the tiglate system (which gives all 2E products and no α-alkylation but some S_N2' products); results are shown in Table II and Scheme I. The extent of electrophile isomerization ranges from 8 to 18% (calculated as isomerized product/total γ-alkylated product) and proceeds roughly to the same extent regardless of whether the allylic electrophile was initially the E or Z geometry. At present, it is not clear at what stage or by what process the isomerization is occurring. It appears not to be occurring in a step separate from alkylation, since excess unreacted allylic bromide that is recovered from the reaction mixture has not undergone isomerization (^1H NMR spectrum). Furthermore, decreasing the stoichiometry of $CuBr \cdot SMe_2$ to 0.5 equiv gave essentially the same extent of isomerization. It is also clear that isomerization is not occurring at the time of allylic bromide formation, since the C-1 methylene resonances of the E and Z isomers of 3-methyl-2-hexenyl bromide can be distinguished by ^1H NMR and the compounds shown to be isomerically pure. Thus, the isomerization most likely occurs during the alkylation process itself and suggests the intermediacy of some species that can undergo rapid isomerization.

(C) Variation in the Structure of the Electrophile Component. Our previous studies[35] on the γ-alkylation of copper dienolates had utilized allylic bromides and methanesulfonates. Further work has been undertaken to examine the range of electrophiles than can be used in this reaction. When the copper dienolate derived from tiglic acid (1) was treated with saturated alkyl bromides, acetic anhydride, 4-bromo-1-butene, benzoyl chloride, or cyclopropylcarbinyl bromide, only unreacted tiglic acid

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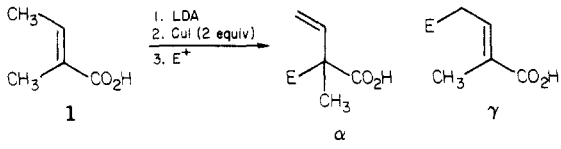
Table III. Treatment of the Copper Dienolate of Tiglic Acid (1) with Nonallylic Electrophiles



electrophile (E^+)	product ratio[a,b] (α:γ)	% yield[b,c]
MeI	57:43 (52:48)	78 (96)
EtI	100:0	67
n-PrI	100:0	40
$BrCH_2CO_2CH_3$	100:0	95
$BrCH_2C_6H_5$	51:49 (60:40)	57 (99)
CH_3CHO	100:0	64

[a] By GLC analysis of the corresponding methyl esters. [b] Numbers in parentheses are for lithium reactions. [c] Isolated yield was based on yield of acidic products. They were shown to consist only of the alkylated products by ^1H NMR and GLC of the corresponding methyl esters.

Table IV. Regioselectivity in the Alkylation of Acid Dienolates with Allyl Electrophiles

acid	electrophile	product ratio[a,b] (α:γ)	% yield[b,c]
1	G	0:100	95
1	H	8:92 (100:0)[a]	91 (84)
1	I	4:96	90
1	J	6:94	79
2	H	13:87	89
2	I	30:70	74
3	H	14:86	93
3	K	3:97	75

[a] Ratio in parentheses is for lithium reactions. [b] Numbers in parentheses are for lithium reactions. [c] Isolated yield was based on the yield of acidic products. They were shown to consist only of the alkylated products by ^1H NMR and GLC of the corresponding methyl esters.

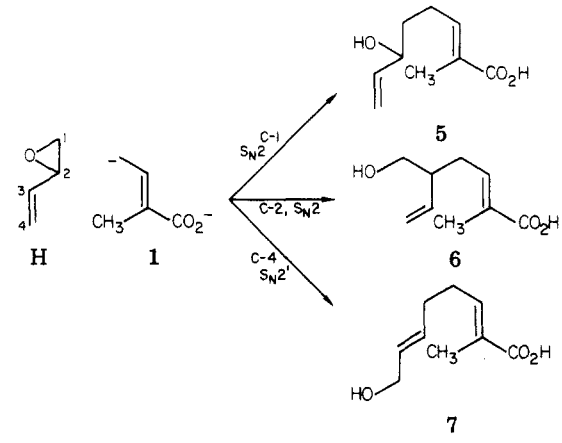
(detected as methyl esters by GLC after methylation with diazomethane) plus a higher boiling component (not identified) were found. Control experiments showed that this latter component is also observed if the dicuprated dianion of tiglic acid was stirred at −78 °C for 4 h before quenching at 0 °C.

Table III summarizes the results obtained when the copper dienolate of tiglic acid (1) was treated with other electrophiles. Except for two cases, only α alkylation was obtained with all the other electrophiles examined. The two exceptions were methyl iodide and benzyl bromide, and in both cases the ratio of α- to γ-alkylated products for the copper dienolate was nearly the same as that for the dilithium dienolate; the yields were better with the lithium reagent. The ratio for α/γ methylation of the lithium dienolate derived from tiglic acid (1) is similar to that reported by Pfeffer[31] (60:40) for the alkylation of the lithium dienolate of crotonic acid (3).

Some variation in the structure of the electrophile can be tolerated provided that it still contains an allylic-type leaving group. Chart II shows the structures of the other allylic electrophiles employed, 2-methoxyallyl bromide (G) and four vinylic epoxides (H–K), and Table IV shows the regioselectivity observed when the copper dienolate derived from an α,β-unsaturated acid was treated with these electrophiles. One can note that regioselectivity was very high in all cases where tiglic acid (I) was alkylated. Crotonic acid (3) and senecioic acid (2) show varying selectivities which depend on the structure of the electrophile.

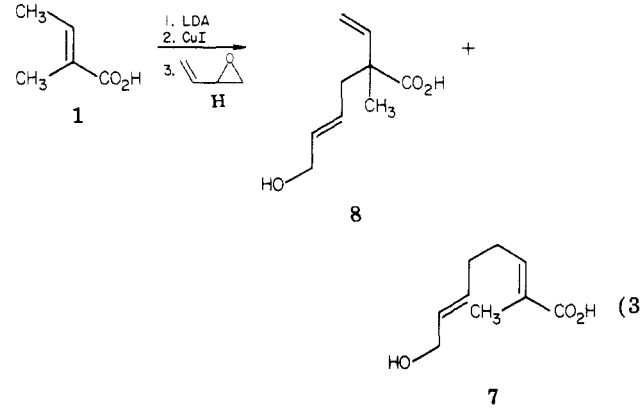
One fact not reflected in Table IV was that in all cases listed except one (1 + J), attack on the epoxide occurred

Scheme II



exclusively in an S_N2' manner. This result was not unexpected, although theoretically, three γ-alkylated products are possible (Scheme II). From previous work on the alkylation of copper dienolates derived from α,β-unsaturated esters[26] and acids[35] it was apparent that there is a tendency for γ alkylation to proceed by attack on the double bond of the electrophile with transposition of the double bond. Also, it is well-known that the reactions of acyclic vinylic epoxides[39] and in some cases cyclic epoxides[40] with organocuprates proceed regiospecifically to yield the S_N2' product. In the case of the alkylation of tiglic acid (1) with 3,4-epoxy-2-methyl-1-butene (J), 14% of the volatile product had a structure derived from S_N2 attack on C-2 of the epoxide 6, the remaining 86% being derived from S_N2' attack on the epoxide 7; no product corresponding to 5 was obtained.

(D) Stereochemistry of the Products Derived from Alkylation of Vinyl Epoxides. With respect to the regioselectivity and yield, the results of the reaction of tiglic acid (1) and butadiene monoxide (H) were encouraging (eq 3). GLC analysis of the products indicated two isomers.



^1H NMR analysis of materials separated by preparative GLC indicated that the first peak had structure 8 and the second structure 7. Each one appeared to be a single isomer at the 6,7 double bond when analyzed by ^1H NMR, since the cis and trans isomers have different resonance positions for the allylic oxymethylene signal; however, because of the coincidence of the two vinylic hydrogens on the disubstitued olefin, it was not apparent which isomer was formed.

Assignment of the trans (*E*) geometry to the 6,7 double bond was made by using the europium shift reagent tris-

(39) (a) Anderson, R. J. *J. Am. Chem. Soc.* **1970**, *92*, 4978; (b) Cahiez, G.; Alexakis, A.; Normant, J. K. *Synthesis* **1978**, 528.
(40) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675.

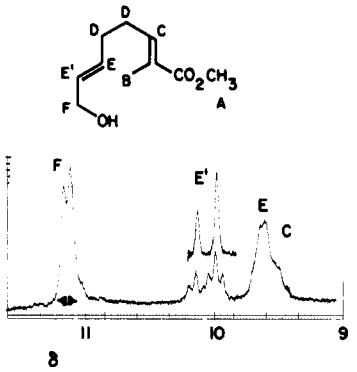


Figure 1. Spectrum of 7 in region of δ 9.0–11.6 with the maximum amount of $Eu(fod)_3$ added.

Table V. Stereochemistry at the 2,3 and 6,7 Double Bonds in 8-Hydroxy-2,6-octadienoic Acids Prepared by the Reaction of Copper Dienolates with Vinylic Epoxides

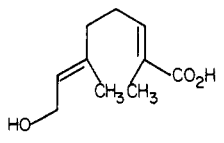
		relative ratio of products,[a] %			
acid	epoxide	2*E*,6*E*	2*E*,6*Z*	2*Z*,6*E*	2*Z*,6*Z*
1	H	100	0	0	0
1	I	81	19	0	0
1	J	81	19	0	0
2	H	19	19	31	31
2	I	0	0	21	79
3	H	100	0	0	0
3	K	100	0	0	0

[a] By GLC analysis in the corresponding methyl esters. Only γ-alkylated products are considered. For yields and byproducts, see the text.

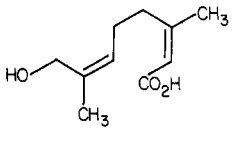
(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium(III) ($Eu(fod)_3$). Figure 1 (bottom) shows an expansion of the region between δ 9.0–11.6 when the maximum amount of shift reagent was added to **7**. The resonance for portion E′ can be seen to be a doublet of triplets as expected, with a doublet coupling of 15 Hz. Decoupling of proton F (oxymethylene protons) reduced the doublet of triplets from the E′ hydrogen to a simple doublet with a coupling constant of 15 Hz (the decoupled spectrum is shown above the nondecoupled one).

Stereochemical results of the reaction of tiglic (**1**), senecioic (**2**), and crotonic (**3**) acids with various vinyl epoxides are summarized in Table V.

Both tiglic (**1**) and crotonic (**3**) acids gave only the isomers with 2*E* stereochemistry. High regioselectivity (α:γ ratio) was also observed with these two acids (greater than 85% γ). The ratio of *E* to *Z* isomers for the 6,7 double bond is variable but strongly in favor of the *E* alcohol (greater than 80% *E* in all cases), and the yields for the alkylations of these two acids range from good (75%) to excellent (93%). The major products of the alkylation of tiglic acid (**1**) with epoxide J (compound **9**) would be useful in the synthesis of terpenoid 1,5 dienes.



