Model Studies of the Biosynthesis of Non-Head-to-Tail Terpenes. Rearrangements of the Chrysanthemyl System[1]

C. Dale Poulter,*[2] Larry L. Marsh, John M. Hughes, J. Craig Argyle, Dennis M. Satterwhite, Robyn J. Goodfellow, and Scott G. Moesinger

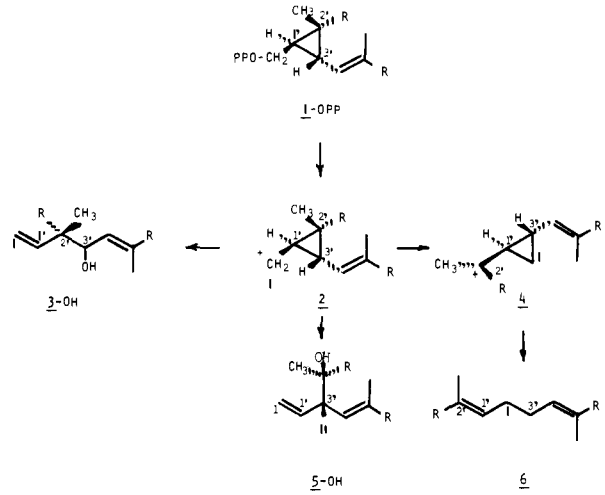
Contribution from the Department of Chemistry, University of Utah, Salt Lake City, Utah 84112. *Received June 16, 1976*

Abstract: A study of the solvolysis reactions of the chrysanthemyl system is reported. In water the chrysanthemyl cation (**2**) gives the naturally occurring monoterpene alcohols chrysanthemol (**1-OH**), artemisia alcohol (**3-OH**), yomogi alcohol (**11-OH**), and santolina alcohol (**5-OH**). Rupture of the C(1′)–C(3′) cyclopropane bond of **2** gives an isomeric allylic cation which reacts with solvent to yield artemisia alcohol (**3-OH**) and yomogi alcohol (**11-OH**). The chrysanthemyl cation also rearranges (cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement) to a tertiary cyclopropylcarbinyl cation, as has been suggested for the head-to-head biosynthetic rearrangements in the sterol and carotenoid pathways. The regiochemistry of **2** for rearrangement and reaction with nucleophiles is presented, and a mechanism for regulation of the rearrangements by an enzyme is discussed.

Terpenes are classified as "irregular" when the attachments of the isoprene units do not follow the common 1′–4 (head-to-tail) pattern.[3] The non-head-to-tail structures are often considered to be chemical and biological curiosities, perhaps because representative monoterpenes are largely confined to a closely related group of plants in the *Compositae* family. However, the discovery of presqualene pyrophosphate[4] and prephytoene pyrophosphate[5] as normal intermediates in the sterol and carotenoid biosynthetic pathways provided a structural link between higher terpenes and irregular monoterpenes. Although biological data for C_{10} compounds are still not conclusive,[6] it is becoming increasingly apparent that non-head-to-tail terpenes are important components in the general terpene biosynthetic pathway. Most current theories place irregular structures after branch points at which two head-to-tail terpene moieties, having double bonds between C(2) and C(3), are coupled.[6,7] The 1′–2 (lavandulyl) and 1′–2–3 (chrysanthemyl) structures have been proposed to be the initial products of the non-head-to-tail condensation reactions,[6a,c] with 1′–3 (artemisyl), 2–1′–3 (santolinyl), and 1′–1 (head-to-head) structures coming from rearrangements of the 1′–2–3 system.[6]

The primary cyclopropylcarbinyl cation **2** is a pivotal intermediate (Scheme I) in the rearrangement paths that have

Scheme I. Proposed Rearrangements of **1**.

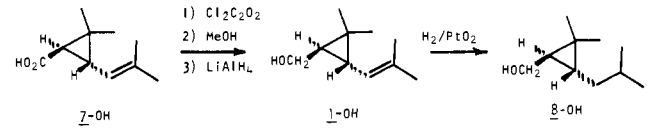


recently been suggested for the biosynthesis of non-head-to-tail terpenes.[6,7] For example, artemisia alcohol (**3-OH**, R = CH_3) is the expected homoallylic product when **2** is captured at C(3′) by water,[6a,b,c] while santolina alcohol (**5-OH**, R = CH_3) would result from capture at C(2′).[6b,c] Formation of the head-to-head terpene squalene (**6**, R = $C_{11}H_{19}$) can be explained by a cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement of **2** to **4** followed by capture of **4** at C(3′) by hydride.[7f,g] In cases where a single reactive intermediate can give more than one product, it is necessary for an enzyme to regulate the regiochemistry of the intermediate in order to obtain the high specificity characteristic of biological reactions. Since the boundary conditions of such regulation are dictated by the chemical properties of the substrate, it is important to know what these properties are when formulating a mechanism for an enzyme-catalyzed reaction.

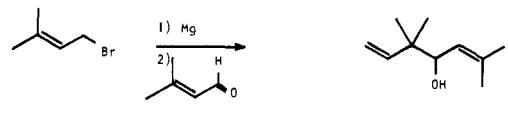
We decided that the chrysanthemyl cation (**2**, R = CH_3) would be ideal for evaluating the rearrangements shown in Scheme I. In those cases where R ≠ CH_3, the size of R, while important in binding between substrate and enzyme, should not alter the chemical properties of the cyclopropylcarbinyl core. When we began our study very little was known about vinyl-substituted cyclopropylcarbinyl cations with structures similar to **2**. The few papers in the literature focused on the chrysanthemyl system (R = CH_3), where it was reported that treatment of chrysanthemol (**1-OH**) with acid gave artemisia triene,[8] while acetolysis of chrysanthemyl tosylate yielded varying amounts of chrysanthemyl acetate and artemisia triene.[9] In this paper we present a detailed study of the cationic rearrangements of the chrysanthemyl system and propose a structure for the chrysanthemyl cation.

Results

Product and Kinetic Studies. (1′*R*,3′*R*)-Chrysanthemol (**1-OH**) and (1′*R*,3′*R*)-dihydrochrysanthemol (**8-OH**) were prepared from (1′*R*,3′*R*)-chrysanthemic acid, 98% enantiomeric excess. Artemisia alcohol (**3-OH**) and yomogi alcohol



(**11-OH**) were obtained as the major products from large scale hydrolyses of chrysanthemyl derivatives. Artemisia alcohol was also prepared by the Grignard addition shown below.



Dinitrobenzoate (ODNB), alkoxypyridinium iodide (OPyI),

Table I. Product Distributions

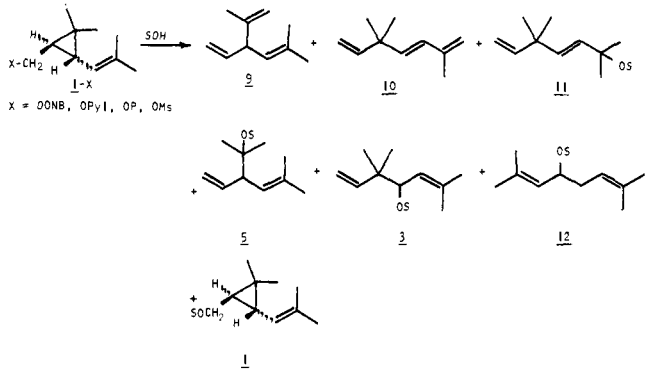
Compd	Solvent	T, °C	Time, h	Composition, %[a] 9	10	11-OS	5-OS	3-OS	12-OS	1-OS
1-ODNB	80% dioxane/water, 2,6-lutidine	100	24	*b*	0.6	81	0.8	17	*b*	0.2
1-OPyI	Water, sodium bicarbonate	25	24	0.07	0.4	81	0.9	17	0.02	0.2
1-OMs	90% acetone/water	0	1	*b*	*b*	83	*b*	17	*b*	*b*
1-OP[c]	Acetic acid, sodium acetate[c]	50	2	1	11	31	0.9	56	*b*	*b*
	Formic acid, sodium formate[c]	0	0.25	*b*	12	16	0.4	71	*b*	*b*
3-ODNB	Methanol, 2,6-lutidine	80	12		9	84	*e*	7		*e*
	50% dioxane/water, 2,6-lutidine	65	12			87	*d*	13		*e*
11-ODNB	50% dioxane/water, 2,6-lutidine	50	22			87		13		

[a] Determined by GLC with a 500 ft × 0.03 in. Carbowax 20M or OV-101 column. Data normalized to 100%. Material balances were >95%. [b] Analysis of trace components was not attempted. [c] The esters were cleaved with lithium aluminum hydride prior to analysis. [d] Not detected and <0.1%. [e] Not detected and <0.01%.

phosphate (OP), and methanesulfonate (OMs) derivatives were prepared by standard procedures.

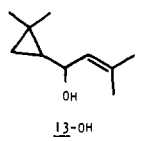
Product studies for chrysanthemyl, artemisyl, and yomogi derivatives are summarized in Table I. Each reaction was carried to at least 95% completion, and control experiments showed that the products are stable to the conditions of the reaction. Alcohols and ethers were analyzed directly, while acetates and formates were reduced to the corresponding alcohols with lithium aluminum hydride prior to spectral or gas chromatographic analysis. Preparative scale solvolyses of **1-OPyl** in water and **1-OP** in acetic acid gave sufficient quantities of products with an artemisia skeleton—artemisia alcohol (**3-OH**), yomogi alcohol (**11-OH**), and artemisia triene (**10**)—to permit isolation by GLC and identification by comparing IR and NMR spectra with those of authentic samples (Scheme II). The products of small scale solvolyses and those

Scheme II. Products from Solvolysis of 1.



