of repressors to the DNA follow a "one-dimensional" diffusion along the chain, in Chou's picture most of the flow of S molecules to the active site comes from the "three-dimensional" diffusion around the E molecule in a spherical shell whose thickness is about the same as, or a little larger than, the range of van der Waals force.[18] With the knowledge about the interfacial diffusion coefficient, especially about the complicated molecular forces and the detailed structure (such as the so-called "icelike" structure) on the surface of an E molecule, not yet sufficiently known, the present calculations and discussions based on Chou's model are rational at least in a sense of approximation.

Second, there will be a reduction (between 25% and 60%) in the rate of diffusion-controlled reaction if the hydrodynamic effect[6,7] is taken into account. But, in comparison with the role of the van der Waals force that gives one order of magnitude in raising the rate from that obtained by the semispherical model, the role of the hydrodynamic effect is relatively small. Besides, what we are interested in here is to compare the semispherical model and the Chou's model so as to disicuss the role of the major protein outside the active site. While the hydrodynamic effect will exert analogous influence on both cases, the principal points discussed here are still valid even without taking the hydrodynamic effect into account.

Third, as regards how to take into consideration diffusion of product (P) molecules away from an E molecule, the reader may refer to the paper by Chou and Forsen.[42] There the diffusion-controlled effects in reversible enzymatic fast reaction systems are discussed, and also it is pointed out that, in such a case, the diffusion-controlled reaction rate is related not only to the diffusion coefficient, the force field, the size of an active site, and so on, but also to the ratio of the concentration of the P molecules to that of the S molecules when the reaction system attains equilibrium. Of course, such an effect will exert the same influence on both the semispherical model and Chou's model, too.

**Acknowledgment.** Valuable discussions with Dr. Theodoor A. J. Payens, Dr. Athel Cornish-Bowden, Professor Xie Si-Dong, and Professor Bjorn Lindman are gratefully acknowledged.

(42) K. C. Chou and S. Forsen, *Biophys. Chem.*, **12**, 255 (1980).

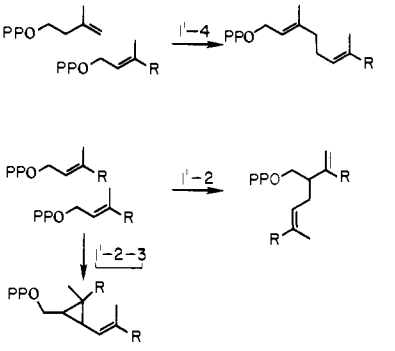
# Model Studies of Terpene Biosynthesis. Intermolecular 1′-2 Electrophilic Condensation of 3-Methyl-2-butenyl Acetate[1,2]

**Chi-Hsin R. King and C. Dale Poulter*[3]**

*Contribution from the Department of Chemistry, University of Utah, Salt Lake City, Utah 84112.* *Received July 1, 1981*

**Abstract:** The stereochemistry of the carbon–carbon bond-forming step in the electrophilic intermolecular 1′–2 condensation of 3-methyl-2-butenyl acetate (**1**-OAc) to yield lavandulyl acetate (**2**-OAc) was studied. Treatment of (1*S*)-[1-$^2$H]3-methyl-2-butenyl acetate ((1*S*)-[1-$^2$H]**1**-OAc) with aluminum trichloride in ethyl acetate gave labeled lavandulyl acetate ([1,3-$^2H_2$]**2**-OAc) (30%) and isoprene (65%) as the major products. The configurations at C(1), C(2), and C(3) and the relative abundances of the diastereomers of [1,3-$^2H_2$]**1**-OAc were determined by converting the mixture to [2,4-$^2H_2$]3-(2′-propyl)-butyrolactone ([2,4-$^2H_2$]**3**). The intensities of $^1$H resonances characteristic of each diastereomer were measured with the aid of Pirkle's chiral shift reagent, (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. The analysis showed that equal amounts of the (1*S*,2*S*,3*R*), (1*S*,2*R*,3*R*), (1*S*,2*S*,3*S*), and (1*S*,2*R*,3*S*) diastereomers of [1,3-$^2H_2$]**2**-OAc were obtained, signifying that the 1′–2 condensation was stereorandom at C(1) of the electrophilic isoprene unit.

Allylic cations are thought to play important roles in the condensation reactions that constitute the major bond-forming reactions in the terpene biosynthetic pathway. Examples include the 1′–4 coupling reaction used to attach isoprenoid residues in a sequential fashion to a growing allylic terpene chain,[4] the 1′–2 coupling reaction which produces the nonhead-to-tail fusion of residues found in some irregular monoterpenes[5] and carotenoids,[6] the 1′–2–3 coupling reaction recently discovered in the sterol[7,8] and carotenoid pathways,[9] and numerous intramolecular cyclizations.[10] The transformations can all be rationalized as electrophilic condensations, and in some instances experiments have confirmed the electrophilic character of the enzyme-catalyzed reactions.[4,11-14]




(1) Taken from the dissertation of C. H. R. King, submitted in partial fulfillment of the requirements for a Ph.D. degree at the University of Utah, 1980.

(2) We wish to acknowledge the National Institutes of Health, GM 21328, for support of this research.

(3) National Institutes of Health Research Career Development Awardee, HL 00084, 1975-1980.

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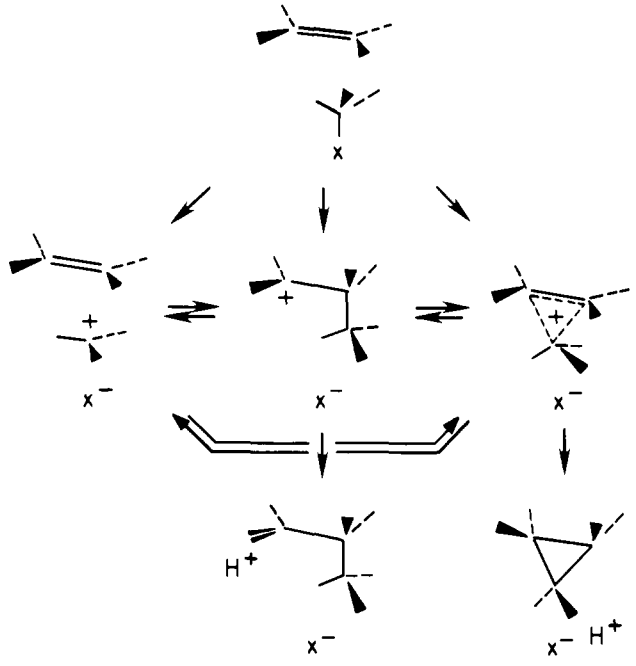
Scheme I. A General Scheme for Electrophilic Condensation Reactions

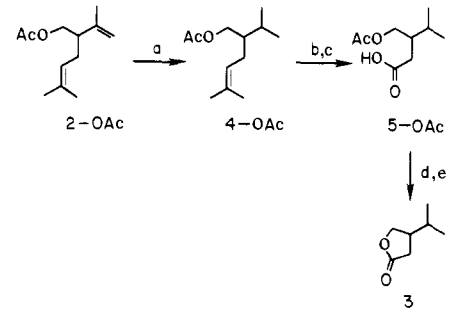


The enzymatic reactions are stereospecific in all of the instances examined thus far.[15] This phenomenon has sometimes been rationalized by assuming that the bond-breaking and bond-making events in the condensation are concerted.[16] Such interpretations are, however, subject to question since stereospecificity may also simply be a result of how the enzyme binds the substrates prior to catalysis.

Scheme I outlines several options for changes in bonding that may occur during an electrophilic condensation. The exact pathway traversed with regard to regiochemistry and concertedness during a specific electrophilic condensation reaction depends on several factors that influence the stability of potential carbocationic intermediates.[17] These include the effect of substituents on the stabilities of developing cationic centers,[18] the nucleophilicity of the double bond, and the orientation of the condensing partners. Negatively charged moieties, for example the leaving group, may also exert a strong influence on the structure of the carbocation through charge–charge interactions in ion pairs.[14,19-22] and assist with quenching the positive charge by removal of a proton or by direct combination.[23,24] Uncharged nucleophiles can also assist with the two latter events. Although substitution patterns exert a dominant influence in solution, the other factors may become much more important for reactions occurring within a highly structured environment such as the active site of an enzyme. It is, therefore, possible that no single mechanism will account for all biological electrophilic condensation reactions.