9



10

The product of the alkylation of senecioic acid (**2**) with isoprene oxide (I, compound **10**) could conceivably also be used in the synthesis of natural isoprenoid products; unexpectedly, however, the major product of alkylation had the 2*Z*,6*Z* geometry (**10**). Regioselectivity was not high, and in this case approximately 30% of the product was α alkylated.

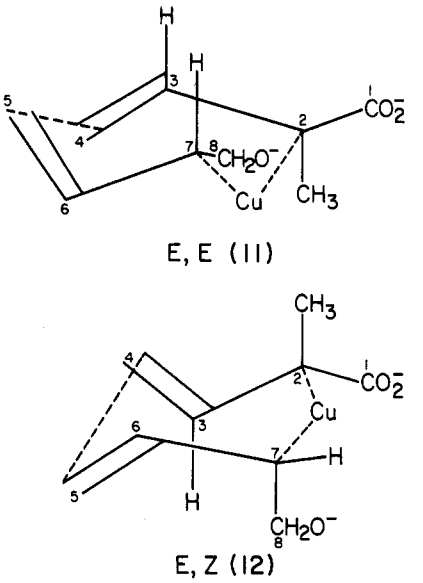


Figure 2. Chair transition states for the alkylation of tiglic acid (**1**) with butadiene monoxide (H).

Although at this point it is not certain what species are involved in the reaction of the copper dienolates with the vinylic epoxides, it is instructive to attempt to rationalize the stereochemical results summarized in Table V on the basis of steric interactions in a metallocycloheptane transition state. Such a metallocycle would result from an oxidative addition of the cuprate to the allylic carbon–oxygen bond of the vinyl epoxide, and thus, it is a reasonable species to consider as a precursor to the γ-alkylated (but not the α-alkylated) products. Figure 2 shows a hypothetical transition state for the alkylation of tiglic acid (**1**) with butadiene monoxide (H). Note that the ring has assumed a chairlike conformation, with the carboxyl anion occupying a pseudoequatorial position (structure **11**). This is probably the most stable conformer available. The reason that crotonic (**3**) and tiglic acids (**1**) both give products only with a 2*E* bond may be because to obtain a 2*Z* double bond either the ring has to assume a boat or twist–boat conformation or the carboxyl anion has to occupy the pseudoaxial position; both of these changes would lead to a less stable transition state.

The reason the *E* geometry is favored for the 6,7 double bond may also be deduced by examining the structures in Figure 2. In the transition state leading to the *E*,*E* product (structure **11**), the carboxyl anion and the methylene oxide occupy pseudoequatorial positions. In this position it can be seen from models that the two groups are as far away from each other as possible and thus have minimized charge repulsion. Only when one replaces the hydrogen on C-7 with a methyl group (such as in J) does one obtain any product with a (*Z*)-6,7 double bond (19%). In this case at least one group, the methyl group or the methylene oxide, must occupy the pseudoaxial position, so that the stereochemical preference is less than that with epoxide H.

A chairlike transition state does not explain the results obtained for the alkylation of senecioic acid (**2**) with vinyl epoxides. With electrophiles H and I, the major product isomers have 2*Z* stereochemistry. One cannot easily rationalize these product distributions on the same basis as the tiglic acid alkylations.

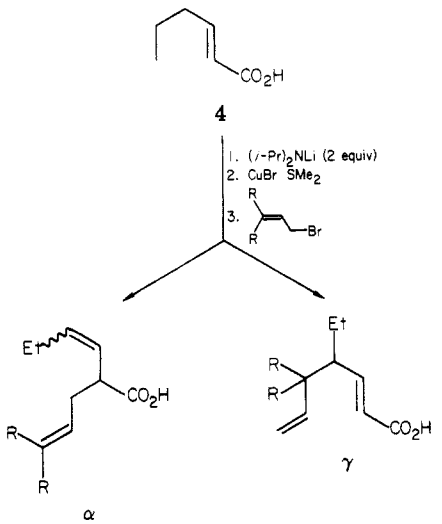
(E) Alteration in the Structure of the α,β-Unsaturated Acid. All of the work discussed previously involved deprotonation and alkylation at a methyl group which occupied the γ site of an α,β-unsaturated acid. We had

Table VI. Product Distribution in the Alkylation of 2-Hexenoic Acid (4) with Allylic Halides

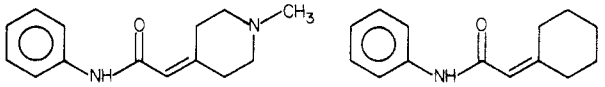
metal	R	ratio[a] of α:γ	% condensation product[a]	% γ[a] direct
Li	H	82:18	10	16
Cu	H	29:71	31	49
Li	Me	78:22	31	15
Cu	Me	59:41	52	13

[a] Determined by GLC analysis of the corresponding methyl esters.

Scheme III

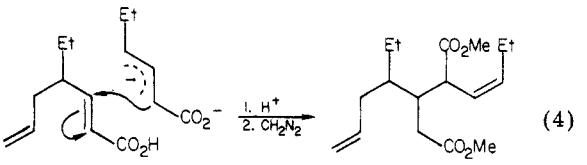


found[35] that in systems where alkylation on a methyl or methylene group was possible, alkylation occurred only on the methyl group. Snieckus and Wu[29] have reported successful γ alkylation on the methylene group of the lithium dienolate dianion of an α,β-unsaturated amide (13),



but it appears that the high γ regioselectivity observed was peculiar to this system, as the lithium dianion of amide 14 underwent exclusive α alkylation with a variety of electrophiles.[30]

Experimental results from the alkylation of the lithium and copper dienolates of 4 are summarized in Table VI and in Scheme III. The results with allyl bromide were encouraging: the relative percentage of γ alkylation rose from 18% with the lithium dienolate to 71% with the copper dienolate of 4; a high-boiling product also became more prominent. A mass spectrum of this material purified by preparative gas chromatography revealed a molecular ion at m/e 296, which would correspond to the condensation of two units of compound 4 and one allylic unit derived from allyl bromide. The ^{1}H NMR of the sample indicates that this compound probably has the structure of a substituted glutaric ester (15) which would result from the Michael addition of the α position of the dienolate of 4 to the unsaturated carboxylate 16 (eq 4) resulting from γ alkylation of another dienolate of 4. Mestres[34] has reported a similar reaction, and Munch-Petersen[41] has found a similar sequence ensues in the conjugate addition reactions



(4)

to tiglate and angelate esters. The extent to which the condensation product 15 was formed was not altered by variations in the experimental conditions, including inverse addition of the copper dienolate to a tenfold excess of neat allyl bromide precooled to −78 °C. While alkylation of acid 4 with allyl bromide (A) gave an appreciable percentage of the desired product (16), when dimethallyl bromide (B) was used to alkylate the copper dienolate of 4, 52% of the volatile material appeared to be the condensation product.

Discussion

It was clear from our previous studies on the alkylation of α,β-unsaturated acids[35] that replacement of the lithium counterion by copper(I) caused a significant shift in the alkylation regioselectivity toward the γ site. The greater γ selectivity in the acid series opened up many opportunities of preparative merit. However, it is important to take note of the scope and limitations of this approach to the isoprenoid 1,5-polyene synthesis.

The γ alkylation approach may be limited to the construction of 1,5-dienes. Nonallylic electrophiles when treated with the copper dienolate may alkylate either at the α-carbon, they may show no more selectivity toward alkylation at the γ position than when treated with lithium dienolates, or they may not react at all. Some interesting terpenoid structures oxygenated at both ends such as structures 8–10 can be prepared by using vinylic epoxides or allylic halides which are also vinyl ethers as electrophiles. These dioxygenated compounds have the potential to be prenylogated again at either end after suitable protection at one end, without need for respositioning the functioning groups. Both high regio- and stereoselectivity are observed when the copper dienolates derived from tiglic (1) and crotonic (3) acids are treated with various allylic epoxides (Tables IV and V), the major isomer observed in all cases being the 2E,6E isomer. The copper dienolate of senecioic acid (2) alkylates with good (87%) to fair (70%) γ selectivity, but gives predominantly Z stereoselectivity at both double bonds (Tables IV and V).

Unfortunately, when the copper dienolate derived from an α,β-unsaturated acid attacks an allylic halide in the direct (S_N2) mode, some isomerization occurs around the double bond in the electrophile-derived portion of the product. Although the percentage of isomerization is small, so that the percentage of the product that retains the original geometry of the bromide is high (Scheme I), the difficulty of the separation of the geometrical isomers clearly makes this a disadvantage for the synthesis of certain isoprenoid 1,5-dienes.

Enhancement of the γ selectivity when the lithium counterion is replaced with cuprous ion is also seen when alkylation occurs on the methylene of 2-hexenoic acid (4). However, copper also accelerates the formation of a side product formed by conjugate addition of the dianion to the 2,3 double bond of the γ-alkylated product. The efficiency of the γ-alkylation process is fair (49%) when the mode of attack on the electrophile is transposed (S_N2') but poor (13%) when it is direct (Table VI).

It is somewhat unclear by what means copper(I) ions are able to effect such a massive alteration in the alkylation regioselectivity of the acid dienolates. As little as 0.1 equiv

(41) Bitsch, V.; Jacobsen, S.; Andersen, I. G. K.; Munch-Petersen, J. *Acta Chem. Scand.* **1963**, *17*, 1433.

of cuprous ion enhances dramatically the γ selectivity for alkylation by allyl bromide. Copper(I) ions are much more effective in this respect than cobalt, magnesium, manganese, silver, iron, zinc, nickel, or cadmium (Table I).

It seems clear that with proper recognition of the constraints discussed above, γ alkylation of acid dienolates can be used as an efficient approach for the construction of certain isoprenoid 1,5-dienes, notably tail-carboxylated structures derived from tiglic acid (1). Some terpenoid 1,5-diene structures oxygenated at both ends (8–10) can also be prepared easily by using this approach; these compounds, while not natural products themselves, could be used as synthetic intermediates in natural product syntheses.

Experimental Section

Analytical gas–liquid phase chromatography (GLC) was performed on a Hewlett-Packard Model 5750 gas chromatograph with a flame-ionization detector and using a carrier gas (nitrogen) flow of 30 mL/min. The following columns were used for analytical work: A, 0.125 in. × 6 ft, 3% OV-17 on 100/120 Supelcoport; B, 0.125 in. × 6 ft, 3% Carbowax 20M on 80/100 Gas Chrom Q; F, 0.125 in. × 12 ft, OV-17 on 100/120 Supelcoport. Preparative GLC was done on a Varian Aerograph gas chromatograph, Model 90-P3, with a thermal-conductivity detector and using helium as a carrier gas at a flow rate of 30 mL/min except as noted. Three columns were used: C, 0.25 in. × 12 ft, 15% SE-30 on 60/80 Chrom W; D, 0.25 in. × 10 ft, 15% Carbowax 20M on 80/100 Chrom Q; E, 0.25 in. × 12 ft, 3% OV-17 on 80/100 Supelcoport. Compounds are listed in order of increasing retention time on the column specified.