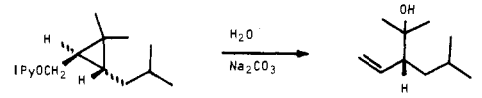
formed in low yield were identified by GC–mass spectrometry and coinjection with authentic samples[10] on 500 ft × 0.03 in. open tubular columns. We previously demonstrated that GC–MS analysis using Carbowax 20M and OV-101 was sufficient for a positive identification of the entries in Table I.[13]

The mixtures of products from hydrolysis and methanolysis of artemisia and yomogi dinitrobenzoates were carefully examined for rearranged products with chrysanthemyl and santolinyl carbon skeletons. No compounds with these structures were found under conditions where controls showed that as little as 0.01% would have been detected. A small peak (0.1%) from the hydrosylate of **1-OPyI** co-chromatographed with an authentic sample of 1-(2′,2′-dimethylcyclopropyl)-3-methyl-2-buten-1-ol (**13-OH**) on Carbowax 20M and OV-101. However, control experiments demonstrated that the alcohol is too reactive to pass through the separator in trace quantities, and we were not able to verify the structure by mass spectrometry.



13-OH

Hydrolysis of dihydrochrysanthemyloxypyridinium iodide gives a single product, **14-OH**, in greater than 98% yield. We

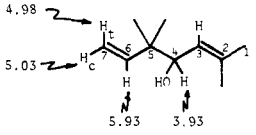


8-OPyI 14-OH

had previously reported that (1′*R*,3′*R*)-**8-OH** rearranges to (*R*)-**14-OH** when treated with aqueous perchloric acid.[14]

First-order rate constants for the hydrolysis of **1-OMs** and **8-OMs** in 90% acetone–water were measured conductiometrically at 0 °C, $k_1 = (2.84 \pm 0.04) \times 10^{-3}$ s^{-1} and $k_8 = (9.41 \pm 0.04) \times 10^{-4}$ s^{-1}. The methanesulfonates rapidly decomposed when concentrated at room temperature, and in view of their reactivity it is doubtful that chrysanthemyl tosylate was prepared and solvolyzed as was previously reported.[9]

Stereochemical Studies. Artemisia alcohol isolated from the hydrolysate of *N*-methyl-4-(1′*R*,3′*R*)-chrysanthemyloxypyridinium iodide has a low, but measurable rotation, $[\alpha]^{26}_D$ +1.06°. In comparison, artemisia alcohol isolated from *Artemisia tridentata tridentata* (giant sage) shows $[\alpha]^{25}_D$ −17.7°.[15] The optical purity of both samples was checked by examining their respective NMR spectra at 100 MHz in the presence of an optically active lanthanide paramagnetic shift reagent. Adding 0.65 M equiv of shift reagent to the alcohol



$^3J_{trans}$ = 16.5 Hz
$^3J_{cis}$ = 10.5 Hz
^2J = 1.5 Hz
$^3J_{3,4}$ = 9.5 Hz
$^4J_{3,1}$ = 1.3 Hz

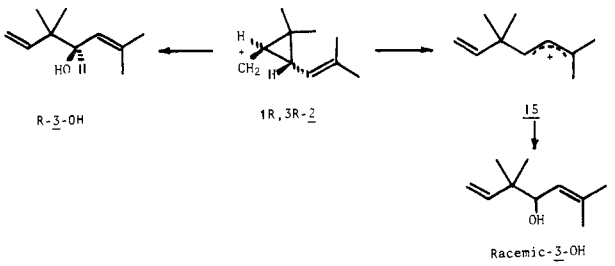
obtained by solvolysis split the resonance at 4.98 ppm (H_t at C(7)) into well-resolved doublets of doublets of approximately equal intensity (J = 17.5 and 1.5 Hz) and shifted the patterns downfield to 6.29 and 6.43 ppm. Also, the resonance at 5.03 ppm (H_c at C(7)) became a pair of doublets of doublets (J = 10.5 and 1.5 Hz) and moved downfield to 5.85 and 5.90 ppm. Comparison of the integrated intensities of the peaks indicated that the alcohol was 98 ± 2% racemic. Addition of 0.58 M equiv of shift reagent to artemisia alcohol from *Artemisia tridentata tridentata* shifted the resonances for protons at C(7), C(6), C(4), and C(3) downfield to 5.73, 6.25, 8.20, and 9.13 ppm, respectively. However, these resonances were single

patterns rather than the duplicate sets obtained for the solvolytic alcohol. No signals for the other enantiomer were seen, even at high spectrum amplitudes where 2% would have been detected.

Comparison of optical rotations, using +17.7° as the maximum rotation of the (+) solvolytic alcohol, indicates that artemisia alcohol obtained by hydrolysis of (1′*R*,3′*R*)-**1-OPyl** is formed with 94% racemization at C(4). The absolute configuration of (+)-artemisia alcohol is not known, although stereochemical work with other alkyl- and vinyl-substituted cyclopropylcarbinyl cations suggests that nucleophiles attack the cyclopropane ring with inversion of configuration.[7f,16] If such is the case, (+)-artemisia alcohol is the *R* enantiomer. In formic acid, a less nucleophilic solvent, ammonium (1′*R*,3′*R*)-chrysanthemyl phosphate gives completely racemic artemisyl formate.

Discussion

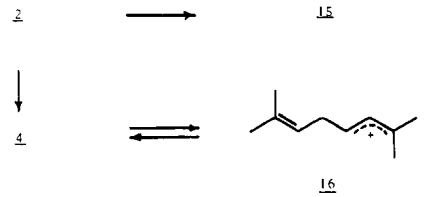
Rearrangements of the Chrysanthemyl Cation. We found that the chrysanthemyl cation (a 1′-2-3 terpene) rearranges under normal solvolysis conditions to irregular terpenes with 1′-3, 2-1′-3, and 1′-1 structures. At least 98% of the products have artemisyl (1′-3) carbon skeletons, with other skeletal classes contributing less than 1% each to the total. Our stereochemical data suggest that the preponderance of artemisyl products is due to a facile fission of the C(1′)-C(3′) cyclopropane bond in **2** to give an isomeric cation, **15**. That portion of artemisia alcohol which is optically active (presumably inverted) comes from capture of the chiral chrysanthemyl cation by water, while racemic **3-OH** results from capture of the planar allylic cation **15**.[17] Isomerization of **2** to **15** is complete before reaction with solvent in formic acid.



Rearrangement of vinyl-substituted cyclopropylcarbinyl cations to their allylic isomers is apparently a general phenomenon. Tertiary cyclopropylcarbinyl cation **4** (Scheme I) also opens up to an allylic cation during solvolysis,[7f] although to a lesser extent than **2**. Equilibration between cyclopropylcarbinyl and homoallylic cations is only found when the homoallylic system is highly stabilized, as is the case for vinyl-substituted cyclopropylcarbinyl cations such as **2** and **4**. For a simple alkyl-substituted system, *trans*-2-methylcyclopropylcarbinyl cation, all of the homoallylic product is inverted,[16] and there is no evidence for isomerization between the cyclopropylcarbinyl and the homoallylic cation prior to reaction with a nucleophile. Two factors are important in determining the degree of equilibration: the relative stabilities of the closed and open cations and the nucleophilicity of the solvent.

The hydrolysates of yomogi and artemisia dinitrobenzoate were carefully examined for the same minor components obtained from chrysanthemyl derivatives, but none were found under conditions where as little as 0.01% would have been detected. Since it was reported that methanolysis of an artemisyl sulfonium salt gave methyl ethers with chrysanthemyl, santolinyl, and head-to-head carbon skeletons,[7a] we solvolyzed artemisyl and yomogi dinitrobenzoates in methanol. Chrysanthemyl methyl ether (**1-OCH$_3$**) and santolinyl methyl ether (**5-OCH$_3$**) were not detected (<0.01%) in the mixture of products. Since the chrysanthemyl cation gives easily detectable amounts of products with chrysanthemyl and santolinyl carbon skeletons, we conclude that allylic cation **15** does not reclose to **2** under our conditions.

