Formal Total Synthesis of (±)-Pseudomonic Acids A and C. The Quasi-Intramolecular Lewis Acid Catalyzed Diels-Alder Reaction

Barry B. Snider,*[1] Gary B. Phillips, and Robert Cordova

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254, and Department of Chemistry, Princeton University, Princeton, New Jersey 08544

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A formal total synthesis of pseudomonic acid A (1) has been achieved by using an ene reaction in sequence with a quasi-intramolecular Lewis acid catalyzed Diels-Alder reaction, which converts **19** to **24**, as the key step. "Quasi-intramolecular" refers to a Diels-Alder reaction in which the Lewis acid binds covalently to the diene and complexes to the dienophile, providing the regiochemical control typical of intramolecular Diels-Alder reactions and the acceleration typical of Lewis acid catalysis. The scope and mechanism of this reaction are explored as well as its potential for control of endo-exo stereochemistry and stereochemistry on a side chain.

Introduction

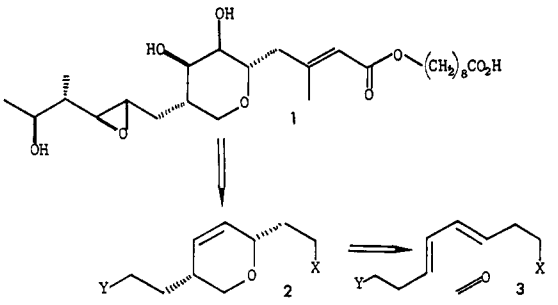
Pseudomonic acid A (1), an antibiotic produced by a strain of *Pseudomonas fluorescens*, functions as a competitive inhibitor of isoleucyl-tRNA synthetase[2] and is an effective antimicrobial agent against Gram-positive bacteria, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and mycoplasmal pathogens.[3] The absolute and relative stereochemistry have been determined by spectroscopic studies[4] and X-ray analysis.[5] More recently, pseudomonic acid C, with a double bond instead of an epoxy group in the side chain, has been isolated.[6] The novel structure and complex stereochemistry and functionality of pseudomonic acid have made it a popular synthetic target.[7,8]

Our approach to pseudomonic acid[9] was based on the retrosynthetic analysis shown in Scheme I. The vicinal diol of 1 can be constructed easily from the double bond of **2**; the two side chains can be elaborated from differently functionalized two-carbon fragments. The dihydropyran **2** can be made by a Diels-Alder reaction of **3** and formaldehyde.[10,11] Unfortunately, control of regiochemistry in the Diels-Alder reaction is likely to be a serious problem since the diene moiety of **3** is virtually symmetrical and separation of regioisomeric adducts is impractical.

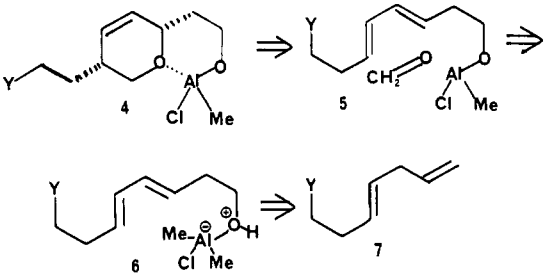
As a solution to this problem, we considered covalently attaching a Lewis acid to the X group, which could then complex to formaldehyde and both direct and accelerate the Diels-Alder reaction. This approach, which we term a quasi-intramolecular Lewis acid catalyzed Diels-Alder reaction, can be easily explored since alkylaluminum halides form complexes with alcohols that spontaneously liberate an alkane, generating a new Lewis acid.[12] For instance, the Me_2AlCl-alcohol complex **6** rapidly loses CH_4 to give **5**, which is a Lewis acid. Complexation of **5** with formaldehyde and Diels-Alder reaction should give **4**. This approach is especially attractive since the complex **6** can be generated in situ by an ene reaction of CH_2O-Me_2AlCl with **7**.[13,14] We have recently shown that CH_2O-Me_2AlCl reacts with a wide variety of alkenes to give a zwitterion, which undergoes a 1,5-proton shift to give an ene adduct and a 1,5-chloride shift to give a γ-chloro alcohol. With monosubstituted alkenes, γ-chloro alcohols are minor products and ene adducts are formed as a 9:1 *E*-*Z* mixture.[13]

Model Studies. The viability of this approach was demonstrated with (*E*)-1,4-hexadiene as a model for **7**. Reaction of (*E*)-1,4-hexadiene with 2 equiv of paraformaldehyde and Me_2AlCl or methylaluminum sesquichloride in CH_2Cl_2 gives a complex mixture of products. The initial addition can occur at three sites. Reaction at C_1 gives

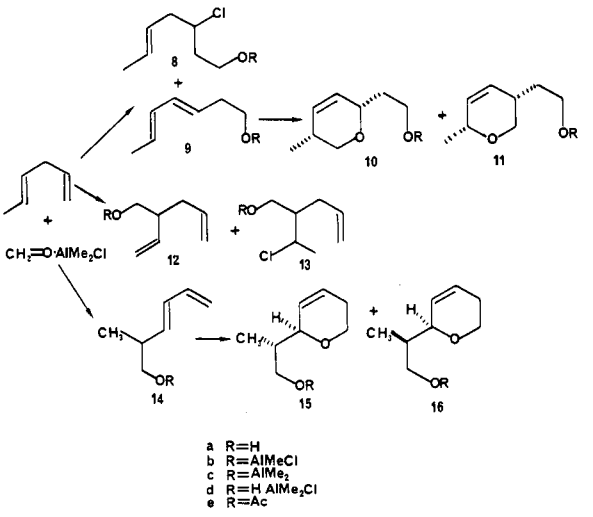
Scheme I



Scheme II



Scheme III



chloroalkoxide **8c** (5%) and ene adduct **9d**, which loses CH_4 to give **9b**, which reacts with another molecule of

* Address correspondence to the Department of Chemistry, Brandeis University, Waltham, MA 02254.

(1) Fellow of the Alfred P. Sloan Foundation, 1979-1983. Camille and Henry Dreyfus Teacher-Scholar, 1982-1987.

(2) Hughes, J.; Mellows, G.; Soughton, S. *FEBS Lett.* **1980**, *122*, 322. Hughes, J.; Mellows, G. *Biochem. J.* **1980**, *191*, 209. Coulton, S.; O'Hanlon, P. J.; Rogers, N. J. *J. Chem. Soc., Perkin Trans 1* **1982**, 729 and references cited therein.

