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Selective γ Alkylation of Dienolate Anions Derived from α,β-Unsaturated Acids. Applications to the Synthesis of Isoprenoid Olefins[1]

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Abstract: Lithium dienolates derived from α,β-unsaturated carbonyl compounds generally undergo alkylation reactions nearly exclusively at the α (rather than the γ) carbon. Changing the counterion from lithium to copper(I), however, has a remarkable effect on the alkylation regioselectivity of these dienolates. A systematic investigation has been made of the reaction of dienolates derived from (*Z*)- and (*E*)-3-methyl-2-hexenoic (**2a** and **3a**) and crotonic (**4a**), senecioic (**5a**), tiglic (**6a**), and angelic (**7a**) acids with a variety of allylic electrophiles. The lithium dianions all undergo exclusive α alkylation, but the dicopper dianions undergo γ-selective alkyation (62–99%). (Lower γ selectivities were found in a previous study of the corresponding esters.[16]) The γ-substituted products of the acids **4a, 6a,** and **7a** were exclusively of the *E* geometry, while 50% and 81% *Z* isomers were found with the acids **5a** and **2a,** respectively. Allylic electrophiles that are unsubstituted at the γ carbon react with the copper dienolates mainly in an S$_N$2′ fashion, giving products in which the allylic portion has been transposed. Those electrophiles that are γ disubstituted react exclusively by direct (S$_N$2) displacement, but those with only one substituent undergo a mixture of S$_N$2 and S$_N$2′ attack. The γ-selective alkylation of copper dienolates can be used as a convenient prenologation process in natural product synthesis. Farnesoic acid has been synthesized from geranyl bromide, and *dl*-lanceol, from an allylic bromide derived from limonene.

Conceptually, one of the simplest approaches to the synthesis of isoprenoid 1,5-polyolefins[2] is the conjoining of two allylic units containing the appropriate olefinic stereochemistry. The biosynthetic condensation of isopentenyl pyrophosphate with an allylic pyrophosate is, in fact, just such a transformation. In terms of laboratory synthesis, however, this approach is fraught with difficulties. If the reaction involves the attack upon an allylic electrophile by an allylic nucleophile, there is positional ambiguity at both reaction centers, as allylic nucleophiles have ambident character,[3] and allylic electrophiles can undergo S$_N$2 or S$_N$2′ attack.[4] Furthermore, the olefinic stereochemistry of the nucleophile is subject to ready isomer equilibration,[5] and the geometric integrity of the electrophile is not certain. When the coupling is radical in nature (Wurtz type[6]) or does not proceed via clearly identifiable electrophiles and nucleophiles (promoted by nickel,[7] titanium,[8] or other metals[9]), additional complications arise in terms of the possibilities for symmetrical vs. unsymmetrical coupling. Solutions to these problems have taken various forms.

We have found that the crossed nature of a Wurtz-type coupling can, in some cases, be improved by the selective generation of an allylic organolithium reagent by reacting allylic mesitoates with lithium metal in tetrahydrofuran, with subsequent coupling to an allylic bromide present in situ.[10] Although the yields of cross-coupled products from this procedure are reasonably high, positional and double-bond isomers of the mesitoate-derived allylic portion (nucleophile) are still produced.

Approaches using a charge-stabilized allylic organometallic reagent,[11,12] generated, for example, from an allylic sufide or phosphonium salt, have been more successful; these reagents can be made to alkylate predominantly at the charge-stabilized site, the final 1,5-diene being generated by reductive cleavage of the sulfide or phosphonium substituent. Although they have not been investigated in depth, the stereochemistry of the anion-derived unit seems to be preserved in the coupling, and double-bond transposition is not a serious problem during the reductive cleavage.

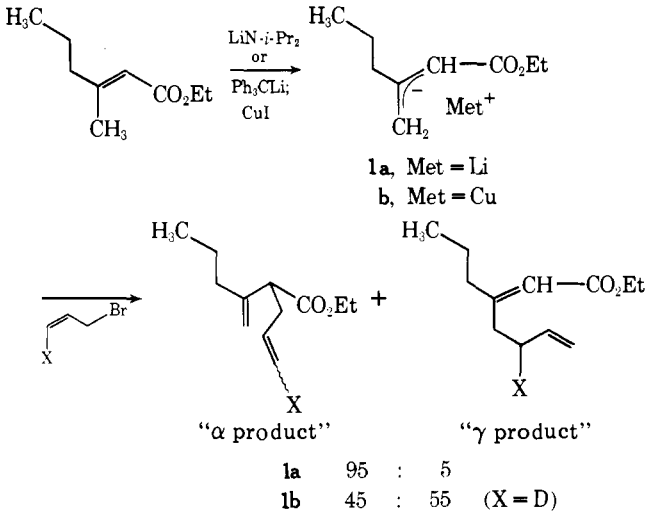
A very different approach to allylic–allylic coupling utilizes [3,3] sigmatropic rearrangements. The Claisen rearrangement,[13] particularly the vinyl acetal modification of Johnson,[13b] has been applied widely to the construction of trisubstituted olefinic systems in a stereoselective fashion; this reaction, however, as well as the related Carroll rearrangement of allylic esters,[14] requires a subsequent series of steps to convert the ketonic or ester products into 1,5-polyenes. The ingenious Claisen–Cope rearrangement of Thomas[15] provides an efficient synthesis of isoprenoid 1,5-dienes.

Although some of the above methods are attractive in terms of their stereoselectivity, many of them suffer from two basic disadvantages. First, the rearrangement reactions are only highly stereoselective when the isoprenoid chain is being constructed in a head-to-tail direction. Second, these and some of the other methods do not produce a product diene that is functionalized in an optimal manner; often several subsequent steps are required in order to transform it into a "natural" type of functionalization.[13a-c]

We have been interested in an allylic–allylic coupling route to isoprenoid 1,5-dienes, which is based on the selective γ alkylation of unsaturated carbonyl compounds. A principal advantage of this approach is that a "natural" oxygenation pattern (at the chain terminus) is maintained whether chain growth proceeds from tail-to-head or vice versa. In order to establish the feasibility of such an approach, many questions concerning positional and stereoselectivity in the γ-alkylation process must, of course, be elucidated.

We have recently reported[16,17] that the copper dienolates (**1b**) derived from unsaturated esters, unlike the lithium enolates (**1a**), will in some cases undergo selective γ alkylation with allylic halides (Scheme I). The action of copper ion is unique, as the alkylation of the alkali metal enolates gives almost exclusively α-alkylated products. Further studies showed that the extent of γ alkylation depended critically on the solvent and substitution pattern of both the dienolate and allylic halide. An additional complication, which made this ester alkylation approach of questionable importance for the preparation of natural terpenoid 1,5-dienes, was the tendency for SN2′ attack upon the allylic halide by the γ center of the copper dienolate. This was evident when alkylation was done with 3-deuterioalkyl bromide (X = D) and it resulted in a transposed geometry in the electrophile-derived portion of the resulting γ-substituted diene ester (Scheme I).

Scheme I. γ Alkylation of Unsaturated Esters



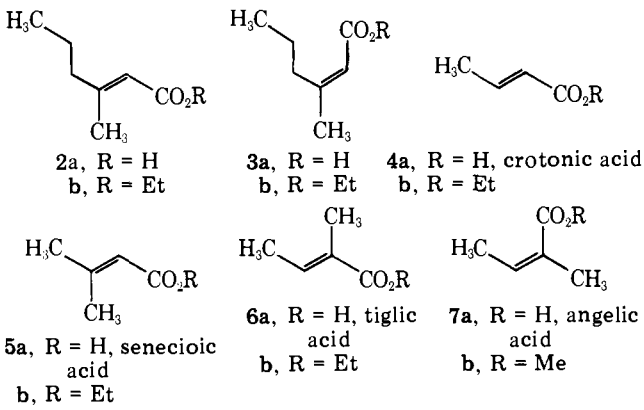
There were a number of reports that suggested that the anionic species derived from α,β-unsaturated acids might undergo alkylation with increased γ regioselectivity. Pfeffer[18,19] found that the dianion derived from crotonic *acid* gave a 60:40 ratio of α- to γ-alkylation products with methyl iodide, while other workers[20] had shown that alkylation of crotonic *ester* enolates gave less than 5% of γ substitution.

The mixed lithium–sodium dianion of senecioic acid was reported by Cainelli[21] to alkylate or condense exclusively at the α position when THF was the solvent, but to give up to 35% γ-alkylated product in the mixed solvent system tetrahydrofuran (THF)/hexamethylphosphoramide (HMPA) (80:20).

A related system, 2-butynoic acid, could be alkylated as the dianion to give a 32:68 α:γ product ratio.[22] In contrast, quenching of methyl 2-butynoate anion with water produced exclusively the allenic ester, methyl 2,3-butadienoate, which arose from protonation at the α carbon.[23] Since the completion of our work, Wu and Snieckus[24] have reported that the dianion derived from an unsaturated carboxamide could be alkylated preferentially at the γ site.

In this report we describe studies on the alkylation of the dienolate dianions derived from the α,β-unsaturated acids shown below (Scheme II). The copper salts of these dianions show a much greater tendency for selective γ alkylation than those derived from the esters. Particular attention has been focused on the stereochemical behavior of the enolate anions and the composition of geometric isomers of the resulting enoate systems. In certain cases, selective γ alkylation can be achieved either without transposition or with complete transposition of the allylic halide; in these instances, or where transposition is of no consequence, γ alkylation of unsaturated acid copper dienolate anions is a very convenient method for isoprenoid natural product synthesis. Syntheses of geranoic and farnesoic acids and *dl*-lanceol are described as illustrations of the utility of these reactions.