Elemental analyses were carried out by the University of Illinois Microanalytical Laboratories.

The proton magnetic resonance ^{1}H NMR spectra were determined on Varian A-60A, HA-100, EM-390, and HR-220 spectrometers. The chemical shifts are expressed as δ values (parts per million downfield from internal tetramethylsilane). Infrared (IR) data were obtained by using a Perkin-Elmer Model 137 spectrometer, and the data are expressed in units of frequency (cm^{-1}).

Chemicals were obtained from the sources noted: butyllithium, sodium hydride, anhydrous cobalt(II) bromide, magnesium chloride, manganese(II) chloride, ferrous(II) chloride, zinc chloride, nickel bromide (Ventron Corp.); tiglic acid, trimethyl phosphonoacetate, senecioic acid, geraniol, crotonic acid, diisopropylamine, dimethyl sulfide, butanal, 4-bromo-1-butene, cyclopropylcarbinol, methyl 2-bromoacetate, piperylene, methacrolein, and Eu(fod)$_3$ (Aldrich); dimethallyl bromide, nerol, butadiene oxide (Chemical Samples Co.); cuprous iodide and bromide (Fisher Scientific Co.); silver tetrafluoroborate (Ozark-Mahoning Co.); cadmium iodide (Allied Chemical); mercurous(I) chloride (J. T. Baker Co.). Diazomethane was prepared from *N*-methyl-*N*-nitrosourea by the procedure of Ardnt.[42] Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. Diisopropylamine was distilled from calcium hydride and stored under dry nitrogen. Isomerically pure samples of ethyl (2*E*)- and (2*Z*)-3-methyl-2-hexenoate were prepared previously.[35] CuBr·SMe$_2$ was synthesized by using the method of House et al.[43] 3-Bromo-2-methoxy-1-propene was prepared according to the method of Jacobson et al.[44] Geranyl, neryl, and cyclopropylcarbinyl bromide were prepared from geraniol, nerol, and cyclopropylcarbinol by the method of Osbond.[45]

Synthesis of 2-Hexenoic Acid (4). Sodium methoxide (8.1 g, 0.15 mol) was suspended in 100 mL of dry DMF under nitrogen. Trimethyl phosphonoacetate (29.3 g, 0.16 mol) was added slowly to the reaction mixture which then was stirred at room temperature for 1 h. Freshly distilled butanal (10.7 g, 0.15 mol) was added slowly to the ylide. Stirring was continued for 6 h, and then the reaction mixture was poured into 500 mL of brine and extracted three times with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Distillation afforded 12.2 g (0.096 mol) of 77% *trans*- and 23% *cis*-methyl 2-hexenoate as a fraction boiling at 132–135 °C (64% yield).

The methyl ester (1 g, 7.81 mmol) was hydrolyzed with 20 mL of 20% NaOH at 80 °C for 1.5 h. The reaction mixture was cooled and extracted twice with ether. The aqueous layer was acidified to pH 2. Product isolation gave 0.70 g (6.14 mmol, 79% yield) of a cis–trans mixture of 2-hexenoic acid: ^{1}H NMR (CCl_4, 90 MHz) δ 12.23 (s, 1), 6.99 (dt, J_1 = 7.5 Hz, J_2 = 15 Hz, 0.80, trans), 6.23 (dt, J_1 = 7.5 Hz, J_2 = 11 Hz, 0.20, cis), 2.61 (q, 0.37, cis), 2.20 (q, 1.63, trans), 1.51 (q, 2), 0.97 (t, 3).

Synthesis of (*Z*)-3-Methyl-2-hexenol. Lithium aluminum hydride (140 mg, 3.5 mmol) was suspended in 10 mL of dry ether. The flask was cooled to 0 °C, and 140 mg (1.1 mmol) of aluminum chloride was added with vigorous stirring. The reaction was stirred for 15 min at 0 °C before the dropwise addition of 750 mg (4.4 mmol) of ethyl (*Z*)-3-methyl-2-hexenoate dissolved in 3 mL of ether. The reaction was stirred at 0 °C for 1 h before being quenched with 5% NaOH. After the mixture was filtered through $MgSO_4$, the solvent was removed under reduced pressure. Short column chromatography (silica, gradient elution with hexane–ether) yielded 366 mg (67% yield) of pure (*Z*)-3-methyl-2-hexanol: ^{1}H NMR (CCl_4, 90 MHz) δ 5.27 (br t, 1), 3.93 (br d, 2), 2.80–2.50 (m, 1), 2.00 (t, 2), 1.67 (s, 3), 1.67–1.10 (m, 2), 0.87 (t, 3).

Synthesis of (*E*)-3-Methyl-2-hexenol. This alcohol was prepared from ethyl (2*E*)-3-methyl-2-hexenoate by the preceeding method. After chromatography, a 91% yield of pure alcohol was obtained: ^{1}H NMR (CCl_4, 90 MHz) δ 5.23 (br t, 1), 3.97 (br d, 2), 2.87–2.38 (m, 1), 1.95 (t, 2), 1.63 (s, 3), 1.63–1.20 (m, 2), 0.87 (t, 3).

Synthesis of (*Z*)-3-Methyl-1-bromo-2-hexene (F). (*Z*)-3-Methyl-2-hexenol (336 mg, 2.9 mmol) was dissolved in 4 mL of dry ether at 0 °C. Then 319 mg (0.113 mL) of PBr_3 was added via syringe. The reaction was stirred at 0 °C for 4 h, poured into ice, and extracted three times with ether. The organic layer was washed with saturated sodium bicarbonate and dried over $MgSO_4$, and the ether was removed under reduced pressure. A total of 308 mg (59% yield) of product was obtained which was used without further purification: ^{1}H NMR (CCl_4, 90 MHz) δ 5.43 (br t, 1), 3.85 (d, 2), 2.08 (t, 2), 1.77 (s, 3), 1.48 (m, 2), 0.93 (t, 3).

Synthesis of (*E*)-3-Methyl-1-bromo-2-hexene (E). This compound was synthesized from (*E*)-3-methyl-2-hexenol by using the preceeding method. Product was isolated in 74% yield and was used without further purification ^{1}H NMR (CCl_4, 90 MHz) δ 5.48 (br t, 1), 3.91 (d, 2), 2.07 (t, 2), 1.77 (s, 3), 1.40 (m, 2), 0.90 (t, 3).

Synthesis of 3,4-Epoxy-2-methyl-1-butene (J). The procedure of Corey[48] was used. Dry dimethyl sulfoxide (50 mL) was added rapidly to 4.26 g of 50% NaH oil dispersion via a dropping funnel. The reaction was mechanically stirred to prevent freezing later on, and a thermometer inserted directly into the reaction medium. The Me_2SO and NaH were heated to 75 °C for 1 h and then cooled to room temperature. Dry THF (50 mL) was then added, and the flask was cooled in an ice–salt bath until the internal temperature reached −10 °C. Trimethylsulfonium iodide (18.1 g), formed from the addition of MeI to Me_2S, recrystallized from 95% ethanol, and stored under vacuum over $CaSO_4$ for 1 week, was dissolved in 59 mL of dry Me_2SO and was slowly added to the Me_2SO anion solution with the internal temperature kept below 5 °C. After the addition was complete, 5.10 g of methacrolein was added at such a rate as to keep the internal temperature below 5 °C. Stirring was continued at ice–salt temperatures for 15 min and then with the bath removed for 45 min. The reaction mixture was poured into 300 mL of ice–water and extracted three times with ether. The organic layer was dried

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(46) Shaw, J. E.; Kunerth, D. C.; Sherry, J. J. *Tetrahedron Lett.* **1973**, 689.
(47) Reist, E. J.; Junga, I. G.; Baker, B. R. *J. Org. Chem.* **1960**, *25*, 1673.
(48) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

with K_2CO_3 and distilled through glass helices. The fraction distilling at 78–85 °C was collected (2.67 g) and found to be a mixture of 23% THF and 77% epoxide J by weight: yield 34%; ^{1}H NMR (CCl_4, 90 MHz) δ 5.07 (s, 1), 4.90 (m, 1), 3.20 (t, 1), 1.59 (d, J = 1.5 Hz, 3).

Synthesis of 3,4 Epoxy-1-pentene (K). *N*-Bromosuccinimide (26 g) was added to a mechanically stirred suspension of 10 g of technical grade piperylene (1,3-pentadiene) and 37 mL of water slowly over a 0.5-h period. After the addition, the reaction mixture was stirred for 2.5 h at 18–25 °C until starch–iodide paper gave a negative test. The organic layer was separated from the water and extracted three times with ether, and the extracts were dried over $MgSO_4$ and concentrated in vacuo. The piperylene bromohydrin thus isolated was added over a 30-min period to 41 mL of 30% sodium hydroxide which had been cooled to 10–15 °C in an ice bath. After the addition was complete, the reaction was stirred at 10 °C for 2 h. The organic layer was then removed and combined with two ether extracts. The combined extract was dried with $MgSO_4$ and distilled through a column of glass helices. The portion that boiled at 83–87 °C was collected, giving a total of 3.53 g (28% yield) of epoxide: ^{1}H NMR (CCl_4, 90 MHz) δ 5.90–5.33 (m, 2), 5.33–5.03 (m, 1), 3.33–2.57 (m, 2), 1.27 (d, 3).

General Method for the Alkylation of the Lithium Dienolate of Tiglic Acid (1). Under a nitrogen atmosphere 10 mmol of butyllithium was added to 1.01 g (10 mmol) of diisopropylamine dissolved in 15 mL of THF at −78 °C. Tiglic acid (0.5 g, 5 mmol) was added, and the reaction mixture was stirred at 9 °C for 30 min. Electrophile dissolved in 5 mL of THF (10 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction was quenched with 5% NaOH when all the yellow color disappeared from the solution. The THF was removed, and the residue was dissolved in 5% NaOH. The basic solution was extracted twice with ether, the pH was adjusted to 2 (concentrated HCl), and the aqueous solution was extracted three times with ether. The organic solution was washed with brine and dried over $MgSO_4$. The ether was removed under reduced pressure to give the crude product. A portion of the crude acid was treated with diazomethane for GLC analysis.