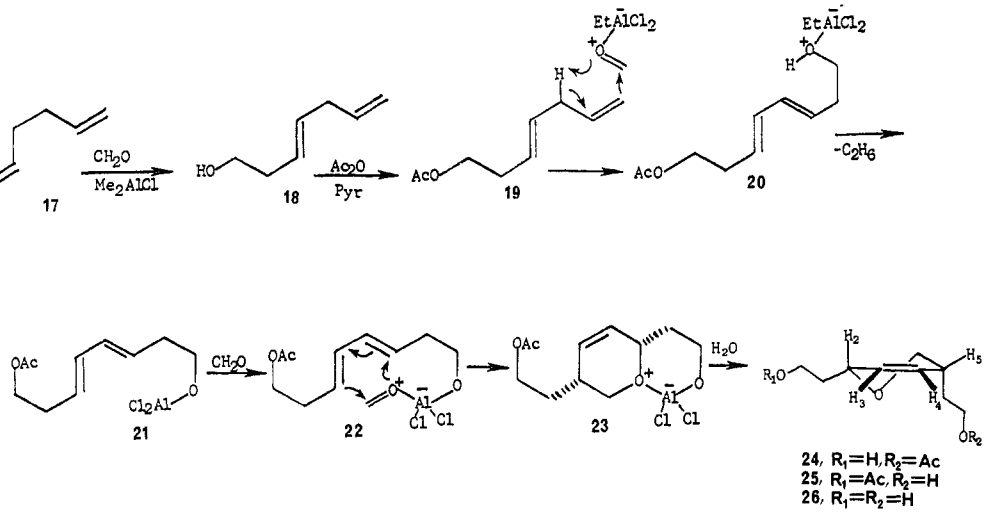
0022-3263/83/1948-3003$01.50/0

Table I. ^{13}C NMR Spectra of Dihydropyrans[a]

compd	C_2	C_3[b]	C_4[b]	C_5	C_6	C_2 subst. C_β	C_2 subst. C_α	C_5 subst. C_β	C_5 subst. C_α	other absorbtions
10a	73.5	131.0	128.6	29.3	68.8	36.8	60.4	18.4		
11a	70.5	132.1	127.3	32.2	68.2	21.0		36.1	59.5	
15a	78.9	128.6	125.1	25.2	63.8	39.4	66.3			13.3(β-Me)
16a	77.3	127.7	126.1	25.2	64.2	39.1	66.0			11.1(β-Me)
24	73.1	130.1	128.4	31.3	67.0	37.0	59.6	32.0	62.4	170.7, 20.8
25	70.9	129.4	128.7	31.5	67.4	33.8	60.8	35.7	59.5	170.7, 20.5
26	73.6	130.1	128.6	31.8	67.9	37.2	60.0	36.0	59.8	
36	72.6	129.6	124.6	24.8	63.0	36.9	59.6			
37	70.3	128.3	126.1	24.9	63.1	40.1	176.3			
39	74.2	131.7	124.2	c	71.0					21.4(C_2-Me)[d]
40	68.4	131.1	123.6	c	67.5					20.0(C_2-Me)[e]
41	75.5	129.4	125.4	32.6	70.3	37.1	61.1			21.7(C_6-Me)
42	72.6	129.0	124.2	31.8	64.4	35.4	61.8			20.4(C_6-Me)

[a] Chemical shifts for 36 and 37 were assigned by using off-resonance decoupling. Other compounds were assigned by analogy. [b] Assignments may be switched. [c] Could not be unambiguously assigned. [d] 36.2, 31.9, 31.2, 29.7, 29.6, 29.3, 25.5, 22.7, 14.1. [e] 35.4, 31.9, 30.7, 29.7, 29.6, 25.6, 22.7, 22.3, 14.1.

Scheme IV



formaldehyde to give Diels–Alder adducts **10b** (25%) and **11b** (3%). Reaction at C_4 gives chloroalkoxide **13c** (1%) and ene adduct **12d**, which loses CH_4 to give **12b** (1%). Reaction at C_5 gives ene adduct **14d**, which loses CH_4 to give **14b**, which reacts with another molecule of formaldehyde to given **15b** (5%) and **16b** (1.5%). Aqueous workup gives **8a**, **10a–13a**, **15a**, and **16a** in the indicated yields. The sequential ene reaction quasi-intramolecular Diels–Alder reaction approach is successful, and the control of regiochemistry (**10a**:**11a** = 8.3:1) is acceptable. The problem here is a lack of selectivity in the initial ene reaction.

The structures of **10a**, **11a**, **15a**, and **16a** were established spectroscopically. γ-Hydroxy ethers **10a**, **15a**, and **16a** show the expected intramolecular hydrogen bond absorption at 3530 cm^{-1} while **11a** absorbs at 3460 cm^{-1}, as expected for a δ-hydroxy ether.[15] The regiochemistry of **10a** and **11a** was established by NMR decoupling experiments. The stereochemistry of **15a** and **16a** was established by ^{13}C NMR spectra: C_2, C_β, and CH_3 absorb upfield in the erythro isomer **16a**[16] (see Table I).

Pseudomonic Acid. The synthesis of the desired starting material **7**, Y = OAc, is easily accomplished by the

(3) Basker, M. J.; Comber, K. R.; Clayton, J. P.; Hannan, P. C. T.; Mizen, L. W.; Rogers, N. H.; Slocombe, B.; Sutherland, R. *Curr. Chemother. Infect. Dis., Proc. Int. Congr. Chemother., 11th* **1979**, *1*, 471.
(4) Chain, E. B.; Mellows, G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 294.
(5) Alexander, R. G.; Clayton, J. P.; Luk, K.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 561.
(6) Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H. *Tetrahedron Lett.* **1980**, *21*, 881.
(7) For total syntheses see: (a) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. I. J. Am. Chem. Soc., **1980**, *102*, 6577. (b) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *Tetrahedron Lett.* **1981**, *22*, 2059.
(8) (a) Sinay, P.; Aburki, S.; Pietraszkiewics, M. "Abstracts of Papers", 178th National meeting of the American Chemical Society, Washington, DC, Sept 1979; American Chemical Society: Washington, DC, **1979**; CARB 29. (b) Curran, D. P. *Tetrahedron Lett.* **1982**, *23*, 4309. (c) Fleet, G. W. J.; Spensley, C. R. C. *Ibid.* **1982**, *23*, 109. (d) Raphael, R. A.; Stibbard, J. H. A.; Tidbury, R. *Ibid. Lett.* **1980**, *21*, 2407. (e) Fleet, G. W. J.; Gough, M. J. *Ibid.* **1982**, *23*, 4509. (f) Schonenberger, B.; Summermatter, W.; Ganter, C. *Helv. Chim. Acta* **1982**, *65*, 2333.
(9) For a prelimary report of a portion of this work see: Snider, B. B.; Phillips, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 1113.
(10) Diels–Alder reactions of simple dienes with unactivated alkenes have been little studied: (a) Hamer, J.; Turner, J. A. In "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1967; p 205. (b) Ansell, N. G.; Charalambrides, A. A. *J. Chem. Soc., Chem. Commun.* **1972**, 739. (c) Dale, W. J.; Sisti, A. J. *J. Am. Chem. Soc.* **1954**, *76*, 81. (d) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
(11) Diels–alder reactions of activated dienes (dienyl ethers) with simple aldehydes and simple dienes with activated aldehydes (e.g., chloral, methyl glyoxylate) are well-known. See ref 10a and: Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358 and references cited therein.
(12) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.
(13) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. C. *J. Am. Chem. Soc.* **1982**, *104*, 555.
(14) For a review of Lewis acid catalyzed ene reactions see: Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.
(15) Aaron, H. S. In "Topics in Stereochemistry", Eliel, E. L.; Alinger, N. L., Eds.; Wiley: New York, **1979**; Vol. 11, pp 1–53. (b) Tichy, M. In "Advances in Organic Chemistry" Raphael, R. A.; Taylor, E. C., Wynberg, H., Eds.; Wiley-Interscience: New York, 1965; vol. 5, p 115.
(16) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

Table II. Reaction of 9a and 9e with Formaldehyde and Me_2AlCl

diene	equiv of Me_2AlCl	reaction time, h	solvent	ratio of products, % 9	10	11	a
9a	1.0	24	CH_2Cl_2	1	80	11	5
9a	1.7	2	CH_2Cl_2	0	70	19	7
9a	1.0	24	1:1 CH_2Cl_2-CH_3NO_2	5	82	2	7
9a	1.7	24[b]	1:1 CH_2Cl_2-CH_3NO_2	0	89	5	4
9e	1.0	24	1:1 CH_2Cl_2-CH_3NO_2	6	37	46	7

[a] Unidentified compound: see Experimental Section. [b] 80% complete after 2 h. Compare to reaction in CH_2Cl_2.

