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)).

Acknowledgment. We wish to thank Professor W. W. Epstein for a generous gift of (*S*)-(+)-2,2,2-trifluoro-1-(9'-anthryl)ethanol.

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

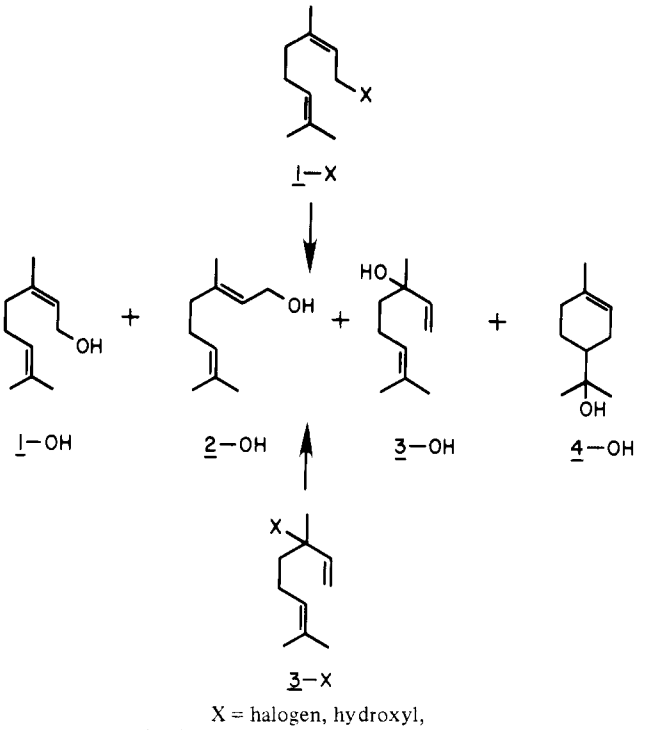
Model Studies of Terpene Biosynthesis. Stereospecific Cyclization of *N*-Methyl-(*S*)-4-([1'-^{2}H]neryloxy)pyridinium Methyl Sulfate to α-Terpineol

C. Dale Poulter* and Chi-Hsin R. King

Department of Chemistry, University of Utah
Salt Lake City, Utah 84112

Received August 10, 1981

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

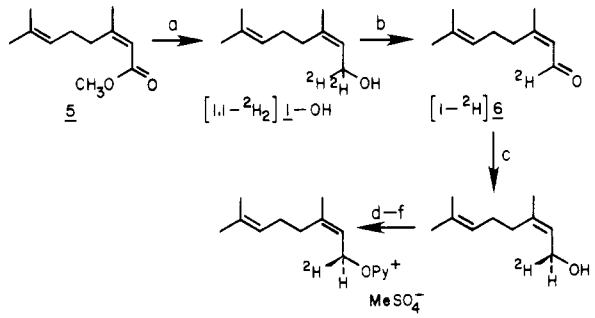


X = halogen, hydroxyl,
p-nitrobenzoate, phosphate, pyrophosphate

(1) See Cane (Cane, D. E. *Tetrahedron* **1980**, *36*, 1109-1159) for a definition of direct and allylic displacements.
(2) Stephan, W. *J. Prakt. Chem.* **1898**, *58*, 109.
(3) Winstein, S.; Valkanas, G.; Wilcox, C. F. *J. Am. Chem. Soc.* **1972**, *94*, 2286-2290.
(4) Godtfredsen, S.; Obrecht, J. P.; Arigoni, D. *Chimia* **1977**, *31*, 62-63.
(5) Rittersdorf, W.; Cramer, F. *Tetrahedron* **1968**, *24*, 43-52.
(6) Coates, R. M. *Prog. Chem. Org. Nat. Prod.* **1976**, *33*, 74-230.
(7) Kitagawa Y.; Hashimoto, S.; Satoshi, I.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1976**, *98*, 5030-5031.
(8) Bunton, C. A.; Cori, O.; Hanchey D.; Leresche, J. P. *J. Org. Chem.* **1979**, *44*, 3238-3244.
(9) Rittersdorf, W.; Cramer, F. *Tetrahedron* **1967**, *23*, 3015-3022.
(10) Ritersdorf, W.; Cramer, F. *Tetrahedron* **1967**, *23*, 3023-3028.
(11) Valenzuela, P.; Cori, O. *Tetrahedron Lett.* **1967**, 3089-3094.
(12) Bunton, C. A.; Leresche, J. P.; Hanchey, D. *Tetrahedron Lett.* **1972**, 2431-2434.