The question of how an isoprenoid allylic cation behaves during a condensation reaction where no prior restrictions exist with respect to the orientation of the reactive partners naturally arises. Beginning with the pioneering work of Schinz and Shappi,[25] several

Scheme II. Synthesis of 3-(2'-Propyl)butyrolactone from Lavandulyl Acetate



[a] $N_2H_2$. [b] $O_3$, −78 °C. [c] $CrO_3/H_2SO_4$. [d] NaOH. [e] 3 N HCl.

groups have studied the intermolecular condensation between 3-methyl-2-butenyl electrophiles and 3-methyl-2-butenyl[26,27] or 3-methyl-3-butenyl partners.[28-30] The yields of condensed material are usually below 40%, but conversions as high as 90% based on the limiting reagent have been found at short reaction times.[28] The regiochemistries of the alkylations are those predicted on the basis of the stability of the open carbocations, and no evidence for products with cyclopropane rings has been found. Stereochemical studies that bear on the timing of the bond-making and bond-breaking events shown in Scheme I have been reported for intramolecular electrophilic olefin cyclizations.[10] In some cases the results are compatible with a concerted process, but no clear general pattern for a family of electrophiles has yet emerged.[31,32] Similar studies for the intermolecular case have not been published. In this paper we present the first such studies for the self-condensation of 3-methyl-2-butenyl acetate (**1**-OAc),[33] a simple biomimetic model for the 1'–2 condensation reaction which places no steric constraints on the orientation of the two reacting partners.

**Strategy for the Stereochemical Analysis.** The 1'–2 condensation reaction produces a carbon–carbon bond between C(1) of the isoprenoid electrophile and C(2) of the isoprenoid nucleophile. In the case of **1**-OAc, C(2) of the product, lavandulyl acetate (**2**-OAc), must be generated in a stereorandom manner since there is no topological distinction between reaction at the *re* and *si* faces of the double bond in the absence of chiral centers in the starting material or reagents. However, the center which becomes C(3)

(R)-2-OAc (S)-2-OAc

will be inverted or racemized, depending on the timing of ionization and condensation. At the two extremes, a concerted reaction requires inversion of the electrophilic center, while a free or symmetrically solvated allylic cationic intermediate will lead to racemization.

If C(1) of the alkylating isoprene unit is labeled with deuterium, the product will contain two chiral centers. Assuming that deuterium will not generate any significant amount of asymmetric induction, formation of the C(2)–C(3) bond in **2**-OAc will be

(15) Several examples of a single plant which synthesizes both enantiomers of certain monoterpenes have been reported. It is not known, however, if a single enzyme synthesizes both enantiomers or if two enzymes are required.
(16) Cornforth, J. W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 903–964.
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(23) This alternative is not shown in Scheme I.
(24) Popjak, G. *Harvey Lect.* **1971**, *65*, 127–156.
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(33) Abbreviations used are acetate, Ac; infrared, IR; pyrophosphate, PP; nuclear Overhauser enhancement, NOE; NMR, nuclear magnetic resonance.

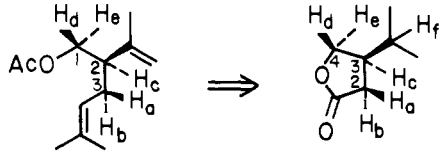
Table I. $^1$H NMR Parameters for 3-(2′-Propyl)butyrolactone[a]

| proton | chemical shifts, ppm | coupling constants, Hz |
|---|---|---|
| $H_a$ | 1.59 | $^2J_{H_a,H_b} = 17.0$ |
| | | $^3J_{H_a,H_c} = 9.8$ |
| $H_b$ | 1.98 | $^3J_{H_b,H_c} = 8.4$ |
| $H_c$ | 1.38 | $^3J_{H_c,H_d} = 8.7$ |
| | | $^3J_{H_c,H_e} = 7.7$ |
| | | $^3J_{H_c,H_f} = 8.4$ |
| $H_d$ | 3.27 | $^2J_{H_d,H_e} = 8.8$ |
| $H_e$ | 3.72 | |
| $H_f$ | 0.87 | $^3J_{H_f,CH_3} = 6.6$ |
| $CH_3$'s | 0.39 | |
| | 0.45 | |

[a] 50 mM solution in benzene-$d_6$, $Me_4Si$ internal standard.

stereorandom at C(2), and C(3) will be inverted or racemized. The diastereotopic hydrogens at C(3) can, in theory, be distinguished from one another on the basis of their chemical shifts, and the distribution of label at C(3) determined by $^1$H NMR. Analytical problems are compounded because the chemical shifts of the protons at C(3) in the (2*R*,3*R*) and (2*R*,3*S*) diastereomers are identical with those in the (2*S*,3*S*) and (2*S*,3*R*) diastereomers, respectively. Since no stereoselectivity is expected at C(2), equal intensities are expected for the protons at C(3) in labeled material irrespective of the stereochemistry of the reaction. Also, the diastereotopic protons at C(3) have almost identical chemical shifts in unlabeled **2**-OAc. Thus, difficulties associated with degenerate chemical shifts and peak assignments in **2**-OAc must be solved.

It occurred to us that the stereochemical analysis would be more tractible if the chiral centers were incorporated in a less flexible molecule with a larger intrinsic difference in the chemical shifts for the protons at C(3). Furthermore, a chiral shift reagent might induce additional nonequivalences which would permit us to measure the relative proportions of the individual diastereomers without resorting to a resolution step. This idea was explored by converting **2**-OAc to 3-(2′-propyl)butyrolactone (**3**) as shown in Scheme II. The disubstituted double bond was selectively hydrogenated with diimide, and the remaining double was cleaved with ozone. An oxidative workup with Jone's reagent gave acetoxyacid **5**-OAc which was converted to lactone **3**. This sequence of reactions translates C(1), C(2), and C(3) of **2**-OAc into C(4), C(3), and C(2) of lactone **3** without changing the configurations of the three centers.




These efforts were rewarded by an NMR spectrum of the lactone in benzene-$d_6$ at 300 MHz in which all eight sets of nonequivalent protons were cleanly resolved (see Table I). The higher field chemical shifts (approximately 0.5 ppm) seen for the isopropyl methyls in benzene-$d_6$ vs. carbon tetrachloride clearly indicate a substantial interaction between the lactone and the aromatic solvent. Each diastereotopic proton at C(2) and C(4) is coupled to its geminal neighbor and the vicinal hydrogen at C(3) and appears as a doublet of doublets (see Figures 1A and 2A). Kendall and Wells[34] assigned the higher field protons in each set to those cis to the isopropyl moiety on the basis of an expected shielding interaction by the alkyl group. We confirmed these assignments with an NOE experiment[35] by repeated integration of the signals at 1.98 ppm ($H_b$, 10 ± 3% enhancement), 3.27 ppm ($H_d$, −3 ± 1% enhancement), and 3.72 ppm ($H_e$, 5 ± 2% en-

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(35) Nachod, E. C.; Zucherman, J. J.; Randall, E. W. "Determination of Organic Structures by Physical Methods", Academic Press: New York, 1976; pp 271–333.

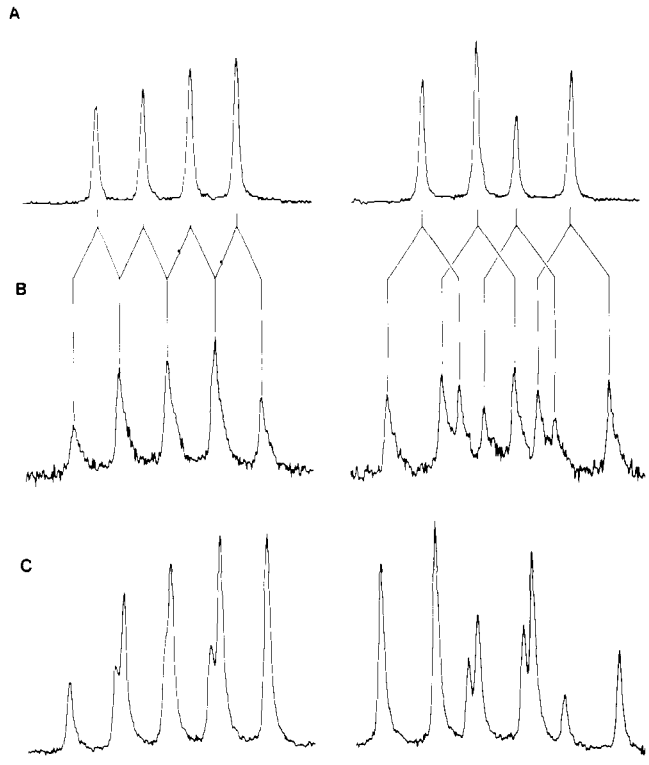



**Figure 1.** $^1$H NMR spectrum of the protons at C(2) in racemic lactone **3** recorded at 300 MHz in benzene-$d_6$ with $Me_4Si$ as an internal standard is shown in part A. The pattern at higher field (right side) is due to $H_a$, and the pattern at lower field (left side) to $H_b$. Part B shows the patterns for $H_a$ and $H_b$ with 5.0 equiv of (*S*)-**6** added to the solution. Part C shows the patterns for $H_a$ and $H_b$ with (*R*)-**3** (70% *R*, 30% *S*) and 5.0 equiv of (*S*)-**6** added to the solution.