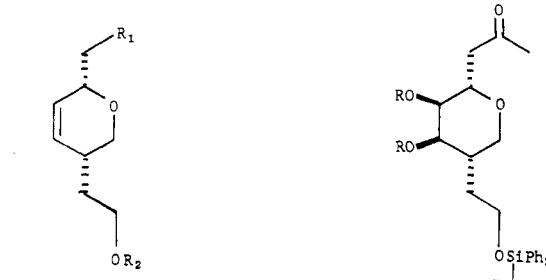
ene reaction of 1,5-hexadiene (17) with CH_2O–Me_2AlCl,[13] which gives 18 as an 8:1 mixture of *E* and *Z* isomers in 81% yield. This mixture is used without purification since only the *E,E* isomer of 22 will undergo the Diels–Alder reaction. Only traces of 2:1 adducts can be obtained in the ene reaction, even when excess CH_2O–Me_2AlCl is used. Electron withdrawal by the aluminum alkoxide deactivates the double bonds of 18 so that addition of the methyl group of Me_2AlCl to formaldehyde occurs much faster than ene reaction of formaldehyde with 18.[12]

Acetylation of 18 gives 19 in 96% yield. The acetate 19 can also be prepared from 17 in one pot. Addition of acetic anhydride to the aluminum alkoxide formed as an intermediate in the preparation of 18 and reaction for 3 days at 25 °C gives a 70% yield of 19.

Attempted reaction of 19 with paraformaldehyde and Me_2AlCl as described above for (*E*)-1,4-hexadiene is unsuccessful. Apparently, complexation of Me_2AlCl to the acetate of 19 decreases the nucleophilicity of the double bonds so that addition of a methyl group to formaldehyde is the only reaction. Use of $EtAlCl_2$, a stronger Lewis acid with a less nucleophilic alkyl group, is successful.[17] Treatment of 19 with 3 equiv of paraformaldehyde and 4.5 equiv of $EtAlCl_2$ in methylene chloride for 1 h at 0 °C gives a 32% yield of a 4:1 mixture of 24 and 25 as determined by analysis of the ^{13}C NMR spectrum. A similar reaction in 1:1 methylene chloride–nitromethane for 12 h at 25 °C gives a 37% yield of a 16:1 mixture of 24 and 25. Use of only 2 equiv of $EtAlCl_2$ gives only 24, but in substantially lower yield. The acetate of 19 is more basic than formaldehyde and complexes to $EtAlCl_2$. This complex selectively reacts with CH_2O–$EtAlCl_2$ at the less deactivated terminal double bond to give ene adduct 20 which loses ethane to give 21. Complexation of 21 with formaldehyde gives 22, which undergoes a quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction to give 23. Aqueous workup gives 24. The minor isomer 25 is presumably formed by a competing intramolecular Diels–Alder reaction.

The cis stereochemistry of 24, which is expected for the Diels–Alder adduct from an (*E,E*)-diene, can be assigned from the coupling constants of the vinylic protons.[18] H_3 is weakly coupled to the vicinal pseudoaxial proton H_2 (≈1 Hz) and to the allylic pseudoequatorial proton H_5 (≈1 Hz). Conversely, H_4 is strongly coupled to the vicinal pseudoequatorial proton, H_5 (4 Hz), and to the allylic pseudoaxial proton, H_2 (2 Hz). If the substituents were trans, H_2 and H_5 would both be pseudoaxial and the coupling constants of the vinylic hydrogens would be similar. The regiochemistry of 24 is established by decoupling experiments on the aldehyde 27. Irradiation of the allylic proton α to the oxygen at δ 4.5 collapses the signal from the methylene group α to the aldehyde at δ 2.51 to a broad singlet. The structure of 25 is established by hydrolysis of the 4:1 mixture of 24 and 25 to give a single diol 26 as determined by ^{13}C NMR analysis.

A formal total synthesis of pseudomonic acid was completed by converting 24 to 32, an intermediate in the



24, R_1=CH_2OH, R_2=Ac
27, R_1=CHO, R_2=Ac
28, R_1=$CHCH_3OH$, R_2=H
29, R_1=$CHCH_3OH$, R_2=$SiPh_2t$-Bu
30, R_1=$COCH_3$, R_2=$SiPh_2t$-Bu

31, R = H
32, R,R = CYCLOHEXYLIDENE

Kozikowski, Schmiesing, and Sorgi syntheses of pseudomonic acids A and C.[7] Oxidation of 24 with buffered pyridinium chlorochromate[19] gives a 74% yield of 27. Addition of crude 27 to methylmagnesium chloride gives a 91% yield of crude 28 as a mixture of diastereomers. Selective silylation of the primary alcohol with *tert*-butyldiphenylsilyl chloride, triethylamine, and 4-(dimethylamino)pyridine[20] gives a 68% yield of 29. Oxidation of 29 with pyridinium chlorochromate gives an 80% yield of 30. Cis hydroxylation from the less hindered side with a catalytic amount of osmium tetraoxide and *N*-methylmorpholine *N*-oxide[21] gives a 91% yield of 31, which is protected as the cyclohexylidene ketal 32 in 92% yield by treatment with cyclohexanone, cupric sulfate, and toluenesulfonic acid. This material is identical with an authentic sample, kindly provided by Professor Kozikowski, by spectral and chromatographic comparison.

The syntheses of pseudomonic acids A and C in optically active form can be achieved by asymmetric induction in the Diels–Alder reaction of 22 to give 23. We therefore investigated the reaction of (*E*)-3,6-heptadien-1-yl *d*-mandelate (54) instead of 19. Unfortunately, the adduct 55, corresponding to 24, is formed in 33% yield as a 1:1 mixture of diastereomers as determined by ^{13}C NMR analysis.

Mechanism. The proposed quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction is probably responsible for the selective formation of 10 and 24. However, adventitious inductive effects may also explain these results.

(17) For more complete studies of $EtAlCl_2$ catalyzed reactions of formaldehyde see: Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1983**, *43* 464.