0002-7863/82/1504-1420$01.25/0

Scheme I. Synthesis of *N*-Methyl-(*S*)-4-([1′-^{2}H]neryloxy)pyridinium Methyl Sulfate



[a] $LiAl^2H_4$, Et_2O, −18 °C, 12 h. [b] MnO_2, CH_2Cl_2, 25 h. [c] Yeast, sucrose. [d] KH, THF, 1 h. [e] 4-Chloropyridine, 12 h. [f] Dimethyl sulfate, Et_2O, 4 h.

in the molecule. In this communication we discuss experiments with chiral, isotopically labeled **1**-OH which permit us to deduce the stereochemistry at C(1) during a direct intramolecular displacement, and in the following communication we address the timing of ionization and cyclization.[13] Our conclusions have important mechanistic implications for electrophilic alkylations of remote double bonds by allylic moieties in biomimetic and enzyme-catalyzed reactions.

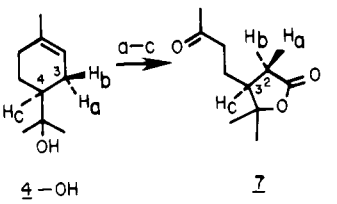
The stereochemistry at C(1) during the direct displacement represented by the neryl to α-terpinyl cyclization was studied by using *N*-methyl-(*S*)-4-([1′-^{2}H]neryloxy)pyridinium methyl sulfate ((*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$), a chiral derivative with a neutral leaving group.[14] The synthesis of (*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$ shown in Scheme I took advantage of the known stereoselectivity of dehydrogenase activity in actively fermenting yeast[15-17] to prepare (*S*)-[1-^{2}H]nerol ((*S*)-[1-^{2}H]**1**-OH)[18] from labeled aldehyde [1-^{2}H]**6**. Hydrolysis of the pyridinium salt in 0.14 M aqueous sodium bicarbonate at 25 °C gave a mixture of labeled **1**-OH (1%), **3**-OH (15%), and **4**-OH (82%), along with some unidentified hydrocarbons (2%).[19] The two major components were purified by GLPC on Carbowax 20M.

Cyclization of (*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$ across C(1) and C(6) gives [3-^{2}H]**4**-OH with chiral centers at C(3) and C(4). Assuming that deuterium does not generate any measurable amount of optical induction during cyclization, C(4) is formed stereorandomly. If cyclization is stereospecific at C(1), [3-^{2}H]**4**-OH consists of a mixture of two stereoisomers, 3*R*,4*R* and 3*R*,4*S* for inversion or 3*S*,4*R* and 3*S*,4*S* for retention. If, however, cyclization is stereoselective or stereorandom, [3-^{2}H]**4**-OH consists of a mixture of all four diastereomers. In the latter case, the selectivity of the reaction can be deduced from the relative proportions of the stereoisomers.

The composition of the stereoisomeric mixture was determined by ^{1}H NMR spectroscopy after conversion of labeled α-terpineol to lactone **7** as shown in Scheme II. This sequence translates C(3) and C(4) of **4**-OH into C(2) and C(3) of **7** without changing the configuration of the chiral centers. Chemical shift assignments of the protons at C(2) and C(3) were made by using unlabeled lactone prepared from racemic α-terpineol and are listed in Table I. A four-line pattern at 2.05 ppm was assigned to H_b on the basis of an 8 ± 2% NOE enhancement when a complex multiplet at 1.49 ppm, assigned to H_c, was irradiated. Upon addition of 7.2 equiv of Pirkle's chiral shift reagent,[20] (*S*)-2,2,2-trifluoro-1-(9′-anthryl)ethanol, to a solution of **7** in benzene-d_6, the four-line patterns at 1.69 and 2.05 ppm assigned to H_a and H_b, respectively, each moved upfield and separated into two well-resolved sets. In a separate experiment (*R*)-**7**, prepared from (*R*)-**4**-OH,[21-23] was mixed with racemic lactone, and the ^{1}H NMR spectrum was recorded in the presence of the chiral shift reagent. Enhanced intensities were seen for peaks in the upfield pattern for H_a and in the downfield pattern for H_b. Thus, we could measure signals from H_a and H_b in (*R*)-**7** and in (*S*)-**7** directly without separating the stereoisomeric lactones.