Scheme II



Scheme III

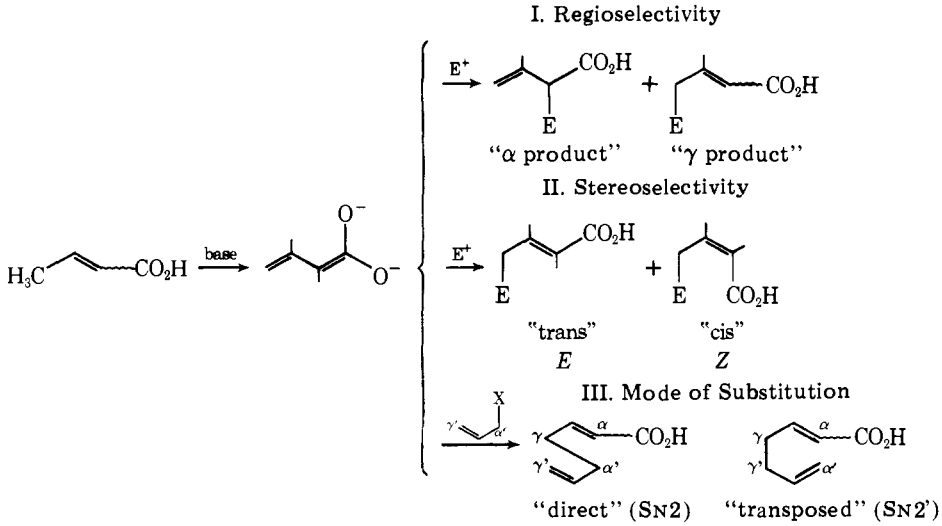
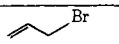
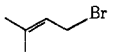
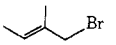
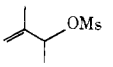
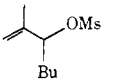
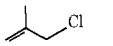


Table I. Regioselectivity, Stereoselectivity, and Mode of Substitution in the Alkylation of Acid Dienolate Anions

Unsaturated system	Alkylating agent	Metal	Regioselectivity[a] α	Regioselectivity[a] γ	γ stereoselectivity,[b] cis/trans	Mode of γ substn[c]	% yield[d]
2	A = 	Li	98 (95)	2 (5)			
		Cu	19 (45)	81 (55)	81/19	T	80–83
	B = 	Li	99 (95)	1 (5)			
		Cu	38 (95)	62 (5)	85/15	D	60–70
3[e]	A	Cu	21	79	85/15	T	70–80
4	A	Li	98	2			90
		Cu	3	97	0/100	T	97
5	A	Li	96	4			93
		Cu	7	93	50/50	T	(90)
	B	Li	99	1			
		Cu	10	90	45/55	D	85
6	A	Li	100 (95)	0 (5)			80–90
		Cu	4 (95)	96 (5)	0/100	T	(95)
	B	Cu	15	85	0/100	D	(68)
	C = 	Cu	0	100	0/100	D-34% T-66%	[78]
	D = 	Cu	0	100	0/100	D-26% T-74% (6Z-79%, 6E-21%)[f]	78
	E = 	Cu	0	100	0/100	T(6E > 95%)[f]	[55]
	F = 	Cu	4	96	0/100		(87)
7	A	Cu	3	97	0/100	T	

[a] Determined by GLC and ^{1}H NMR analysis of the corresponding methyl esters. See Experimental Section. [b] Stereoselectivity refers to geometry about the 2,3-double bond in the γ-alkylated product (see Scheme IV). Data in parentheses are for the corresponding esters. See ref 16. [c] Mode of substitution refers to the attack on the allylic bromide. D = direct (SN2) and T = transposed (SN2'). [d] Yields are from the weight of the total isolated acid (base-soluble) fraction. Yields in parentheses are determined by GLC with an internal standard. Yields in square brackets are of isolated, purified product. [e] Acid 3a contains ca. 15% of 2a. [f] Data are explained more fully in Scheme VII.

Results

The regioselective and stereoselective consequences of the reaction of a dienolate dianion with an allylic electrophile can be considered in three stages (see Scheme III). The first stage concerns the distribution of products between the α-alkylated and γ-alkylated types (regioselectivity); the second deals with the geometry (cis *Z* or trans *E*) of the γ-alkylated product (stereoselectivity); and the third deals with the mode of substitution experienced by the allylic electrophile (direct or transposed). The presentation of the results of our study will follow the outline of this scheme.

Regioselectivity in the Alkylation of Dienolate Dianions. The distribution of α- vs. γ-substituted products, subsequent to the reaction of the copper or lithium dienolate derivatives with various allylic electrophiles, is summarized in Table I. Data from our previous study[16] of the alkylation of the corresponding esters are given in parentheses. As noted previously,[16] the γ-substituted products do not arise via a Cope rearrangement from the α-substituted isomers.

There are several notable patterns in the regioselectivity data. All the lithium enolates give predominantly α-alkylated products. Despite the reports of others,[18,21,24] we find no evidence that the acid-derived lithium dienolates give increased γ selectivity when compared to the esters, in the cases where we have made comparisons (see Table I, **2** and **6**).

The preference for selective γ alkylation with the copper dienoates, while evident to some extent in the ester series (**2A**), is most notable in the acids. Of particular significance is the nearly complete reversal of product distributions seen upon going from tiglic ester to tiglic acid (**6A**) and the acceptable yields of γ-alkylated products in the systems alkylated with the 3,3-disubstituted allylic bromide (**2B**, **5B**, **6B**). These are systems that are of potential use in the synthesis of naturally-occurring isoprenoid dienes.

In general, high yields of the isomeric product mixtures were obtained, and few problems were encountered in their separation. All the isomers (save the *Z* and *E* γ-substituted isomers from **2A** and **3A**, vide infra) were cleanly resolved on analytical or preparative GLC, and this technique was generally used for isomer analysis. With care, liquid chromatographic separation between the α- and γ-substituted derivatives and the γ-cis and trans isomers on a preparative scale could be achieved.

The success of the selective γ alkylation of the copper dienolate dianions depends quite critically upon the homogeneity of the reaction mixture and upon adequate temperature control. Although we have experienced no difficulty in generating the reagents derived from the acids **2a–4a, 6a** and **7a,** problems were encountered with the senecioic acid system (**5A**). Generation of the dilithium salt with 2 equiv of lithium diisopropylamide in THF at −78 °C produced a white precipitate. If this suspension was reacted further with cuprous iodide, the γ-selective alkylation was severely compromised. Addition of hexamethylphosphoramide to the insoluble dilithium enolate did solubilize it, but when this species was converted to the dicopper salt, it gave predominantly α alkylation.

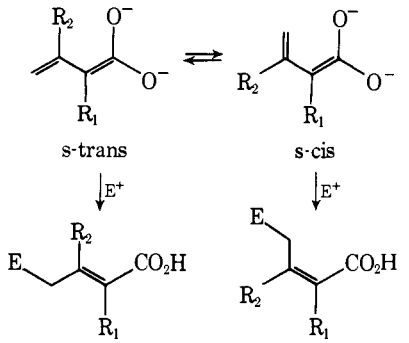
A soluble dianion of this system with suitable reactivity could be prepared using mixed counterions.[21] The sodium carboxylate (from the acid and sodium hydride) was treated with 1 equiv of lithium diisopropylamide and the homogeneous dianion was then converted to the copper salt with 2 equiv of cuprous iodide.

Occasionally, the generation of a suitably reactive dicopper dienolate was erratic; however, characteristic color changes enabled one to follow this process. After formation of the dilithium or lithium–sodium dianion, which should be a clear,

yellow solution, free from suspended or colloidal matter, the reaction mixture is cooled to −78° and cuprous iodide is added with stirring. After 1-2 h at this temperature, the slurry should be pale to bright yellow. If it is grayish white, the product ratio will more closely resemble that of the lithium dianion (mainly α substitution), and if it is black, starting material will be recovered. One cause of unsuccessful copper complex formation was found to be the use of old bottles of butyllithium, regardless of the titer. (The butyllithium is used to generate the lithium amide base which in turn generates the acid dianion.) Once the copper dienolate has been successfully generated, the appropriate halide is added at −78° and the temperature is allowed to warm overnight to room temperature.

Stereochemistry of the γ-Substituted Enoates. The ratio of cis to trans isomers (stereoselectivity) that results from the γ alkylation of the various acids is also summarized in Table I. Although the structures of the products from dimethacrylic acid (**5a**) do not permit one to decide whether the product mixtures arise from isomerization of the dienolate between s-cis and s-trans forms (Scheme IV) or from competitive deprotonation from the two γ-methyl groups, the fact that both the isomeric acids tiglic (**6a**) and angelic (**7a**) and **2a** and **3a** give the same product mixtures clearly establishes the ready interconversion of the two enolate forms. There is, in fact, a reasonable progression in the stereoselectivity of the γ-alkylation process that follows the expected relative stability of s-cis and s-trans enolates. As the size of substituent R_2 is increased from hydrogen to methyl to propyl, the percent cis product increases from 0 to 50 to 81%. This presumably represents increasing allylic strain (between R_2 and O^- in the s-trans form) that is reflected as an increased transition state energy upon going to the γ-trans product.

Scheme IV



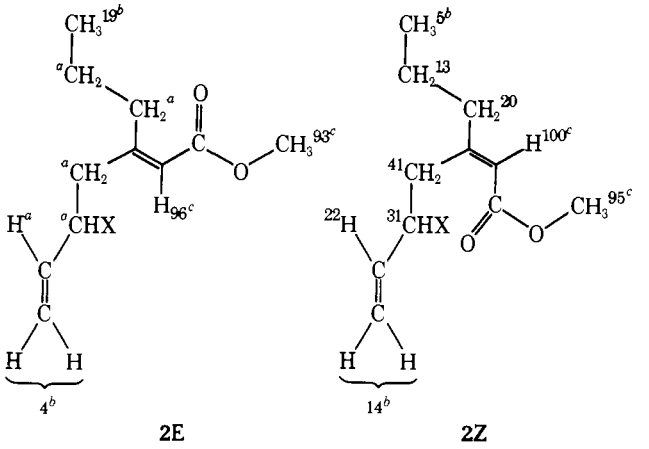
Acid	R_1	R_2	Trans/cis
4a, **6a**, or **7a**	H or CH_3	H	100/0
5a	H	CH_3	50/50
2a or **3a**	H	$CH_3CH_2CH_2$	19/81

Although acids **2a** and **3a** present two alternative sites for γ deprotonation, methylene and methyl, the products found are derived exclusively from methyl deprotonation. Thus, there is no evidence for an internal base effect which would lead to preferential deprotonation from the methylene center in **3a**.

While the isomeric products derived from acids **4a**–**7a** are readily separable by preparative and analytical GLC and have distinct and unambiguous NMR spectra (vide ante), the γ-substituted product isomers obtained from **2a** and **3a**, have nearly identical ^1H NMR spectra and are not easily separable by GLC. The distribution of isomeric forms, however, can readily be ascertained using a europium shift reagent tris(1,1,1,2,2,3,3,7,7,8,8,9,9,9-tetradecafluoro-4,6-nonadione)europium(III) ($Eu(tfn)_3$; Scheme V).