(18) The conformation shown for 24 minimizes 1,3-diaxial interactions. In cyclohexanes, the vicinal coupling constant of the vinylic proton is larger for a pseudoequatorial proton, which has a dihedral angle closer to the optimal 0°. The allylic coupling constant is larger for the pseudoaxial proton, which has a dihedral angle closer to the optimal 90°. See: (a) Abraham, R. J.; Gottschalk, H.; Paulsen, H.; Thomas, W. A. *J. Chem. Soc.*, **1965**, 6268. (b) Francois, P.; Lablache-Combier, A.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1965**, 2588. See 2a and 4a.

(19) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

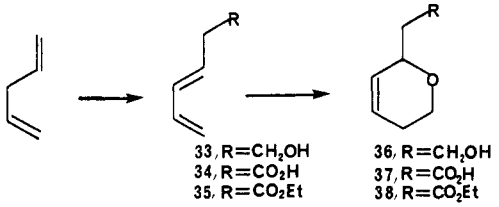
(20) Chaudhary, S. K.; Hernandez, O. *Tetrahedron* Lett. **1979**, 99.

(21) VanRheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

Mechanistic investigations were carried out on pure **9a**, prepared in 38% yield as a 4.7:1 3-*E* and 3-*Z* mixture by the Wittig reaction of lithium triphenylphosphoranylidenepropoxide[22] with crotonaldehyde. Selective formation of the *E* isomer may result from alkoxide catalyzed isomerization of the betaine.[23]

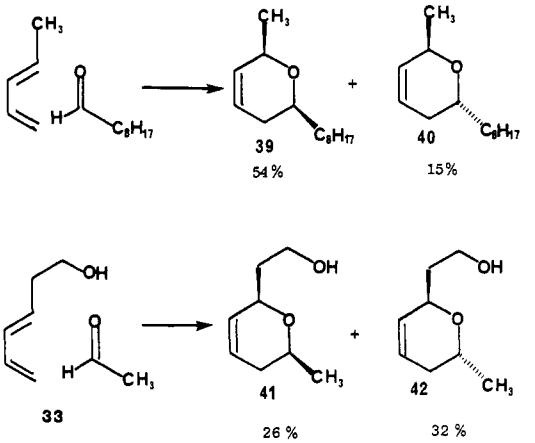
The results of the reaction of **9a** with CH_2O, shown in Table II, indicate that the quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction is occurring. Reaction of **9a** with 1 equiv of Me_2AlCl gives **9b**, which reacts with paraformaldehyde to give a 7.3:1 mixture of **10a** and **11a** in methylene chloride and a 41:1 mixture in 1:1 methylene chloride–nitromethane. When excess Me_2AlCl (1.7 equiv) is used, an intermolecular reaction competes. Selectivity drops to 3:1 in methylene chloride and to 18:1 in 1:1 methylene chloride–nitromethane. The reactions in nitromethane–methylene chloride are slower, possibly due to nitromethane competing with formaldehyde for the Lewis acid. This competition may be responsible for the enhanced selectivity. Reaction of the acetate **9e** under optimal conditions for **9a** gives a 1:1.3 mixture of **10e** and **11e**, indicating that inductive effects are as expected[17] and that the free hydroxyl group that reacts with Me_2AlCl to give a new Lewis acid is necessary for the quasi-intramolecular reaction.

Directing Groups. The reactions of **33**,[24] **34**,[24] and **35**[24,25] were studied to determine the scope of directing groups. Reaction of (*E*)-3,5-hexadien-1-ol (**33**) with paraformaldehyde and Me_2AlCl gives a 68% yield of **36**. Reaction of 1,4-pentadiene with paraformaldehyde and Me_2AlCl, which generates **33** in situ, gives a 37% yield of **36**. The acid **34** is less reactive than **33**, giving a 35% yield of **37** with 45% recovered **34**. The ester **35**, which is inductively deactivating and cannot direct the reaction, is even less reactive. No reaction occurred with Me_2AlCl. With 3 equiv of $EtAlCl_2$ a 63% yield of **38** is obtained.



Endo–Exo Selectivity. The directing effect in the quasi-intramolecular reaction may allow the control of endo–exo selectivity with aldehydes. Relatively little is known about the Diels–Alder reactions of aldehydes with simple nonoxygenated dienes.[10] We found that treatment of (*E*)-1,3-pentadiene with nonanal and 1 equiv of methylaluminum sesquichloride gives a 3.7:1 mixture of **39** and **40** in 69% yield and 2-decanol in 9% yield. Use of the more nucleophilic Me_2AlCl gives a 46% yield of a 3.6:1 mixture of **39** and **40** and 43% of 2-decanol. Reaction of **33** with acetaldehyde (as paraldehyde) and 1 equiv of Me_2AlCl gives a 57% yield of a 1:1.2 mixture of **41** and **42**. Attempted reaction of **34** or **35** with acetaldehyde was unsuccessful.

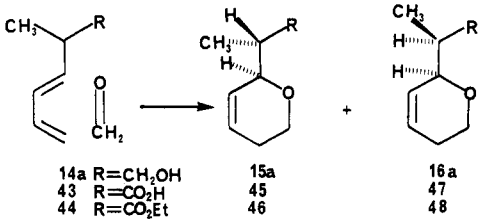
The structures of **39–42** were assigned by analyses of the ^{13}C NMR spectra (Table I). Either the C_2 or C_6 substituent must be pseudoaxial in the trans isomers **40** and



42. This leads to enhanced γ shielding of C_2, C_6, and the substituent carbons (C_6-Me and C_β in **42** and C_2-Me in **40**).

The quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction thus has a marked directing effect for the exo isomer, although this is not synthetically useful in these examples. Endo–exo selectivity in these reactions is a result of steric interactions rather than secondary orbital overlap. The diene interacts both with the substituent on the aldehyde and the Lewis acid, which is presumably complexed to the less hindered oxygen lone pair.

Control of Stereochemistry on the Side Chain. Diels–Alder adducts **15a** and **16a** are minor products in the reaction of (*E*)-1,4-hexadiene with formaldehyde. Their formation in a 3.7:1 ratio suggests that the quasi-intramolecular reaction may be useful for control of stereochemistry on a side chain. Dienes **14a**, **43**, and **44** were synthesized to study this possibility. Methylation of the dianion of sorbic acid gives **43**.[26] Methylation of the anion of ethyl sorbate[27] gives **44** in 71% yield. In both

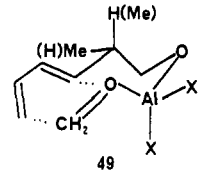


cases, the 2,2-dimethyl compound is a significant byproduct. Lithium aluminum hydride reduction of **44** gives a 68% yield of **14a**.

Reaction of **14a**, **43**, or **44** with paraformaldehyde using conditions developed for **33–35** gives disappointing results. The alcohol **14a** gives a 3.0:1 ratio of threo adduct **15a** to erythro adduct **16a** while **43** and **44** give a 2.2:1 ratio of threo to erythro adducts.

The structures of adducts **45–48** were established by interconversion of the esters and acids and reduction of the mixture of esters to **15a** and **16a**. The coupling constants, $J_{\beta,2}$ = 7 Hz and $J_{\beta,2}$ = 5 Hz for **45** and **46**, respectively, are consistent with the expected values for intramolecularly hydrogen bonded threo and erythro β-alkoxy carboxylic acids.[28] Examination of the transition state **49** suggests that the *threo* isomer will be favored since the alkyl group should prefer to occupy the pseudoequatorial position. Models suggest, and results indicate, that this preference should be small since 1,3-diaxial interactions with the two oxygens are minimal.