[3-^{2}H]α-Terpineol obtained from solvolysis of (*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$ was then converted to [2-^{2}H]**7** for the NMR measurements. The signals for H_b are shown in Figure 1a. The six-line pattern at 2.01 ppm is characteristic of a large vicinal coupling to H_c ($^3J_{H_a,H_c}$ = 8.0 Hz) and a small geminal coupling to the deuteron ($^2J_{H_a,H_b}$ = 2.4 Hz). Addition of 7.2 equiv of chiral shift reagent to the solution shifted the pattern upfield to 1.57 ppm, along with some loss of resolution. It is apparent, however, from examination of the spectrum shown in Figure 1b that the resonance for H_b did not separate into enantiotopic pairs as we had previously observed with racemic, unlabeled lactone. Finally, 1.5 equiv of labeled lactone prepared from [3-^{2}H]**4**-OH obtained by cyclization of (*R*,*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$ were added to the sample. The broad doublet at 1.57 ppm became the three-line

Scheme II. Conversion of α-Terpineol to 3-(3′-Oxobutyl)-4,4-dimethylbutyrolactone



[a] O_3, −78 °C. [b] Jones reagent. [c] C_6H_6, Δ.

Table I. NMR Parameters for H_a, H_b, and H_c in 3-(3′-Oxobutyl)-4,4-dimethylbutyrolactone

compd	chemical shifts, δ^a	δ_{3R}	δ_{3S}	$\delta_R - \delta_S$, Hz	coupling constants, Hz
7					
H_a	1.69	1.11[b]	1.22[b]	−33.0	$^2J_{H_a,H_b}$ = 17.0
					$^3J_{H_a,H_c}$ = 11.6
H_b	2.05	1.57[b]	1.55[b]	6.4	$^3J_{H_b,H_c}$ = 8.0
H_c	1.49				
[2-^{2}H]**7**					
H_a	1.66	*d*	1.23[c]		$^2J_{H_a,H_b}$ = 2.4
					$^3J_{H_a,H_c}$ = 11.6
H_b	2.01	1.57[c]	1.55[c]	6.2	$^3J_{H_b,H_c}$ = 8.0
H_c	1.49				

[a] Recorded at 300 MHz, 84 mM solution in benzene-d_6 with Me_4Si internal standard. [b] Measured for **7** using a 90 mM solution of a mixture containing 1 part (*R*)-**7**, 2 parts (*R*,*S*)-**7**, and 7.2 equiv of (*S*)-2,2,2-trifluoro-1-(9′-anthryl)ethanol. [c] Measured for [2-^{2}H]**7** using a 74 mM solution of a mixture containing 1 part of [2-^{2}H]**7** from (*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$, 1.5 parts of [2-^{2}H]**7** from (*R*,*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$, and 11.2 equiv of (*S*)-2,2,2-trifluoro-1-(9′-anthryl)ethanol. [d] Obscured by signals from the butyl side chain between 1.05-1.15 ppm.

(13) Poulter, C. D.; King, C. H. R. *J. Am. Chem. Soc.* **1982**, *104*, 1422-1426.
(14) This derivative was selected in order to minimize stereorandomization of the label by ionization and internal return.
(15) Althouse, V. E.; Feigl, D. M.; Sanderson, W. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1966**, *88*, 3595-3599.
(16) Poulter, C. D.; Hughes, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 3824-3829.
(17) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274-275.
(18) All labeled compounds gave satisfactory IR and NMR spectra. Incorporation of deuterium in (*S*)-[1-^{2}H]**1**-OH was greater than 99%, as determined by mass spectrometry.
(19) The absence of trace quantities of geraniol (**2**-OH), commonly found with anionic leaving groups, indicates that internal return had been suppressed.
(20) Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384-387.
(21) (*R*)-**4**-OH was obtained by oxymercuration of (*R*)-limonene[22,23] [Aldrich, $[\alpha]^{24}_D$ +106° (*c* 1, EtOH)].
(22) Brown, H. C.; Geoghegan, P. J.; Lynch, G. J.; Kurek, J. T. *J. Org. Chem.* **1972**, *37*, 1941-1947.
(23) Bambagiotti, A. M.; Vincieri, F. F.; Coran, S. A. *J. Org. Chem.* **1974**, *39*, 680-682.