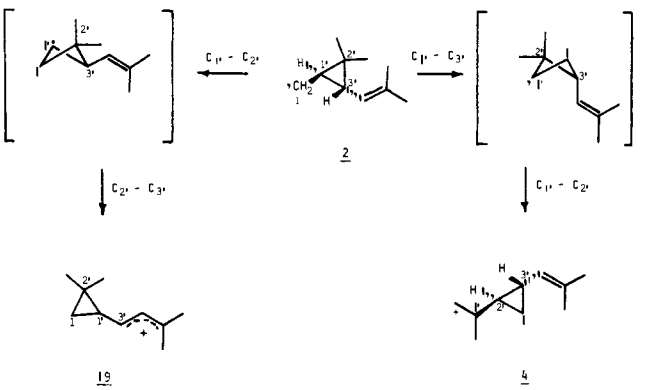
One can estimate the relative free energies of cations **2, 4, 15,** and **16** from data in the literature. We showed that **4** and **16** readily interconvert during solvolysis in aqueous solvents.[7f]



Thus, the two cations must have comparable free energies. The difference between **2** and **4** has not been accurately measured, since there is no report of a tertiary cyclopropylcarbinyl cation isomerizing to its primary isomer by a cyclopropylcarbinyl-cyclopropylcarbinyl rearrangement. Hehre and Hilberty[18] estimate that the difference between primary and tertiary cyclopropylcarbinyl isomers is *ca.* 17 kcal/mol. Although one hesitates to extrapolate calculated ΔH's (a gas-phase estimate) into solution, recent estimates of ΔH for rearrangement of *sec*-butyl to *tert*-butyl cation in solution and in the gas phase by mass spectrometry or molecular orbital methods yield similar values.[19] If the proposal of Schleyer and coworkers[20] that "the degree of electrostatic solvation varies little between carbonium ions of similar structure" is valid for cyclopropylcarbinyl cations, 17 kcal/mol should be a reasonable approximation for the enthalpy difference between **2** and **4**. Allylic cations **15** and **16** should have similar free energies. Both are trisubstituted allylic cations which differ only in the attachment of the isoprene moiety to the monosubstituted terminal allylic carbon. The "tertiary" attachment in **15** may be slightly more stabilizing than the corresponding primary attachment in **16** with regard to dispersal of positive charge. However, we estimate the side chain in **16** to be ca. 1 kcal/mol more stable than the isomeric side chain in **15**.[21] If the free energy differences for **4** ⇄ **16** and **15** ⇄ **16** are small and **2** is much less stable than **4, 2** is also much less stable than **15**. Thus, closure of **2** to **15** during solvolysis is not anticipated.

The chrysanthemyl cation also rearranges via the cyclopropylcarbinyl-cyclopropylcarbinyl rearrangement. The process is thought to proceed through a cyclobutyl species (intermediate or transition state) by a ring expansion-ring contraction sequence.[7f] Rearrangement initiated by migration of the C(1′)-C(3′) cyclopropane bond leads to **4** (Scheme III),

Scheme III. Cyclopropylcarbinyl–Cyclopropylcarbenyl Rearrangement.

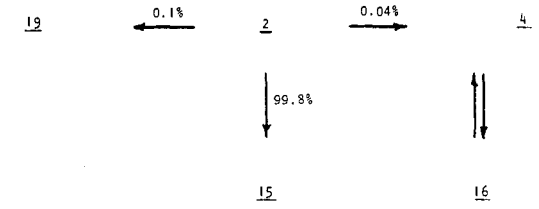


which we have shown gives head-to-head alcohol **12-OH**.[7c,f,g] In a similar rearrangement, migration of the C(1′)-C(2′) cyclopropane bond would yield **19**. Although it is reasonable that **2** → **19** competes with **2** → **15**, evidence for the former rear-

rangement is tenuous, since we could not unambiguously confirm the structure of **13-OH**.

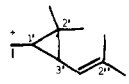
The rearrangements of **2** in water are summarized in Scheme IV. The value of 99.8% for **2** → **15** assumes that

Scheme IV. Rearrangements of the Chrysanthemyl Cation



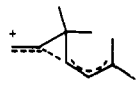
fragmentation of the C(1′)-C(3′) cyclopropane bond is not concerted with ionization, in agreement with our recent studies of the stereochemistry at C(1) during head-to-head rearrangement.[12,23]

The chrysanthemyl cation can, in theory, react with nucleophiles—at the carbinyl carbon, at both rear cyclopropane

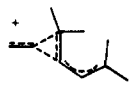


carbons, and at C(2″) of the double bond. We have already described how the amounts of products arising from capture at C(2′) and C(3′) were determined. Unfortunately, such estimates cannot be made for capture at C(1) and C(2″). Primary cyclopropylcarbinyl derivatives can undergo substitution at C(1) by a k_s process,[24] and we have not separated the relative contributions of k_s and k_Δ. Yomogi alcohol is achiral, so the method used to estimate the proportion of artemisia alcohol coming from **2** is not applicable. If the double bond interacts weakly with the rest of the chrysanthemyl cation as experiment and theory[25] suggest (see below), the proportion of yomogi alcohol coming directly from **2** will be small. The regiochemistry of the chrysanthemyl cation for rearrangement and substitution is summarized in Table II.

Structure of the Chrysanthemyl Cation. The chrysanthemyl cation presents an interesting structural problem with regard to how effectively the cyclopropane ring transmits positive charge from C(1) into the vinyl substituent at C(3). The recent work of Wilcox and coworkers[25] suggests that poor orbital overlap between the double bond and the cyclopropane ring severely restricts conjugative interaction between the two moieties. However, Sasaki and coworkers[26] recently argued that the 2-methyl-1-propenyl group represents a sufficiently large perturbation to alter the expected bisected geometry to that of a homopentadienyl cation. We feel that a critical ex-



homopentadienyl



bisected

amination of all of the data for **2** supports a bisected structure. At a superficial level, the distribution of solvolysis products from the various derivatives of **1** suggests that C(3′) is much more susceptible to nucleophilic attack than C(2′). However, only a small percentage of 1′-3 products actually comes from **2**, and when a correction is made for that proportion derived from allylic cation **15**, it is apparent that santolina and artemisia substitution products are found in equal amounts. Also, the double bond at C(3′) only provides a threefold rate enhancement.

Biosynthetic Implications. All of the rearrangements shown in Scheme I are available to the chrysanthemyl cation; however, Table II shows that opening of the C(1′)-C(3′) cyclopropane bond is by far the most facile reaction. Once the bond is cleaved, products from **2** are limited to 1′-3 terpenes. Thus,

Table II. Regiochemistry for Rearrangement and Substitution for the Chrysanthemyl Cation

Reaction	$\Delta(\Delta G^{\ddagger})$,[b] kcal/mol
2 → **15**	0
2 → **18**	4.1
2 → **4**	4.6
2 → **3-OH**	2.7
2 → **5-OH**	2.7
2 → **1-OH**	4.1

[a] In 0.25 M sodium bicarbonate solution at 25 °C. [b] Relative to **2** → **15**.

control of C(1′)-C(3′) fission in **2** is a process which must be regulated during enzyme-catalyzed reactions that yield 2-1′-3 or 1′-1 terpenes.

We presented a mechanism based on oriented intimate ion pairs for the stereospecific, regiospecific 1′-2-3 → 1′-1 rearrangements catalyzed by squalene synthetase and phytoene synthetase[7f,g] and pointed out that rearrangements of the type **2** → **15** and **2** → **18** could in theory be suppressed because only **2** → **4** maintains close proximity of positive and negative centers. It was estimated that the barrier for **2** → **4** was reduced by 8-15 kcal/mol relative to **2** → **15** in the intimate ion pair. A change of this magnitude should be enough to make the **2** → **4** rearrangement dominate. Premature capture of **2** by NADPH during biosynthesis of squalene can be prevented by proper placement of the "nucleophile" relative to presqualene pyrophosphate prior to ionization.

Santolina (2-1′-3) monoterpenes must come from **2** before rearrangement. A likely mechanism would involve an oriented ion pair to prevent rupture of the C(1′)-C(3′) cyclopropane bond with the nucleophile (most likely water) positioned for attack at C(2′). This mechanism predicts that the 1′-2-3 and 2-1′-3 structures have the same absolute configuration at the 1′ position, in agreement with the absolute configurations of chrysanthemol[6d] and santolina alcohol[11] isolated from closely related plants. Similar predictions cannot be made for artemisia alcohol because the immediate precursor could be **2** or **15**. However, we found that artemisia alcohol from natural sources and that portion which came from **2** during solvolysis had opposite configurations. If (1′*R*,3′*R*)-**1-OPP** is the precursor of artemisia alcohol in the plant, the stereochemistry of natural **3-OH** suggests that the enzyme-catalyzed conversion proceeds via **15** and stereospecificity found at C(4) in artemisia alcohol is imposed solely by the enzyme.

It is interesting to note that 1′-3 terpenes are not confined to the C_{10} series. Oil of bergamot is reported to contain C_{20} terpenes with 1′-3 and 1′-1 attachments.[27] A primitive algae, *Botryococcus braunii*, synthesizes large quantities of a C_{34} terpene, botryococcene,[28] which logically results from a 1′-3 coupling of two molecules of farnesyl pyrophosphate via presqualene pyrophosphate, followed by methylation of the isoprenoid chains.

Experimental Section

General. Melting points were obtained on a Fisher–Johns melting point stage or in open capillaries in a Thomas-Hoover melting point apparatus and are uncorrected. Carbon–hydrogen microanalyses were performed by Chemalytics, Inc., Tempe, Arizona.