(22) Leppard, D. G.; Raynolds, P. W.; Chapelo, C. B.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 695.
(23) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 792.
(24) Martin, S. F.; Tu, C.;Chow, T. *J. Am. Chem. Soc.* **1980**, *102*, 5274.
(25) Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *J. Am. Chem. Soc.* **1976**, *98*, 6317.
(26) For a similar procedure see: Savu, P. M.; Katzenellenbogen, J. *J. Org. Chem.* **1981**, *46*, 239.
(27) For a similar procedure see: Kieczykowski, G. R.; Quesada, M. L.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 782.
(28) Maskins, K.; Polgar, N. *J. Chem. Soc., Perkin Trans. 1* **1973**, 109.



49

Conclusion. The synthesis of **24** in three steps from 1,5-hexadiene demonstrates the utility of the quasi-intramolecular Lewis acid catalyzed Diels–Alder reaction. We are presently exploring the application of this concept to other types of reactions.

Experimental Section

NMR spectra were determined on a Perkin-Elmer R32, Varian EM390, Bruker WH90, Jeol FX90Q or a homemade 270 MHz NMR spectrometer. Mass spectra were obtained on an AEI MS9 mass spectrometer. GC analyses were performed on 10-ft 10% Carbowax 20M(A), 15-ft 7% DEGS(B), or 9-ft 10% DEGS(C) on 60/80 Chromosorb WNAW on $^1/_4$-in. columns at flow rates of ≈50 mL/min. Analyses were performed by Galbraith Laboratories.

All alkylaluminum halides were purchased from Texas Alkyls Inc. in the following forms: Me_2AlCl, 15% in heptane (1.14 M) or 25% in hexane (1.9 M); $EtAlCl_2$, 25% in heptane (1.54 M) or neat; $MeAlCl_2$, 21% in hexane (1.40 M). $Me_3Al_2Cl_3$ was prepared by mixing equimolar amounts of $MeAlCl_2$ and Me_2AlCl. $EtAlCl_2$ in CH_2Cl_2 solution was prepared by dilution of neat $EtAlCl_2$.

CH_2Cl_2, diisopropylamine, paraldehyde, triethylamine, and (*E*)-1,3-pentadiene were distilled from CaH_2. THF and ether were distilled from sodium–benzophenone ketyl. HMPA, nitromethane, crotonaldehyde, and nonanal were fractionally distilled under N_2. Cyclohexanone was distilled from anhydrous $CuSO_4$. Sorbic acid was dried overnight in vacuo.

All air-sensitive reactions were run in flame-dried glassware under N_2.

Preparation of Starting Materials. Ethyl 3,5-hexadienoate (**35**), 3,5-hexadienoic acid (**34**), and 3,5-hexadien-1-ol (**33**) were prepared by literature methods.[24,25]

2-Methyl-3,5-hexadienoic acid (43).[26] Sorbic acid (3.9 g, 35 mmol) in 50 mL of THF was added to a solution of lithium diisopropylamide (83 mmol) in 100 mL of THF at −78 °C over a period of 20 min. The solution was stirred 1 h at −78 °C and treated with methyl iodide (12.08 g, 85 mmol). After 10 min, 100 mL of 5% NaOH solution was added and the mixture was warmed to 25 °C. The layers were separated and the aqueous phase was washed with ether, acidified with 200 mL of 10% hydrochloric acid, and extracted with three portions of ether. The ether layer was dried (Na_2SO_4) and evaporated to give 4.4 g of crude product which was a 4:1 mixture of **43** and **51**. Medium pressure chromatography of 4.1 g on silica gel (1:1 ether–hexane) gave 26 mg of a 1:9 mixture of **43** and 2,2-dimethyl-3,5-hexadienoic acid (**51**),[29] 1.45 g of a 1:1 mixture of **43** and **51**, 2.2 g of a 9:1 mixture of **43** and **51**, which was used for further reactions, and 90 mg of a 20:1 mixture of **43** and **51**. These mixtures and 3,5-hexadienoic acid were stored as 1 M solutions in CH_2Cl_2 at −20 °C. The pure acids polymerized even at −20 °C.

The data for **43** follow: NMR ($CDCl_3$) δ 11.4 (s, 1), 6.6–5.6 (m, 3), 5.4–5.0 (m, 2), 3.23 (dq, 1, *J* = 7, 7 Hz), 1.32 (d, 3, *J* = 7 Hz); IR (neat) 3600–2300, 1705, 1649, 1605, 1009 cm^{-1}.

Ethyl 2-Methyl-3,5-hexadienoate (44).[27] Ethyl sorbate (6.3 g, 45 mmol) was added dropwise to a solution of lithium diisopropylamide (50 mmol) in 90 mL of THF and 11 g of HMPA at −78 °C. The solution was stirred 1 h at −78 °C, giving a deep red solution. Methyl iodide (8.46 g, 60 mmol) was added rapidly. The solution was stirred 30 min and quenched by pouring into a mixture of 400 mL of water and 100 mL of saturated NH_4Cl solution. Normal workup gave 6.5 g of crude ester. Fractional distillation of 5.3 g gave 4.0 g (71%) of a 4:1 mixture of **44** and ethyl 2,2-dimethyl-3,5-hexadienoate (**52**): bp 91 °C (15 torr); NMR ($CDCl_3$) δ 6.55–5.65 (m, 3), 5.35–5.00 (m, 2), 4.15 (q, 2, *J* = 7.5 Hz), 3.16 (dq, 1, *J* = 7, 7.5 Hz, **44**), 1.31 (s, 6, **52**), 1.28 (d, 3, *J* = 7 Hz, **44**), 1.25 (t, 3, *J* = 7.5 Hz); IR (neat) 1730, 1647, 1603, 1007 cm^{-1}.

2-Methyl-3,5-hexadien-1-ol (14a). The 4:1 mixture of **44** and **52** (1.9 g, ~12 mmol) was reduced with lithium aluminum hydride (0.6 g, 16 mmol) in 20 mL of ether as described for the preparation of **33**[24] to give 1.47 g of crude **14a** and 2,2-dimethyl-3,5-hexadien-1-ol (**50**). Medium-pressure chromatography of 1.37 g on silica gel (2:1 hexane–ether) gave 185 mg (13%) of **50** and 859 mg (68%) of **14a**.

The data for **50** follow: NMR ($CDCl_3$) δ 6.60–5.50 (m, 3), 5.25–4.95 (m, 2), 3.35 (s, 2), 2.22 (s, 1, OH), 1.02 (s, 6); IR (neat) 3320, 1646, 1603, 1386, 1362, 995 cm^{-1}. An analytical sample was prepared by evaporative distillation (35 °C, 0.05 torr). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.11; H, 11.30.

The data for **14a** follow: NMR ($CDCl_3$) δ 6.60–4.95 (m, 5), 3.51 (d, 2, *J* = 6.5 Hz), 2.41 (ddq, 1, *J* = 6.5, 6.5, 6.5 Hz), 1.03 (d, 3, *J* = 6.5 Hz); IR (neat) 3320, 1649, 1604, 995 cm^{-1}. The alcohol was distilled (65–66 °C, 10 torr) prior to use.