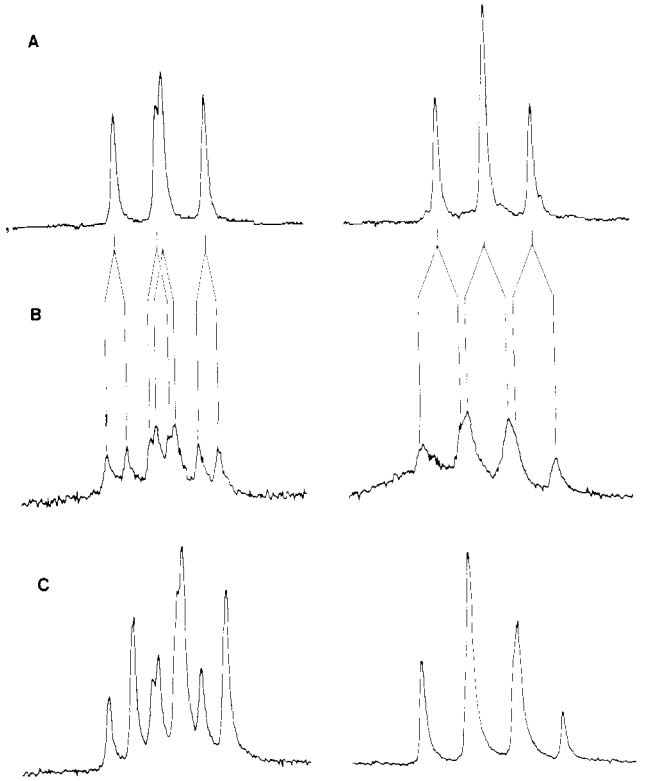



**Figure 2.** $^1$H NMR spectrum of the protons at C(4) in racemic lactone **3** recorded at 300 MHz in benzene-$d_6$ with $Me_4Si$ as internal standard is shown in part A. The pattern at higher field (right side) is due to $H_d$, and the pattern at lower field (left side) to $H_e$. Part B shows the patterns for $H_d$ and $H_e$ with 5.0 equiv of (*S*)-**6** added to the solution. Part C shows the patterns for $H_d$ and $H_e$ with (*R*)-**3** (70% *R*, 30% *S*) and 5.0 equiv of (*S*)-**6** added to the solution.

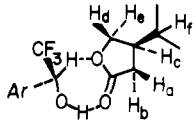
Table II. Chemical Shift Differences and Assignments for (*R*)- and (*S*)-3-(2′-Propyl)butyrolactone in the Presence of (*S*) 2,2,2-Trifluoro-1-(9′-anthryl)ethanol[a]

| protons | chemical shifts, ppm *R* | *S* | $\delta_R - \delta_S$, Hz |
|---|---|---|---|
| $H_a$ | 1.20 | 1.15 | 15.7 |
| $H_b$ | 1.54 | 1.58 | −9.7 |
| $H_c$ | 0.95 | 0.99 | −11.7 |
| $H_d$ | 2.94 | 2.91 | 7.8 |
| $H_e$ | 3.37 | 3.39 | −4.4 |
| $H_f$ | 0.55 | 0.52 | 7.6 |
| $CH_3$'s | 0.16 | 0.15 | 3.6 |
| | 0.19 | 0.18 | 3.6 |

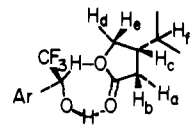
[a] 55 mM solution of (±)-**3** in the presence of 5 equiv of (*S*)-**6** at 300 MHz.

hancement) of a degassed sample of **3** with and without irradiation of the signal at 1.38 ppm ($H_c$). The multiplet at 1.59 ppm ($H_a$) was too close to the decoupling field for the Overhauser experiment and was assigned by the process of elimination.

Signals for enantiotopic hydrogens in **3** were resolved with (*S*)-2,2,2-trifluoro-1-(9′-anthryl)ethanol ((*S*)-**6**), a chiral shift reagent developed by Pirkle and co-workers[36] that is particularly effective for γ-lactones. Addition of 5.0 equiv of (*S*)-**6** to a 55 mM solution of **3** in benzene-$d_6$ resulted in separate sets of signals for the two enantiomers of the lactone (see Table II). Of special importance to us, the signals for the protons at C(2) and C(4) were particularly well-resolved (see Figures 1B and 2B). Pirkle developed a model to predict the effect of the reagent on enantiomeric lactones based on hydrogen bonding of the hydroxyl proton and the hydrogen at C(1) in the reagent with the carbonyl and alkoxy oxygens, respectively, in the lactone. In this complex,

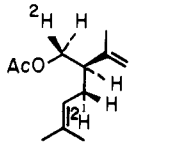


(S)-6:(R)-3

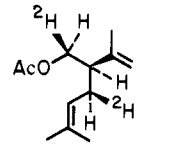


(S)-6:(S)-3

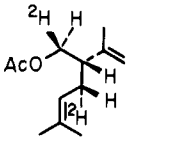
the aromatic rings in the anthryl group shield the lactone hydrogens, with those on the side of the lactone ring syn to the anthryl group experiencing the greatest upfield shift. Based on this model, $H_b$, $H_c$, and $H_e$ are the higher field signals in each pair for (*R*)-**3**, while $H_a$, $H_d$, $H_f$, and the methyl hydrogens are at higher field in (*S*)-**3**.



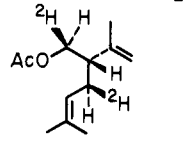
(1S,2R,3R)-[1,3-$^2H_2$]2-OAc



(1S,2R,3S)-[1,3-$^2H_2$]2-OAc



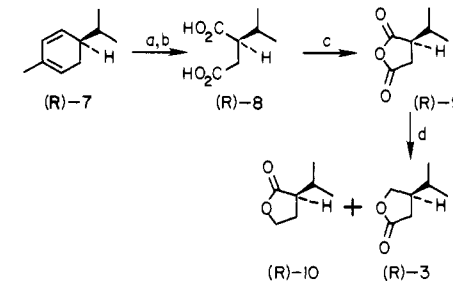
(1S,2S,3R)-[1,3-$^2H_2$]2-OAc



(1S,2S,3S)-[1,3-$^2H_2$]2-OAc

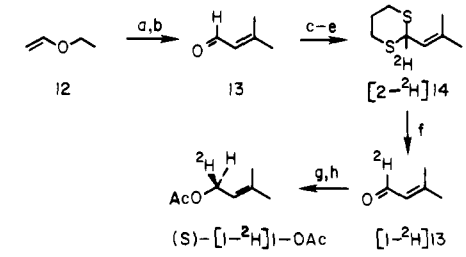
Since the assignments listed in Table II are critical, they were verified with (*R*)-3-(2′-propyl)butyrolactone ((*R*)-**3**) synthesized from (*R*)-α-phellandrene ((*R*)-**7**)[37-39] as outlined in Scheme III. The diene was treated with ozone, and the intermediate ozonide

Scheme III. Synthesis of (*R*)-3-(2′-Propyl)butyrolactone from (*R*)-α-Phellandrene



[a] $O_3$, −78 °C. [b] $CrO_3/H_2SO_4$. [c] 3 N HCl. [d] $LiAlH_4$.

Scheme IV. Synthesis of (*S*)-[1-$^2$H]3-Methyl-2-butenyl Acetate



[a] 2,2-Dimethoxypropane, $BF_3 \cdot Et_2O$. [b] AcOH/NaOAc. [c] 1,3-Propanedithiol, $BF_3 \cdot Et_2O$. [d] BuLi. [e] $^2H_2O$. [f] HgO, $BF_3 \cdot Et_2O$. [g] Yeast. [h] $Ac_2O$, pyridine.

was oxidized to (*R*)-(2′-propyl)succinic acid[34] ((*R*)-**8**). The dicarboxylic acid was cyclized to anhydride (*R*)-**9** before reduction with lithium aluminum hydride, to afford (*R*)-3-(2′-propyl)butryolactone[34] ((*R*)-**3**) and (*R*)-2-(2′-propyl)butryolactone[34] ((*R*)-**10**) in a 4:1 ratio. Chemical shift studies were then conducted with the chiral shift reagent and a 2.3 to 1 mixture of (*R*) and (*S*) lactones obtained by mixing (*R*)-**3** with racemic **3**. The results for $H_a$, $H_b$, $H_d$, and $H_e$ are shown in Figures 1C and 2C. Although the magnitudes of the shifts are slightly different in Figures 1B and 2B relative to those in Figures 1C and 2C, resulting in somewhat different patterns, the chemial shifts of protons in the two enantiomers can be easily assigned on the basis of differences in intensity. In agreement with the predictions based on Pirkle's model, enhanced signals were seen for the higher field components of $H_b$, $H_c$, and $H_e$ and the lower field components of $H_a$, $H_d$, $H_f$, and the methyl hydrogens. This observation removes any ambiguity concerning the assignments presented in Table II.