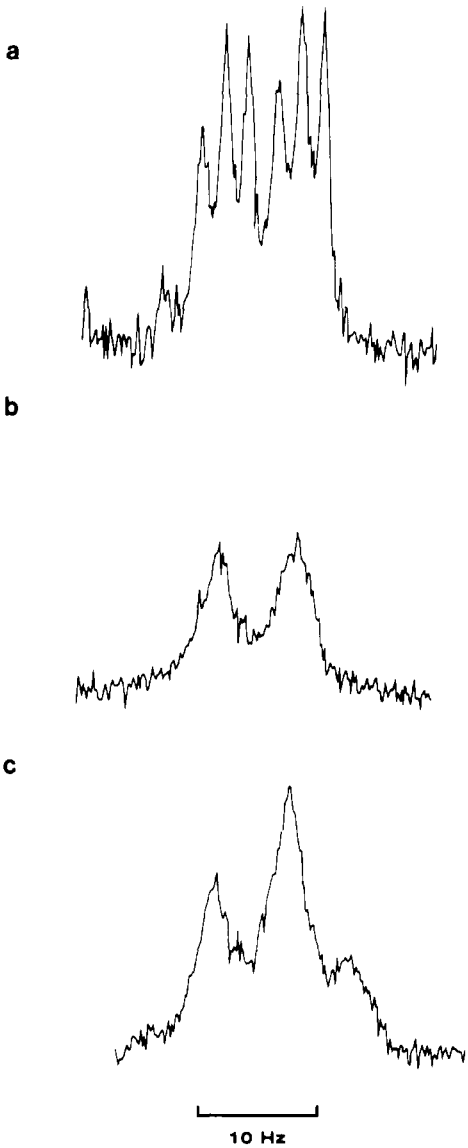
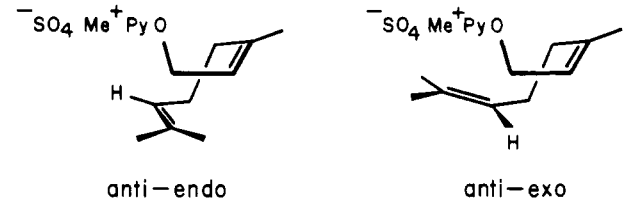


Figure 1. ^1H NMR spectra for H_b in [2-^{2}H]**3**-(3′-oxobutyl)-4,4-dimethylbutyrolactone] ([2-^{2}H]**7**) recorded in benzene-d_6 at 300 MHz. (a) [2-^{2}H]**7** from [3-^{2}H]**4**-OH obtained during solvolysis of (*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$; (b) same as (a) with 7.2 equiv of (*S*)-2,2,2-trifluoro-1-(9′-anthryl)ethanol added; (c) same as (a) with 1.5 equiv of [2-^{2}H]**7** obtained from (*R*,*S*)-[1-^{2}H]**1**-OH and 11.2 equiv of (*S*)-2,2,2-trifluoro-1-(9′-anthryl)ethanol added.

pattern shown in Figure 1c, formed from overlapping doublets (J = 8 Hz) with the low field pattern being more intense. Similar behavior was seen for H_a. According to the assignments presented in Table I, the deuteron in [2-^{2}H]**7** is cis to H_c when C(3) is *S* and trans when C(3) is *R*. These experiments clearly establish that [2-^{2}H]**7** obtained from (*S*)-[1-^{2}H]**1**-OH is a mixture of only the 2*S*,3*R* and 2*S*,3*S* diastereomers.[24] Labeled α-terpineol derived from (*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$ must, therefore, consist of only the 3*R*,4*R* and 3*R*,4*S* stereoisomers. The obvious conclusion is that cyclization is stereospecific at C(1) and proceeds with inversion of configuration.