3,5-Heptadien-1-ol (9a).[30] Butyllithium (24 mL, 1.48 M in hexane, 35 mmol) was added to a solution of (3-hydroxypropyl)triphenylphosphonium bromide[22] (6.42 g, 16 mmol) in 80 mL of THF at −78 °C. The solution was slowly warmed to 25 °C and stirred 1 h, giving a deep red solution of the alkoxide ylide. The solution was cooled to −35 °C and treated dropwise with crotonaldehyde (1.12 g, 16 mmol). The solution was stirred 2.5 h at −35 °C and then 15 h at 25 °C. Normal workup gave 4.19 g of crude product. Chromatography of 4.13 g on silica gel (2:1 hexane–ether) gave 679 mg (38%) of a 4.75:1 mixture of **9a** and 3-*Z*-**9a** as determined by 270 MHz NMR analysis. The mixture was inseparable by GC. Spectral data were determined from the mixture. NMR ($CDCl_3$) δ 3-*Z*-**9a** 6.30 (dd, 1, *J* = 11, 15 Hz, H_5), 6.1–5.9 (m, 1, H_4), 5.68 (dq, 1, *J* = 15, 6 Hz, H_6), 5.25 (dt, 1, *J* = 10.5, 6.5 Hz, H_3), 3.67 (t, 2, *J* = 6 Hz), 2.39 (dt, 2, *J* = 6.5, 6 Hz, H_2), 1.74 (d, 3, *J* = 6 Hz); **9a** 6.1–5.9 (m, 2), 5.58 (dq, 1, *J* = 14, 6 Hz, H_6), 5.48 (dt, 1, *J* = 14.5, 5.5 Hz, H_3), 3.67 (t, 2, *J* = 6 Hz), 2.27 (dt, 2, *J* = 5.5, 6 Hz, H_2), 1.70 (d, 3, *J* = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 3-*Z*-**9a** 130.1, 126.6, 124.5, 61.8, 31.0, 18.1, one peak is obscured by the major isomer; **9a** 132.9, 131.1, 127.8, 127.0, 61.8, 35.7, 17.8; IR (neat) 3320, 1032, 985 cm^{-1}; GC (A, 170 °C) t_R = 7.7 min. In addition to $J_{3,4}$, the chemical shift of H_2 is consistent with that observed in (*E*)-[24] and (*Z*)-3,5-hexadien-1-ol.[31] The alcohol **9a** was distilled (89 °C, 16 torr) prior to use.

3,5-Heptadien-1-yl Acetate (9e). Treatment of the 4.75:1 mixture of (*E,E*)- and (*Z,E*)-3,5-heptadien-1-ol (220 mg, 2.0 mmol) with acetic anhydride (310 mg, 3.0 mmol) and pyridine (240 mg, 3.0 mmol) for 1 day at 25 °C gave 310 mg (100%) of a 4.75:1 mixture of acetates **9e** and 3-*Z*-**9e**:[32] NMR ($CDCl_3$) δ 6.5–5.1 (m, 4), 3.66 (t, 2, *J* = 6 Hz), 2.47 (dt, 2, *J* = 7, 6 Hz, H_2, **9e**), 2.37 (dt, 2, *J* = 6, 6 Hz, H_2, 3-*Z*-**9e**), 2.02 (s, 3), 1.77 (d, 3, *J* = 7 Hz, **9e**) 1.72 (d, 3, *J* = 7 Hz, 3-*Z*-**9e**); GC (A, 140 °C) t_R = 14.6 min.

General Procedure for Diels–Alder Reactions. Dienes without Hydroxyl or Carboxyl Groups. Alkylaluminum halide was added rapidly to a stirred mixture of diene and aldehyde (paraformaldehyde does not dissolve until the Lewis acid is added) in CH_2Cl_2. The reaction was quenched by slow addition of water (5 mL/mmol) followed by 10% hydrochloric acid (1 mL/mmol) to dissolve the precipitate. The layers were separated and the aqueous phase extracted with three portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo.

Dienes with Hydroxyl or Carboxyl Groups. A 1 M solution of the diene in CH_2Cl_2 was slowly added to a solution of Me_2AlCl in the remaining CH_2Cl_2 at 0 °C. If nitromethane was used, it was then added. The aldehyde was then added rapidly. The solution was quenched and worked up as described above except that Na_2SO_4 was the drying agent.

Reaction of *trans*-1,4-Hexadiene with Formaldehyde. $Me_3Al_2Cl_3$ (10 mL, 0.5 M in hexane, 5 mmol, 10 mmol of Al) was

(29) Bigley, D. B.; Weatherhead, R. H. *J. Chem. Soc., Perkin Trans. 2* **1976**, 704.

(30) Mauldin, C. H. Biehl, E. R.; Reeves, D. C. *Tetrahedron Lett.* **1972**, 2955.

(31) Winter, M.; Naf, F.; Furrer, A.; Pickenhagen, W.; Giersch, W.; Meister, A.; Wilhalm, B.; Thommen, W.; Ohloff, G. *Helv. Chim. Acta* **1979**, *62*, 135.

(32) Tolstikov, G. A.; Dzhemilov, U. M.; Khusnutdinov, R. I. *J. Gen. Chem. USSR (Engl. Trans.)* **1975**, *45*, 1296.

added to a solution of (*E*)-1,4-hexadiene (410 mg, 5.0 mmol) and paraformaldehyde (300 mg, 10 mmol) in 15 mL of CH_2Cl_2 at 0 °C. Workup after 2 min gave 670 mg of crude product. Medium pressure chromatography of 465 mg on silica gel (2:1 hexane–ether) gave, in order of elution, 10 mg (2%) of a 2.5:1 mixture of 2-(1-chloroethyl)-4-penten-1-ol (**13a**) and 2-vinyl-4-penten-1-ol (**12a**),[33] 23 mg (4.5%) of (*E*)-3-chloro-5-hepten-1-ol (**8a**), 30 mg (6%) of (*E*)-6-chloro-3-hepten-1-ol (**53**), 33 mg (6.5%) of a 3.7:1 mixture of *threo*- and *erythro*- 5,6-dihydro-β-methyl-2*H*-pyran-2-ethanol (**15a** and **16a**), 120 mg (25%) of *cis*-5,6-dihydro-5-methyl-2*H*-pyran-2-ethanol (**10a**), and 14 mg (3%) of *cis*-5,6-dihydro-2-methyl-2*H*-pyran-5-ethanol (**11a**).

The data for the mixture of **12a** and **13a** follow: NMR (CCl_4) δ **13a** 6.0–5.4 (m, 1), 5.3–4.8 (m, 2), 4.22 (dq, 1, J = 7, 7 Hz), 2.49–1.65 (m, 3), 1.54 (d, 3, J = 7 Hz); **12a**[33] 6.0–5.4 (m, 2), 5.3–4.8 (m, 4), 3.67 (d, 2, J = 7 Hz); IR (neat) 3360, 3080, 1642, and 912 cm^{-1}.