Nuclear magnetic resonance (NMR) spectra were obtained on Varian Associates A-60, EM-360, EM-390, and XL-100 spectrometers and are reported in parts per million (δ, ppm) downfield from tetramethylsilane (Me_4Si) internal standard. Unless otherwise indicated, NMR spectra were obtained in carbon tetrachloride (Mallinkrodt, SpectrAR grade) containing 1 vol % tetramethylsilane (Diaprep, Inc.) and chloroform (Mallinkrodt, SpectrAR grade) as internal standards. NMR solvent giving equally intense Me_4Si and

chloroform resonances of amplitude suitable for use with 10% solutions was prepared by adding 0.5 mL (0.32 g, 3.68 mmol, 44.2 mmol of protons) of Me_4Si and 5.30 g (44.2 mmol) of chloroform to 50 mL of carbon tetrachloride. Spectra were corrected when necessary for nonlinearity using the 436-Hz (at 60 MHz) singlet resonance of chloroform. Infrared (IR) spectra were obtained on a Beckman IR-5 spectrophotometer. Optical rotations were measured using a Perkin-Elmer Model 141 digital polarimeter operating at 589 nm (sodium D line), employing the specified solvent and a 1-dm water-jacketed cell thermostated to 25 ± 0.1 °C. Optical rotations are reported as specific rotations ($[\alpha]^{25}_D$) and concentrations in grams per 100 mL of solvent, e.g. (*c* 5, $CHCl_3$).

Analytical gas–liquid chromatography was performed on a Varian-Aerograph Model 1200 instrument equipped with a flame ionization detector and an Autolab Model 6300 digital integrator. Repetitive injections showed that the system's reproducibility averaged ±0.5% and never exceeded ±2%. Analytical separations were achieved using 500 ft × 0.03 in. (i.d.) stainless steel open tubular columns prepared and coated as previously reported,[29] utilizing the stationary phases Carbowax 20M (recrystallized from ethanol), 95:5 OV-101/Igepal CO-880 (both obtained from Analabs, Inc.), or SF-96 (viscosity 50 cSt at 25 °C; Analabs, Inc.) as indicated and operated at the specified temperature at a nitrogen flow rate of 10 mL/min.

Preparative gas–liquid chromatographic separations were performed on a Varian-Aerograph Model A90-P3 thermal conductivity instrument, using 12 ft × ¼ in. (o.d.) glass columns packed with 10% Carbowax 20M on 60/80 mesh Anakrom ABS diatomaceous earth support, or on a 3 ft × ¼ in. (o.d.) stainless steel column packed with 10% 95:5 OV-101/Igepal CO-880 on 50–60 mesh Anakrom ABS.

Thin-layer chromatography was carried out on 75 × 25 mm "Bakerflex" precoated silica gel 1B-F sheets (silica gel G with fluorescer; J. T. Baker Co.) in vapor-saturated tanks, visualizing the developed spots first with 254-nm light and then with iodine staining.

Sodium (1*R*,3*R*)-2′,2′-Dimethyl-3′-(2″-methyl-1″-propenyl)-cyclopropylcarboxylate, Sodium (1′*R*,3′*R*)-Chrysanthemate (7-ONa). To a well-stirred suspension of 6.14 g (0.114 mol) of sodium methoxide powder in 800 mL of distilled pentane was added dropwise over 10 min 15.99 g (0.095 mol) of freshly distilled (1′*R*,3′*R*)-chrysanthemic acid (McLaughlin, Gormley, King), $[\alpha]^{26}_D$ +25.0 (*c* 2, $CHCl_3$) [lit.[30] $[\alpha]^{23}_D$ +25.9° (*c* 3, $CHCl_3$)], in 250 mL of pentane. The resulting fluffy white crystals were removed by filtration, washed with dry ether to remove traces of color, and dried in vacuo over phosphorus pentoxide to give 17.19 g (0.090 mol, 95%) of the salt; NMR (D_2O vs. internal DSS at 0.0 ppm) 1.08 and 1.13 (6, pr of s, methyls at C(2′)), 1.28 (1, d, *J* = 5.5 Hz, H at C(1′)), 1.68 (6, d, *J* = 1.5 Hz, CH_3's at C(2″)), 1.88 (1, d of d, H at C(3′)), 4.92 ppm (1, d of septets, *J* = 8.5 Hz, H at C(1″)); IR (KBr) 2940, 1675, 1550 (s), 1425, 1380, 1290, 1240, 1115, 1060, 953, 858 cm^{-1}.

Methyl (1′*R*,3′*R*)-2′,2′-Dimethyl-3′-(2″-methyl-1″-propenyl)-cyclopropylcarboxylate, Methyl (1′*R*,3′*R*)-Chrysanthemate (7-OMe). To a rapidly stirred slurry of 43.1 g (0.227 mol) of sodium (1*R*,3*R*)-chrysanthemate in 200 mL of dry benzene was added 30.2 g (0.238 mol) of oxalyl chloride in 200 mL of anhydrous ether over 1 h. The mixture was allowed to stir for 30 min, then 25 mL of absolute methanol was added over 30 min and the reaction mixture brought to reflux and allowed to stir for 30 min before being neutralized with powdered sodium bicarbonate. The mixture was filtered, the filtrate washed with saturated sodium bicarbonate solution, and the organic layer washed with water until the aqueous washes were neutral. The organic layer was dried over anhydrous magnesium sulfate and solvent was removed at reduced pressure to afford 32.5 g (79%): bp 58–60 °C (3 mm); $[\alpha]^{26}_D$ +24.63° (*c* 4, cyclohexane). NMR[31] and IR[32] spectra were in accord with those in the literature.

(1′*R*,3′*R*)-2′,2′-Dimethyl-3′-(2″-methyl-1″-propenyl)cyclopropylmethanol, (1′*R*,3′*R*)-Chrysanthemol (1-OH). A slurry of 3.21 g (84.6 mmol, 2 equiv) of lithium aluminum hydride (Alfa-Ventron) in 200 mL of anhydrous ether was prepared in an oven-dried 500-mL three-neck flask equipped with a Friedrich condenser, 250-mL addition funnel, dry nitrogen atmosphere, and mechanical stirring. A solution of 15.4 g (84.6 mmol) of methyl (1′*R*,3′*R*)-chrysanthemate in 125 mL of dry ether was added at a rate sufficient to maintain slow self-reflux over 3 h. The stirred mixture was heated at mild reflux for 24 h. Excess hydride was destroyed and the salts were hydrolyzed by the dropwise addition with vigorous stirring of saturated ammonium chloride solution until the inorganic salts precipitated cleanly. The reaction mixture was filtered through sintered glass with suction and the solids were washed with 200 mL of ether in several portions. The combined filtrates were dried (magnesium sulfate), concentrated at reduced pressure, and distilled, affording 10.95 g (85%): bp 57–58 °C (0.9 mm); $[\alpha]^{26}_D$ +46.85° (*c* 5, $CHCl_3$). The NMR spectrum was identical with those previously reported.[31a,33]

4-[(1′*R*,3′*R*)-2′,2′-Dimethyl-3′-(2″-methyl-1″-propenyl)cyclopropylmethoxy]pyridine, 4-[(1′*R*,3′*R*)-Chrysanthemyloxy]pyridine (20). A slurry of 0.415 g (17.3 mmol) of sodium hydride in 20 mL of dry dimethyl sulfoxide was allowed to stir for 30 min at room temperature before heating to 65 °C for 2 h. To the resulting green mixture was added 1.97 g (12.8 mmol) of (1′*R*,3′*R*)-chrysanthemol in 15 mL of dry dimethyl sulfoxide, and stirring was allowed to continue at 65 °C for 1 h before adding 1.475 g (13.0 mmol, 1 equiv) of freshly-prepared 4-chloropyridine[34] in 10 mL of dimethyl sulfoxide. After 24 h, the light brown reaction mixture was allowed to cool and then was poured into 100 mL of water. Extraction with three 50-mL portions of pentane, washing the combined organic layers with 50 mL of water, drying (magnesium sulfate), and solvent removal at reduced pressure afforded 2.714 g (11.8 mmol, 92% crude) of a clear, light yellow oil. Short-path distillation gave 1.738 g (7.53 mmol, 60%) of a colorless oil: bp 133–134 °C (2.6 mm); IR (CCl_4) 3320, 2920, 2860, 1585, 1560, 1550, 1378, 1285, 1215, 1117, 1005, 815 cm^{-1}; NMR ($CDCl_3$) 1.07 (3, methyl at C(2′)), 1.13 (3, methyl at C(2′)), 0.73–1.48 (2, m, H at C(1′) and C(3′)), 1.63 (6, br, CH_3's at C(2″)), 3.83 (2, H at C(1)), 4.85 (1, d of septets, H at C(1″), *J* = 7.5 and 1.5 Hz), 6.63 (2, m, H at C(2) and C(6) of pyridine), 8.20 ppm (2, m, H at C(3) and C(5) of pyridine).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.93; H, 8.97.

***N*-Methyl-4-[(1′*R*,3′*R*)-2′,2′-dimethyl-3′-(2″-methyl-1″-propenyl)-cyclopropylmethoxy]pyridinium Iodide, *N*-Methyl-4-[(1′*R*,3′*R*)-chrysanthemyloxy]pyridinium Iodide (1-OPyI).** To 1.738 g of alkoxypyridine (**20**) was added 2.213 g (15.7 mmol, 100% excess) of iodomethane (MCB). The mixture immediately began to yellow and thicken, and had become a solid yellow mass in 30 min. The mixture was allowed to stand at −10 °C for 24 h and was then dissolved in a minimum of dichloromethane. Trituration to cloudiness with ether and clarification by mild heating afforded 1.30 g of off-white powdery crystals, mp 115–116 °C. Further crystallization from 5% dichloromethane–ethyl acetate afforded second and third crops totalling 0.46 g, for an overall yield of 63%: NMR ($CDCl_3$) 1.06 and 1.14 (6, s, methyls at C(2′)), 1.0–1.4 (2, m, H at C(1′) and C(3′)), 1.67 (6, d, allylic methyls), 4.20 (2, m, H at C(1)), 4.37 (3, s, methyl at N), 4.77 (1, d of septets, olefinic H, *J* = 8 and 1.5 Hz), 7.25 (2, m, H at C(3) and C(5) of pyridinium ring), 8.87 ppm (2, m, H at C(2) and C(6) of pyridinium ring); IR (KBr) 2850, 1640 (s), 1575 (w), 1520 (s), 1385 (br), 1330, 1210, 1188, 862, 846, 832 (w) cm^{-1}; $[\alpha]^{25}_D$ +2.80° (*c* 2.7, $CHCl_3$).