**Stereochemistry of the 1′–2 Condensation.** After considerable experimentation, we found that treatment of a concentrated solution of **1**-OAc in ethyl acetate with anhydrous aluminum chloride consistently gave 30% yields of lavandulyl acetate (**2**-OAc). A similar procedure was used by Takabe and co-workers[26] in the self-condensation of 3-methyl-2-butenyl thioacetate. The other major component in our reaction was isoprene (65%). A minor product (<1%) had a retention time similar to that of lavandulyl acetate (**2**-OAc). Although the material was not identified, it was not chrysanthemyl acetate (**11**-OAc), the expected product of a 1′–2–3 condensation, as determined by coinjection with an authentic sample.[40] A careful search for **11**-OAc was unsuccessful, although control experiments showed that as little as 0.01% could have easily been detected. Approximately 5% of the starting material could not be accounted for and presumably had polymerized.

(*S*)-[1-$^2$H]3-Methyl-2-butenyl acetate ((*S*)-[1-$^2$H]**1**-OAc) needed for the stereochemical studies was prepared as outlined in Scheme IV. Although the synthesis of 3-methyl-2-butenal (**13**) from ethyl vinyl ether (**12**) was not particularly efficient, the starting materials were cheap, and the procedure was easy to run

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on large scales.[41] Deuterium was introduced by conversion of aldehyde **13** to 1,3-dithiane **14**, followed by deprotonation of **14** with butyl lithium, treatment of the resulting anion with deterium oxide, and removal of the dithiane moiety with mercuric oxide.[42] An NMR spectrum of [2-$^2$H]**14** showed that the doublet at 4.85 ppm for the allylic methine hydrogen in unlabeled **14** had disappeared. Also, the ratio of the molecular ions at $m/z$ 175 and $m/z$ 174 for labeled and unlabeled material, respectively, indicated 97 ± 1% incorporation of deuterium. Aldehyde [1-$^2$H]**13** was reduced by actively fermenting yeast to a 1:1 mixture of (*S*)-[1-$^2$H]3-methyl-2-butenol and (*S*)-[1-$^2$H]3-methylbutanol.[43-45] Carbon–carbon double-bond reduction was recently reported for cinnamaldehyde[46] and was attributed to yeast enzymes other than the alcohol dehydrogenases. The mixture of $C_5$ alcohols was acetylated and (*S*)-[1-$^2$H]**1**-OAc was purified by gas chromatography. Labeled acetate was treated with aluminum trichloride as previously described to yield lavandulyl acetate bearing deuteruim at C(1) and C(3). Assuming that C(1) in (*S*)-[1-$^2$H]**1**-OAc was not racemized prior to condensation, the acetate was a mixture of perhaps as many as four diastereomers. The distribution of diastereomers was measured by conversion of the labeled acetate to [2,4-$^2H_2$]**3** as outlined in Scheme II. At 300 MHz in benzene-$d_6$, signals for $H_a$ and $H_b$ appeared as doublets of triplets, and each integrated to 0.5 protons (see Figure 3A). The 1:1:1 triplet patterns were a result of the geminal coupling between hydrogen and deuterium at C(2). The value measured for $^2J_{H,^2H}$ (see Table III) was close to the theoretical value calculated from $^2J_{H_a-H_b}$ = 17.0 Hz.[47] The signals for the hydrogens at C(4) were broad doublets, and each pair integrated to 0.5 protons (see Figure 4A). In this case the geminal coupling interaction was too small to be resolved.

Upon addition of 4.8 equiv of (*S*)-2,2,2-trifluoro-1-(9′-anthryl)ethanol ((*S*)-**6**) to the labeled lactone, the pattern at 1.52 ppm moved upfield and separated into a pair of doublets of triplets centered at 1.21 ppm ($\delta_R - \delta_S$ = 13.8 Hz, Figure 3B). Similar behavior was seen for the pattern at 1.92 ppm, which moved upfield to 1.60 ppm ($\delta_R - \delta_S$ = −9.1 Hz). The relative intensities of the overlapping sets of signals were deduced by cutting and weighing photocopies of the spectra. After making a correction for the slightly greater intensity of the higher field set of triplets in each pair, each gave identical integrated intensities. In contrast, the broad doublets at 3.20 and 3.66 ppm for the hydrogens at C(4) did not separate upon addition of (*S*)-**6**, although the signals moved upfield to 2.94 and 3.41 ppm, respectively (Figure 4B). Based on our results with unlabeled material, it is evident that the [2,4-$^2H_2$]**3** was an *equal* mixture of (2*S*,3*S*,4*S*), (2*S*,3*R*,4*S*), (2*R*,3*S*,4*S*), and (2*R*,3*R*,4*S*) diastereomers. Since the degadation of lavandulyl acetate did not alter the configurations of the chiral centers, labeled lavandulyl acetate obtained form the 1′–2 condensation of (1*S*)-[1-$^2$H]**1**-OAc is an equal mixture of (1*S*,2*S*,3*R*), (1*S*,2*R*,3*R*), (1*S*,2*S*,3*S*), and (1*S*,2*R*,3*S*) diastereomers.

## Discussion

Julia[28-30] and Takabe[26] studied the 1′–2 condensation reaction with various derivatives of the 3-methyl-2-butenyl system. Proton-catalyzed reactions were very sensitive to specific conditions, partly because the initial 1′–2 products were unstable to the acid catalysts.[28-30] The cross condensation between **1**-OAc and 3-methyl-2-butenyl thioacetate catalyzed by aluminum trichloride gave acceptible (ca. 19%) yields of lavandulyl thioacetate.[26] The major product was, however, 3-methyl-2-butenyl sulfide, presumably formed by alkylation at sulfur rather than the C(2)–C(3) double bond.

These results led us to study the self-condensation of 1-OAc in ethyl acetate with aluminum trichloride as a catalyst. Although a substantial portion of the allylic acetate underwent elimination to give isoprene, the yield of **2**-OAc was acceptible, and the condensation was highly regioselective. Maximum yields of **2**-OAc were achieved after about 30 min, and the product slowly decomposed upon prolonged exposure to the catalyst. Ethyl acetate had an important moderating influence on the reaction, which improved the selectivity for condensation vs. decomposition by presumably coordinating with aluminum trichloride.

The complete loss of stereochemistry at C(1) of the electrophilic isoprenoid unit during 1′–2 condensation requires that carbon–oxygen bond cleavage and carbon–carbon bond formation be two distinct steps or that C(1) is completely racemized via ion pair return prior to condensation. In a poorly ionizing solvent such as ethyl acetate, it is likely that the allylic cation and aluminate anion remain paired. Since the rotational barrier about the C(1)–C(2) bond in the cation is too high (~23 kcal/mol[48]) for a simple rotational isomerization, loss of stereochemical integrity at C(1) without internal return would necessitate migration of the aluminate counterion to the opposite face of the allylic system

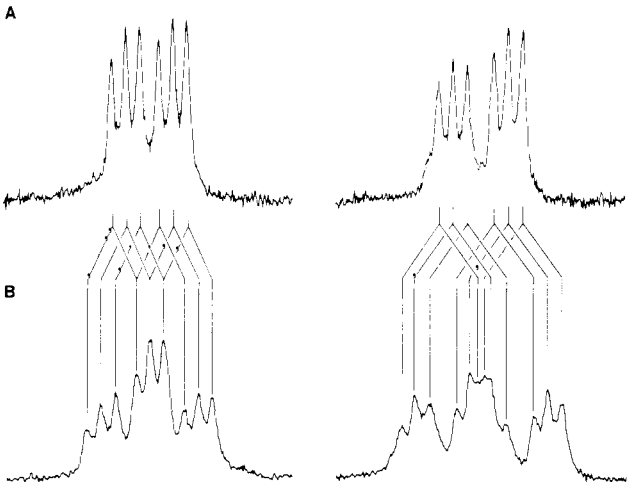


**Figure 3.** $^1$H NMR spectrum of the protons at C(2) in lactone [2,4-$^2H_2$]**3** recorded at 300 MHz in benzene-$d_6$ with $Me_4Si$ as an internal standard is shown in part A. The pattern at higher field (right side) is due to $H_a$, and the pattern at lower field (left side) to $H_b$. Part B shows the patterns for $H_a$ and $H_b$ with 4.8 equiv of (*S*)-**6** added to the solution.