The data for **8a** follow: NMR ($CDCl_3$) δ 5.55 (m, 2), 4.35–3.90 (m, 1), 3.86 (t, 2, J = 7 Hz), 2.48 (br t, 2, J = 5.5 Hz), 2.5–1.5 (m, 2), 1.70 (br d, 3, J = 5 Hz); IR (neat) 3320, 3010, 1670, and 968 cm^{-1}.

The data for **53** follow: NMR ($CDCl_3$) δ 5.56 (m, 2), 4.09 (tq, 1, J = 6.5, 6.5 Hz), 3.65 (t, 2, J = 6 Hz), 2.45 (m, 2, $J_{5,6}$ = 6.5 Hz, H_5), 2.29 (m, 2, $J_{1,2}$ = 6 Hz, H_2), 1.66 (s, 1, OH), 1.51 (d, 3, J = 6.5 Hz), coupling constants were determined by irradiation at H_3, H_4, and H_7; IR (neat) 3330 and 974 cm^{-1}.

The data for **14a** and **15a** follow: NMR ($CDCl_3$) δ **14a** 5.91 (m, 1), 5.72 (br d, 1, J = 10.5 Hz), 4.03 (m, 2), 3.74–3.55 (m, 3), 2.95 (s, 1, OH), 2.33 (m, 1), 2.00–1.75 (m, 2), 1.00 (d, 3, J = 7 Hz); **15a** 5.62 (br d, 1, J = 10.5 Hz), 4.32 (m, 1), 4.03 (m, 1), 0.91 (d, 3, J = 7 Hz) the remaining peaks are the same as **14a**; IR (neat) 3380, 3030, 1648, and 1063 cm^{-1}; IR (CCl_4) 3630 (w), 3530 (s) cm^{-1}; GC (A, 170 °C) t_R = 14.5 min.

The data for **10a** follow: NMR ($CDCl_3$) δ 5.84 (ddd, 1, J = 10, 2, 1 Hz, H_3), 5.56 (ddd, 1, J = 10, 4.5, 2.5 Hz, H_4), 4.31 (m, 1, H_2), 3.98–3.50 (m, 4), 3.0 (br s, 1, OH), 2.18 (m, 1), 1.79 (dt, 2, J= 7, 7 Hz), 1.08 (d, 3, J = 7 Hz); IR (neat) 3400, 3055, 1655, and 720 cm^{-1}; IR (CCl_4) 3630 (w), 3530 (s) cm^{-1}; GC (A, 170 °C), t_R = 14.2 min. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.31; H, 10.05.

The data for **11a** follow: NMR ($CDCl_3$) δ 5.72 (br s, 2), 4.23 (br dq, 1, J = 3,7 Hz, H_2) 3.87 (dd, 1, J = 11.5, 1 Hz, H_6), 3.79 (dd, 1, J = 11.5, 3.8 Hz, H_6), 3.74 (ddd, 1, J = 11.5, 8, 4 Hz, H_α), 3.64 (ddd, 1, J = 11.5, 5, 5 Hz, H_α), 3.12 (br, 1, OH), 2.25 (m, 1, H_5), 1.76 (m, 2, Hβ), 1.25 (d, 3, J = 6.5 Hz); IR (neat) 3600, 3020, and 1058 cm^{-1}; IR (CCl_4) 3630 (w), 3460 (s) cm^{-1}; GC (A, 170 °C) t_R = 18.6 min.

Synthesis of 3,6-Heptadien-1-ol (18). A 250-mL flask containing paraformaldehyde (2.26 g, 75 mmol) was flame-dried, filled with N_2, and cooled to 0 °C. 1,5-Hexadiene (5.7 g, 57 mmol) and CH_2Cl_2 (50 mL) were added. Me_2AlCl (80 mL of 1.14 M in heptane, 91 mmol) was added slowly with concomittant foaming. The solution became clear after 2 min. After 38 min the reaction was quenched slowly with saturated NaH_2PO_4 solution followed by enough 1 M HCl to dissolve the precipitate. The layers were separated and the aqueous layer was extracted twice with 25 mL of ether. The combined organic layers were dried (Na_2SO_4) and evaporated to give 5.166 g (81%) of **18**, as an 86:14 *E*–*Z* mixture, which contained a small amount (≈5%) of a polar impurity: NMR (CCl_4) δ 5.4–6.1 (m, 3), 5.0 (br d, 1, J = 16 Hz), 4.96 (br d, 1, J = 11 Hz), 3.55 (t, 2, J = 6 Hz), 3.00 (br s, 1, OH), 2.75 (dd, 2, J = 6, 6 Hz), 2.31 (m, 2); IR (neat) 3340, 3080, 2930, 1638, 1430, 1050, 992, 968, 910cm^{-1}; MS m/e (relative intensity, %) 112 (4, M^+), 94 (25), 81 (54), 79 (100); GC (C, 125 °C) t_R = 16.1 (*E*) and 17.6 (*Z*) min; mol wt calcd for $C_7H_{12}O$ 112.0888, found 112.0888.

A similar reaction mixture was "quenched" with 3.6 equiv of acetic anhydride and stirred for 3 days. Normal workup gave a 70% yield of a 10:1 mixture of **19** and **18**.

Synthesis of 3,6-Heptadien-1-yl Acetate (19). Crude **18** (4.42 g, 39.4 mmol), acetic anhydride (6.0 g, 59 mmol), and pyridine (3.4 g, 41.3 mmol) were stirred 14 h at 25 °C. Water was added and the reaction was stirred 9 h to hydrolyze excess acetic anhydride. Normal workup gave 5.84 g (96%) of **19** which was ≈95% pure by NMR analysis: NMR (CCl_4) δ 5.3–6.1 (m, 3), 4.98 (br d, 1, J = 15 Hz), 4.96 (br d, 1, J = 11 Hz), 4.02 (t, 1, J = 6 Hz), 2.75 (m, 2), 2.35 (dd, 2, J = 6, 6 Hz), 1.98 (s, 3); IR (neat) 3090, 2970, 1745, 1640, 1240, 1040, 995, 972cm^{-1}.

Synthesis of 24. A 250-mL flask containing paraformaldehyde (2.439 g, 81.2 mmol) was flame-dried, filled with N_2 and cooled to 0 °C. 3,6-Heptadien-1-yl acetate (**19**)(4.102 g, 26.6 mmol), 18 mL of CH_2Cl_2, and 30 mL of nitromethane were added via syringe. $EtAlCl_2$ (45 mL, 2.62 M in Ch_2Cl_2, 120 mmol) was added slowly. The reaction mixture was allowed to warm to 25 °C and stirred overnight. The reaction was quenched by slow addition of saturated NaH_2PO_4 solution followed by 1 M HCl to dissolve the precipitate. The layers were separated, and the aqueous layer was extracted with two 50-mL portions of ether. The combined organic layers were dried ($MgSO_4$) and evaporated to give 6.38 g of crude product. Medium-pressure chromatography of 5.770 g on silica gel (ether) gave 1.946 g (37%) of a 16:1 mixture of pyrans **24** and **25** as determined by ^{13}C NMR analysis: NMR (CCl_4) δ 5.88 (ddd, 1, J = 10, 4, 2 Hz), 5.64 (br d, 1, J = 10 Hz), 4.30 (m, 1), 4.18 (t, 2, J = 6 Hz), 3.4–4.0 (m, 4), 2.55 (br s, 1, OH), 2.1 (m, 1), 2.07 (s, 3), 1.0–2.0 (m, 4); IR (neat) 3420, 2940, 1737, 1250, and 1050 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.53; H, 8.42.