General Method for Alkylation of Tiglic Acid (1) Copper Dienolate. To a solution of 1.01 g (1.5 mL, 10 mmol) of diisopropyl amine in 15 mL of THF under N_2 at −78 °C was added *n*-butyllithium (10 mmol). The pale yellow solution was stirred for about 10 min, and 0.50 g (5 mmol) of tiglic acid dissolved in 10 mL of THF was added. This was stirred was 30 min at 0 °C, forming a clear yellow solution. Then the reaction mixture was cooled to −78 °C, the proper copper (or other metal) salt was added, and the resulting suspension was stirred rigorously for 1 h at −78 °C. Then 2 equiv of electrophile was added, and the reaction was stirred overnight and allowed to warm slowly to room temperature. The alkylation was quenched with 1 mL of 5% NaOH, and the THF was removed on a rotary evaporator. About 50 mL of 5% NaOH was added, and the suspension was filtered through a pad of Celite. The clear, light blue solution was extracted twice with 50 mL of ether, adjusted to pH 2 with concentrated HCl, and extracted three times with 50 mL of ether. The extract was washed with saturated NaCl and dried over $MgSO_4$, and the ether was removed, giving a yellow oil. A portion of the oil was dissolved in ether and treated with diazomethane for GLC analysis.

Alkylation of Tiglic Acid (1) with Allyl Bromide (A) Using CuBr·SMe$_2$. By use of the general method, 0.125 g (1.25 mmol) of tiglic acid was alkylated with 0.45 g (2.5 mmol) of allyl bromide. CuBr·SMe_2 (0.513 g, 2.5 mmol) was added to the dienolate dianion of tiglic acid at −78 °C before the addition of allyl bromide. A total of 0.121 g of product was isolated. GLC analysis of the methyl esters (column A, 80–275 °C, 20 °C/min, 1-min postinjection interval) revealed one peak (150 °C) whose retention time matched that of the γ-alkylated product.

Alkylation of Senecioic Acid (2) Copper Dienolate with Geranyl Bromide (C). By use of the general procedure outlined for senecioic acid, the copper dienolate formed from 25 g (0.25 mol) of senecioic acid and 0.50 mmol of CuI was treated with 65 g (0.28 mol) of geranyl bromide. The reaction mixture was stirred at −78 °C overnight with warming and was quenched at room temperature with 5% HCl. Ether was added, and the organic layer was extracted twice with saturated NH_4Cl. The ether phase was dried ($MgSO_4$) and concentrated to give the crude alkylated product.

This material was esterified by using the method of Shaw, Kunerth, and Sherry.[46] It was dissolved in 500 mL of hexamethylphosphoramide, 200 mL of 20% NaOH (0.5 mol) was added, and the reaction mixture was stirred for 1.5 h. MeI (134 g) was then added, the reaction was stirred for 2 h, and then it was poured into 1 L of 5% HCl. The aqueous layer was extracted three times with ether, and the organic layer was washed with brine and then dried ($MgSO_4$). Removal of ether gave the crude methyl esters which were chromatographed on silica gel (10% ether/hexane) to give 30.03 g of product (48% yield). GLC analysis (column A, 175 °C) revealed four peaks, A (4.5 min), B (5.4 min), C (6.1 min), and D (7.2 min) in a ratio of 12:11:38:39. The purified esters were distilled by using a Nester-Faust Teflon annular spinning-band column at a vacuum pressure of 0.2 mm and a reflux ratio of (60–300):1. Fractions were analyzed by GLC. A total of 5.63 g of peak D was isolated in pure form (9% yield) and was identified by ^{1}H NMR analysis as the 2*E*,6*E*, γ-alkylated material, methyl (2*E*,6*E*)-farnesoate: ^{1}H NMR (CCl_4, 100 MHz) 5.57 (br s, 1), 5.05 (m, 2), 3.60 (s, 3), 2.13 (d, J = 0.5 Hz, 7), 1.96 (m, 4), 1.65 (s, 3), 1.58 (s, 6). Anal. ($C_{16}H_{26}O_2$) C, H.

Peak A was found to be the α-alkylated material, methyl (4*E*)-5,9-dimethyl-2-(2-propenyl)-4,8-decadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 4.98 (br t, 2), 4.80 (s, 2), 3.60 (s, 3), 2.93 (dt, J_1 = 3 Hz, J_2 = 9 Hz, 1), 2.63–2.20 (m, 2), 2.03 (t, 4), 1.63 (s, 3), 1.58 (s, 6), 1.50 (s, 3).

Peak B was found to be the 2*Z*,6*Z*, γ-alkylated material, methyl (2*Z*,6*Z*)-farnesenate: ^{1}H NMR (CCl_4, 90 MHz) δ 5.55 (br s, 1), 5.27–4.80 (m, 2), 3.60 (s, 3), 2.60 (br t, 2), 2.33–2.03 (m, 2), 1.98 (d, 4), 1.88 (s, 3), 1.68 (s, 6), 1.57 (s, 3).

Peak C was found to be the 2*Z*,6*E*, γ-alkylated material, methyl (2*Z*,6*E*)-farnesoate: ^{1}H NMR (CCl_4, 90 MHz) δ 5.55 (br s, 1), 5.23–4.73 (m, 2), 3.60 (s, 3), 2.60 (br t, 2), 2.30–2.03 (m, 2), 1.98 (m, 4), 1.88 (d, J = 2 Hz, 3), 1.65 (s, 3), 1.60 (s, 6).

Alkylation of the Copper Dienolate of Tiglic Acid (1) with Geranyl Bromide (C). The copper dienolate formed from 5 mmol of tiglic acid and 10 mmol (2.06 g) of CuBr·SMe_2 was treated with 5.5 mmol (1.20 g) of geranyl bromide. The reaction mixture was stirred for 1.5 h at −78 °C and 30 min at 0 °C before being quenched with 5% HCl. Ether was added, and the organic layer was washed twice with saturated NH_4Cl and dried over $MgSO_4$. The ether was then removed, furnishing the crude acid that was esterified by using the method of Shaw, Kunerth and Sherry.[46] sherry.[46] After short-column chromatography (silica, 20% ether/hexane), a total of 1.16 g (93% yield) of alkylated material was isolated. GLC analysis (column F, 200 °C) revealed three peaks, A (10.6 min), B (13.9 min), and C (15.2 min) in a ratio of 17:15:68, respectively. Preparative GLC (column E, 175 °C, gas flow rate of 16 mL/min) afforded pure samples of two of the three isomers. Peak A (retention time 26 min) was found to be the S_N2' product, methyl (2*E*)-2,5,9-trimethyl-5-vinyl-2,8-decadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.61 (br t, 1), 5.69 (dd, J_1 = 10.5 Hz, J_2 = 15 Hz, 1), 5.10–4.73 (m, 3), 3.63 (s, 3), 2.13 (d, 4), 1.80 (s, 3), 1.63 (s, 3), 1.57 (s, 3), 1.30 (m, 2), 1.01 (s, 3).

Peak B had the same retention time as the major isomer (2*E*,6*Z*, γ isomer) of the alkylation of tiglic acid with neryl bromide (see below); peak C (retention time 43 min) was found to be the 2*E*,6*E*, γ product, methyl (2*E*,6*E*)-2,7,11-trimethyl-2,6,10-dodecatrienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.00 (br t, 1), 5.01 (m, 2), 3.63 (s, 3), 2.13 (br t, 4), 1.97 (br s, 4), 1.79 (s, 3), 1.65 (s, 3), 1.60 (s, 6). Anal. ($C_{16}H_{28}O_2$) C, H.

Alkylation of the Copper Dienolate of Tiglic Acid (1) with Neryl Bromide (D). The copper dienolate formed from 5 mmol of tiglic acid and 10 mmol of CuBr·SMe_2 was treated with 1.20 g of neryl bromide. The reaction was performed, worked up, and chromatographed as described for the alkylations of tiglic acid with geranyl bromide. After chromatography, 1.16 g (93% yield) of alkylated material was isolated. GLC analysis (column F, 200 °C) revealed three peaks, A (10.6 min), B (13.9 min), and C (15.2 min) in a ratio of 9:81:10. Preparative GLC (column E, 175 °C, gas flow rate of 16 mL/min) afforded pure samples of two of the isomers. Peak A was found to be the S_N2' isomer and had a ^{1}H NMR spectrum identical with that described previously in the alkylation of tiglic acid with geranyl bromide. Peak B (retention time 35 min was found to be the 2*E*,6*Z*, γ-alkylated isomer, methyl

(2*E*,6*Z*)-2,7,11-trimethyl-2,6,10-dodecatrienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.63 (br t, 1), 5.05 (m, 2), 3.63 (s, 3), 2.13 (br t, 4), 2.01 (d, 4), 1.80 (s, 3), 1.70 (s, 6), 1.60 (s, 3). Anal. ($C_{16}H_{26}O_2$) C, H.

Peak C was found to have the same retention time as the major isomer (2*E*,6*E*, γ isomer) of the alkylation of tiglic acid with geranyl bromide (vide ante).

Alkylation of the Copper Dienolate of Tiglic Acid (1) with (*E*)-3-Methyl-1-bromo-2-hexene (E). The copper dienolate formed from 4 mmol of tiglic acid and 8 mmol (1.65 g) of $CuBr{\cdot}SMe_2$ was treated with 4.4 mmol (780 mg) of (*E*)-3-methyl-1-bromo-2-hexene (E). The reaction mixture was stirred for 1.5 h at −78 °C and then 30 min at 0 °C and gave after product isolation 610 mg (78% yield) of crude alkylated acid that was methylated with diazomethane. GLC analysis (column F, 2-min postinjection interval, 160–180 °C, 2 °C/min) revealed two peaks, A (184 °C) and B (194 °C) in a ratio of 19:81. Peak B was very broad and appeared to have a shoulder on its leading edge. Further GLC analysis (Varian Model 3700 gas chromatograph, capillary column, 0.25 mm i.d. × 25 m, OV-101, split ratio of 100:1, 130–240 °C, 4 °C/min) revealed that peak B consisted of two peaks (180 °C), C and D; the ratio of C to D was 8:92. Preparative GLC (column E, 150 °C, gas flow rate of 19 mL/min) afforded separation of peaks A and B. Peak A was found to be the S_N2' isomer, methyl (2*E*)-2,5-dimethyl-5-propyl-2,6-heptadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.61 (dt, J_1 = 2 Hz, J_2 = 7.5 Hz, 1), 5.67 (dd, J_1 = 12 Hz, J_2 = 18 Hz, 1), 5.07–4.70 (m, 2), 3.63 (s, 3), 2.13 (d, 2), 1.79 (s, 3), 1.27 (m, 4), 0.99 (s, 3), 0.99–0.80 (m, 3).

Peak B was found to be an isomeric mixture of 2*E*,6*E* and 2*E*,6*Z* γ-alkylated material, with the major isomer being the 2*E*,6*E* isomer, methyl (2*E*,6*E*)-2,7-dimethyl-2,6-decadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.60 (br t, 1), 5.03 (m, 1), 3.63 (s, 3), 2.20–1.80 (m, 6), 1.77 (s, 3), 1.57 (s, 3), 1.53–1.00 (m, 2), 0.83 (t, 3). Anal. ($C_{13}H_{22}O_2$) C, H.