Table III. $^1$H NMR Parameters for [2,4-$^2H_2$]3-(2′-Propyl)butryolactone[a]

| protons | chemical shifts, ppm | relative intensities | coupling constants, Hz |
|---|---|---|---|
| $H_a$ | 1.52 | 0.5 | $^2J_{H_a,^2H}$ = 2.5 |
| | | | $^3J_{H_a,H_c}$ = 9.9 |
| $H_b$ | 1.92 | 0.5 | $^2J_{H_b,^2H}$ = 2.5 |
| | | | $^3J_{H_b,H_c}$ = 8.6 |
| $H_c$ | 1.30 | 1.0 | $^3J_{H_c,H_d}$ = 8.6 |
| | | | $^3J_{H_c,H_e}$ = 7.6 |
| | | | $^3J_{H_c,H_f}$ = 8.4 |
| $H_d$ | 3.20 | 0.5 | $^2J_{H_d,^2H} \leq 1.0$ |
| $H_e$ | 3.66 | 0.5 | $^2J_{H_e,^2H} \leq 1.0$ |
| $H_f$ | 0.82 | 1.0 | $^3J_{H_f,CH_3}$ = 6.6 |
| $CH_3$'s | 0.36 | 3.0 | |
| | 0.41 | 3.0 | |

[a] 64 mM solution in benzene-$d_6$, $Me_4Si$ internal standard.

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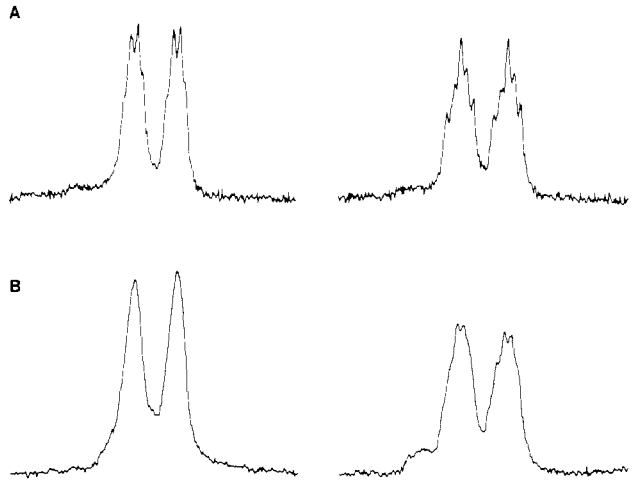


**Figure 4.** $^1$H NMR spectrum of the protons at C(4) in lactone [2,4-$^2H_2$]**3** recorded at 300 MHz in benzene-$d_6$ with $Me_4Si$ as an internal standard is shown in part A. The pattern at higher field (right side) is due to $H_d$, and the pattern at lower field (left side) to $H_e$. Part B shows the patterns for $H_d$ and $H_e$ with 4.8 equiv of (*S*)-**6** added to the solution.

much faster than condensation. As an alternative, ion pair return to the allylically rearranged tertiary system followed by rotation about the C(1)–C(2) bond and reionization would also scramble the label at C(1). We could not distinguish between the two possibilities for stereorandomization if internal return occurred exclusively to a chloride in the aluminate because allylic chlorides are more reactive than the corresponding acetates. We can, however, rule out internal return to acetate prior to condensation. Since the 3-methylbutenyl cation gives approximately a 1:2 ratio of primary and tertiary products with oxygen nucleophiles, a significant amount of internal return would have resulted in substantial racemization of (*S*)-[1-$^2$H]**1**-OAc as the reaction proceeded, with concomitant racemization at C(1) of [1,3-$^2H_2$]**2**-OAc. An NMR spectrum of [2,4-$^2H_2$]**3** (Figure 4B) clearly indicates, however, that [1,3-$^2H_2$]**2**-OAc is formed with retention at C(1). The simplest explanation of our data is that ionization is not assisted by intermolecular double bond participation and that racemization occurs in the carbocation–aluminate ion pair before condensation.

The absence of intermolecular $\pi$ participation during the electrophilic condensation of **1**-OAc has a biological parallel in the 1′–4 condensation catalyzed by farnesyl pyrophosphate synthetase. We recently reported linear free-energy correlations for the enzyme-catalyzed reaction which indicate that carbon–oxygen bond cleavage and carbon–carbon bond formation are distinct steps.[13] Thus, even in a case where the enzyme presumably binds the substrates in an orientation favorable for $\pi$ participation, the developing allyl cation is not significantly stabilized by the adjacent double bond.

## Experimental Section

**General.** Boiling points were uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on Varian Associates EM-390, XL-100, and SC-300 spectrometers and are reported in parts per million ($\delta$, ppm) downfield from tetramethylsilane, internal standard. Unless otherwise indicated, NMR spectra were obtained in carbon tetrachloride (Mallinkrodt, SpectrAR grade) containing 1% tetramethylsilane (Diaprep. Inc.) and 4% chloroform (Mallinkrodt, SpectrAR grade) as internal standards. Infrared (IR) spectra were obtained on Beckman Acculab 3 and Perkin-Elmer 299 infrared spectrophotometers. Optical rotations were measured with a Perkin-Elmer Model 141 digital polarimeter operating at 589 nm (sodium D line) in a 1-dm water jacketed cell. Optical rotations are reported as specific rotation ($[\alpha]^{25}_D$) and concentrations in grams per 100 mL of solvent. Mass spectra (chemical ionization and electron impact) were obtained on a Varian MAT 112-S mass spectrometer.

Analytical gas–liquid chromotography was performed on a Varian-Aerograph Model 1200 instrument equipped with a flame ionization detector and a Hewlett-Packard Model 3370 B digital integrator. Reproducibility of identical runs averaged ±0.5% and never exceeded ±2%. Analytical separations were achieved with 500 ft × 0.03 in. (i.d.) stainless steel open tubular columns coated with Carbowax 20 M (recrystallized from ethanol) or SF-96 (Analabs Inc.). Preparative separations were performed on a Gow-Mac Series 550 gas chromatograph, with use of 4 ft × 0.25 in. glass columns packed with 10% Carbowax 20 M on 60/80 mesh Chromosorb W-AW, 10% DEGS on 60/80 mesh Chromosorb W-AW, and 3.3% 10:1 SF 96/Igepal on 60/80 mesh Chromosorb W-AW, or a 4 ft × 0.25 in. copper column packed with 15% DC-200 on 80/100 mesh Chromosorb P. Thin-layer chromatography was carried out on 75 × 25 mm "Bakerflex" precoated silica gel 1B-F sheets (silica gel G with fluorescent; J. T. Baker Co.), in vapor-saturated tanks, and visualized first with 254-nm light followed by staining with iodine.

**2-(2′-Propyl)-5-methyl-4-hexenyl Acetate, Dihydrolavandulyl Acetate (4-OAc).** Following the procedure of Hamersma and Snyder,[49] 2.5 mL of glacial acetic acid was added over 30 min to a stirred suspension containing 1.0 g (5.1 mmol) of lavandulyl acetate (Givaudan) and 8.3 g (42.7 mmol) of potassium azodicarboxylate in 166 mL of anhydrous pyridine at 50 °C. The reduction was followed by GLC (500 ft SF-96, 140 °C) and additional 2.5-mL portions of glacial acetic acid were added after 6, 18, 24, 30, 44, and 54 h, and 2-g and 1-g portions of potassium azodicarboxylate were added after 30 and 54 h, respectively. After 81 h, the reaction mixture was allowed to cool to room temperature and poured into 150 mL of diethyl ether. The solution was extracted with 5 N hydrochloric acid until the aqueous layer remained acidic. The ether layer was then washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure to give 0.99 g (98%, crude) of light yellow oil. Gas chromatography indicated that the crude product contained dihydrolavandulyl acetate (70%), tetrahydrolavandulyl acetate (16%), and lavandulyl acetate (14%). Analytical samples were collected by GLC (Carbowax 20 M, 140 °C); IR ($CCl_4$) 2940, 2900, 1730, 1460, 1375, 1362, 1240, 1040 cm$^{-1}$; NMR ($CCl_4$) 0.92 (6, d, $^3J$ = 6 Hz, methyls of isopropyl group), 1.58 (3, s, methyl at C(5)), 1.68 (3, s, methyl at C(5)), 1.95 (3, s, acetoxy methyl), 1.1–2.6 (4, m, H at C(2), C(3) and methine H of isopropyl group), 3.78 (1, d of d, $^2J_{gem}$ = 11 Hz, $^3J$ = 6 Hz, H at C(1)), 3.92 (1, d of d, $^2J_{gem}$ = 11 Hz, $^3J$ = 6 Hz, H at C(1)), 5.04 (1, t, vinyl H); mass spectrum (CI, methane, 70 eV) *m/z* (relative intensity) 199 (28, M + 1).