Quantitation of the stereoisomeric mixture could be done by comparison of the integrated intensities of the signals due

Scheme V



[a] Signals not definitively identifiable. [b] Signals useful for isomer identification (X = H, D). [c] Signals useful for isomer quantitation. The numbers represent the shift sensitivities relative to the C-2 hydrogen on the **2Z** isomer.

to the two methyl groups (ester and chain terminus) and the vinyl hydrogen at C-2; the signals of each isomer are nicely separated in the presence of the shift reagent, and by all three methods an 81:19 mixture was evident. The assignment of the major isomer as **2Z** can be made in two ways. The relative shift sensitivities of the different hydrogens of the two isomers (see Scheme V) indicated that the more abundant isomer had a larger shift in the terminal vinyl hydrogens and smaller shift in the chain terminal methyl, and thus was **2Z**. The ^1H NMR of the specifically deuterated products also confirmed this assignment (note position of X = D in Scheme V). It was clearly evident, even in the absence of shift reagents, that the signal of the downfield γ-methylene group (i.e., the one cis to the carbomethyoxy group) in the major isomer changed from a triplet to a doublet upon deuterium substitution, as expected for **2Z**, but not **2E**.

Mode of Substitution. From our previous work on the alkylation of lithium and copper dienolates derived from esters,[16] it was apparent that there is a tendency for γ alkylation to proceed by an SN2′ attack on the allylic double bond, giving γ-substituted products in which the electrophile-derived portion has undergone double-bond transposition. Evidence of this process was obtained by NMR analysis of products derived by alkylation with (*Z*)-3-deuterioallyl bromide (Scheme I); further, the reluctance of 3,3-dimethylallyl bromide to undergo γ attack in the ester series was consistent with the steric hindrance involved in SN2′ attack in this system. The lithium derivatives showed less preference for double-bond transposition in γ alkylation.[16] (The extent of γ alkylation with the lithium derivatives is, of course, very small.)

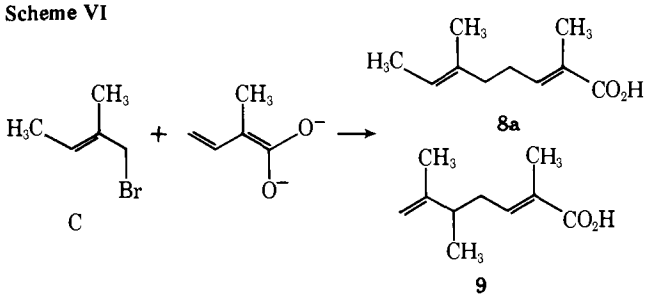
Studies using the same specifically labeled deuterioallyl bromide in the acid series gave similar results. The γ-substituted products obtained from the reaction of acids **2a**–**6a** with deuterioallyl bromide all had undergone complete double-bond transposition in the allyl portion. In contrast to the ester series, the acid dianion copper salts underwent γ alkylation with 3,3-dimethylallyl bromide in the three cases that were studied (**2a**, **5a**, and **6a**). It was thus with considerable interest that we examined in detail the question of double-bond transposition in these cases.

GLC analysis of the products derived from senecioic acid (**5a**) and 3,3-dimethylallyl bromide (B) indicated that only two γ-substituted products were present. NMR analysis showed these to be the 2,3 cis and trans isomers, both of which had the allylic bromide portion incorporated *without double-bond transposition.* It is apparent in the acid series, where γ-alkylation products predominate for primarily electronic reasons

(see Discussion), that the steric demands of the dimethylallyl electrophile are sufficient to prevent SN2′ attack; γ alkylation then proceeds without double-bond transposition by a different mechanism.

The results of the reaction of acid **6a** with 2,3-dimethylallyl bromide (C) are more complex (Scheme VI). GLC analysis

Scheme VI



of the reaction mixture showed two γ-substituted products (**8a** and **9**). These were both 2,3 trans isomers, but they differed in the methyl substitution pattern in the electrophile-derived portion of the diene, the result of partial double-bond transposition in the substitution process. This result is not surprising, as the unsubstituted system (A) undergoes complete transposition, but the 3,3-dimethyl-substituted system (B), only direct displacement.

As the generation of a mixture of structural isomers is clearly a disadvantage in terms of the preparative utility of this reaction, we investigated an alternative approach to the synthesis of the system which bears the distribution of methyl substituents found in natural isoprenoid 1,5-dienes (**8a**).

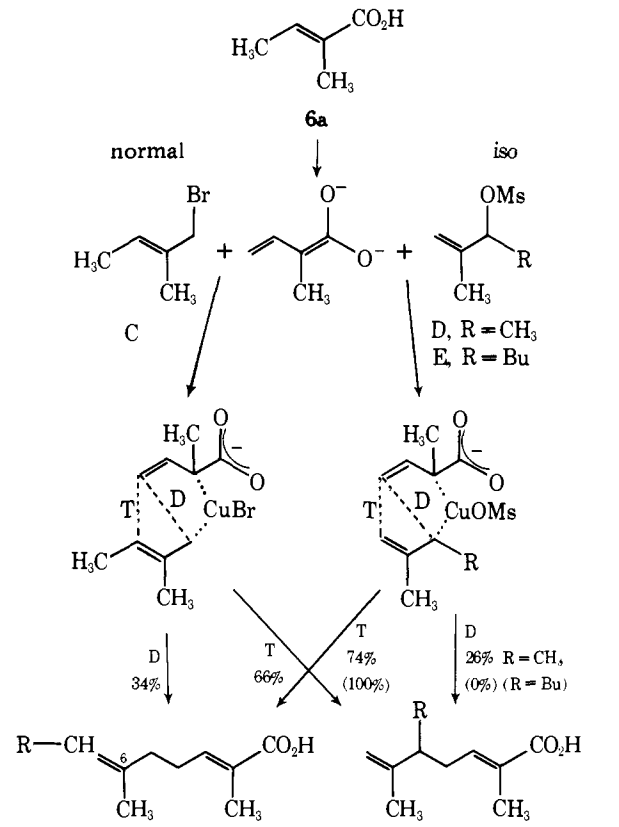
The isomeric allylic bromide, 1,2-dimethylallyl bromide, was sought in place of C in the hope that removal of a substituent from the γ′ position (Scheme VII, normal) and addition of it to the α′ position (Scheme VII, iso) should lead to complete double-bond transposition in the substitution process. An additional ambiguity in this approach is the generation of a new olefinic center at C-6, the stereochemistry of which depends upon the geometry of the SN2′ displacement process.

In practice, it is very difficult to prepare 1,2-dialkyl allylic bromides because they readily undergo rearrangement to the 2,3-dialkyl isomers. In fact, despite reports by Snyder[25] that 1,2-dialkyl allylic chlorides could be prepared cleanly using triphenylphosphine–carbon tetrachloride, we were unable to get the desired allylic chloride completely free from its allylic isomer (type C) and other aliphatic impurities. Further, difficulty was encountered in freeing the volatile chloride from carbon tetrachloride, which had a detrimental effect on the course of the coupling reaction.

These problems were solved simply by using the easily obtainable methanesulfonate (D), prepared from the alcohol with methanesulfonyl chloride–triethylamine and used without purification.[26] The results are summarized in Scheme VII. Repositioning of the methyl substituent from the γ′ (C) to the α′ (D) site causes a significant increase in the extent of SN2′ attack (from 66% in C to 74% in D), so that the γ-substituted product with the desired structure **8** now predominates. However, the stereoselectivity of the formation of the new 6,7 double bond in the product **8** (derived from **6a** and D by SN2′ attack) is low; a 71:29 cis/trans mixture is obtained. (The difference in leaving groups in C (Br) and D (OMs) prevents direct comparison of the effect of the methyl repositioning on the extent of SN2 vs. SN2′ reaction.)

Consideration of the probable transition state for γ alkylation with allylic transposition in this system **6a** + D (Scheme VIII) indicates that the geometry of the 6,7 double bond is determined by the positioning of the α′-alkyl group R in a pseudoequatorial (gives *E*) vs. a pseudoaxial (gives *Z*) configuration. Where alkylation was done using 1-methyl-2-

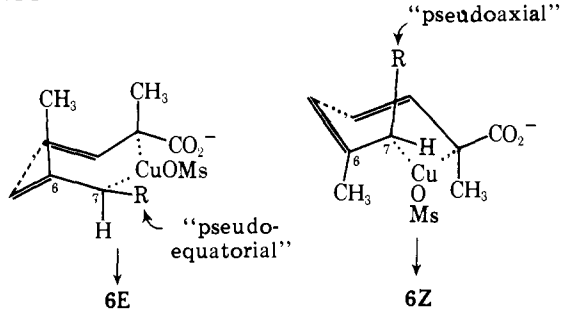
Scheme VII



Electrophile	Δ⁶ in 8 *Z*	Δ⁶ in 8 *E*
C	0	100
D	71	29
E	<5	>95

D = direct (SN2)
T = transposition (SN2′)
Ms = methanesulfonyl

Scheme VIII



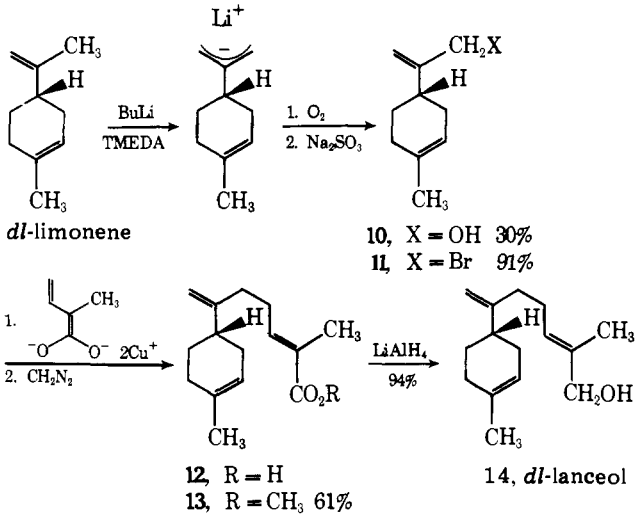
butylallyl methanesulfonate (E), which is, in fact, a better model for the synthesis of naturally occurring isoprenoid systems, transposition was the exclusive mode of substitution, and the stereoselectivity was improved to the point that 95% of the **6E** isomer was produced. Thus, it appears that this approach to isoprenoid 1,5-diene synthesis can be made to operate in a highly regioselective and stereoselective manner when chain elongation is proceeding in the head-to-tail direction.