The crystalline material could be stored at −10 °C for up to 1 month without visible discoloration. Decomposition was more rapid at room temperature, and a satisfactory combustion analysis could not be obtained. The salt used in solvolysis experiments was recrystallized just prior to each run.

Dicyclohexylammonium (1′*R*,3′*R*)-2′,2′-Dimethyl-3′-(2″-methyl-1″-propenyl)cyclopropylmethyl Phosphate, Dicyclohexylammonium (1′*R*,3′*R*)-Chrysanthemyl Phosphate (1-OP). To 2.00 g (13.0 mmol) of *trans*-chrysanthemol (**1-OH**) and 11.26 g (78.0 mmol) of trichloroacetonitrile was added over a 4-h period 9.36 g (31.2 mmole) of ditriethylammonium phosphate dissolved in 200 mL of acetonitrile. The yellow solution was allowed to stand overnight at room temperature.

The reaction mixture was diluted with 100 mL of dilute ammonium hydroxide and extracted with 200 mL of diethyl ether. Cyclohexylamine (2.5 mL) was added to the aqueous phase and excess water was removed at reduced pressure. When approximately 75 mL of solvent remained in the flask, a sudden crystallization occurred, and the flask was placed in the refrigerator for 24 h. The white crystals were collected by filtration. The mother liquor was evaporated, and a second crop was obtained. The two crops were combined and recrystallized from distilled water, giving a combined yield of 0.877 g (15.5%) of a white powder: mp 182–184 °C; R_f 0.74 on buffered (pH 6.5) silica gel H (50:50:10 chloroform/methanol/water); R_f 0.35 for chrysanthemyl pyrophosphate;[35] IR (KBr) 3500, 3360–2475 (s), 2250 (w), 1615, 1525, 1440, 1380, 1152, 1088, 1048–990 (s), 914, 826 cm^{-1}; NMR (D_2O) 0.87 and 0.97 (6, two s, methyls at C(2′)), 1.53 (6, br s, olefinic methyls), 0.65–2.21 (22, br m, hydrogens on cyclopropyl

and cyclohexyl rings), 3.43–4.11 (2, m, H at C(1)), 4.55 (6, s, $-NH_3^+$), 4.85 ppm (1, d of septets, J = 7.5 and 1.5 Hz, olefinic H). Analysis for phosphate gave 96% of the theoretical value.[36]

(1′*R*,3′*R*)-2′,2′-Dimethyl-3′-(2″-methyl-1″-propenyl)cyclopropylmethyl Dinitrobenzoate, (1′*R*,3′*R*)-Chrysanthemyl Dinitrobenzoate (*1*-ODNB). To a solution of 100 mg (0.65 mmol) of chrysanthemol in 0.5 mL of anhydrous pyridine was added 165 mg (0.72 mmol) of 3,5-dinitrobenzoyl chloride. After heating at 55 °C for 5 h the solution was poured into anhydrous ether, and the tannish precipitate which formed was removed by centrifugation. Ether and pyridine were removed on a rotary evaporator. The ether solution was extracted in succession with 2 N HCl, saturated $NaHCO_3$, and water. After being dried over $MgSO_4$ the solvent was removed to give a crystalline residue. Recrystallization from pentane gave 220 mg of colorless crystals: mp 108–109.5 °C; IR (CS_2) 3090, 2900, 1725, 1630, 1340, 1265, 1062, 920, 738, 721 cm^{-1}; NMR ($CDCl_3$) 1.10 and 1.25 (6, s, CH_3 at C(2″)), 0.9–1.3 (2, m, H at C(1′) and C(3′)), 1.75 (6, two br s, allylic CH_3), 4.52 (2, m, H at C(1)), 4.93 (1, d of septets, H at C(1″), J = 1.5 and 8 Hz), 9.15 ppm (3, m, aromatic H).

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.62; H, 5.79. Found: C, 58.79; H, 5.91.

(1′*R*,3′*R*)-2′,2′-Dimethyl-3′-(2″-methyl-1″-propyl)cyclopropylmethanol, (1′*R*,3′*R*)-Dihydrochrysanthemol (8-OH). A solution of 3.9 g (0.0253 mol) of (1′*R*,3′*R*)-**1-OH** in 100 mL of glacial acetic acid and 0.1 g of PtO_2 was placed in a Parr hydrogenation bottle. The mixture was hydrogenated under 35 psi hydrogen for 5 h. The reaction mixture was filtered through sintered glass, and the filtrate neutralized with saturated sodium bicarbonate solution. The aqueous solution was extracted three times with ether, and the combined ether extracts were washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The ether was removed at reduced pressure on a rotary evaporator, leaving 3.54 g (88%) of yellowish liquid. The crude hydrogenated product was purified by short-path distillation to give 2.1 g of a colorless liquid. GLC analysis showed that the distilled product was 96% pure: bp 73–75 °C (4 mm); $[\alpha]^{23}_D$ +10.5° (*c* 4.2, cyclohexane); IR (CCl_4) 3600, 3390, 2940, 1465, 1380, 1015 cm^{-1}; NMR (CCl_4) 0.16–0.63 (2, m, cyclopropyl), 0.78–1.72 (9, m), 1.02 and 1.06 (3, s, C(2) methyls), 2.49 (1, s, hydroxyl H), 3.09–3.76 ppm (2, m, hydroxymethyl); mass spectrum (70 eV) *m/e* (rel intensity) 138 (2), 125 (17), 95 (12), 82 (19), 81 (26), 71 (18), 70 (10), 69 (100), 67 (21), 57 (19), 55 (26), 43 (31), 41 (40).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.87; H, 13.08.

***N*-Methyl-4-[(1′*R*,3′*R*)-dimethyl-3′-(2″-methyl-1″-propyl)cyclopropylmethoxy]pyridinium Iodide, *N*-Methyl-4-[(1′*R*,3′*R*)-dihydrochrysanthemyloxy]pyridinium Iodide (7-OPyI).** To a suspension of 0.45 g (11.2 mmol) of potassium hydride in 15 mL of dry tetrahydrofuran containing 1.84 g (10.3 mmol) of hexamethylphosphoramide was added dropwise 1.21 g (7.76 mmol) of 1′*R*,3′*R*-dihydrochrysanthemol. Stirring was allowed to continue for 30 min before dropwise addition of 1.1 mL (10 mmol) of freshly prepared 4-chloropyridine. After 12 h, 0.2 mL of saturated ammonium chloride solution was added. The reaction mixture was poured into 100 mL of pentane and extracted with eight 30-mL portions of distilled water. After drying the organic layer over 1 g of anhydrous magnesium sulfate, solvent was removed at reduced pressure, affording 1.60 g (88.4% crude) of a light yellow oil of which 70% was dihydrochrysanthemyloxypyridine by NMR.

To 1.0 g (4.3 mmol) of colorless alkoxypyridine, which had been purified by bulb-to-bulb transfer under high vacuum, was added 5 mL of dry diethyl ether and 0.913 g (6.4 mmol) of methyl iodide. The mixture was allowed to stand for 2 h at room temperature, and 0.20 g of additional methyl iodide added to the now yellow solution. After an additional 2 h the reaction mixture began to separate into two liquid layers. The flask was stored for 12 h at −20 °C, during which time the product crystallized. The crystals were filtered and washed with 10 mL of cold dry ether. Thin layer chromatography (chloroform/2-propanol, 10:1), visualized with iodine vapor, showed a single component, the pyridinium iodide, R_f 0.15 (dihydrochrysanthemyloxypyridine R_f 0.7). The crystals were dried under vacuum for 15 min at room temperature, giving 0.90 g (56%) of light yellow powder which failed to improve in color after three recrystallizations from acetone/ether: mp 77–79 °C; IR (KBr) 3060, 3000, 2890, 1645, 1515, 1505, 1318, 1295, 1220, 1192, 968, 850, 827 cm^{-1}; NMR (acetone-d_6) 0.5–0.8 (2, m, cyclopropyl H), 0.8–1.9 (3, m, H at C(1″) and C(2″), 0.90 (3, s, H at C(2′)), 0.98 (3, s, H at C(2′)), 1.15 (6, d, J = 7 Hz, H at C(2″) methyl and C(3″)), 4.47 (3, s, N methyl), 4.3–4.75 (2, m, H at C_1), 7.68 (2, d, H at C(2), C(6) of pyridine), 9.06 ppm (2, d, H at C(3), C(5) of pyridine).

The salt was handled as previously described for **1-OPyI.** The material did not survive shipment and a satisfactory combustion analysis could not be obtained.