**3-(Acetoxymethyl)-4-methylpentanoic Acid (5-OAc).** A solution of 50 mg (0.25 mmol) of dihydrolavandulyl acetate in 12 mL of methylene chloride was cooled to −78 °C (dry ice–2-propanol), and a stream of 2% ozone in oxygen (generated with a Welsbach T-23 ozonizer operating at 90 V and 4.2 psi of dry oxygen) was bubbled into the solution until the deep-blue color of ozone appeared. The solution was allowed to stir at −10 °C for 1 h before excess ozone was removed at that temperature with a stream of dry nitrogen. The solution was allowed to warm to room temperature, and the solvent was removed at reduced pressure. The residue was dissolved in 2 mL of acetone and placed in an ice–water bath. Standard Jone's reagent (0.35 mL, 26.72 g of crominum trioxide in 23 mL of concentrated sulfuric acid diluted to 100 mL with water) was added dropwise. The resulting mixture was allowed to stir at 0 °C for 30 min and at room temperature for 30 min. Excess Jone's reagent was destroyed by addition of 2-propanol, and the reaction mixture was extracted with ether. The combined extracts were washed with 10 mL of saturated brine and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure, and the residue was dissolved in ethyl acetate. The resulting solution was extracted with saturated sodium carbonate solution twice, and the aqueous extracts were chilled in ice and acidified with 3 N hydrochloric acid. The acidic solution was extracted with ethyl acetate, and the extract was dried over magnesium sulfate. Solvent was removed at reduced pressure, giving 33.4 mg (71%) of a clear liquid; IR (neat) 3400–2400 (br), 2940, 2900, 1735, 1702, 1460, 1396, 1235 (br), 1042 cm$^{-1}$; NMR ($CDCl_3$) 0.92 (6, d, $^3J$ = 6 Hz, methyls at C(4)), 1.07–1.89 (2, m, H at C(3) and C(4)), 2.00 (3, s, acetoxy methyl), 2.32 (2, m, H at C(2)), 3.91 (1, d of d, $^2J$ = 12 Hz, $^3J$ = 6 Hz, H at C(1)), 4.14 (1, d of d, $^2J$ = 12 Hz, $^3J$ = 6 Hz, H at C(1)), 8.22 (1, s, br, carboxylic H).

**3-(2′-Propyl)butyrolactone (3).** 3-(Acetoxymethyl)-4-methylpentanoic acid (40 mg, 0.21 mmol) was dissolved in 10 mL of 5% aqueous potassium hydroxide solution and allowed to stir at 65 °C for 16 h. The reaction mixture was acidified with 3 N hydrochloric acid and continuously extracted with benzene. Benzene was removed at reduced pressure, and the crude product was purified by GLC (Carbowax 20 M, 150 °C), giving 18 mg (67%) of a colorless liquid; IR (neat) 2950, 1770, 1462, 1420, 1390, 1365, 1293, 1233, 1177, 1148, 1050, 1018, 860, 830, 690 cm$^{-1}$; NMR[34] ($C_6D_6$, 300 MHz) 0.39 (3, d, $^3J$ = 6.6 Hz, methyl),

(49) Hamersma, J. W.; Snyder, E. I. *J. Org. Chem.* **1965**, *30*, 3985–3988.

0.45 (3, d, $^3J$ = 6.6 Hz, methyl), 0.87 (1, d of heptet, $^3J$ = 6.6 Hz, $^3J$ = 8.4 Hz, methine H of isopropyl), 1.38 (1, m, $^3J$ = 8.4 Hz, $^3J$ = 9.8 Hz, $^3J$ = 8.4 Hz, $^3J$ = 8.7 Hz, $^3J$ = 7.7 Hz, H at C(3)), 1.59 (1, d of d, $^2J$ = 17.0 Hz, $^3J$ = 9.8 Hz, H at C(2) trans to H at C(3)), 1.98 (1, d of d, $^2J$ = 17.0 Hz, $^3J$ = 8.4 Hz, H at C(2) cis to H at C(3)), 3.27 (1, d of d, $^2J$ = 8.8 Hz, $^3J$ = 8.7 Hz, H at C(4) trans to H at C(3)), 3.72 (1, d of d, $^2J$ = 8.8 Hz, $^3J$ = 7.7 Hz, H at C(4) cis to H at C(3)).

**Condensation of 2-Methyl-2-butenyl Acetate (1-OAc).** To a vigorously stirred solution containing 0.205 g (1.6 mmol) of 3-methyl-2-butenyl acetate[26,28] and 0.025 g (0.13 mmol) of tetradecane (internal standard for GLC analysis, response factor for lavandulyl acetate, 1.42) in 0.4 g of ethyl acetate was added 0.104 g (0.78 mmol) of anhydrous aluminum chloride (MCB) over 5 min at room temperature. The reation mixture was periodically sampled by injecting a 0.1-mL portion into 1 mL of saturated brine. The mixture was shaken thoroughly and extracted with a 1-mL portion of pentane. The pentane extract was analyzed by GLC. The presence of isoprene and lavandulyl acetate was verified by coinjection of authentic samples. Also, an analytical sample collected by GLC (Carbowax 20 M, 140 °C) gave IR and NMR spectra indentical with those reported for lavandulyl acetate.

**(*R*)-(−)-2-(2′-Propyl)succinic Acid ((*R*)-8).** A solution containing (*R*)-(−)-α-phellandrene (2.8 g, 20.6 mmol), $[\alpha]^{24}_D$ − 140° (*c* 6.4, chloroform), in 130 mL of methylene chloride was cooled to −78 °C (dry ice–2-propanol). A stream of ozone in oxygen was bubbled through the solution until the deep-blue color of excess ozone appeared. The resulting mixture was allowed to stand at −78 °C for 10 min before excess ozone was removed with a stream of dry nitrogen, and the solvent was removed at reduced pressure. The residue was dissolved in 150 mL of acetone and placed in an ice–water bath before treatment with 50 mL of standard Jone's reagent as described for 3-(acetoxymethyl)-4-methylpentanoic acid. The same workup was used to obtain 1.64 g (50%) of a colorless viscous liquid. Analytical samples were purified by column chromatography on silica gel (60–200 mesh, chloroform saturated with 88% formic acid, $R_f$ 0.09); IR (neat) 3600–3200 (br), 1710, 1465, 1425, 1395, 1375, 1250 (br), 1190 (br), 1045, 940, 850, 760 cm$^{-1}$; NMR[34] ($CDCl_3$) 0.96 (3, d, $^3J$ = 6.8 Hz, methyl), 1.00 (3, d, $^3J$ = 6.8 methyl), 1.8–2.3 (1, m, methine H of isopropyl), 2.3–2.9 (3, m, H at C(2) and C(3)), 10.4 (2, br s, carboxylic H); $[\alpha]^{24}_D$ −14.73° (*c* 7.8, chloroform) (ref 31).

**(*R*)-(+)-2-(2′-Propyl)succinic Anhydride ((*R*)-9).** A solution containing 1.00 g (6.3 mmol) of (*R*)-(−)-2-(2′-propyl)succinic acid in 15 mL of benzene was heated at reflux for 20 h. Solvent was removed at reduced pressure to afford 0.84 g (95%) of a crude product. Analytical samples were purified by GLC (DEGS, 175 °C); IR[31] (neat) 2960, 2840, 1850, 1780, 1460, 1410, 1390, 1375, 1280, 1220, 1095, 1065, 1045, 1020, 980, 960, 920, 840, 800, 730 cm$^{-1}$; NMR ($CDCl_3$) 1.00 (3, d, $^3J$ = 6.8 Hz, methyl), 1.05 (3, d, $^3J$ = 6.8 Hz, methyl), 2.05–2.46 (1, m, methine H of isopropyl), 2.46–3.19 (3, m, H at C(2) and C(3)); $[\alpha]^{24}_D$ +7.14° (*c* 0.78, chloroform).

**(*R*)-(+)-3-(2′-Propyl)butyrolactone ((*R*)-3).** A suspension of 0.16 g (4.0 mmol) of lithium aluminum hydride in 12 mL of tetrahydrofuran was heated at reflux for 30 min. The mixture was then cooled to −55 °C (dry ice–acetone) and 0.84 g (5.9 mmol) of (*R*)-(+)-2-(2′-propyl)-succinic anhydride in 9 mL of tetrahydrofuran was added dropwise over 20 min. After the addition was complete, the solution was allowed to warm up to 0 °C and maintained at 0 °C for an additional 15 min. The sample was quenched with 2.4 mL of 6 N hydrochloric acid and extracted with two 25-mL portions of ether. The combined organic layers were washed with water and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure to give 0.8 g of a viscous brown oil which upon analysis by GLC (DC 200, 150 °C) was found to contain a mixture of (*R*)-(+)-3-(2′-propyl)butyrolactone[34] and (*R*)-(+)-2-(2′-propyl)butyrolactone[34] (4:1). A sample of (+)-3-(2′-propyl)butyrolactone was purified by GLC; $[\alpha]^{24}_D$ +14.7° (*c* 0.91, chloroform); lit.[34] $[\alpha]^{23}_D$ −14.2° ($CCl_4$) for (*S*)-**3**. NMR and IR spectra were identical with those for (±)-3-(2′-propyl)butyrolactone.