Synthesis of Isoprenoid 1,5-Diene Natural Products. Although the stereoselectivity and regioselectivity of the alkylation of the copper dienolate derived from senecioic acid (**5a**) are not high, reaction with 3,3-dimethylallyl bromide (B) and geranyl bromide provides an extremely rapid route to the geranoic and farnesoic acid systems, respectively. The isolated

yield of methyl geranate (prepared by methylation of the crude alkylation product with diazomethane) was about 80% (cf. Table I, **5B**). Methyl (*E,E*)-farnesoate could be isolated chromatographically from the alkylated product mixture after methylation with either diazomethane or methyl iodide in dimethylformamide.[27] The composition of the farnesoate product mixture was 10:36:54, α alkylated/γ cis alkylated/γ trans alkylated ((*E,E*)-farnesoate).

γ alkylation of tiglic acid (**6a**) copper dienolate provides a convenient synthesis of *dl*-lanceol (Scheme IX). *dl*-Limonene

Scheme IX



was converted to the allylic alcohol **10** using the selective metalation–oxidation procedure of Crawford.[28] The corresponding bromide **11** reacted with the tiglate dicuprate to give the acid **12** which was esterified with diazomethane (yield of **13**, 61%). As this allylic bromide (**10**) is symmetrical with respect to allylic transposition, the mode of attack in this coupling (SN2 or SN2′) is of no consequence. Reduction of **13** with lithium aluminum hydride gave *dl*-lanceol in 94% yield.[29]

Discussion

While it was clear from our previous studies on the alkylation of unsaturated esters[16] that replacement of the lithium counterion by copper(I) caused a significant shift in alkylation regioselectivity towards the γ site, none of the reactions in the ester series that gave naturally occurring isoprene carbon skeletons were of sufficient selectivity and efficiency to make the γ-alkylation approach of preparative utility. The greater γ selectivity in the acid series, however, opens up numerous opportunities of preparative merit. One must still, however, make appropriate note of the applicability of the γ-alkylation approach in the differing situations encountered in isoprenoid 1,5-polyene synthesis.

In conversions that involve lengthening of the isoprenoid chain in a tail-to-head direction, where the appropriate acids will be of the 3-alkyl-2-butenoic type, the following constraints apply: (1) the γ regioselectivity will not be absolute, but should fall within the 60–90% range; (2) the stereoselectivity will depend upon the size of the 3-alkyl group and can vary over a considerable range (Scheme IV); and (3) the mode of substitution with 3,3-disubstituted allylic halides should clearly be exclusively direct. To counterbalance these restrictions are the convenience of this method of prenologation, the relative ease with which the reaction products may be separated, and the possibilities for repetitive application of the reaction (in a cycle: alkylation–reduction–bromination–alkylation) without the need for the repositioning of functional groups at intermediate or final stages.

In the alternative application, increasing the isoprenoid chain head-to-tail, 2-alkyl-2-butenoic acids are used. Here, high γ regioselectivity and *E* stereoselectivity are to be expected, but the extent of direct vs. transposed substitution on the allylic electrophile may vary. In a model system, however, by using the 1,2- rather than the 2,3-substituted allylic alkylating agent, we have been successful in achieving both clean transposition and generation of a new olefinic structure with high stereoselectivity.

At present it is unclear by what means the copper(I) counterions are able to effect such a dramatic alteration in alkylation regioselectivity of the acid dienolates (cf. Table I, **2A**, **4A**, **5AB**, **6A**). We have not made an exhaustive search, but copper(I) ions are clearly much more effective in this respect than sodium, potassium, magnesium bromide, manganese, cobalt, silver and iron ions.[30] Further, it is not clear whether it is more appropriate to formulate the dienolates in O-copper or C-copper species.[31] The greater γ selectivity in the acid vs. ester series can be rationalized simply on the basis of the greater negative charge density expected at the γ site in the dianionic (acid) species vs. the monoanionic (ester) one.

Using isotopically substituted allyl bromide as the electrophile, we determined[16] that there was a stereoelectronic preference for γ alkylation of the copper dienolates to proceed with allylic transposition (γ-γ' coupling). From the present investigations, it is clear that steric effects can operate to reinforce (**6E**), partially reverse (**6C** and **6D**), or completely reverse (**2B**, **5B**, **6B**) this electronic effect.

It seems clear that, simply by replacement of counterions, γ alkylation of dienolates, normally considered an exceedingly inefficient process,[32] can be made into a synthetic method of great potential. We are actively pursuing additional applications and extensions of this methodology.

Experimental Section

General. Analytical gas–liquid phase chromatography (GLC) was performed on the Hewlett-Packard Model 5750 gas chromatograph with a flame ionization detector, using a carrier gas (nitrogen) flow of 30 ml/min. The following columns were used for analytical work: A, 0.125 in. × 10 ft, 5% SE-30 on Gas-Chrom Q; B, 0.125 in. × 5 ft, 3% OV-17 on Gas-Chrom Q. Preparative GLC was done on the Varian Aerograph gas chromatograph Model 90-P3, with a thermal conductivity detector, using helium as a carrier gas. Two columns were used: C, 0.375 in. × 12 ft, 15% SE-30 on Chromosorb W, and D, 0.375 in. × 5 ft, 15% Carbowax on Chromosorb W. Where GLC analysis was employed, compounds are listed in order of increasing retention time on the column specified.

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

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

Solvents and Commercial Chemicals. The supplier of *n*-butyllithium and phenyllithium was Ventron Corp. Methanesulfonyl chloride, triethyl phosphonoacetate, *dl*-limonene, 2-pentanone, triphenylmethane, allyl alcohol, tiglic acid, propargyl alcohol, senecioic acid, geraniol, and crotonic acid were purchased from Aldrich. Matheson Coleman and Bell supplied allyl bromide and triethylamine. Crotyl bromide and dimethylallyl bromide came from the Chemical Samples Co., and isocrotyl chloride and phosphorus tribromide were from Eastman Co. Cuprous iodide from Fisher Scientific Co. was used without further purification. Eu(tfn)$_3$ was from Kary Laboratories (Anderson, S.C.). Diazomethane was prepared from *N*-methyl-*N*-nitrourea by the procedure of Arndt.[33] Tetrahydrofuran (THF) was distilled from sodium naphthalide, and ether was dried by storage over sodium.

Unless indicated otherwise, all reactions were quenched in water and products were isolated in a standard fashion: extraction with an organic solvent, washing extract with aqueous solutions (e.g., brine, bicarbonate), drying with anhydrous salts, filtration, and removal of

solvent under vacuum by rotary evaporation. In each case the solvents, etc., used in the procedure are given in parentheses.

Ethyl (*E*)-3-Methyl-2-hexenoate (2b) and Ethyl (*Z*)-3-Methyl-2-hexenoate (3b). To a suspension of 6.0 g (0.24 mol) of NaH in THF at 25° under N_2 was added 56.0 g (0.25 mol) of triethyl phosphonoacetate in 50 ml of THF. After the mixture was stirred for 1 h, 22 g (0.256 mol) of 2-pentanone was added, and the reaction was stirred overnight. The THF was removed via distillation, and the residue was poured into water, extracted with two portions of ether, washed twice with equal volumes of saturated NaCl solution, and dried over $MgSO_4$. According to GLC analysis, a 4:1 mixture of trans/cis isomers was obtained. The solvent was removed in vacuo, and the residue was distilled on a Nester–Faust Teflon annular spinning band column. Second spinning band distillation of cis-enriched fractions was required to obtain pure **3b**. Compound **2b**: ^{1}H NMR ($CDCl_3$) δ 5.6 (m, 1), 4.1 (q, 2), 2.3–1.9 (m, 2), 2.2 (s, 3), 1.7–1.2 (m, 2), and 0.95 (t, 3).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.15; H, 10.28.

Compound **3b**: ^{1}H NMR ($CDCl_3$) δ 5.6 (m, 1), 4.1 (q, 2), 2.6 (t, 2), 1.9 (d, 3), 1.8–1.2 (m, 2), 1.23 (t, 3), and 0.95 (t, 3).

(*E*)-3-Methyl-2-hexenoic Acid (2a). In a flask containing 30 ml of 20% KOH and 5 ml of EtOH was added 6.8 g (0.044 mol) of **2b**. This mixture was refluxed over steam for 1 h and poured into 20 ml of ice water. Product isolation (Et_2O, brine, $MgSO_4$) gave the acid **2a**, which crystallized upon cooling. Recrystallization from ethanol–water gave 5.1 g (89%) of **2a**: mp 39–40 °C (Fisher-Johns, corrected); ^{1}H NMR (CCl_4) δ 10.57 (s, 1), 5.67 (s, 1), 2.1 (s, 3), 2.2–2.0 (m, 2), 1.8–1.1 (m, 2), and 0.90 (t, 3).

(*Z*)-3-Methyl-2-hexenoic Acid (3a). Hydrolysis of **3b** by the above procedure gave an oil that was shown to be an 85:15 mixture of **3a**/**2a** by GLC analysis (column A, 120 °C) after methylation with diazomethane.

Ethyl Tiglate (6b). A mixture of 75 g (0.75 mol) of tiglic acid (**6**), 148 ml of absolute ethanol, 300 ml of benzene, and 15 ml of concentrated sulfuric acid was refluxed for 3 days in a flask with a Dean–Stark water separator. The majority of the solvent was removed in vacuo and an equal volume of water was added. Product isolation (Et_2O, 10% aqueous Na_2CO_3, brine, $MgSO_4$) gave an oil that was distilled (bp 152–157 °C (760 mm)), affording 64 g (67%) of material whose properties agreed with those cited for ethyl tiglate:[13b] ^{1}H NMR ($CDCl_3$) δ 6.85 (m, 1), 4.25 (q, 2), 1.9 (s, 3), 1.8 (d, 3), and 1.2 (t, 3).

Angelic Acid (7a). Angelic acid was prepared from tiglic acid by the procedure of Buckles and Mock.[34]

(*Z*)-3-Deuterioallyl Bromide. The procedure of McMichael[35] was used to obtain 3-deuterioallyl alcohol. Propargyl alcohol (8 g, 0.14 mol) was added to a stirred solution of 5.7 g (0.15 mol) of $LiAlH_4$ in 70 ml of Et_2O at 0° under N_2. After 13 h at 0°, 11 ml of D_2O was added, and stirring continued for another 10 h at 25°. The salts were removed by adding 11 ml of 10% NaOH and 11 ml of H_2O, and filtering. Product isolation ($MgSO_4$) gave an oil that was distilled (bp 91–94 °C (760 mm)) to give 2.8 g (35.8%) of deuterated alcohol: ^{1}H NMR (CCl_4) δ 4.05 (m, 2), 4.6 (t, 1), 5.05–5.3 (m, 1), and 5.9 (m, 1).