It follows that the fraction of **1**-OPy$^+$MeSO$_4^-$ which cyclizes to α-terpineol must do so from a conformation where the remote double bond is positioned at the backside of C(1). Two limiting orientations which accomodate this restriction are shown below. Although we cannot distinguish between the anti-endo and anti-exo modes, the topologically related linalyl system is known to cyclize preferentially from an anti-endo conformation,[4] and a similar preference is expected for its allylic isomer. The stereoselectivity



we observed at C(1) for the direct process is measurably higher than the preference reported for the anti-endo mode in the allylic displacement. The difference might indicate that allylic cyclization can also occur by competing anti-exo or syn modes. The former possibility cannot be detected by the technique we employed, and the latter is precluded for a direct displacement. Linalyl *p*-nitrobenzoate was, however, used to study the allylic displacement,[4] and loss of stereocontrol could have resulted from internal return of the anionic leaving group.

As mentioned earlier, a concerted mechanism offers an attractive rationale for the stereochemistry of direct and allylic displacements. It must be emphasized, however, that while a concerted electrophilic cyclization requires stereospecificity, the converse—that stereospecificity establishes concertedness—does not hold. A stepwise process where cyclization is faster than reorientation of the side chain is also consistent with the stereochemistry of the electrophilic cyclizations. This question is addressed in the following communication.

Acknowledgment. This work was supported by the Institute of General Medical Science of the National Institutes of Health, GM 21328.

Registry No. **1**-OPy$^+$MeSO$_4^-$, 80387-02-6; α-terpineol, 98-55-5; (3*R*,4*R*)-[3-^{2}H]-**4**, 80375-27-5; (3*R*,4*S*)-[3-^{2}H]-**4**, 80408-85-1; (2*S*,3*R*)-[2-^{2}H]-**7**, 80375-28-6; (2*S*,3*S*)-[2-^{2}H]-**7**, 80408-86-2; (*R*)-**7**, 38746-47-3; (*S*)-**7**, 80408-87-3; ((*S*)-[1′-^{2}H]**1**-OPy$^+$MeSO$_4^-$), 80387-04-8.

(24) We saw no peaks for the 2*R*,3*R* and 2*R*,3*S* stereoisomers, even at high spectrum amplitudes, and conservatively estimate that they constituted less than 5% of the mixture.

Model Studies of Terpene Biosynthesis. A Stepwise Mechanism for Cyclization of Nerol to α-Terpineol

C. Dale Poulter* and Chi-Hsin R. King

Department of Chemistry, University of Utah
Salt Lake City, Utah 84112

Received August 10, 1981

Electrophilic alkylations of remote double bonds by allylic moieties are important carbon–carbon bond forming reactions in terpene metabolism and related biomimetic olefin cyclizations.[1-4] The enzymatic and nonenzymatic reactions are both characterized by a high degree of stereoselectivity. Two explanations have evolved for this phenomenon.[5] One is the reactions are concerted. This is attractive since stereospecificity is a logical result of the synchronous changes in bonding that occur in concerted reactions. The other explanation is a nonconcerted process involving a series of conformationally rigid intermediates where topology is maintained between the initiation and termination steps.[2,3,5-10]

(1) Coates, R. M. *Prog. Chem. Org. Nat. Prod.* **1976**, *33*, 74–230.
(2) Poulter, C. D.; Rilling, H. C. *Acc. Chem. Res.* **1978**, *11*, 307–313.
(3) Cane, D. E. *Tetrahedron* **1980**, *36*, 1109–1159.
(4) Poulter, C. D.; Rilling, H. C. "Biosynthesis of Isoprenoid Compounds"; Porter, J. W., Ed., Wiley: New York, 1981; Vol. 1, pp 161–224.
(5) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9–17.
(6) Poulter, C. D.; Wiggins, P. L.; Le, A. T. *J. Am. Chem. Soc.* **1981**, *103*, 3926–3927.
(7) Mash, E. A.; Gurria, G. M.; Poulter, C. D. *J. Am. Chem. Soc.* **1981**, *103*, 3927–3929.

0002-7863/82/1504-1422$01.25/0