**3-Methyl-2-butenal (13).** According to the procedure of Julia and co-workers,[41] the boron trifluoride–diethyl ether complex (3.1 g, 21.9 mmol) was added to 250 g (2.07 mol) of 2,2-dimethoxypropane dropwise over 5 min at 0 °C. The brown reaction mixture was cooled to −10 °C before 130 g (1.8 mol) of ethyl vinyl ether was added. After the addition was complete, the reaction mixture was allowed to stir for 30 min at −5 °C an then quenched by addition of 1.30 g (24 mmol) of sodium methoxide in methanol. The resulting solution was distilled, giving 154 g (49%), bp 73–76 °C (11 mm), of a colorless oil.

The product (118.5 g, 0.673 mol) was dissolved in 308 mL of glacial acetic acid containing 34.9 g of sodium acetate and 27 mL of water, and the resulting mixture was heated at reflux for 15 h. The reaction mixture was allowed to cool to 35 °C and carefully poured into 300 g of ice in 400 mL of saturated aqueous sodium bicarbonate solution. Powdered sodium bicarbonate was added until evolution of carbon dioxide ceased, and the mixture was extracted with ether. The combined organic layers were carefully washed with saturated sodium bicarbonate and saturated brine and dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure, and the residue was rapidly distilled to afford 37 g (65%) of a colorless liquid, bp 115–125 °C [lit.[50] bp 133 °C (730 mm)].

**2-(2′-Methylpropen-1′-yl)-1,3-dithiane (14).** The dithiane was prepared from aldehyde **12** (44.3 g, 0.53 mmol) according to the procedure of Poulter and Hughes[51] giving 67.2 g (73%) of a colorless oil, bp 84–86 °C (0.2 mm) [lit.[51] bp 84–86 °C (0.2 mm)].

**[2-$^2$H]2-(2′-Methylpropen-1′-yl)-1,3-dithiane ([2-$^2$H]14).** 2-(2′-Methylpropen-1′-yl)-1,3-dithiane (23.7 g, 0.14 mol) was dissolved in 105 mL of anhydrous tetrahydrofuran and cooled to −40 °C (dry ice–acetone) before addition of 60.7 mL (2.4 M, 0.15 mol) of *n*-butyllithium in hexane solution. The reaction mixture was allowed to stir for 2 h at −25 °C, before 6 mL (Stohler Isotopic Chemicals, 99.8% $^2$H) of deuterium oxide was added. Stirring was continued for 20 min at −30 °C and for 15 min at room temperature. The resulting mixture was extracted with pentane, the organic solution was dried over anhydrous magnesium sulfate, and solvent was removed at reduced pressure. Distillation of the residue afforded 22.58 g (95%) of a pale yellow liquid, bp 125–127 °C (4 mm); IR (neat) 2950, 1655, 1445, 1425, 1398, 1378, 1244, 1200, 1170, 1127, 1061, 1040, 910, 895, 872, 834, 813 cm$^{-1}$; NMR ($CCl_4$) 1.72 (6, d, $^4J$ = 1.5 Hz, two methyls), 1.82–2.15 (2, m, $^3J$ = 4 Hz, H at C(5)), 2.65–2.98 (4, m, H at C(4) and C(6)), 5.02 (1, br s, vinyl H); mass spectrum (70 eV) *m/z* (relative intensity) 177 (6.25), 175 (62.5 M), 174 (1.15), 160 (3.12), 159 (0.12), 106 (46), 101 (38), 100 (78), 86 (100), 46 (40), 45 (49), and 41 (48); incorporation of $^2H_1$ 97 ± 1% (calculation based on M and M − $CH_3$ peaks).

**[1-$^2$H]3-Methyl-2-butenal ([1-$^2$H]13).** [2-$^2$H]2-(2′-Methylpropen-1′-yl)-1,3-dithiane (1.8 g, 10 mmol) in 5 mL of tetrahydrofuran was slowly added to a vigorously stirred suspension of 4.3 g (20 mmol) of red mercuric oxide and 2.8 g (20 mmol) of boron trifluoride etherate in 23 mL of 15% aqueous tetrahydrofuran.[42] The mixture was allowed to stir for 30 min at room temperature and then extracted with ether. The combined organic layers were washed in succession with saturated sodium bicarbonate solution and brine and dried over magnesium sulfate. Solvent was removed at reduced pressure to give 0.57 g (67% crude yield) of a sample judged to be 90% pure by NMR. Analytical samples were purified by GLC (Carbowax 20 M) and the bulk of the material was used directly for the yeast reduction; IR (neat) 2980, 2958, 2850, 2170, 2150, 1665, 1640, 1468, 1385, 1336, 1202, 1170, 1008, 902, 845, 810 cm$^{-1}$; NMR ($CDCl_3$) 1.97 (3, d, $^4J$ = 1 Hz, methyl), 2.15 (3, d, $^4J$ = 1 Hz, methyl), 5.85 (1, br s, $^4J$ = 1 Hz, H at C(2)).

**(*S*)-[1-$^2$H]3-Methyl-2-buten-1-ol ((*S*)-[1-$^2$H]1-H).**[43–45] A solution containing 262 g of Fleishmann's baker's yeast and 262 g of sucrose in 2700 mL of water was warmed to 40 °C. Fermentation was monitored by evolution of carbon dioxide and foaming was controlled by frequent swirling and by addition of a few drops of octanol. After fermentation had commenced, 4.45 g (52 mmol) of [1-$^2$H]3-methyl-2-butenal ([1-$^2$H]**13**) in 15 mL of 95% ethanol was added, and the mixture was allowed to incubate at room temperature for 60 h. Solid material was removed by centrifugation, and the supernatant was steam distilled. Two 800-mL portions of distillate were collected, combined, and extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate, and solvent was removed by distillation. The residue was distilled to yield 2.36 g of a colorless liquid, bp 130–136 °C. Analysis by GLC (SF 96, 99 °C) indicated that the distillate was a mixture of (*S*)-[1-$^2$H]3-methyl-2-buten-1-ol (55%) and [1-$^2$H]isoamyl alcohol (45%). Analytical samples were purified by GLC; IR (neat) 3300 (br), 2960, 2905, 2860, 2140, 1670, 1450, 1380, 1200, 1115, 1050, 945, 900, 840 cm$^{-1}$; NMR ($CDCl_3$) 1.59 (1, s, hydroxyl H), 1.68 and 1.74 (6, s, two methyls), 4.06 (1, br d, $^3J$ = 7 Hz, H at C(1)), 5.37 (1, br d, $^3J$ = 7 Hz, H at C(2)); mass spectrum (70 eV) *m/z* (relative intensity) 88 (1.17), 87 (19.49 M), 86 (3.62), 72 (100), 71 (2.88), 69 (19), 68 (15), 54 (26), 44 (33), 42 (32), 41 (35), 40 (13), and 39 (24); GC–MS–SIM, *m/z* (integration) 72 (0.2715 × 10$^5$), 71 (0.1767 × 10$^4$); incorporation of $^2H_1$, 94%.

**(*S*)-[1-$^2$H]3-Methyl-2-butenyl Acetate ((*S*)-[1-$^2$H]1-OAc).** (*S*)-[1-$^2$H]3-Methyl-2-buten-1-ol ((1*S*)-[1-$^2$H]**15**) was acetylated with acetic anhydride in pyridine at 0 °C. Analytical samples were purified by GLC (Carbowax 20 M, 90 °C); IR (neat) 2960, 2180, 1742, 1670, 1445, 1378, 1248, 1030, 930 cm$^{-1}$; NMR ($CDCl_3$) 1.70 (3, s, methyl), 1.75 (3, s, methyl), 2.04 (3, s, acetoxy methyl), 4.53 (1, br d, $^3J$ = 7.8 Hz, H at C(1)), 5.32 (1, br d, $^3J$ = 7.8 Hz, H at C(2)); mass spectrum (70 eV) *m/z* (relative intensity) 129 (1.05, M), 87 (8), 86 (6), 72 (15), 71 (1.31),

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70 (25), 69 (61), 68 (34), 67 (21), 54 (14), 53 (14), 43 (100), 42 (35), 41 (32), and 39 (16); GC-MS-SIM $m/z$ (integration) 72 (0.1584 × $10^5$), 71 (0.1911 × $10^4$); incorporation of $^2H_1$, 94.8%.