Phosphorus tribromide (2.71 g, 0.01 mol) was added to 1.8 g (0.03 mol) of the above alcohol in ether at 0° under N_2, in the absence of light. After stirring for 3 h, the product was isolated (ice water, Et_2O, saturated aqueous $NaHCO_3$, brine, $MgSO_4$), with solvent removal by careful distillation. Since the boiling point of allyl bromide is low, it was difficult to remove the ether completely. This solution was used to alkylate various cuprous and lithium enolates: ^{1}H NMR (CCl_4) δ 5.9 (m, 1), 5.09 (m, 1), and 3.9 (d, 2).

(*E*)-2-Methyl-2-butenyl Bromide (C). Using an excess of diazomethane in ether, 4 g (0.04 mol) of tiglic acid (**6a**), dissolved in a minimum of Et_2O, was methylated. After the solution had turned from yellow to clear, the ester was obtained quantitatively ($MgSO_4$) and used without further purification: ^{1}H NMR ($CDCl_3$) δ 6.85 (m, 1), 3.65 (s, 3), 1.82 (s, 3), and 1.77 (d, 3).

To a slurry of 1.38 g (0.036 mol) of $LiAlH_4$ in 30 ml of anhydrous Et_2O at 0° under N_2 was added 1.6 g (0.012 mol) of $AlCl_3$. After stirring for 30 min at 25° and cooling to 0°, 2.6 g of methyl tiglate (0.228 mol) in 5 ml of Et_2O was added slowly via syringe. The mixture stirred for 1 h at 25° and was quenched with 1 ml of H_2O, followed by 1 ml of 15% KOH and 3 ml of H_2O. Product isolation (saturated aqueous $NaHCO_3$, brine, $MgSO_4$) and distillation (bp 122–127 °C) gave 1.33 g (68%) of (*E*)-2-methyl-2-buten-1-ol: ^{1}H NMR (CCl_4) δ 6.8 (m, 1), 3.8 (br s, 1), 3.65 (s, 2), 1.80 (s, 3), and 1.73 (d, 3); ir (neat) 3350 (O–H), 2900 (C–H), 1670 (C=C), 1450 (C=C), and 1050 (C–O) cm^{-1}.

The above alcohol was converted to the bromide (C) by placing 1.3 g (0.155 mol) in a flask with 20 ml of anhydrous Et_2O at 0° under N_2 in the absence of light. Using a syringe, 1.62 g (0.006 mol) of PBr_3 was added slowly, and the reaction was stirred at 0° for 2 h. Product isolation (ice water, Et_2O, brine, $MgSO_4$) gave 1.82 g of C (74%): ir (neat) 2900 (C–H), 1670 (C=C), and 1450 (C=C) cm^{-1}.

2-Methyl-1-buten-3-yl Methanesulfonate (D). Methyllithium (0.1 mol) was added to a flask containing 50 ml of anhydrous Et_2O at 0° under N_2. Then 7 g (0.1 mol) of methacrolein in 10 ml of Et_2O was added slowly via dropping funnel. After 1 h, the reaction was quenched by addition of 20 ml of water. Product isolation (Et_2O, brine, $MgSO_4$) gave 6 g (69%) of 2-methyl-buten-3-ol (bp 110–113 °C): ^{1}H NMR (CCl_4) δ 4.8 (d, 2), 4.1 (m, 1), 4.05 (s, 1), 1.8 (s, 3), and 1.2 (d, 3); ir (neat) 3400 (O–H), 2900 (C–H), 1650 (C=C), and 1050 (C–O) cm^{-1}.

This alcohol (3 g, 0.035 mol) was placed in a flask containing 3.63 g (0.036 mol) of triethylamine and 30 ml of CH_2Cl_2 under N_2 at 0°. While stirring, 4.10 g (0.036 mol) of methanesulfonyl chloride was added dropwise. After another 15 min, the reaction was poured into ice water. Product isolation (Et_2O, 5% HCl, saturated aqueous $NaHCO_3$, brine, $MgSO_4$) gave 3.2 g (66%) of D which was used without further purfication, since it easily decomposed: ir (neat) 2900 (C–H), 1650 (C=C), 1350 (S=O), and 1170 (S=O) cm^{-1}.

2-Methyl-1-hepten-3-yl Methanesulfonate (E). To a flask containing 0.35 mol of *n*-butyllithium in 100 ml of ether at 0° under N_2 was added dropwise 24 g (0.35 mol) of methacrolein in 25 ml of ether. The reaction was stirred for 2 h at 0° and was quenched by careful addition of water. Product isolation (Et_2O, brine, $MgSO_4$) gave 23 g (72%) of crude 2-methyl-1-hepten-3-ol, which was purified further by chromatography on silica gel. The alcohol (16 g, 51%) eluted with ether–hexane (35:65): ^{1}H NMR ($CDCl_3$) δ 4.83 (d, 2), 4.0 (m, 1), 3.1 (br s, 1), 1.7 (s, 3), and 1.6–0.8 (m, 9); ir (neat) 3300 (O–H), 2900 (C–H), 1650 (C=C), and 1050 (C–O) cm^{-1}.

This alcohol (2.5 g, 0.0295 mol) was added to a flask with 20 ml of CH_2Cl_2 and 2.02 g (0.02 mol) of triethylamine. After flushing the flask with N_2 and reducing the temperature to 0°, 2.28 g (0.02 mol) of methanesulfonyl chloride was added slowly. After 1 h at 0°, the mixture was poured into ice water. Product isolation (Et_2O, saturated aqueous $NaHCO_3$, $MgSO_4$) gave an oil which was not further purified, as it decomposed readily: ir (neat) 2900 (C–H), 1650 (C=C), 1350 (S=O), and 1180 (S=O) cm^{-1}.

General Method for Lithium Dienolate Formation from Unsaturated Esters (Method I). In a nitrogen atmosphere, 1.21 mmol of *n*-butyllithium was added to a solution of 0.122 g (1.21 mmol) of diisopropylamine in THF at −78 °C. To this was added 0.156 g (1.0 mmol) of **2b**, and the reaction was warmed to room temperature. After 1 h, the ester monolithium dienolate was ready for further reaction (see below). If it was quenched with water, analysis via GLC (column A, 125 °C) of the material obtained after isolation (ether, brine, $MgSO_4$) showed two peaks in the ratio of 93:7. They were isolated by GLC (column C): peak 1 (ethyl 3-propyl-3-butenoate): ^{1}H NMR ($CDCl_3$) δ 5.0 (s, 2), 4.25 (q, 2), 3.05 (s, 2), 2.15 (t, 2), and 1.6–0.9 (m, 8); peak 2: spectral data matched that of starting material.

General Method for Cuprous Dienolate Formation from Unsaturated Esters (Method II). Phenyllithium (7 mmol) was added to 1.7 g (7 mmol) of triphenylmethane in 30 ml of THF at 25 °C under N_2 and the solution was stirred for 2 h.[36] The red solution was titrated with 1.08 g (7 mmol) of **2b** and cooled to −78 °C, whereupon 1.236 g (7 mmol) of CuI was added. The reaction was stirred for 2 h at −78°, and the ester monocopper dienolate was then ready for further reaction. It could be quenched in 5% HCl to give the same two products that were isolated from the lithium enolate (see above) in a 81:19 ratio, respectively.

General Method for Alkylation of Ester Monolithium Dienolates (Method A). The lithium enolate of **2b** was generated as described in method I on a 7-mmol scale. After stirring at 25° for 2 h, 2.58 g (20 mmol) of allyl bromide was added, and the reaction was stirred for another hour. Product isolation (Et_2O, brine, $MgSO_4$) and GLC analysis (column A, 140 °C) showed two peaks in the ratio of 90:10. Using ethyl 3-methyl-2-hexenoate as an internal standard, a 43% yield of the α-allylated product, ethyl 2-(1′-penten-2′-yl)-4-pentenoate, and a more slowly eluting isomer (γ-alkylated product) was estimated.

Isolation of the first peak (α-substituted product) was accomplished via GLC (column C): ^{1}H NMR ($CDCl_3$) δ 5.7 (m, 1), 4.95 (m, 4), 4.1 (q, 2), 2.95 (t, 1), 2.6–1.9 (m, 4), 1.5 (m, 2), 1.2 (t, 3), and 0.9 (t, 3).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.50; H, 10.21. Found: C, 73.41; H, 10.39.

General Method for Alkylation of Ester Monocopper Dienolates (Method B). The cuprous enolate of **2b** (7 mmol) was formed via method II, and after stirring at −78° for 2 h, 2.58 g (20 mmol) of allyl bromide was added. The mixture was stirred at −50 to −40 °C for 1 h and then warmed to room temperature. Product isolation (ether, saturated aqueous NH_4Cl, aqueous 5% $NaHCO_3$, brine, $MgSO_4$) and GLC analysis (column A, 130 °C) gave peaks that matched those formed in the lithium enolate alkylation (above), except that they were in the ratio of 43.6:56.4 (α-allylated/γ-allylated products, respectively). The mixture was diluted to fill a 25-ml volumetric flask and, using tridecane as an internal standard, the yield of the combined products was estimated at 65%. Solvent was removed, and the remaining dark yellow oil was purified by elution from a silica gel column with petroleum ether. The isolated yield of the combined products was 66%. The spectroscopic data of the isomer that eluted more rapidly on GLC matched that of the α-allylated ester (see preceding procedure). The γ-allylated isomer, ethyl 3-propyl-2,6-heptadienoate showed ^{1}H NMR ($CDCl_3$) δ 5.8 (m, 1), 5.6 (s, 1), 5.0 (t, 2), 4.1 (q, 2), 2.9–2.1 (m, 6), 1.8–1.6 (m, 2), 1.2 (t, 3), and 1.0 (t, 3).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.79; H, 10.31.

When the monocopper enolate generated from **3b** was reacted with allyl bromide, the same two products were obtained, in a 60:40 ratio (α- to γ-substituted).