Alkylation of the Copper Dienolate of Tiglic Acid (1) with (*Z*)-3-Methyl-1-bromo-2-hexene (F). The copper dienolate formed from 1.58 mol of tiglic acid and 0.65 g of $CuBr{\cdot}SMe_2$ was treated with 1.75 mol (308 mg) of (*Z*)-3-methyl-1-bromo-2-hexene. The reaction mixture was stirred at −78 °C for 1.5 h and then 30 min at 0 °C before being quenched. Product isolation gave 255 mg (82% yield) of crude alkylated acid that was methylated with diazomethane. GLC analysis (column F, 2-min postinjection interval, 160–180 °C, 2 °C/min) revealed two peaks, A (187 °C) and B (194 °C) in a ratio of 15:85. Peak B appeared to have a shoulder on its tailing edge. Further GLC analysis (Varian Model 3700 gas chromatograph, 0.25 mm × 25 m, OV-101, split ratio of 100:1, 130–240 °C, 4 °C/min) revealed that peak B consisted of two peaks (180 °C): C and D in a ratio of 83:17. Preparative GLC (column E, 148 °C, gas flow rate of 19 mL/min) afforded separation of peaks A and B. Peak A was found to be the S_N2' isomer (vide ante). Peak B was found to be an isomeric mixture of 2*E*,6*E* and 2*E*,6*Z* γ-alkylated material with the major isomer being the *E*,*Z* isomer, methyl (2*E*,6*Z*)-2,7-dimethyl-2,6-decadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.61 (br t, 1), 5.05 (m, 1), 3.63 (s, 3), 2.20–1.83 (m, 6), 1.79 (s, 3), 1.65 (s, 3), 1.69–1.03 (m, 2), 0.89 (t, 3). Anal. ($C_{13}H_{22}O_2$) C, H.

Alkylation of Tiglic Acid (1) Copper Dienolate with *n*-Propyl Iodide. The copper dienolate formed from 5 mmol of tiglic acid and 10 mmol of CuI was treated with 50 mmol of *n*-propyl iodide. A total of 0.37 g (2.6 mmol, 53% yield) of material was isolated and was treated with diazomethane. GLC analysis (column A, 75–300 °C, 20 °C deg/min, 1-min postinjection interval) showed one peak (100 °C). Isolation by preparative GLC (column C, 100 °C) and ^{1}H NMR analysis showed this material to be the α-propylated tiglate ester, methyl 2-methyl-2-propyl-3-butenoate: ^{1}H NMR (CCl_4, 60 MHz) δ 5.92 (dd, J_1 = 10 Hz, J_2 = 18 Hz, 1), 5.19 (d, J = 2 Hz, 1), 4.95 (dd, J_1 = 2 Hz, J_2 = 5 Hz, 1), 3.67 (s, 3), 1.7–0.8 (m, 10).

Alkylation of Tiglic Acid (1) Copper Dienolate with Ethyl Iodide. The copper dienolate formed from 2.5 mmol of tiglic acid and 5 mmol of $CuBr{\cdot}SMe_2$ was alkylated with 7.1 g (50 mmol) of ethyl iodide. The reaction mixture was stirred at −78 °C for 4 h and at 0 °C for 30 min and then was quenched. Product isolation gave 0.32 g of crude acid that was treated with diazomethane. GLC analysis (column A, 70 °C) revealed two peaks, A (1.3 min) and B (3.4 min) in a ratio of 30:70, respectively. Peak A was found to have the same retention time as methyl tiglate. Preparative GLC (column E, 80 °C) yielded a pure sample of B (retention time 12 min) which was found to be the α-alkylated product, methyl 2-methyl-2-ethyl-3-butenoate: ^{1}H NMR (CCl_4, 90 MHz) δ 5.90 (dd, J_1 = 10.5 Hz, J_2 = 18 Hz, 1), 5.05 (d, 1), 4.90 (dd, J_1 = 2 Hz, J_2 = 6 Hz, 1), 3.63 (s, 3), 1.63 (m, 2), 1.21 (s, 3), 0.80 (t, 3).

Alkylation of Tiglic Acid (1) Lithium Dienolate with Methyl Iodide. The lithium dienolate formed from 2.5 mmol of tiglic acid (1) was treated with 3.0 g (21 mmol) of methyl iodide. Product isolation gave 0.272 g (96% yield) of material that was treated with diazomethane. GLC analysis (column F, 70 °C) of the methyl esters revealed two peaks [A (2.8 min) and B (7.3 min) in a ratio of 52:48] that were subsequently separated by preparative GLC (column E, 73 °C). ^{1}H NMR revealed A to be the α-alkylation product methyl 2,2-dimethyl-3-butenoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.00 (dd, J_1 = 9 Hz, J_2 = 18 Hz, 1), 5.11 (d, 1), 4.95 (br s, 1), 3.63 (s, 3), 1.30 (s, 6). Characterization of the material in peak B (γ-alkylated product) is discussed below. Anal. ($C_7H_{12}O_2$) C, H.

Alkylation of Tiglic Acid (1) Copper Dienolate with Methyl Iodide. The copper dienolate formed from 15 mmol of tiglic acid (1) and 30 mmol of $CuBr{\cdot}SMe_2$ was alkylated with 7.0 g (49.5 mmol) of methyl iodide. Product isolation gave 1.33 g of material that was treated with diazomethane. GLC analysis of the methyl esters (column F, 70 °C) revealed two peaks [A (2.8 min) and B (7.3 min) in a ratio of 57:43] that were separated by preparative GLC (column E, 85 °C). Peak A had the same retention time as material previously shown to be the α-alkylated product. ^{1}H NMR revealed B to be the γ-alkylated product, methyl (2*E*)-2-methyl-2-pentenoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.60 (qt, J_1 = 2 Hz, J_2 = 7.5 Hz, 1), 3.63 (s, 3), 2.15 (d, 2), 1.77 (s, 3), 1.05 (t, 3). Anal. ($C_7H_{12}O_2$) C, H.

Alkylation of Tiglic Acid (1) Copper Dienolate with Acetaldehyde. The copper dienolate formed from 5 mmol of tiglic acid and 10 mmol of CuI was treated with 12 mmol of freshly distilled acetaldehyde. A total of 0.46 g (64% yield) of material was isolated, and GLC analysis of the methyl esters (column A, 75–300 °C, 20 °C/min, 1-min postinjection interval) revealed one peak (132 °C) that was subsequently isolated in pure form via preparative GLC (column C, 150 °C) and shown to be the α-alkylation product, methyl 3-hydroxy-2-methyl-2-vinylbutanoate: ^{1}H NMR (CCl_4, 100 MHz) δ 6.3–5.76 (m, 1), 5.38–5.04 (m, 2), 4.18–3.88 (dq, J_1 = 3 Hz, J_2 = 4 Hz, 1), 3.74 (s, 3), 2.80–2.45 (br s, 1), 1.26 (d, J = 1 Hz, 3), 1.10 (d, J = 3 Hz, 3). Anal. ($C_8H_{14}O_3$) C, H.

Alkylation of Tiglic Acid (1) Copper Dienolate with Methyl 2-Bromoacetate. The copper dienolate formed from 5 mmol of tiglic acid and 10 mmol of CuI was treated with 10 mmol of methyl 2-bromoacetate. A total of 0.864 g (4.97 mmol, 99% yield) of material was isolated, and GLC analysis of methyl esters (column A, 75–300 °C, 20 °C/min, 1-min postinjection interval) revealed three products, A (94 °C), B (102 C), and C (116 °C) in a ratio of 22:13:65. The major product was isolated in pure form by preparative GLC (column A, 99 °C) and found to be the α-alkylated product, dimethyl 2-methyl-2-vinylsuccinate: ^{1}H NMR (CCl_4, 90 MHz), 5.95 (dd, J_1 = 10 Hz, J_2 = 18 Hz, 1), 5.10 (d, 1), 4.95 (d, 1), 3.63 (s, 3), 3.57 (s, 3), 2.60 (AB q, $\Delta\nu$ = 0.33 ppm, J = 17 Hz, 2), 1.33 (s, 3). Anal. ($C_9H_{14}O_4$) C, H.

Alkylation of Tiglic Acid (1) Lithium Dienolate with Benzyl Bromide. Tiglic acid lithium dienolate (5 mmol) was treated with 11 mmol (1.88 g) of benzyl bromide. A total of 0.824 g (4.96 mmol) of material was isolated (99% yield), and GLC analysis of the methyl esters (column A, 188–250 °C, 10 °C/min, 1-min postinjection interval) revealed two peaks [A and B in a ratio of 60:40] that were subsequently isolated by preparative GLC (column C, 163 °C). Peak A was found to be the α-benzylated tiglate ester, methyl 2-benzyl-2-methyl-3-butenoate: ^{1}H NMR (CCl_4, 60 MHz) δ 7.20 (m, 5), 6.15 (m, 1), 5.21 (d, J = 2.5 Hz, 1), 4.99 (dd, J_1 = 1 Hz, J_2 = 7 Hz, 1), 3.66 (s, 3), 2.93 (AB q, $\Delta\nu$ = 0.33 ppm, J = 14 Hz, 2), 1.20 (s, 3). Anal. ($C_{13}H_{16}O_2$) C, H.

Peak B was the γ-benzylated product, methyl (2*E*)-2-methyl-5-phenyl-2-pentenoate: ^{1}H NMR (CCl_4, 60 MHz) δ 7.20 (m, 5), 6.80 (m, 1), 3.70 (s, 3), 2.66 (m, 4), 1.75 (m, 3). Anal. ($C_{13}H_{16}O_2$) C, H.

Alkylation of Tiglic Acid (1) Copper Dienolate with Benzyl Bromide. The copper dienolate formed from 5 mmol

of tiglic acid and 10 mmol of CuI was treated with 11 mmol (1.88 g) of benzyl bromide. Product isolation afforded 0.476 g (2.9 mmol) of material (57% yield), and GLC analysis of the methyl esters (column A, 188–250 °C, 10 °C/min, 1-min postinjection interval) revealed two peaks in a 51:49 ratio which had identical retention times with the α-benzylated and γ-benzylated tiglate esters, respectively.