**[1,3-$^2H_2$]2-(2′-Propenyl)-5-methyl-4-hexenyl Acetate, [1,3-$^2H_2$]Lavandulyl Acetate ([1,3-$^2H_2$]2-OAc).** To a vigorously stirred solution containing 0.33 g (2.56 mmol) of (*S*)-[1-$^2$H]3-methyl-2-butenyl acetate in 0.66 g of ethyl acetate at 0 °C was added 0.17 g (1.28 mmol) of anhydrous aluminum chloride. The reaction mixture was allowed to warm to room temperature and stirring was continued for 110 min before 2 mL of saturated brine was added. The resulting solution was extracted with pentane, and the combined organic layers were dried over anhydrous magnesium sulfate. Solvent was removed at reduced pressure, giving 76 mg (30%) of a colorless liquid. Analytical samples were purified by GLC (Carbowax 20 M, 140 °C); IR ($CCl_4$) 3060, 2955, 2905, 2850, 2310, 1737, 1640, 1445, 1372, 1240, 1100, 1045, 900, 825 $cm^{-1}$; NMR ($CDCl_3$) 1.58 (3, s, methyl), 1.68 (6, s, two methyls), 2.00 (3, s, acetoxy methyl), 2.07 (1, d of d, $^3J$ = 9 Hz, $^3J$ = 6 Hz, H at C(3)), 2.34 (1, d of d, $^3J$ = 9 Hz, $^3J$ = 6 Hz, H at C(2)), 3.99 (1, br d, $^3J$ = 6 Hz, H at C(1)), 4.70 (1, br s, olefinic methylene), 4.78 (1, br s, olefinic methylene), 5.02 (1, br d, $^3J$ = 6 Hz, H at C(4)); mass spectrum (70 eV) $m/z$ (relative intensity), 139 (2), 138 (8), 123 (13), 95 (47), 84 (22), 83 (10), 81 (14), 75 (15), 70 (100), 69 (57), and 68 (23); GC-MS-SIM (CI, isobutane) $m/z$ (integration) 199 (0.1422 × $10^5$, M + 1), 198 (0.8298 × $10^3$), 197 (0.1968 × $10^3$); incorporation of $^2H_2$, 93.4%.

**[2,4-$^2H_2$]3-(2′-Propyl)butyrolactone ([2,4-$^2H_2$]3).** Following the procedures described previously for preparation of 3-(2′-propyl)butyrolactone from lavandulyl acetate, 76 mg (0.38 mmol) of [1,3-$^2H_2$]lavandulyl acetate ([1,3-$^2H_2$]2-OAc) was converted into [2,4-$^2H_2$]3-(2′-propyl)butrolacetone ([2,4-$^2H_2$]3). The crude product was purifed by GLC (Carbowax 20 M, 140 °C) to yield 15.4 mg (31%) of a colorless oil; NMR ($C_6D_6$, 300 MHz), 0.36 (3, d, $^3J$ = 6.6 Hz, methyl), 0.41 (3, d, $^3J$ = 6.6 Hz, methyl), 0.82 (1, d of heptets, $^3J$ = 6.6 Hz, $^3J$ = 6.6 Hz, $^3J$ = 8.4 Hz, methine H of isopropyl), 1.30 (1, br m, $^3J$ = 8.4 Hz, $^3J$ = 9.9 Hz, $^3J$ = 8.6 Hz, $^3J$ = 7.6 Hz, H at C(3)), 1.52 (0.5, d of t, $^3J$ = 9.9 Hz, $^2J$ = 2.5 Hz, H at C(2) trans to H at C(3)), 1.92 (0.5, d of t, $^3J$ = 8.6 Hz, $^2J$ = 2.5 Hz, H at C(2) cis to H at C(3)), 3.20 (0.5, br d, $^3J$ = 8.6 Hz, H at C(4) trans to H at C(3)), 3.66 (0.5, br d, $^3J$ = 7.6 Hz, H at C(4) cis to H at C(3)).

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**Registry No. 1**-OAc, 1191-16-8; (1*S*)-[1-$^2H$]1-H, 55833-58-4; (1*S*)-[1-$^2H$]**1**-OAc, 80410-17-9; **2**-OAc, 25905-14-0; (1*S*,2*R*,3*R*)-[1,3-$^2H_2$]**2**-OAc, 80410-18-0; (1*S*,2*R*,3*S*)-[1,3-$^2H_2$]**2**-OAc, 80446-34-0; (1*S*,2*S*,3*R*)-[1,3-$^2H_2$]**2**-OAc, 80446-35-1; (1*S*,2*S*,3*S*)-[1,3-$^2H_2$]**2**-OAc, 80446-36-2; (*R*)-**3**, 80410-19-1; (*S*)-**3**, 53657-15-1; (±)-**3**, 80446-37-3; (2*S*,3*S*,4*S*)-[2,4-$^2H_2$]**3**, 80410-20-4; (2*S*,3*R*,4*S*)-[2,4-$^2H_2$]**3**, 80446-38-4; (2*R*,3*S*,4*S*)-[2,4-$^2H_2$]**3**, 80446-39-5; (2*R*,3*R*,4*S*)-[2,4-$^2H_2$]**3**, 80446-40-8; **4**-OAc, 74912-37-1; **5**-OAc, 80410-21-5; (*R*)-**7**, 4221-98-1; (*R*)-**8**, 1187-69-5; (*R*)-**9**, 80410-22-6; (*R*)-**10**, 80410-23-7; **12**, 109-92-2; **13**, 107-86-8; [1-$^2H$]**13**, 21849-61-6; **14**, 19860-69-6; [2-$^2H$]**14**, 80410-24-8; (1*S*)-[1-$^2H$]**15**, 55833-58-4; tetrahydrolavandulyl acetate, 40853-55-2; 3-methyl-2-butenyl acetate, 3814-41-3; 2-(2′-methylpropen-1′-yl)-1,3-dithiane, 19860-69-6; [1-$^2H$]isoamyl alcohol, 53939-07-4.

# *Communications to the Editor*

## Model Studies of Terpene Biosynthesis. Stereospecific Cyclization of *N*-Methyl-(*S*)-4-([1′-$^2$H]neryloxy)pyridinium Methyl Sulfate to α-Terpineol

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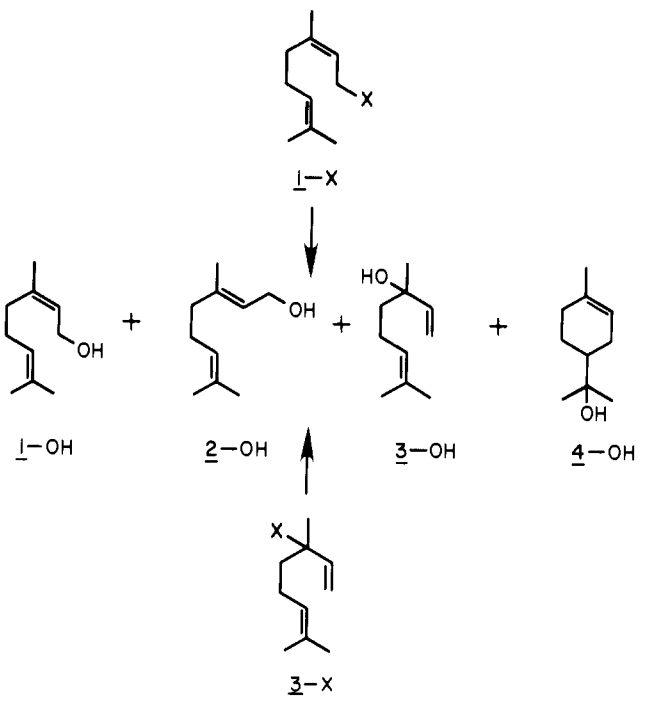
Much of the structural diversity found in the terpene biosynthetic pathway is introduced by olefin cyclization reactions of a few common acyclic precursors. The basic strategy involves intramolecular electrophilic alkylation of remote double bonds by allylic pyrophosphate esters. Treatment of the acyclic terpenes nerol (**1**-OH) and linalool (**3**-OH) with acid or solvolysis of appropriate derivatives gives a complex mixture of products containing **1**-OH, **3**-OH, geraniol (**2**-OH), and α-terpineol (**4**-OH). Formation of the cyclic isomer from neryl and linalyl precursors is commonly assumed to be a good model for related biological direct and allylic displacements.[1] As early as 1898, Stephan[2] reported optical induction in the acid-catalyzed cyclization of **3**-OH to **4**-OH, and enantiomeric excesses of up to 90% were found during the cyclization of linalyl *p*-nitrobenzoate (**3**-OpNB).[3] Arigoni and co-workers,[4] in a particularly elegant piece of work, recently deduced which conformation of the linalyl skeleton was preferred during cyclization. Several groups have commented on the attractiveness of a concerted reaction with π participation by the remote double bond to explain the stereoselectivity observed for the allylic displacement.[3-8] Although the isomeric neryl system has been studied extensively,[3,5-12] there are no reports of stereochemical studies for cyclization of **1**-OH to **4**-OH, presumably because of difficulties associated with the lack of a chiral center




X = halogen, hydroxyl,
*p*-nitrobenzoate, phosphate, pyrophosphate

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