Alkylation of Ester 2b with Dimethylallyl Bromide (B) (Method B). The cuprous enolate of **2b** (7 mmol) was generated (method II) and a two fold excess of dimethylallyl bromide was added (method B). Two peaks were observed on GLC (column A, 160°) in an approximate ratio of 95:5. The major peak was isolated by preparative GLC and shown to be the α-substituted product, ethyl 2-(1′-penten-2′-yl)-5-methyl-4-hexenoate: ^{1}H NMR ($CDCl_3$) δ 4.9 (m, 3), 4.1 (q, 2), 2.85 (t, 1), 2.6–1.9 (m, 4), 1.67 (s, 3), 1.63 (s, 3), 1.45 (m, 2), 1.2 (t, 3), and 0.9 (t, 3).

The minor product was thought to be the γ-alkylated isomer, but was present in such small amounts that it could not be isolated.

General Method for Dilithium Dienolate Formation from Unsaturated Acids (2–4, 5, 7) (Method III). To a 2.02 g (0.020 mol) of diisopropylamine in 25 ml of THF under nitrogen at −78°, was added *n*-butyllithium (0.020 mol). The pale yellow solution was stirred for about 10 min, and 0.01 mol of the desired acid, dissolved in 10–15 ml of THF, was added slowly. This solution was stirred for 30 min at 0°, forming a clear yellow solution.

General Method for Lithium–Sodium Dienolate Formation from Unsaturated Acids (Method IV). The sodium salt of the acid to be alkylated was formed by adding dropwise 0.01 mol of the acid in 5 ml of THF to a slurry of NaH (0.012 mol) in 15 ml of THF under nitrogen at 0°. This was heated over a steam bath for 10 min or until formation of a thick white mixture. While this was heating, 1 equiv of lithium diisopropylamide was generated by adding 0.010 mol of *n*-butyllithium to a flask containing 1.01 g (0.010 mol) of diisopropylamine in 20 ml of THF under a nitrogen atmosphere at −78°.

The thick white slurry was cooled to 0° and the lithium amide solution (at −78°) was slowly siphoned into this mixture while rapidly stirring, preferably using an overhead stirrer. Stirring was continued at 0° for 15 min, then at 25° until dianion formation was complete. This is indicated by a clear (or translucent if running a large-scale reaction) yellow solution. If a white colloidal solution persists after stirring at 25° for more than 30 min, the salt of the acid has probably precipitated to some extent, and complete dianion generation will be impossible. Should this occur, it is best to abort the run and to repeat the process taking care (1) not to overheat the sodium salt of the acid, (2) to use a fresh bottle of *n*-butyllithium, (3) to maintain rapid stirring of the sodium salt of the acid while lithium diisopropylamide is being siphoned in, and (4) to add the lithium diisopropylamide slowly.

General Method for Alkylation of Acid Dilithium or Lithium–Sodium Dienolates (Method C). The acid dienolate was formed by method III or IV, depending on the acid, and the appropriate allylic halide (1–3 equiv) was added dropwise to the acid dienolate at 0° under nitrogen atmosphere. There should be a color change from yellow to colorless. This mixture is stirred at 25° for 1 h and quenched.

General Method for Alkylation of Acid Dicopper Dienolates (Method D). After the dienolate of the acid (0.010 mol) is generated via the appropriate method (III or IV), the solution is cooled to −78°. Maintaining a nitrogen atmosphere, 3.89 g (0.020 mol) of cuprous iodide was added, and the slurry was stirred rapidly at −78° for 1 h. The copper dienolate is formed successfully if the slurry is pale to bright yellow in color. If it is a pale grayish white, the lithium (or lithium–sodium) dienolate predominates, and if it is black, the dienolate has decomposed, and subsequent γ-selective alkylation will be impossible. The halide is added at −78° and stirring is continued overnight (16 h), during which time the reaction mixture warms to 25°.

Acid Product Isolation 1. If the acid product was C_{10} or less, the reaction was quenched with H_2O, stirred, and filtered through Celite. Sodium hydroxide solution was added to pH 12, causing more copper salts to precipitate; these were removed by filtration through Celite. The mixture was then extracted with two equal volumes of ether to remove the nonacidic organic residues. The combined aqueous layers were acidified to pH 3 (acid to Congo Red paper), and were extracted with two equal volumes of Et_2O. These extracts were washed with brine and dried over $MgSO_4$, and the product acid was obtained after removal of the solvent under vacuum.

Acid Product Isolation 2. An acid of C_{11}–C_{14} was isolated by quenching the reaction with 5% HCl, acidifying with 6 N HCl to below pH 3, and filtering through Celite. The acid product was obtained by extracting with ether, drying the extracts with brine and $MgSO_4$, and removing the solvent under vacuum.

Acid Product Isolation 3. The cleanest workup involved product acids of C_{15} and more. Dilute HCl (3%) was added to quench the alkylation, and saturated NH_4Cl solution was added until all of the copper salts were dissolved. The product was removed via extraction with ether. Salt (NaCl) was added to the blue NH_4Cl layer, and any residual acid product was extracted with more ether. The combined extracts were dried (brine, $MgSO_4$) and evaporated to give the acid product.

Alkylation of (*E*)-3-Methyl-2-hexenoic Acid (2a) with Allyl Bromide (A) (Method C). Acid **2a** (0.05 mol) was alkylated with 1.01 g (0.01 mol) of allyl bromide (A) by generating the lithium–sodium dienolate (method IV) and alkylating via method C. After isolation 1, the crude acid was methylated with excess diazomethane, producing 0.70 g (83%) of an oil. GLC analysis (column A, 140 °C) showed two peaks, A and B, in the ratio 98:2. Peak A (retention time of 6.4 min) was isolated on preparative GLC (column C) and assigned the structure of the α-allylated product methyl 2-(1′-penten-2′-yl)-4-pentenoate: ^{1}H NMR (CCl_4) δ 5.9–5.4 (m, 1), 5.1–4.8 (overlapping doublets, 4), 3.56 (s, 3), 2.95 (s, 1), 2.6–2.2 (m, 2), 2.0 (t, 2), 1.65–1.3 (m, 2), and 0.9 (t, 3).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.13; H, 9.73.

Peak B had the same retention time (10.3 min) as the γ-allylated product that was synthesized in method D (following procedure).

The above reaction was repeated using deuterioallyl bromide in place of allyl bromide. The GLC analysis was identical with that of the protio case. Isolation of the major product (by preparative GLC, column C) provided the following ^{1}H NMR spectrum, consistent with the 5-deuterio substituted α-allylated product (nontransposed): ^{1}H NMR ($CDCl_3$) δ 5.8–5.5 (m, 1), 5.15–4.9 (overlapping doublets, 3), 3.65 (s, 3), 3.10 (t, 1), 2.7–2.1 (m, 2), 2.0 (t, 2), 1.65–1.3 (m, 2), and 0.9 (t, 3).

Alkylation of 2a with Allyl Bromide (Method D). The lithium–sodium dienolate of **2a** (1.28 g, 0.01 mol) was generated using method IV. Cuprous iodide (3.89 g, 0.02 mol) was added according to alkylation D to form the copper dienolate for subsequent alkylation with 2.00 g (0.02 mol) of allyl bromide. After isolation and methylation (with diazomethane), 1.5 g (82%) of product was obtained. GLC analysis (column A, 140 °C) showed two product peaks, A and B, in the ratio 19.4:80.6. Peak A (retention time of 6.4 min) was identified as the α-allylated product by ^{1}H NMR analysis (see preceding procedure, method C). Peak B (retention time of 10.3 min) was isolated by preparative GLC (column C) and assigned the structure of the γ-allylated product, methyl 3-propyl-2,6-heptadienoate: ^{1}H NMR (CCl_4) δ 6–5.6 (m, 1), 5.54 (s, 1), 5.1–4.8 (overlapping doublets, 2), 5.58 (s, 3), 2.66 (t, 2), 2.3–2.0 (m, 4), 1.65–1.4 (m, 2), and 0.9 (t, 3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 71.99; H, 9.89.

The preceding procedure was repeated using 1.01 g of 3-deuterioallyl bromide (0.01 mol). GLC analysis showed identical product ratio. The minor product (retention time of 6.4 min) gave a ^1H NMR spectrum identical with that shown for the major product of the alkylation of **2a** with 3-deuterioallyl bromide via method C (see above). The major product (retention time of 10.3 min) had the following ^1H NMR consistent with the 5-deuterio-γ-allylated product (transposed): ^1H NMR ($CDCl_3$) δ 6–5.65 (m, 1), 5.6 (s, 1), 5.1–4.85 (overlapping doublets, 2), 3.65 (s, 3), 2.66 (m, 2), 2.3–2.0 (m, 3), 1.7–1.4 (m, 2), and 0.9 (t, 3).

Using the above ^1H NMR sample (32.5 mg of deuterated γ-allylated product in 0.5096 g $CDCl_3$), 28 mg of $Eu(tfn)_3$ were added. The HA-100 ^1H NMR spectrum then indicated that two isomers were present. Successive amounts of additional $Eu(tfn)_3$ were added (20, 21.6, and 39.7 mg), and by comparison of their relative shift sensitivities additional peaks were assigned, and the relative amount of each isomer was estimated; the ratio of **2E** to **2Z** isomers was 19:81.

Alkylation of Crotonic Acid (4a) with Allyl Bromide (A) (Method C). The lithium dienolate of **4a** was generated via method III using 0.43 g (0.05 mol) of crotonic acid in 3 ml of THF and 1.01 g (0.01 mol) of diisopropylamine and 0.01 mol *n*-butyllithium in 20 ml of THF. This dienolate was alkylated with 2.8 g (0.02 mol) of allyl bromide using alkylation C and isolated as outlined in isolation 1. The crude acid was methylated with diazomethane, yielding 0.65 g (90%) of ester. GLC analysis (column A, 120 °C) showed a major product, 98% (retention time of 2.9 min), which was isolated via preparative GLC (column C) and identified as the α-allylated product, methyl 2-vinyl-4-pentenoate: ^1H NMR (CCl_4) δ 7–6.8 (m, 2), 5.8–5.6 (m, 2), 5.2–4.9 (m, 2), 3.65 (s, 3), 2.95 (m, 1), and 2.25 (m, 2).

The minor product (2%, retention time of 6 min), was later identified by GLC comparison as the γ-allylated isomer (see method D, below).