Alkylation of Tiglic Acid (1) Lithium Dienolate with Butadiene Oxide (H). The lithium dienolate formed from 5 mmol of tiglic acid was treated with 0.69 g (10 mmol) of butadiene oxide. The reaction mixture was stirred for 3 h at −78 °C, the dry ice bath was removed, and the reaction was allowed to warm to room temperature before being quenched. A total of 0.72 g (84% yield) of material was isolated, and GLC analysis of the methyl esters (column A, 70–300 °C, 20 °C/min, 1-min postinjection interval) revealed peaks at 150, 156, 160, 180 (major), and 195 °C. The methyl esters were chromatographed on preparative silica gel TLC plates (50% ether/hexane), and the band that stained with iodine was removed. The major isomer in the chromatographed material was then isolated by preparative GLC (column C, 135 °C) and shown to be methyl (4*E*)-6-hydroxy-2-methyl-2-vinyl-4-hexenoate (cf. 8): ^{1}H NMR (CCl_4, 100 MHz) δ 5.95 (dd, J_1 = 5 Hz, J_2 = 9 Hz, 1), 5.64–5.44 (m, 2), 5.12 (d, 1), 4.97 (dd, J_1 = 1 Hz, J_2 = 3 Hz, 1), 3.96 (br d, 2), 3.64 (s, 3), 2.60–2.10 (m, 2), 1.54 (br t, 1), 1.22 (s, 3). Anal. ($C_{10}H_{16}O_3$) C, H.

Alkylation of Copper Dienolate of Tiglic Acid (1) with Butadiene Monoxide (H). The copper dienolate formed from 5 mmol of tiglic acid and 10 mmol of CuI was treated with 0.69 g (10 mmol) of butadiene oxide. The reaction mixture was stirred for 3 h at −78 °C and then for 0.5 h at 0 °C before being quenched at 0 °C. A total of 0.77 g (91% yield) of product was isolated, and GLC analysis of the methyl esters (column A, 70–300 °C, 20 °C/min, 1-min postinjection interval) revealed two peaks, A (180 °C) and B (210 °C) in a ratio of 9:92. The retention time of peak A matched that of the α-alkylated product. The methyl esters were chromatographed on preparative silica gel TLC plates (50% ether/hexane), and the major isomer (peak B) was isolated in pure form after preparative GLC (column C, 135 °C) and found to be methyl (2*E*,6*E*)-8-hydroxy-2-methyl-2,6-octadienoate (cf. 7): ^{1}H NMR (CCl_4, 100 MHz) δ 6.66 (m, 1), 5.60 (br t, 2), 3.98 (m, 2), 3.68 (s, 3), 2.22 (m, 5), 1.80 (s, 3); IR (CS_2) 3660–3240 (OH), 2960 (CH), 1723 (C=O), 1658 (C=C), 1270 (CO), 748 (HC=CH trans, out of plane bending) cm^{-1}. Anal. ($C_{10}H_{16}O_3$) C, H.

Alkylation of the Copper Dienolate of Senecioic Acid (2) with Butadiene Oxide (H). The procedure followed for the generation of the copper dienolate of senecioic acid is somewhat different from that employed for tiglic acid due to the insolubility of the dilithium senecioic acid dianion in THF. NaH (0.24 g of 50% oil dispersion, 5 mmol, washed free from oil) was slurried in 15 mL of dry THF under nitrogen at 0 °C. Mechanical stirring is absolutely necessary in order to form the mixed sodium–lithium salt successfully. Senecioic acid (0.50 g, 5 mmol) was dissolved in 8 mL of THF and added to the slurry, and the reaction mixture was stirred at room temperature until a white precipitate formed. In another flask, 5 mmol of lithium diisopropylamide was generated in 10 mL of THF at −78 °C under nitrogen. The sodium salt was cooled at 0 °C, and the LDA (at −78 °C) was siphoned over under nitrogen. The reaction mixture was stirred for 30 min at 0 °C and then cooled to −78 °C. CuI (1.96 g, 10 mmol) was then added and stirred for at least 1 h at −78 °C until a bright green-gold precipitate formed. Butadiene oxide (0.69 g, 10 mmol) was added, and the reaction mixture was stirred for 3 h at −78 °C and then 0.5 h at 0 °C before being quenched at 0 °C. A total of 0.753 g (98% yield) of product was isolated after the standard workup. GLC analysis of the methyl esters (column A, 155 °C) revealed three products, A (2.3 min), B (3.3 min), and C (5.5 min) in a ratio of 13:33:54. The methyl esters were chromatographed on preparative silica gel TLC plates (50% ether/hexane), and the three components were subsequently separated by preparative GLC (column C, 143 °C). Peak A was the α-alkylated material, methyl (4*E*)-6-hydroxy-2-(isopropenyl)-4-hexenoate: ^{1}H NMR (CCl_4, 100 MHz) δ 5.70–5.10 (m, 2), 4.84 (m, 2), 4.80–3.84 (m, 2), 3.60 (s, 3), 3.12–2.90 (m, 1), 2.84–2.00 (m, 3), 1.72 (m, 3). Anal. ($C_{10}H_{16}O_3$) C, H.

Peak B was a 50:50 mixture of the 2*Z*,6*E* and 2*Z*,6*Z* isomers of the γ-alkylated product, methyl 8-hydroxy-3-methyl-2,6-octadienoate: ^{1}H NMR (CCl_4, 100 MHz) δ 5.74–5.40 (m, 3), 4.06 (d, J = 2.5 Hz, 1 (cis)), 3.95 (m, 1 (trans)), 3.60 (m, 3), 2.80–2.54 (m, 2), 2.42 (br s, 1), 2.36–2.04 (m, 2), 1.88 (s, 3). Anal. ($C_{10}H_{16}O_3$ C, H.

Peak C was a 50:50 mixture of the 2*E*,6Z and 2*E*,6*E* isomers of the γ-alkylated product: ^{1}H NMR (CCl_4, 100 MHz) δ 5.64–5.48 (m, 3), 4.06 (d, 1, cis), 3.96 (m, 1, trans), 3.60 (s, 3), 2.20 (m, 4), 2.12 (d, 3), 1.32 (br s, 1). Anal. ($C_{10}H_{16}O_3$) C, H.

Alkylation of Crotonic Acid (3) Copper Dienolate with Butadiene Oxide (H). The copper dienolate formed from 1.00 g (11.6 mmol) of crotonic acid and 4.80 g (23.2 mmol) of $CuBr{\cdot}SMe_2$ was treated with 2.10 g (30.4 mmol) of butadiene oxide. Twice as much THF was used as in the case of the tiglic acid copper dienolate alkylations. The reaction mixture was stirred at −78 °C for 3 h and then for 0.5 h at 0 °C before being quenched at 0 °C. A total of 3.37 g (93% yield) of product was isolated, and GLC analysis of the methyl esters (column A, 155 °C) revealed two peaks [A (1.9 min) and B (5.4 min) in a ratio of 14:86] that were subsequently separated by preparative GLC (column C, 143 C). Peak A was the α-alkylated material methyl (4*E*)-6-hydroxy-2-vinyl-4-hexenoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.00–5.43 (m, 3), 5.23 (d, 1), 5.00 (d, 1), 3.97 (m, 2), 3.63 (s, 3), 3.20–2.70 (m, 1), 2.67–1.90 (m, 4). Anal. ($C_9H_{14}O_3$) C, H.

Peak B was the γ-alkylated product methyl (2*E*,6*E*)-octadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.80 (dt, J_1 = 7.5 Hz, J_2 = 15 Hz, 1), 5.67 (d, 1), 5.57 (m, 2), 3.97 (m, 2), 3.60 (m, 3), 2.23 (m, 4), 1.95 (s, 1). Anal. ($C_9H_{14}O_3$) C, H.

Alkylation of Tiglic Acid (1) Copper Dienolate with Isoprene Oxide (I). Isoprene oxide was synthesized according to the method of Reist, Junga, and Baker.[47] The copper dienolate formed from 5 mmol (0.5 g) of tiglic acid and 10 mmol of CuI was treated with 12 mmol (1.00 g) of isoprene oxide. The reaction mixture was stirred for 3 h at −78 °C and then for 0.5 h at 0 °C before being quenched at 0 °C. A total of 0.826 g of product (90% yield) was isolated, and GLC analysis of the methyl esters (column A, 165 °C) revealed three peaks [A (3.6 min), B (4.5 min), and C (5.3 min) in a ratio of 4:18:78] that were subsequently separated by preparative GLC on Carbowax column (column D, 15 mL/min gas flow rate, 210 °C). Peak A because of its retention time was assumed to be the α-alkylated material. Peak B was the 2*E*,6*Z* γ-alkylated material, methyl (2*E*,6*Z*)-2,7-dimethyl-8-hydroxy-2,6-octadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.60 (m, 1), 5.20 (m, 1), 3.97 (s, 2), 3.67 (s, 3), 2.17 (m, 4), 1.77 (s, 6), 1.20 (s, 1). Anal. ($C_{11}H_{18}O_3$) C, H.

Peak C was the 2*E*,6*E* isomer: ^{1}H NMR (CCl_4, 90 MHz) δ 6.60 (m, 1), 5.30 (m, 1), 3.87 (s, 2), 3.67 (s, 3), 2.17 (m, 4), 1.77 (s, 3), 1.63 (s, 3), 1.30 (s, 1). Anal. ($C_{11}H_{18}O_3$) C, H.

Alkylation of Senecioic Acid (2) Copper Dienolate with Isoprene Oxide (I). The copper dienolate formed from 5 mmol of senecioic acid and 10 mmol of CuI was treated with 12 mmol (1.00 g) of isoprene oxide. The reaction mixture was stirred for 3 h at −78 °C and then for 0.5 h at 0 °C before being quenched at 0 °C. A total of 0.683 g (74% yield) of material was isolated, and GLC analysis of the methyl esters (column B, 155 °C) revealed four peaks, A (2.6 min), B (3.2 min), C (4.7 min), and D (5.3 min) in a ratio of 30:9:55:6, respectively. Preparative GLC (column D, 15 mL/min helium flow rate, 210 °C) led to separation of the four peaks. Peak A was the α-alkylated material, methyl 6-hydroxy-5-methyl-2-isopropenyl-4-hexenoate: ^{1}H NMR (CCl_4, 90 MHz) δ 5.03 (br t, 1), 4.80 (m, 2), 3.97 (dd, J_1 = 12 Hz, J_2 = 0.9 Hz, 2), 360 (s, 3), 3.20–2.40 (m, 2), 2.30–1.83 (m, 1), 1.73 (m, 7). Anal. ($C_{11}H_{18}O_3$) C, H.

Peak B was found to be the 2*Z*, 6*E*, γ-alkylated compound in which the hydroxyl group was also methylated by the diazomethane used to methylate the acid, methyl (2*Z*,6*E*)-8-methoxy-3,7-dimethyl-2,6-octadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 5.47 (m, 1), 5.27 (br t, 1), 3.80 (s, 2), 3.60 (s, 3), 3.17 (s, 3), 2.73–2.43 (br t, 2), 2.33–1.98 br t, 2), 1.83 (s, 3), 1.67 (s, 3).