(1′*R*,3′*R*)-2′,2′-Dimethyl-3′-(2″-methyl-1″-propenyl)cyclopropylmethyl methanesulfonate, (1′*R*,3′*R*)-Chrysanthemyl Methanesulfonate (1-OMs). A solution of 1 mL of anhydrous pentane, 1 mL of anhydrous benzene, and 0.100 g (0.657 mmol) of methanesulfonylchloride was allowed to stir at −10 °C for 10 min before 0.110 g (1.07 mmol) of dry triethylamine was added. During the next 10 min, a white precipitate slowly formed. The precipitate was removed by filtration, and the clear solution was used for the kinetic runs.

For characterization by NMR, the methanesulfonate was prepared in anhydrous carbon tetrachloride containing 3% Me_4Si from 0.100 g (0.657 mmol) of chrysanthemol, 0.74 g (0.646 mmol) methanesulfonyl chloride, and 0.066 g (0.654 mmol) triethylamine: NMR (−20 °C) 0.6–1.0 (2, m, H at C(1′) and C(3′)), 1.09 and 1.20 (6, two s, CH_3's at C(2′)), 1.68 (6, br s, CH_3's at C(2″)), 2.93 (3, s, sulfonyl methyl), 4.05 (1, d of d, J = 9 and 11 Hz, *pro R* H at C(1)), 4.42 (1, d of d, J = 7 and 11 Hz, *pro S* H at C(1)), 4.80 ppm (1, d, J = 8 Hz, H at C(1″)).

(1′*R*,3′*R*)-2′,2′-Dimethyl-3′-(2″-methyl-1″-propyl)cyclopropylmethyl Methanesulfonate, (1′*R*,3′*R*)-Dihydrochrysanthemyl Methanesulfonate (8-OMs). A solution of 1 mL of anhydrous pentane, 1 mL of anhydrous benzene, 0.120 g (0.779 mmol) of (1′*R*,3′*R*)-dihydrochrysanthemol, and 0.081 g (0.711 mmol) of methanesulfonyl chloride was allowed to stir at −10 °C for 10 min before 0.128 g (1.25 mmol) of dry triethylamine was added. The reaction mixture was worked up as described for **1-OMs.**

For characterization by NMR the methanesulfonate was prepared from 0.100 g (0.649 mmol) of dihydrochrysanthemol as described for **1-OMs:** NMR (−20 °C) 0.4–0.7 (2, m, H at C(1′) and C(3′)), 0.90 (6, d of d, J = 1.5 and 7 Hz, CH_3's at C(2″)), 1.07 and 1.12 (6, two s, CH_3's at C(2′)), 1.0–1.7 (3, m, H at C(1″) and C(2″)), 2.90 (3, s, sulfonyl methyl), 4.01 (1, d of d, J = 9.5 and 10.5 Hz, *pro R* H at C(1)), 4.33 ppm (1, d of d, J = 8.5 and 10.5 Hz, *pro S* H at C(1))

2,5,5-Trimethylhepta-2,6-dien-4-ol, Artemisia Alcohol (3-OH). Activated magnesium was prepared by the Rieke procedure[37] from 3.00 g (77 mmol) of freshly cut potassium metal, 3.80 g (40 mmol) of anhydrous magnesium chloride (Alfa-Ventron), and 3.32 g (20 mmol) of granular potassium iodide in 60 mL of dry tetrahydrofuran. After heating at reflux for 5 h, the black suspension was cooled to 20 °C and 2.98 g (20 mmol) of 1-bromo-3-methyl-2-butene (Chemical Samples Co.) in 10 mL of tetrahydrofuran was added by syringe. After 1 h, 1.00 g (20 mmol) of 3-methyl-2-butenal in 5 mL of tetrahydrofuran was added and the resulting suspension was allowed to stir overnight. The reaction was quenched with saturated ammonium chloride. The resulting suspension was filtered through Celite and diluted with 100 mL of ether. The resulting solution was washed with saturated sodium chloride and dried over magnesium sulfate. Solvent was removed at reduced pressure, giving 2.54 g (69%) of a fragrant, light yellow oil. A portion of the major component (91% of the mixture) was purified by preparative GLC and had an IR spectrum identical with that reported for artemisia alcohol.[38]

***trans*-2,5,5-Trimethylhepta-3,6-dien-2-yl Dinitrobenzoate, Yomogi Dinitrobenzoate (11-ODNB).** Following the procedure described for **1-ODNB,** 100 mg (0.65 mmol) of yomogi alcohol obtained by solvolysis of **1-OPy** and purified by GLC (Carbowax 20M and SF-96-50) was converted into its dinitrobenzoate ester, yielding 62.3 mg (28%): mp 69–70 °C; IR (CCl_4) 2960, 2865, 1722, 1632, 1540, 1460, 1343, 1178, 1125, 1070, 952, 908, 775, 732, 721 cm^{-1}; NMR ($CDCl_3$) 1.15 (6, methyls at C(5)), 1.73 (6, methyls at C(2)), 4.92 (2, m, H at C(7)), 5.77 (3, H at C(3), C(4), and C(6)), 9.18 ppm (3, aromatic H).

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.62; H, 5.79. Found: C, 58.43; H, 5.71.

2,5,5-Trimethylhepta-1,5-dien-4-yl Dinitrobenzoate, Artemisia Dinitrobenzoate (3-ODNB). Following the procedure outlined for **1-ODNB,** 154 mg (1.0 mmol) of artemisia alcohol was converted into 180 mg (49%) of the corresponding dinitrobenzoate: mp 87.5–88 °C; NMR ($CDCl_3$) 1.09 and 1.13 (6, s, methyls at C(5)), 1.76 and 1.85 (6, s, methyls at C(2)), 4.98 and 5.19 (2, m, H at C(1)), 5.24 (1, d of septets, H at C(3), J = 10 and 1.5 Hz), 5.63 (1, d, H at C(4), J = 10 Hz), 5.94 (1, m, H at C(6)), 9.10 (2, m, ortho protons), 9.14 ppm (1, m, para proton); IR (KBr) 3055, 3044, 2985, 2960, 2945, 1718 (s),

1630 (m), 1548 (s), 1460 (m), 1347 (s), 1285 (s), 1178, 1080, 1020, 950, 924 (s), 840, 780, 740 (s), 728 (s) cm^{-1}.

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.62; H, 5.79. Found: C, 58.57; H, 5.86.

***trans*-2,5,5-Trimethylhepta-1,3,6-triene, Artemisia Triene (10).** Artemisia triene was prepared from chrysanthemol according to the procedure of Crombie and co-workers.[7b]

2',2'-Dimethyl-3'-(2''-methyl-1''-propenyl)cyclopropylmethyl Methyl Ether, Chrysanthemyl Methyl Ether (1-OCH_3). To 180 mg (7.5 mmol) of sodium hydride was added 4 mL of dry dimethyl sulfoxide. The mixture was stirred at room temperature for 2 h before 440 mg (2.85 mmol) of **1-OH** in 1 mL of dimethyl sulfoxide was added. After 1 h 650 mg (4.6 mmol) of methyl iodide was added and stirring was continued at room temperature for 16 h. The mixture was diluted with water and extracted with pentane. The pentane extracts were washed with water and dried over magnesium sulfate. Solvent was removed at reduced pressure to give 310 mg (65%) of a colorless oil that was 92% pure by GLC. The major component was obtained pure by GLC: NMR ($CDCl_3$) 0.54–1.25 (2, m, protons at C(1') and C(3')), 1.05 and 1.12 (6, two s, methyls at C(2')), 1.68 (6, br s, CH_3's at C(2'')), 3.32 (3, s, methoxy protons), 3.44 (2, m, H at C(1)), 4.89 ppm (1, d of septets, J = 8 and 1.5 Hz, H at C(1'')).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.59; H, 11.98. Found: C, 78.60; H, 12.02.

4-Methoxy-2,5,5-trimethylhepta-2,6-diene, Artemisia Methyl Ether (3-OCH_3). To 60 mg (1.5 mmol) of potassium hydride in 3 mL of pentane and 125 mg of hexamethylphosphoramide was added 110 mg (0.71 mmol) of artemisia alcohol. The suspension was stirred at room temperature for 1 h before 125 mg (0.88 mmol) of methyl iodide was added. After stirring overnight, the product was isolated as described for **1-OCH_3**, yielding 35 mg (24%) of material after purification by GLC: NMR ($CDCl_3$) 0.94 and 0.98 (6, two s, methyls at C(5)), 1.65 and 1.74 (6, br s, methyls at C(2)), 3.18 (3, s, methoxy protons), 3.48 (1, d, J = 9 Hz, H at C(5)), 4.82–5.14 (3, m, H at C(3) and C(7)), 5.92 ppm (1, m, H at C(6)).

2-Methoxy-2,5,5-trimethylhepta-3,6-diene, Yomogi Methyl Ether (11-OCH_3). Following the procedure described for **3-OCH_3**, 25 mg (0.16 mmol) of **11-OH** (same source as for **11-ODNB**) was converted to 10 mg (37%) of GLC-purified **11-OCH_3**: IR (CS_2) 3112, 3000, 2960, 2915, 2897, 1652, 1392, 1376, 1275, 1234, 1190, 1172, 1152, 1096, 1061, 1020, 1002, 934, 880, 830, 761, 711 cm^{-1}; NMR (CS_2) 1.02 and 1.06 (12, s, methyls at C(2) and C(5)), 2.94 (3, s, methoxy protons), 4.92 and 4.94 (2, m, H at C(7)), 5.27 and 5.46 (2, AB quartet, H at C(3) and (C4), J = 16.5 Hz), 5.70 ppm (1, m, H at C(6)).