Alkylation of Crotonic Acid (4a) with Allyl Bromide (Method D). Method III was used to form 0.005 mol of the lithium dienolate of crotonic acid as described above. Addition of cuprous iodide and alkylation with 2.8 g (0.02 mol) of allyl bromide was done according to alkylation method D. Isolation 1 gave a yellow oil that was methylated with diazomethane, yielding 0.69 g (97%) of ester. GLC analysis (column A, 120 °C) indicated two peaks, A and B, in the ratio of 3:97. The minor product (retention time of 2.9 min) was shown to be the α-allylated product by GLC comparison with the major product of the preceding reaction (method C above). The major product in this case (retention time of 6 min) was isolated by preparative GLC (column C) and shown to be the γ-allylated product, methyl (*E*)-2,6-heptadienoate: ^1H NMR (CCl_4) δ 6.9–6.7 (m, 1), 5.9–5.6 (m, 2), 3.65 (s, 3), and 2.24 (m, 4).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.50; H, 8.58. Found: C, 68.21; H, 8.75.

Alkylation of Senecioic Acid (5a) with Allyl Bromide (A) (Method C). The lithium–sodium dianion of senecioic acid (1 g, 0.01 mol) was generated via method IV with 0.43 g (0.01 mol) of NaH and 0.01 mol of lithium diisopropylamide. Excess allyl bromide (2.02 g, 0.022 mol) was added according to alkylation method C. Using isolation 1 and diazomethane methylation, 1.43 g (93%) of ester was obtained as a yellow oil. GLC analysis (column A, 115 °C) indicated two peaks, A and B, in the ratio 95.5:4.5. PEAK A was isolated by preparative GLC (column C) and shown by ^1H NMR to be the α-allylated product, methyl 2-isopropenyl-4-pentenoate: ^1H NMR (CCl_4) δ 5.9–5.4 (m, 1), 5.1–4.9 (overlapping doublets, 2), 4.85 (d, 2), 3.62 (s, 3), 3.01 (t, 1), 2.7–2.1 (m, 2), and 1.7 (d, J = 0.5 Hz, 3).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.02.

Peak B was assigned as the cis γ product by GLC comparison with the products from the following reactions (method D).

Alkylation of Senecioic Acid (5a) with Allyl Bromide (A) (Method D). The dianion generation from 1 g (0.01 mol) of senecioic acid was repeated (method IV), and 3.89 (0.02 mol) of cuprous iodide was added. Subsequently, alkylation with 2.02 g (0.022 mol) of allyl bromide according to alkylation method D, and isolation 1, gave an oil that was methylated with diazomethane. The yield was determined to be 89.5% (GLC with internal standard), and by GLC (column A, 115 °C) three peaks, A, B, and C, were evident in the ratio 7.2:46:47. All three were isolated by preparative GLC (column C). Peak A was identical with the α-allylated product whose preparation is described in the preceding procedure (method C). Peaks B and C are the γ-cis- and γ-trans-allylated products, respectively. Peak B (methyl (*Z*)-3-methyl-2,6-heptadienoate): ^1H NMR (CCl_4) δ 5.9–5.6 (m, 1), 5.57 (s, 1), 5.1–4.8 (overlapping doublets, 2), 3.65 (s, 3), 2.68 (t, 2), 2.2 (m, 2), and 1.84 (d, J = 0.5 Hz, 3).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.00; H, 9.12.

Peak C (methyl (*E*)-3-methyl-2,6-heptadienoate): ^1H NMR (CCl_4) δ 5.9–5.6 (m, 1), 5.57 (s, 1), 5.1–4.8 (overlapping doublets, 2), 3.65 (s, 3), 2.2 (d, 4), and 2.1 (d, J = 0.5 Hz, 3).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.97; H, 9.10.

Alkylation of Tiglic Acid (6a) with Allyl Bromide (A) (Method C). The lithium dienolate of 0.5 g (0.005 mol) of tiglic acid was generated with 1.01 g (0.01 mol) of diisopropylamine and 0.01 mol of *n*-butyllithium as in method III. The dienolate was then alkylated with 1.4 g (0.011 mol) of allyl bromide according to alkylation C and isolated according to 1. After methylation with diazomethane, a yellow oil (0.705 g, (90%)) gave one peak on GLC (column A, 105 °C), which was shown to be the α-allylated product, methyl 2-methyl-2-vinyl-4-pentenoate: ^1H NMR ($CDCl_3$) δ 6.07 (d of d, J_1 = 17 Hz and J_2 = 10 Hz, 1), 5.8–5.45 (m, 1), 5.2–4.9 (overlapping doublets, 4), 3.65 (s, 3), 2.38 (m, 2), and 2.24 (s, 3).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.02.

The above procedure was repeated using 1.4 g (0.011 mol) of 3-deuterioallyl bromide. The results were essentially identical, except that the product had a deuterium in the vinylic 5 position (nontransposed): ^1H NMR ($CDCl_3$) δ 6.07 (d of d, J_1 = 17 Hz and J_2 = 10 Hz, 1), 5.8–5.45 (m, 1), 5.2–4.9 (overlapping doublets, 3), 3.65 (s, 3), 2.38 (m, 2), and 2.24 (s, 3).

Alkylation of Tiglic Acid (6a) with Allyl Bromide (A) (Method D). Using 1.01 g (0.01 mol) of diisopropylamine, 0.01 mol of *n*-butyllithium, 25 ml of THF, and 0.5 g (0.005 mol) of tiglic acid, dienolate generation by method III was performed. The anion was alkylated using method D with 1.4 g (0.011 mol) of allyl bromide. Isolation 1 was used to give the crude acid. After methylation with diazomethane, the oil was analyzed on GLC (column A, 110 °C) and the yield was determined to be 95% by internal standard (cyclohexylcarboxylic acid was added to the reaction after quenching but before workup). Two product peaks in a 4:96 ratio were found; the first (retention time 4.8 min) was the α-allylated product (cf., preceding procedure, method C). The second (retention time 11.9 min) was isolated by preparative GLC (column C) and shown to be the trans γ-allylated product, methyl (*E*)-2-methyl-2,6-heptadienoate: ^1H NMR ($CDCl_3$) δ 6.75 (t, 1), 6–5.6 (m 1), 5.2–4.9 (overlapping doublets, 2), 3.65 (s, 3), 2.22 (m, 4), and 1.83 (d, J = 0.5 Hz, 3).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.25; H, 9.67.

The previous experiment was duplicated using 3-deuterioallyl bromide instead of allyl bromide. In this case, the deuterium appeared on the methylene carbon at the 5 position of the γ-allylated product (transposed): ^1H NMR ($CDCl_3$) δ 6.75 (t, 1), 6–5.6 (m, 1), 5.2–4.9 (overlapping doublets, 2), 3.65 (s, 3), 2.22 (m, 3), and 1.83 (d, J = 0.5 Hz, 3).

Alkylation of Tiglic Acid (6a) with Dimethylallyl Bromide (B) (Method D). The dienolate of tiglic acid (0.5 g, 0.005 mol) was generated using method III, and alkylation with dimethylallyl bromide (1.92 g, 0.013 mol) proceeded as described in alkylation D. After isolation 2, the crude acid mixture was methylated with diazomethane and analyzed on GLC (column B, 140 °C). Two major product peaks, A (retention time of 3.2 min) and B (retention time of 5.6 min) in a ratio of 15:85 were isolated by preparative GLC (column C), and identified as the α- and γ- substituted esters. The yield was determined to be 68% via GLC internal standard. Methyl 2,5-dimethyl-2-vinyl-4-hexenoate (α-substituted product): ^1H NMR (CCl_4) δ 6.07 (d of d, J_1 = 17 Hz and J_2 = 10 Hz, 1), 5.06 (d, 1), 4.92 (d, 2), 3.65 (s, 3), 2.25 (m, 2), 1.67 (s, 3), 1.58 (s, 3), and 1.17 (s, 3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.48; H, 9.98.

Methyl (*E*)-2,7-dimethyl-2,6-octadienoate (γ-substituted product): ^1H NMR (CCl_4) δ 6.65 (m, 1), 5.05 (m, 1), 3.65 (s, 3), 2.1 (m, 4), 1.77 (d, J = 0.5 Hz, 3), 1.66 (s, 3), and 1.58 (s, 3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.01; H, 9.88.

Alkylation of Tiglic Acid (6a) with (*E*)-1-Bromo-2-methyl-2-butene

(C) (**Method D**). Tiglic acid (0.5 g, 0.005 mol) was lithiated (dienolate generation III), complexed with 1.89 g (0.01 mol) of cuprous iodide, and alkylated with 0.5 g (0.003 mol) of C via alkylation D. After isolation 2, the crude acids were methylated with diazomethane, yielding 0.45 g (78%) of the methyl esters. There were two products via GLC (column B, 125 °C) in the ratio 65.6:34.4, A (retention time of 2.4 min) to B (retention time of 3.6 min). The products were isolated on preparative GLC (column D) and both shown to be γ-alkylation products: A was **9**, derived from SN2′ attack, and B was **8a**, from SN2 attack.

Peak A, methyl (*E*)-2,5,6-trimethyl-2,6-heptadienoate (**9**) (substitution with transposition): ^{1}H NMR (CCl_4) δ 6.59 (br t, 1), 4.66 (d, J = 0.5 Hz, 2), 3.63 (s, 3), 2.2 (m, 3), 1.77 (d, J = 0.3 Hz, 3), 1.67 (d, J = 0.5 Hz, 3), and 1.3 (d, J = 6 Hz, 3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 71.95; H, 9.81.

Peak B, methyl (*E,E*)-2,6-dimethyl-2,6-octadienoate (**8a**) direct substitution): ^{1}H NMR (CCl_4) δ 6.6 (br t, 1), 5.2 (br q, 1), 3.63 (s, 3), 2.3–2.2 (m, 4), 1.78 (d, J = 0.3 Hz, 3), 1.59 (s, 3), and 1.56 (d, 3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.42; H, 9.89.

Alkylation of Tiglic Acid (6a) with 2-Methyl-1-buten-3-yl Methanesulfonate (D) (Method D). Tiglic acid (0.5 g, 0.005 mol) was metalated (method III), complexed with 1.89 g of cuprous iodide, and alkylated with 1.5 g (0.009 mol) of D (alkylation D). After isolation 2, the acids were methylated with diazomethane, yielding 0.75 g (78%) of the combined esters. GLC analysis (column **B**, 110 °C) showed three products, A, B, and C, in the ratio 26:21.5:52.5. The material in peak A was **9** and peak C was **8a** (by GLC and ^{1}H NMR comparison). Peak B from this reaction appeared as a shoulder on peak C (**8a**) and was difficult to separate it by preparative GLC. The ^{1}H NMR spectrum of a mixture of 65% B in C showed only one additional signal, a broad singlet at δ 1.68; thus it appears that the material in peak B is the **6Z** isomer of **8a**: methyl (*E,Z*)-2,6-dimethyl-2,6-octadienoate.