Peak C was found to be 2*Z*,6*Z* γ-alkylated material as the free alcohol, methyl (2*Z*,6*Z*)-8-hydroxy-3,7-dimethyl-2,6-octadienoate (cf. 10): ^{1}H NMR (CCl_4, 90 MHz) δ 5.55 (m, 1), 5.20 (br t, 1), 3.95 (s, 2), 3.60 (s, 3), 2.74–2.40 (br t, 2), 2.33–1.95 (br t, 2), 1.97 (m, 4), 1.73 (s, 3). Anal. ($C_{11}H_{18}O_3$) C, H.

Peak D was found to be the 2Z,6E, γ-alkylated material as the free alcohol: ^{1}H NMR (CCl_4, 90 MHz) δ 5.55 (m, 1), 5.33 (br t, 1), 3.83 (s, 2), 3.60 (s, 3), 2.80–2.50 (br t, 2), 2.33–2.07 (br t, 2), 1.87 (s, 3), 1.80–1.60 (m, 4).

Alkylation of Crontonic Acid (3) Copper Dienolate with Epoxide K. The copper dienolate formed from 0.86 g (10 mmol) of crotonic acid and 20 mmol of CuBr·SMe_2 was treated with 20 mmol (1.69 g) of epoxide K. The reaction mixture was stirred for 5 h at −78 °C and for 0.5 h at 0 °C before being quenched at 0 °C. A total of 1.37 g (75% yield) of product was isolated and GLC analysis of the methyl esters (column G, 115–173 °C, 8 °C/min, 1-min postinjection interval) revealed three peaks, A (129 °C), B (138 °C), and C (172 °C) in a ratio of 10:4:86. Preparative GLC (column D, 185 °C for 40 min, then 200 °C) was used to separate the three peaks. Peak A was presumed to be the E,E, γ-alkylated compound with the hydroxyl methylated because on column A, the order of elution was B, A, C, with A having a retention time very similar to that of C. This behavior was observed in the case of the 2Z,6E ester, the methyl ether, and the 2Z,6E ester-free alcohol which were the products of alkylation of senecioic acid with isoprene oxide.

Peak B was found to be the α-alkylated material, methyl 6-hydroxy-2-vinyl-4-heptenoate: ^{1}H NMR (CCl_4, 90 MHz) δ 5.93–5.33 (m, 3), 5.15 (d, 1), 5.00 (m, 1), 4.15 (m, 1), 3.63 (s, 3), 3.16–2.90 (m, 1), 2.67–2.13 (m, 2), 1.40 (s, 1), 1.17 (d, 3).

Peak C was found to be the 2E,6E, γ-alkylated material, methyl (2E,6E)-8-hydroxy-2,6-nonadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.83 (dt, J_1 = 6 Hz, J_2 = 15 Hz, 1), 5.72 (d, J = 15 Hz, 1), 5.50 (m, 2), 4.15 (m, 1), 3.67 (s, 3), 2.23 (m, 4), 1.57 (br s, 1), 1.17 (d, 3).

Alkylation of Copper Dienolate of Tiglic Acid (1) with Epoxide J. The copper dienolate formed from 5 mmol of tiglic acid and 10 mmol of CuBr·SMe_2 was treated with 1.12 g of 77% epoxide J in THF (10 mmol). The reaction mixture was stirred for 3 h at −78 °C and then for 0.5 h at 0 °C before being quenched at 0 °C. A total of 0.728 g (79% yield) of product was isolated, and GLC analysis of the methyl esters (column B, 170–190 °C, 2 °C/min, 1-min postinjection interval) revealed four peaks, A (4.3 min), B (6.2 min), C (7.9 min), and D (9.4 min) in a ratio of 6:14:15:65. Preparative gas chromatography of the methyl esters on column D failed to achieve separation of peaks C and D, but treatment of the methyl esters–alcohols with BSA [N,O-bis(trimethylsilyl)acetamide] gave the methyl esters–trimethyl silyl ethers which were separated by preparative GLC (column E, 15 mL/min helium flow rate, 165 °C). Peak A was presumed to be the α product because of its retention time and the R_f of the free alcohol in several solvent systems.

Peak B was found to be the product of direct attach on C-2 of epoxide J, methyl (2E)-6-hydroxy-2-methyl-5-vinyl-2-hexenoate, and was isolated as the free alcohol from the other three isomers after column chromatography (50% ether/hexane, neutral alumina, grade 1): ^{1}H NMR (CCl_4, 90 MHz) δ 6.57 (br t, 1), 4.80 (br d, 2), 3.63 (s, 3), 3.47 (br d, 2), 2.27 (br d, 2), 1.80 (s, 3), 1.70 (br s, 4).

Peak C was found to be the 2E,6Z, γ-alkylated product, methyl (2E,6Z)-8-[(trimethylsilyl)oxy]-2,6-dimethyloctadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.57 (br t, 1), 3.90 (d, 2), 3.63 (s, 3), 2.17 (m, 4), 1.77 (s, 3), 1.70 (s, 3).

Peak D was found to be the 2E,6E, γ-alkylated product (cf. **9**): ^{1}H NMR (CCl_4, 90 MHz) δ 6.59 (br t, 1), 5.23 (br t, 1), 4.01 (d, 2), 3.63 (s, 3), 2.13 (m, 4), 1.77 (s, 3), 1.60 (s, 3); IR (CCl_4) 2960 (CH), 1720 (C=O), 1655 (C=O), 1268 cm^{-1} (CO). Anal. ($C_{14}H_{26}O_3Si$) C, H.

Alkylation of the Copper Dienolate of Tiglic Acid (1) with 3-Bromo-2-methoxy-1-propene (G). The copper dienolate formed from 5 mmol of tiglic acid and 10 mmol (2.06 g) of CuBr·SMe_2 was treated with 2.5 g of 60% 3-bromo-2-methoxy-1-propene (10 equiv; the remaining 40% consisted of 24% 1-bromo-2-methoxy-1-propene and 17% of 1-bromo-2,2-dimethoxypropane). The reaction mixture was stirred for 1.5 h at −78 °C then for 30 min at 0 °C before being quenched. Product isolation gave 740 mg of alkylated acid (95% yield) that was methylated with diazomethane. GLC analysis (column A, 1-min postinjection interval, 70–300 °C, 20 °C/min) revealed one peak (195 °C) that was identified as the E, γ-alkylated product, methyl (2E)-2-methyl-6-oxo-2-heptenoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.50 (br t, 1), 3.63 (s, 3), 2.43 (m, 4), 2.07 (s, 3), 1.80 (s, 3). An analytical sample was prepared by preparative GLC (column E, 145 °C, retention time of 13 min); IR (CCl_4) 2960 (CH), 1723 (C=O), 1655 (C=C), 1438 (CH_3, asymmetric bending), 1265 cm^{-1} (CO). Anal. ($C_8H_{14}O_3$) C, H.

Alkylation of the Lithium Dienolate of 2-Hexenoic Acid (4) with Allyl Bromide (A). The lithium dienolate of 2-hexenoic acid (4) was generated by the same method used for the lithium dienolate of tiglic acid (1) except that twice as much solvent per millimole of acid was used. Care had to be taken to add the acid very slowly to the lithium diisopropylamide solution to prevent the dilithium salt from precipitating. The lithium dianion of 2-hexenoic acid (205 mg, 1.8 mmol) was treated with 1.2 g (10 mmol) of allyl bromide at 0 °C. The reaction was allowed to warm to room temperature over 1 h and then was quenched with 5% NaOH. Product isolation gave 275 mg (99% yield) of crude acid that was methylated with diazomethane. GLC analysis (column A, 2-min postinjection interval, 75–275 °C, 15 °C/min) revealed four peaks, A (134 °C), B (137 °C), C (150 °C), and D (235 °C) in a ratio of 41:33:16:10. Preparative GLC (column E, 95 °C, gas flow rate of 17 mL/min) afforded samples of peaks A and B together and peak C. Peaks A and B were the E and Z α-alkylated material, methyl 2-allyl-3-hexenoate: ^{1}H NMR (CCl_4, 90 MHz) δ 5.90–5.30 (m, 3), 5.27–4.83 (m, 2), 3.63 (S, 3), 3.47–2.77 (m, 1), 2.63–1.87 (m, 4), 1.00 (t, 3). Anal. ($C_{10}H_{16}O_2$) C, H.

Peak C was the 2E, γ-alkylated product, methyl (2E)-4-ethyl-2,6-heptadienoate (cf. **16**): ^{1}H NMR (CCl_4, 90 MHz) δ 6.63 (m, 1), 5.87–5.33 (m, 2), 5.00 (d, 1), 4.85 (m, 1), 3.63 (s, 3), 2.11 (d, 3), 1.67–1.15 (m, 2), 0.87 (t, 3). Anal. ($C_{10}H_{16}O_2$) C, H.

Peak D was later found to have the same retention time as structure **16** isolated from the alkylation of the copper dienolate of 2-hexenoic acid with allyl bromide (see below).

Alkylation of the Copper Dienolate of 2-Hexenoic Acid (4) with Allyl Bromide (A). By use of the general method described for the generation of the tiglic acid copper dienolate from the lithium dienolate, the copper dienolate formed from 200 mg (1.75 mmol) of 2-hexenoic acid (4) and 720 mg of CuBr·SMe_2 was treated with 1.2 g (10 mmol) of allyl bromide. Product isolation followed by short-column chromatography (silica, ether) gave 179 mg (64% yield) of crude acid that was methylated with diazomethane. GLC analysis (column A, 2-min postinjection interval, 75–275 °C, 15 °C/min) revealed four peaks, A (134 °C), B (137 °C), C (150 °C), and D (235 °C) in a ratio of 11:9:49:31. Preparative GLC (column E, 118 °C for 40 min, then 200 °C, gas flow rate of 17 mL/min) led to isolation of peaks C and D. Peaks A and B had the same retention time as that of material shown above to be E and Z α-alkylated products. Peak C was found to be the 2E, γ-alkylated material discussed previously. Peak D was found to be dimethyl 2-(1-buten-1-yl)-3-(1-hexen-4-yl)-glutarate (**15**): mass spectrum (10 eV), m/e (relative intensity) 296 (M^+, 3.6), 222 (64.1), 183 (69.3), 182 (76.2), 128 (100), 127 (42.3), 109 (77.2); ^{1}H NMR (CCl_4, 220 MHz) δ 5.83–5.10 (m, 3), 4.96 (m, 2), 3.60 (overlapping singlets, 6), 2.88 (m, 1), 2.50–1.87 (m, 6), 1.19 (m, 4), 0.97 (t, 3), 0.85 (br t, 3).