2-Methoxy-2,5-dimethyl-3-(ethenyl)hex-4-ene, Santolina Methyl Ether (5-OCH_3). Following the procedure described for **3-OCH_3**, 25 mg (0.16 mmol) of santolina alcohol[39] was converted to 7 mg (27%) of GLC-purified **6-OCH_3**: IR (CS_2) 3090, 3000, 2950, 2930, 2850, 1640, 1390, 1375, 1274, 1244, 1214, 1197, 1160, 1095, 1015, 924, 828, 678 cm^{-1}; NMR (CS_2) 0.98 and 1.02 (6, s, methyls at C(2)), 1.56 and 1.69 (6, d, olefinic methyls, J = 1.5 Hz), 2.88 (1, d of d, H at C(3), J = 9 and 7 Hz), 3.07 (3, s, methoxy group), 4.83 (1, d of d of d, trans H at C(2'), J = 18, 2.5, and 1.4 Hz), 4.88 (1, d of d of d, cis H at C(2'), J = 10, 2.5, and 1.2 Hz), 5.07 (1, d of septets, H at C(4), J = 9 Hz), 5.78 ppm (1, d of d of d, J = 18, 10, and 7 Hz).

1-(2',2'-Dimethylcyclopropyl)-3-methyl-2-buten-1-ol (13-OH). To a vigorously stirred suspension of 425 mg (61.2 mmol) of finely divided lithium wire (1% sodium) in anhydrous ether was added 1.85 g (20.4 mmol) of 1-chloro-2-methyl-1-propene followed by 1 drop of methyl iodide. The suspension was stirred at room temperature for 22 h. The dark gray suspension was cooled to 0 °C and a solution of 200 mg (2.0 mmol) of 2,2-dimethylcyclopropylcarboxaldehyde[26] in 5 mL of dry ether was added. After 3 h saturated ammonium chloride was added until the inorganic salts precipitated from solution. The ether layer was decanted and the residue washed with ether. The combined ether fractions were dried over magnesium sulfate and solvent was removed at reduced pressure. The residue was chromatographed on a short silica gel column and the product was eluted with 1:1 pentane/ether. Solvent was removed at reduced pressure to give 193 mg (61%) of a light yellow oil which could not be distilled without decomposition: IR (CCl_4) 3340, 2940, 2850, 1675, 1454, 1357, 1125, 1025, 1010, 860 cm^{-1}; NMR (CCl_4) 1.03 and 1.08 (6, s, methyls at C(2')), 0.23–1.4 (3, m, H at C(1') and C(3')), 1.67 and 1.77 (6, br s, methyls at C(3)), 3.77 (1, m, H at C(1)), 5.23 ppm (1, d of septets, H at C(2), J = 7.5 and 1.5 Hz).

Hydrolysis of 1-OPyl. A 0.05 M solution of **1-OPyl** in 0.25 M aqueous sodium bicarbonate was allowed to stand for 24 h. The solution was extracted with ether; the ether extracts were washed with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The products were concentrated by distilling the solvent, and the pot residue (about 1:1 products and solvent) was distilled bulb-to-bulb under high vacuum. Analytical runs were analyzed directly by GLC. In preparative runs the products were collected from a 12 ft × ¼ in. 10% Carbowax 20M on Anakrom ABS column. All products were reinjected to check their stability to the collection conditions. It was essential to keep the columns, injector, and detector free of acidic material.

Hydrolysis of 1-ODNB, 1-OMs, 3-ODNB, 8-OMs, and 11-ODNB. Approximately 0.05 M solutions of the esters and a threefold molar excess of 2,6-lutidine in the appropriate solvents were heated for the times indicated in Table I. The aqueous mixtures were extracted with ether and the ether extracts were washed in succession with cold 1 M hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, products were separated from solvent as described for **1-OPyl.** Control experiments with the products, an equimolar amount of the appropriate acid, and a threefold excess of 2,6-lutidine indicated that the products were stable to the reaction conditions.

Methanolysis of 3-ODNB. A methanolic solution of **3-ODNB** (ca. 0.05 M) containing a threefold molar excess of 2,6-lutidine was heated (bath temperature, 80 °C) for 12 h. The methanolic solution was diluted with water and extracted with ether. The combined extracts were washed successively with cold 1 M hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution before drying over anhydrous magnesium sulfate. The mixture was analyzed and products were purified as described for **1-OPyl.**

Acetolysis and Formolysis of 1-OP. Approximately 0.05 M solutions of **1-OP** were solvolyzed in acetic and formic acids as indicated in Table I. The mixtures were diluted with water and extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered. A twofold equivalent excess of lithium aluminum hydride was added and the suspension was stirred for 4 h. Excess hydride was carefully destroyed and the inorganic salts were precipitated with saturated ammonium chloride solution. The mixture was analyzed and the products were purified as described for **1-OPyl.**

Stereochemical Studies. (a) Optical Rotations. Artemisia alcohol (**3-OH**) isolated from the hydroyslate of **1-OPyl** had a low, but easily measured rotation, $[\alpha]^{26}_D$ +1.06° (*c* 1.23, CCl_4), while **3-OH** from formolysis of **1-OP** gave no measurable rotation, $[\alpha]^{26}_D$ 0.00 (*c* 5.1, CCl_4). Artemisia alcohol isolated from *Artemisia tridentata tridentata* gave $[\alpha]^{25}_D$ −17.7° (*c* 0.35, CCl_4).

(b) Shift Reagent. The NMR spectra of both natural and solvolytic artemisia alcohol were examined in the presence of an optically active lanthanide paramagnetic shift reagent, "Europium Optishift" (Willow Brook Laboratories). Each sample of alcohol was dissolved in 0.25 mL of carbon tetrachloride NMR solution, the initial spectrum was taken, and then approximately 20-mg portions of shift reagent were added until one or more resonances were resolved into duplicate patterns which were sufficiently separated for integration of each. Best results in each case were obtained with approximately 0.6 M equiv of shift reagent, which resulted in 1 ppm downfield shifts for most resonances. The largest chemical shift separation observed for protons in enantiomers of solvolytic **3-OH** was 0.12 ppm for the methylene protons at C(7). The diastereotopic methyl groups at C(5) were expected to be well-resolved, but were obscured by reasonances arising from the shift reagent. Only single patterns were obtained for **3-OH** from natural sources.

Kinetic Analyses. Kinetic runs were carried out in a 10-mL (1-cm path) platinum electrode conductivity cell which was equipped with a magnetic stir bar. In a typical run, a stirred solution of 90% acetone/water (8.6 mM in γ-collidine) was cooled to 0 °C in an ice/water bath. A 20-μL portion of the pentane/benzene solution of methanesulfonate (ca. 0.7 mM during the run) was injected into the cell through a 0.2-mm i.d. Teflon capillary tube. The change in conductivity was measured with a Radiometer-Copenhagen CDM-3 conductivity meter. The data were evaluated on a Hewlett-Packard Model 9810A computer-plotter.

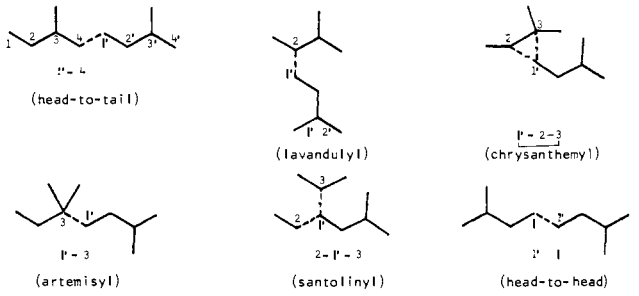
Acknowledgment. We wish to thank Drs. Roy Teranishi, Dick Mon, and Dale Black at the Western Regional USDA

Laboratory in Albany, California for their advice and assistance with open tubular columns and GC–mass spectrometry. C.D.P. was a visiting scientist at the Albany laboratory, September, 1975.

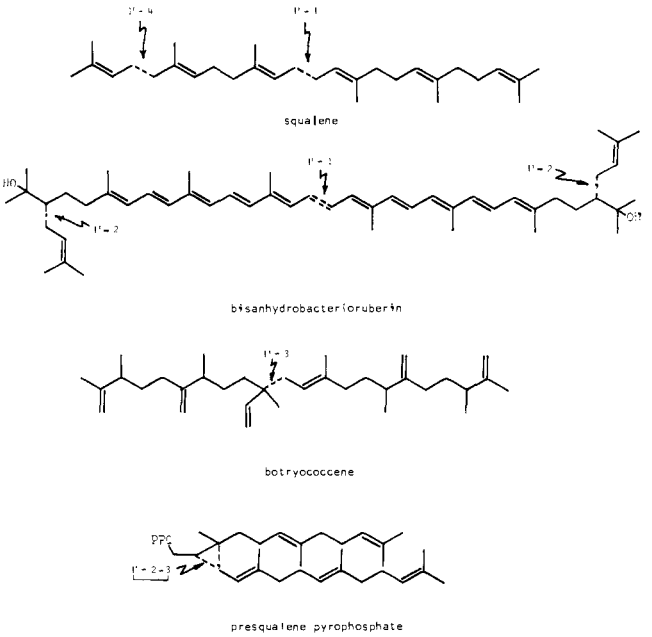
Appendix

Non-head-to-tail terpenes are commonly classified by relating the carbon skeleton to the name of a natural product (i.e., artemisyl-artemisia ketone, santolinyl-santolina triene, etc.). As the number of known irregular terpenes expands, especially into higher terpenes with one or more irregular attachments, this procedure becomes cumbersome. Also, there is still disagreement about what constitutes the head and what constitutes the tail of an isoprene unit or a polyisoprenoid chain.