Alkylation of Tiglic Acid (6a) with 2-Methyl-1-hepten-3-yl Methanesulfonate (E) (Method D). Using enolate generation III and alkylation D, the dienolate of 0.5 g (0.005 mol) of tiglic acid was complexed with 1.89 g (0.01 mol) of cuprous iodide and alkylated at −79° with 2.69 g (0.021 mol) of E. After isolation of the crude acids via 3 and methylation with diazomethane, the ester was analyzed on GLC (column B, 110 °C). Since there was only one major product (retention time of 12.2 min), the crude product was purified by preparative TLC (ether–hexane 15:85), which gave 0.58 g (55%) of the γ-transposed product, methyl (*E,E*)-2,6-dimethyl-2,6-undecadienoate (**8b**), which was further purified on preparative GLC (column D): ^{1}H NMR (CCl_4) δ 6.62 (br t, 1), 5.1 (br t, 1), 3.64 (s, 3), 2.3–1.9 (m, 6), 1.79 (d, J = 0.3 Hz, 3), 1.60 (d, J = 0.5 Hz, 3), 1.4–1.2 (m, 4), and 0.9 (t, 3).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.40; H, 10.87.

Alkylation of Tiglic Acid (6a) with 2-Methyl-2-propenyl Chloride (F) (Method D). The copper dienolate of tiglic acid (0.005 mol) was generated in the usual manner (dienolate generation, method III, and alkylation D) and alkylated with 0.9 g (0.01 mol) of 2-methyl-2-propenyl chloride. Product was isolated according to 1 and was methylated with excess diazomethane. GLC analysis (column A, 140 °C) showed two products in the ratio of 4.5:95.5 (A, retention time of 3.2 min; B, retention time of 6 min) with a combined yield of 87% (GLC with cyclohexylcarboxylic acid as internal standard). The two products were isolated on preparative GLC (column C) and identified as the α-substituted ester, methyl 2,4-dimethyl-2-vinyl-4-pentenoate (peak A): ^{1}H NMR (CCl_4) δ 6.08 and 5.89 (doublets, AB pattern, 1), 5.08 (d, 2), 4.95–4.6 (overlapping doublets, 2), 2.5 (d, J = 12 Hz, 1), 2.2 (d, J = 12 Hz, 1), 1.62 (s, 3), and 1.22 (s, 3).

The γ-substituted ester, methyl (*E*)-2,6-dimethyl-2,6-heptadienoate (peak B): ^{1}H NMR (CCl_4) δ 6.62 (t, 1), 4.66 (s, 2), 3.65 (s, 3), 2.16 (m, 4), 1.77 (s, 3), and 1.70 (s, 3).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.45.

Alkylation of Angelic Acid (7a) with Allyl Bromide (A) (Method D). The dienolate of 0.5 g (0.005 mol) of angelic acid was generated with 1.01 g (0.01 mol) of diisopropylamine and 0.01 mol of *n*-butyllithium via method III. Alkylation was carried out with 1.4 g (0.011 mol) of allyl bromide as in alkylation D; the reaction was quenched and the crude acids were isolated by procedure 1 and methylated with diazomethane (0.71 g, 92%). GLC analysis showed two peaks, A and B, (column A, 110 °C) matching the retention times of the α- (4.8 min) and γ-allylated (11.9 min) tiglic esters (vide ante), in the ratio 9.5:90.5. Peak B was isolated on preparative GLC and had a ^{1}H NMR identical with that of the γ-substituted product from the reaction of **6a** and A, implying that the conjugated double bond in the latter compound was now of the *E* configuration.

Alkylation of Senecioic Acid (5a) with Geranyl Bromide, Farnesoic Acids (Method D). The copper dienolate from 1 g (0.01 mol) of senecioic acid (**5a**) was formed by initial mixed dienolate generation (method IV) and subsequent addition of 3.89 g (0.02 mol) of cuprous iodide, and 5.0 g (0.025 mol) of geranyl bromide was added as in alkylation D. Isolation by procedure 3 and methylation with diazomethane produced 2.06 g (80%) of a mixture of esters. Using GLC analysis (column B, 145 °C), three major product peaks were found in a ratio of 10:36:54, A (retention time of 4 min), B (retention time of 6.2 min), C (retention time of 7.3 min). Peak A was presumed to be the α product, and peaks B and C were identified as the isomeric γ products by ^{1}H NMR[37] after isolation by preparative GLC (column D). Methyl (*Z,E*)-farnesoate (peak B): ^{1}H NMR (CCl_4) δ 5.55 (s, 1), 5.1–4.9 (m, 2), 3.54 (s, 3), 2.58 (t, 2), 2.2–1.9 (m, 6), 1.82 (d, J = 0.5 Hz, 3), 1.6 (s, 3), and 1.4 (s, 6).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.43; H, 10.38.

Methyl (*E,E*)-farnesoate (peak C): ^{1}H NMR (CCl_4) δ 5.55 (s, 1), 5.1–4.9 (m, 2), 3.54 (s, 3), 2.2–1.9 (m, 8), 1.6 (s, 3), and 1.4 (s, 6).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.97; H, 10.45.

2-(1′-Methylcyclohexen-4′-yl)-2-propen-1-ol (10). A complex of *n*-butyllithium tetramethylethylenediamine (TMEDA) was formed by dropwise addition of 8.77 g (0.075 mol) of TMEDA to 0.075 mol of *n*-butyllithium at 25° under an N_2 atmosphere. This yellow solution was used to metalate 21 g (0.154 mol) of limonene by dropwise addition of the limonene to the *n*-BuLi–TMEDA solution at 25°. The dark red reaction mixture was stirred overnight and cooled to below −40°, and dry air was slowly bubbled through, taking care to maintain the temperature below −20°. When the exothermic reaction was complete, the vessel was warmed to 25°, and 15 ml of H_2O and 70 ml of 25% sodium sulfite solution were added. After vigorous stirring for 24 h, the layers were separated. Distillation of the product after isolation (Et_2O, 5% aqueous HCl, 5% aqueous KOH, brine) gave 3.42 g (30%) of the alcohol containing an aromatic impurity, bp 74–77 °C (0.12 mm) (lit.[28] 66–71 °C (0.10 mm)).

Additional purification of the alcohol was done by $AgNO_3$ complexation. A 7.0-g portion of distilled alcohol (combined from two runs) was dissolved in 50 ml of pentane and extracted three times with 20-ml portions of half saturated aqueous $AgNO_3$. The combined $AgNO_3$ fractions were washed with 20 ml of pentane and poured slowly into an equal volume of concentrated aqueous NH_4OH at 0°. This was extracted twice with 30-ml portions of pentane, which were dried over $MgSO_4$. After solvent removal in vacuo, 2.5 g of alcohol was isolated (35.7%), making the overall isolated yield about 10.7%: ^{1}H NMR (CCl_4) δ 5.40 (br s, 1), 4.8–5.0 (overlapping doublets, 2), 3.98 (s, 2), 3.43 (s, 1), 2.2–1.85 (m, 7), 1.7 (m, 2), and 1.62 (s, 3); ir (neat) 3300 (O–H), 2900 (C–H), 1650 (C=C), 1430 (C=C), and 1050 (C=O) cm^{-1}.

2-(1′-Methylcyclohexen-4′-yl)-2-propenyl Bromide (11). In a flask containing 60 ml of anhydrous ether and 1.03 g (0.0037 mol) of PBr_3 at 0° in the absence of light was added, dropwise, 2.2 g (0.143 mol) of alcohol **10**. After stirring for 2 h, the reaction was poured into ice water. A 90.5% yield (2.815 g) of bromide **11** was isolated (Et_2O, saturated aqueous $NaHCO_3$, brine, $MgSO_4$): ir (neat) 2900 (C–H), 1650 (C=C), and 1430 (C=C) cm^{-1}.

Alkylation of Tiglic Acid (6a) with 11 (Method D). After forming the copper dienolate of 0.6 g (0.006 mol) of tiglic acid (dienolate method III, alkylation D), 1.4 g (0.0065 mol) of **11** was added slowly. After the reaction was complete, it was quenched with 10 ml of 5% HCl, and isolation procedure 3 was employed. The crude acid was methylated with excess diazomethane and the solvent was reduced in vacuo. Only one product peak was seen on GLC (column B, 150 °C). The product was purified by preparative TLC using ether–hexane, (15:85, two developments), which gave 0.63 g (61%) of the ester **13**:[29a] ^{1}H NMR (CCl_4) δ 6.62 (t, 1), 5.3 (m, 1), 4.72 (d, 2), 3.65 (s, 3), 2.3–1.85 (m, 11), 1.77 (d, J = 0.5 Hz, 3), and 1.6 (s, 3).

***dl*-Lanceol[29] (14).** Ester **13** was reduced to the alcohol using alu-

minum hydride. Lithium aluminum hydride (0.082 g, 2.1 mmol) was slurried in 15 ml of anhydrous ethyl ether under N_2 at 0°, and 0.0939 g (0.7 mmol) of aluminum chloride was added. After stirring at 25° for 30 min, the temperature was once more lowered to 0°, and 0.186 g (0.75 mmol) of ester **13** in 2 ml of ethyl ether was added dropwise with a syringe. After stirring 30 min at 25°, 0.5 ml of H_2O was slowly added, followed by 0.5 ml of 15% KOH and 1.5 ml of H_2O. The heavy white precipitate was removed by filtration and washed with 15 ml of ether. Product isolation (Et_2O, brine, $MgSO_4$) and purification by preparative TLC (ether–hexane 30:70, two developments) gave 0.15 g (93.7%) of *dl*-lanceol (**14**): ^1H NMR ($CDCl_3$) δ 5.38 (m, 2), 4.7 (m, 2), 3.96 (s, 2), 2.2–1.8 (m, 10), and 1.62 (s, 6); ir (neat) 3400 (O–H), 2900 (C–H), 1640 (C=C), 1415 (C=C), 1050 (C–O), and 890 (C=C) cm^{-1}.

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