Alkylation of the Lithium Dienolate Derived from 2-Hexenoic Acid (4) with Dimethallyl Bromide (B). The lithium dienolate derived from 200 mg (1.75 mmol) of 2-hexenoic acid (4) was treated with 1.4 g (7 mmol) of dimethallyl bromide at 0 °C. The reaction was stirred for 1 h with warming to room temperature. Product isolation gave 256 mg (80% yield) of crude acid that was methylated with diazomethane. GLC analysis (column A, 2-min postinjection interval, 75–275 °C, 15 °C/min) revealed three peaks: A (157 °C), B (175 °C), and C (250 °C) in a ratio of (A + B):C of 69:31. Further GLC analysis (column F, 130 °C) revealed that peak A actually consisted of two peaks with a ratio of A_1:A_2:B of 51:27:22. Preparative GLC (column E, 130 °C, gas flow rate of 17 mL/min) led to isolation of peaks A and B.

Peak A was found to be the E and Z α-alkylated product, methyl 2-(1-buten-1-yl)-5-methyl-4-hexenoate: ^{1}H NMR (CCl_4, 90 MHz) δ 5.57–5.07 (m, 2), 4.97 (br t, 1), 3.63 (s, 3), 3.20 (dd, J_1 = 6 Hz, J_2 = 15 Hz, 1), 2.75–1.85 (m, 4), 1.69 (s, 3), 1.60 (s, 3), 0.98 (t, 3). Anal. ($C_{12}H_{20}O_2$) C, H.

Peak B was found to be the 2E-γ-alkylated product, methyl (2E)-4-ethyl-7-methyl-2,6-octadienoate: ^{1}H NMR (CCl_4, 90 MHz) δ 6.63 (m, 1), 5.61 (d, J = 15 Hz, 1), 4.99 (br t, 1), 3.63 (s, 3), 2.05

(m, 3), 1.69 (s, 3), 1.59 (s, 3), 1.59–1.10 (m, 2), 0.87 (t, 3).

Peak C was assumed to have the structure corresponding to **15** with two more methyl groups because of its GLC retention time.

Alkylation of the Copper Dienolate of 2-Hexenoic Acid (4) with Dimethallyl Bromide (B). The copper dienolate formed from 200 mg (1.75 mmol) of 2-hexenoic acid and 720 mg $CuBr \cdot SMe_2$ was treated with 1.40 g (7 mmol) of dimethallyl bromide. Product isolation gave the crude acid that was methylated with diazomethane. GLC analysis (column A, 2-min postinjection interval, 75–275 °C, 15 °C/min) revealed four peaks, A (157 °C), B (164 °C), C (175 °C) and D (250 °C) in a ratio of (A + B + C):D of 48:52. Further GLC analysis (column F, 130 °C) revealed that peak A consisted of two peaks (A_1 and A_2, retention times 8.6 and 9.2 min), that peak B had a retention time of 10.1 min, and that peak C had a retention time of 14.2 min; the ratio of A_1:A_2:B:C was 34:25:13:28. Peak A had the same retention time as that of material previously shown to be the *E* and *Z* α-alkylated products. Peak C had the same retention time as that of the material previously shown to be the 2*E* γ-alkylated product. Because of its retention time, peak B was presumed to be the γ S_N2' isomer, and peak D was assumed to be the dimethylated structure corresponding to **15**.

Registry No. **1**, 80-59-1; **2**, 541-47-9; (*E*)-**3**, 107-93-7; *cis*-**4**, 1577-28-2; *trans*-**4**, 13419-69-7; *cis*-**4** methyl ester, 13894-64-9; *trans*-**4** methyl ester, 13894-63-8; (*E*)-**6** methyl ester, 75716-89-1; (2*E*,6*E*)-**7** methyl ester, 75716-90-4; (*E*)-**8** methyl ester, 75716-91-5; (2*E*,6*Z*)-**9** methyl ester trimethylsilyl ether, 75716-92-6; (2*E*,6*E*)-**9** methyl ester trimethylsilyl ether, 75716-93-7; (2*Z*,6*Z*)-**10** methyl ester, 75716-94-8; (2*Z*,6*E*)-**10** methyl ester, 75716-95-9; **15**, 75716-96-0; (*E*)-**16** methyl ester, 75716-97-1; A, 106-95-6; B, 870-63-3; C, 6138-90-5; D, 25996-10-5; E, 75716-98-2; F, 75716-99-3; G, 26562-24-3; H, 930-22-3; I, 1838-94-4; J, 7437-61-8; K, 6790-37-0; trimethyl phosphonoacetate, 5927-18-4; butanal, 123-72-8; ethyl (*Z*)-3-methyl-2-hexenoate, 22210-22-6; (*Z*)-3-methyl-2-hexenol, 30804-76-3; (*E*)-3-methyl-2-hexenol, 30801-96-8; ethyl (2*E*)-3-methyl-2-hexenoate, 22210-21-5; methacrolein, 78-85-3; THF, 109-99-9; piperylene, 504-60-9; methyl (2*E*,6*E*)-farnesenate, 3675-00-1; methyl (4*E*)-5,9-dimethyl-2-(2-propenyl)-4,8-decadienoate, 61264-06-0; methyl (2*Z*,6*Z*)-farnesenate, 4176-78-7; methyl (2*Z*,6*E*)-farnesenate, 4176-77-6; methyl (2*E*)-2,5,9-trimethyl-5-vinyl-2,8-decadienoate, 75717-00-9; methyl (2*E*,6*E*)-2,7,11-trimethyl-2,6,10-dodecatrienoate, 55786-72-6; methyl (2*E*,6*Z*)-2,7,11-trimethyl-2,6,10-dodecatrienoate, 55786-73-7; methyl (2*E*)-2,5-dimethyl-5-propyl-2,6-heptadienoate, 75717-01-0; methyl (2*E*,6*E*)-2,7-dimethyl-2,6-decadienoate, 75717-02-1; methyl (2*E*,6*Z*)-2,7-dimethyl-2,6-decadienoate, 75717-03-2; propyl iodide, 107-08-4; methyl 2-methyl-2-propyl-3-butenoate, 75717-04-3; ethyl iodide, 75-03-6; methyl 2-methyl-2-ethyl-3-butenoate, 75717-05-4; methyl iodide, 74-88-4; methyl 2,2-dimethyl-3-butenoate, 19757-86-9; methyl (2*E*)-2-methyl-2-pentenoate, 1567-14-2; acetaldehyde, 75-07-0; methyl 3-hydroxy-2-methyl-2-vinylbutanoate, 75717-06-5; methyl 2-bromoacetate, 96-32-2; dimethyl 2-methyl-2-vinylsuccinate, 70912-92-4; benzyl bromide, 100-39-0; methyl 2-benzyl-2-methyl-3-butenoate, 75717-07-6; methyl (2*E*)-2-methyl-5-phenyl-2-pentenoate, 75717-08-7; methyl (4*E*)-6-hydroxy-2-(isopropenyl)-4-hexenoate, 75717-09-8; methyl (2*Z*,6*E*)-8-hydroxy-3-methyl-2,6-octadienoate, 75750-97-9; methyl (2*Z*,6*Z*)-8-hydroxy-3-methyl-2,6-octadienoate, 75717-10-1; methyl (2*E*,6*Z*)-8-hydroxy-3-methyl-2,6-octadienoate, 75717-11-2; methyl (2*E*,6*E*)-8-hydroxy-3-methyl-2,6-octadienoate, 75717-12-3; methyl (4*E*)-6-hydroxy-2-vinyl-4-hexenoate, 75717-13-4; methyl (2*E*,6*E*)-octadienoate, 25172-05-8; methyl (2*E*,6*Z*)-2,7-dimethyl-8-hydroxy-2,6-octadienoate, 75717-14-5; methyl (2*E*,6*E*)-2,7-dimethyl-8-hydroxy-2,6-octadienoate, 75717-15-6; methyl 6-hydroxy-5-methyl-2-isopropenyl-4-hexenoate, 75717-16-7; methyl (2*Z*,6*E*)-8-methoxy-3,7-dimethyl-2,6-octadienoate, 75717-17-8; methyl (2*E*,6*E*)-8-methoxy-2,6-nonadienoate, 75717-18-9; methyl 6-hydroxy-2-vinyl-4-heptenoate, 75717-19-0; methyl (2*E*,6*E*)-8-hydroxy-2,6-nonadienoate, 75717-20-3; methyl (2*E*)-2-methyl-6-oxo-2-heptenoate, 75717-21-4; methyl (*E*)-2-allyl-3-hexenoate, 62243-61-2; methyl (*Z*)-2-allyl-3-hexenoate, 75717-22-5; methyl (*E*)-2-(1-buten-1-yl)-5-methyl-4-hexenoate, 75717-23-6; methyl (*Z*)-2-(1-buten-1-yl)-5-methyl-4-hexenoate, 75717-24-7; methyl (2*E*)-4-ethyl-7-methyl-2,6-octadienoate, 75717-25-8; methyl 2,5-dimethyl-6-hydroxy-2-vinyl-4-hexenoate, 75717-26-9; methyl 2,4-dimethyl-6-hydroxy-2-vinyl-4-hexenoate, 75717-27-0; methyl 2-methyl-2-vinyl-4-pentenoate, 66052-30-0; methyl (*E*)-2-methyl-2,6-heptadienoate, 66052-31-1; CuI, 7681-65-4; $CoBr_2$, 7789-43-7; $MgCl_2$, 7786-30-3; $MnCl_2$, 7773-01-5; $AgBF_4$, 14104-20-2; $FeCl_2$, 7758-94-3; $ZnCl_2$, 7646-85-7; $NiBr_2$, 13462-88-9; CdI_2, 7790-80-9; $HgCl_2$, 7487-94-7; Li, 7439-93-2.

Ozonation of Organic Compounds. 4. Ozonolysis of α,β-Unsaturated Carbonyl Compounds in Protic Solvents

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Ozonolysis of mesityl oxide, crotonic acid, and maleic acid was carried out in protic solvents such as methanol, *tert*-butyl alcohol, water, and acetic acid at 30 °C. Anomalous ozonolysis products were obtained in every solvent except in methanol and the ratio of anomalous ozonolysis to total ozonolysis was determined. It was suggested that these anomalous products were formed mostly by the rearrangement of carbonyl oxides of methylglyoxal and glyoxylic acid, **2c** and **2d**, because α-acetoxyalkyl and α-carboxylalkyl hydroperoxides were relatively stable at 30 °C.

It is well recognized that the ozonolysis of olefins in protic solvents proceeds as shown in Scheme I by a Criegee mechanism.[1,2] It has been argued whether primary ozonide **1** decomposes to carbonyl oxide **2** or singlet biradical **3**.[2,3] However, **2** is considered to be more stable than **3** in protic solvents.[4] In methanol, therefore, **2** reacts with alcohol to form methoxyalkyl hydroperoxides **4w**.[1] Similarly hydroxyalkyl and acetoxyalkyl hydroperoxides (**4x** and **4y**, respectively) are produced in the ozonolysis in water[5] and acetic acid,[6] respectively. Accordingly, *tert*-butylalkyl hydroperoxide **4z** must be formed when ozo-

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