We propose a simple method for describing how terpene units are joined to one another for the attachments shown below. The numbering of the isoprene unit is based on the fact



that the intermediates in the terpene biosynthetic pathway bear reactive substituents at C(1), and when terpene units are polymerized, C(1) of one of the terpene partners is always involved in bonding. The isoprene unit is numbered as one would number the carbon atoms in 3-methyl-2-butenyl pyrophosphate. The prime designation is given to the unit whose number one carbon is attached to or embedded in the other terpene unit. The method can be used to unambiguously designate irregular terpene attachments as illustrated below.



References and Notes

(1) We wish to acknowledge the National Institutes of Health (GM 19557), the Research Corporation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society for support.

(2) (a) Alfred P. Sloan Fellow, 1975–1977. (b) Career Development Award from the National Institutes of Health (HL 00084), 1975–1980.
(3) See the Appendix for a brief description of this method for denoting attachments between terpenes.
(4) (a) H. C. Rilling, C. D. Poulter, W. W. Epstein, and B. Larsen, *J. Am. Chem. Soc.*, **93**, 1783 (1971); (b) L. J. Altman, R. C. Kowerski, and H. C. Rilling, *ibid.*, **93**, 1782 (1971); (c) R. M. Coates and W. H. Robinson, *ibid.*, **93**, 1785 (1971); (d) F. Muscio, J. P. Carlson, L. Kuehl, and H. C. Rilling, *J. Biol. Chem.*, **249**, 3746 (1974); (e) G. Popjak, H. Ngan, and W. Agnew, *Bioorg. Chem.*, **4**, 279 (1975); (f) R. V. M. Campbell, L. Crombie, D. A. R. Findley, R. W. King, G. Pattenden, and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 897 (1975); (g) E. J. Corey and R. P. Volante, *J. Am. Chem. Soc.*, **98**, 1291 (1976).
(5) (a) L. J. Altman, L. Ash, R. C. Kowerski, W. W. Epstein, B. R. Larsen, H. C. Rilling, F. Muscio, and D. E. Gregonis, *J. Am. Chem. Soc.*, **94**, 3257 (1972); (b) D. E. Gregonis and H. C. Rilling, *Biochemistry*, **13**, 1538 (1974).
(6) (a) R. B. Bates and S. K. Paknikar, *Tetrahedron Lett.*, 1453 (1965); (b) C. D. Poulter, S. G. Moesinger and W. W. Epstein, *ibid.*, 67 (1972); (c) W. W. Epstein and C. D. Poulter, *Phytochemistry*, **12**, 737 (1973); (d) K. Alexander and W. W. Epstein, *J. Org. Chem.*, **40**, 2576 (1975).
(7) (a) B. M. Trost, P. Conway, and R. Stanton, *Chem. Commun.*, 1639 (1971); (b) L. Crombie, P. A. Firth, R. P. Houghton, D. A. Whiting, and D. K. Woods, *J. Chem. Soc., Perkin Trans. 1*, 642 (1972); (c) C. D. Poulter, O. J. Muscio Jr., C. J. Spillner, and R. J. Goodfellow, *J. Am. Chem. Soc.*, **94**, 5921 (1972); (d) R. M. Coates and W. H. Robinson, *ibid.*, **94**, 5920 (1972); (e) B. M. Trost and W. G. Biddlecom, *J. Org. Chem.*, **38**, 3438 (1973); (f) C. D. Poulter, O. J. Muscio Jr., and R. J. Goodfellow, *Biochemistry*, **13**, 1530 (1974); (g) C. D. Poulter, *J. Agric. Food Chem.*, **22**, 167 (1974).
(8) L. Crombie, R. P. Houghton, and D. K. Woods, *Tetrahedron Lett.*, 4553 (1967).
(9) R. B. Bates and D. Feld, *Tetrahedron Lett.*, 4875 (1967).
(10) (a) A sample of santolina triene (**9**) which was isolated from *Artemisia tridentata tridentata* and gave IR and NMR spectra identical with those previously reported[11] was provided by Professor Epstein in this department. (b) Samples of 2,7-dimethylocta-2,6-dien-4-ol (**12-OH**) were available from two independent syntheses of the alcohol carried out in our laboratory.[7f,12] Methyl ethers **1-OCH$_3$**, **3-OCH$_3$**, **5-OCH$_3$**, and **11-OCH$_3$** were prepared from the corresponding alcohols by a Williamson ether synthesis.
(11) Y. Chretien-Bessiere, L. Peyron, L. Benezet, and J. Garnero, *Bull. Chim. Soc., Fr.*, 2018 (1968).
(12) C. D. Poulter and J. M. Hughes, *J. Am. Chem. Soc.*, **99**, 3824 (1977).
(13) W. W. Epstein, L. McGee, C. D. Poulter, and L. L. Marsh, *J. Chem. Eng. Data*, **21**, 500 (1976).
(14) C. D. Poulter, R. J. Goodfellow, and W. W. Epstein, *Tetrahedron Lett.*, 71 (1972).
(15) We wish to thank Dr. Earl H. Hoerger for a generous gift of naturally occurring artemisia alcohol.
(16) C. D. Poulter and C. J. Spillner, *J. Am. Chem. Soc.*, **96**, 7591 (1974).
(17) Since the leaving group, *N*-methyl-4-pyridone, is neutral, it is unlikely that loss of asymmetry at C(4) resulted from internal return to an artemisia or yomogi derivative, followed by reionization. We were able to exclude an S_N2' contribution to the inversion at C(3') in a less hindered system.[7f]
(18) W. J. Hehre and P. C. Hiberty, *J. Am. Chem. Soc.*, **96**, 302 (1974).
(19) E. W. Bittner, E. M. Arnett, and M. Saunders, *J. Am. Chem. Soc.*, **98**, 3734 (1976).
(20) J. L. Fry, J. M. Harris, R. C. Bixigham, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **92**, 2540 (1970).
(21) The heats of formation for 2-methyl-2-pentene and 3,3-dimethyl-1-butene are −15.98 and −14.70 kcal/mol, respectively.[22] If one considers bonding between an allylic isoprene radical and a methyl group, attaching the methyl group at C(1) is 1.28 kcal/mol more stable than at C(3). Thus, the side chains should make similar contributions to the free energies of **15** and **16**.
(22) S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).
(23) C. D. Poulter and J. M. Hughes, *J. Am. Chem. Soc.*, **99**, 3830 (1977).
(24) P. v. R. Schleyer and Z. Majerski, *J. Am. Chem. Soc.*, **93**, 665 (1971).
(25) C. F. Wilcox, L. M. Loew, and R. Hoffmann, *J. Am. Chem. Soc.*, **95**, 8192 (1973).
(26) T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, *Chem. Lett.*, 503 (1972).
(27) M. Soucek, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **26**, 2551 (1961).
(28) R. F. Cox, A. L. Burlingame, D. M. Wilson, G. Eglinton, and J. R. Maxwell, *J. Chem. Soc., Chem. Commun.*, 284 (1973).
(29) T. R. Mon, *Res./Dev.*, **22**, 14 (1971).
(30) I. G. M. Campbell and S. H. Harper, *J. Sci. Food Agric.*, **3**, 189 (1952).
(31) (a) A. F. Bramwell, L. Crombie, P. Hemesley, G. Pattenden, M. Elliott, and N. F. Janes, *Tetrahedron*, **25**, 1727 (1969); (b) E. J. Corey and M. Jautelat, *J. Am. Chem. Soc.*, **89**, 3912 (1967).
(32) (a) Y. Inouye and M. Ohno, *Bull. Agric. Chem. Soc., Jpn.*, **20**, 25 (1956); (b) T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, *J. Org. Chem.*, **36**, 1968 (1971).
(33) J. L. Pierre, R. Perraud, and P. Arnaud, *Bull. Soc. Chim. Fr.*, 1539 (1970).
(34) M. Vogel and J. D. Roberts, *J. Am. Chem. Soc.*, **88**, 2262 (1966).
(35) W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, **245**, 4597 (1970).
(36) O. C. Richards and P. D. Boyer, *J. Mol. Biol.*, **11**, 327 (1965).
(37) R. D. Rieke and S. E. Bales, *J. Am. Chem. Soc.*, **96**, 1775 (1974).
(38) T. Takemoto and T. Nakajima, *Yakugaku Zasshi*, **77**, 1307 (1957).
(39) Isolated from the essential oil of *Ormenis multicaulis*.[11,40]
(40) C. D. Poulter, R. J. Goodfellow, and W. W. Epstein, *Tetrahedron Lett.*, 71 (1972).