A similar reaction of paraformaldehyde (300 mg, 10 mmol), 3,6-heptadienl-yl acetate (**19**) (515 mg, 3.34 mmol), and $EtAlCl_2$ (9.8 mL, 1.53 M in heptane, 1.51 mmol) in 5 mL of Ch_2Cl_2 at 0 °C for 1 h gave 703 mg of crude product. Chromatography of 485 mg as above gave 161 mg (33%) of a 4:1 mixture of **24** and **25** as determined by ^{13}C NMR analysis.

Hydrolysis of a 4:1 Mixture of Pyrans 24 and 25. The 4:1 mixture of **24** and **25** from the preceding reaction (51 mg) and KOH (200 mg) were dissolved in 3 mL of MeOH. The mixture was stirred 5 h at 25 °C and evaporated in vacuo. Saturated NaCl solution was added to the residue. The resulting solution was extracted 6 times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated to give 38 mg (94%) of **26**: NMR ($CDCl_3$) δ 5.88 (br d, 1, J = 11 Hz), 5.67 (br d, 1, J = 11 Hz), 4.32 (m, 1), 3.5–4.0 (m, 6), 2.9 (br s, 2, OH), 2.25 (m, 1), 2.0–1.6 (m, 4); IR (neat) 3400, 3030, 2960, and 1655 cm^{-1}.

Oxidation of 24. Alcohol **24** (212 mg, 1 mmol) in CH_2Cl_2 (2.5 mL) was added to a suspension of NaOAc (0.43 mmol), Celite (2.5 g), and pyridinium chlorochromate (425 mg, 1.97 mmol) in 11 mL of CH_2Cl_2 under N_2. The mixture was stirred for 3 h and evaporated in vacuo. Ether was added and the solution was filtered through a pad of $MgSO_4$, Celite, and Florisil. The solvent was evaporated to give 156 mg (75%) of crude aldehyde **27**: NMR ($CDCl_3$) δ 9.72 (t, 1, J = 2 Hz), 5.90 (ddd, 1, J = 1.8, 4, 10 Hz), 5.67 (ddd, 1, J = 1, 2, 10 Hz), 4.58 (br t, 1, J = 6 Hz), 4.11 (t, 2, J = 7 Hz), 3.74 (m, 2), 2.57 (dd, 2, J = 2.2, 5.9 Hz), 2.00 (s, 3), 1.9–2.1 (m, 1), 1.0–2.0 (m, 2); when the signals at δ 4.58 is irradiated the signals at 2.5–2.6 collapse to a broad singlet; ^{13}C NMR ($CDCl_3$) δ 200.2, 170.3, 129.1, 128.6, 69.4, 66.8, 61.8, 47.8, 31.6, 31.0, 20.4; IR (neat) 3040, 2970, 1734, 1720 cm^{-1}.

Addition of MeMgCl to 27. Crude aldehyde **27** (148 mg, 0.695 mmol) in 1 mL of THF was added to MeMgCl (1.0 mL of 2.9 M in THF) in 3 mL of THF at 0 °C. The reaction was stirred for 1 h at 0 °C and poured into ice water. Normal workup gave 118 mg (91%) of **28** as a mixture of diastereomers: NMR ($CDCl_3$) δ 5.85 (br d, 1, J = 11 Hz), 5.63 (d, 1, J = 11 Hz), 4.33 (br, 1), 4.05 (m, 1), 3.8 (m, 2), 3.69 (t, 2, J = 7 Hz), 3.25 (br, s, 2, OH), 2.2 (br, 1), 1.5–1.9 (m, 4), 1.20 (2d, 3, J = 6 Hz); IR (neat) 3500, 3035, 2940 cm^{-1}.

***tert*-Butyldiphenylsilylation of 28.** 2-(Dimethylamino)-pyridine (2 mg), triethylamine (94 mg, 0.93 mmol), and *tert*-butyldiphenylsilyl chloride (0.19 g, 0.69 mmol) were added to a solution of diol **28** (118 mg, 0.63 mmol) in 2 mL of CH_2Cl_2. The solution was stirred for 13 h, and CH_2Cl_2 (1 mL), triethylamine (20 mg, 0.2 mmol), and *tert*-butyldiphenylsilyl chloride (40 mg, 0.2 mmol) were added. The solution was stirred 1 day and the solvent was removed in vacuo. Pentane was added and the solution was filtered to remove solids. The filtrate was evaporated to give 345 mg of crude product. Chromatography on silica gel (4:1 pentane–ether) gave 183 mg (68%) of pure **29**: NMR ($CDCl_3$) δ 7.65 (m, 4), 7.42 (m, 6), 5.8 (m, 1), 5.53 (d, 1, J = 10.5 Hz), 4.4 (br, 1), 4.0 (m. 1), 3.73 (t, 2, J = 6 Hz), 3.6–3.8 (m, 2), 3.6 (br s, 1, OH), 2.4–2.9 (m, 4), 2.2 (br, 1), 1.20 (d, 3 x 0.35, J = 6 Hz), 1.17

(33) Kazansky, B. A.; Bubnov, Y. N.; Zotova, S. U.; Abromova, N. M.; Kiselar, N. G.; Mikailov, B. M. *Tetrahedron Lett.* **1974**, 567.

(d, 3 x 0.65, J = 6 Hz), 1.05 (s, 9); IR (CCl_4) 3540, 3080, 2935, and 1430 cm^{-1}.

Oxidation of 29. Alcohol **29** (180 mg, 0.43 mmol) in 3 mL of CH_2Cl_2 was added to a stirred suspension of pyridinium chlorochromate (258 mg, 1.20 mmol) in 1 mL of CH_2Cl_2. The reaction was stirred 12 hr, 6 mL of ether was added, and the solution was filtered with suction through a pad of Celite and Florisil. Evaporation of the solvent gave 217 mg. Chromatography on silica gel (4:1 pentane–ether) gave 144 mg (80%) of pure ketone **30**: NMR (CCl_4) δ 7.63 (m, 4), 7.37 (m, 6), 5.80 (br d, 1, J = 10 Hz), 5.55 (d, 1, J = 10 Hz), 4.40 (br t, 1, J = 6 Hz), 3.73 (t, 2, J = 6 Hz), 3.6 (m, 2), 259 (dd, 1, J = 6, 15 Hz), 2.32 (dd, 1, J = 6, 15 Hz), 2.2 (m, 1), 2.09 (s, 3), 1.7 (m, 2), 1.06 (s, 9); ^{13}C NMR ($CDCl_3$) δ 206.7, 135.6, 133.9, 130.0, 129.6, 128.7, 127.6, 70.6, 67.2, 61.7, 48.9, 36.0, 31.3, 30.8, 26.9, 19.2; IR (CCl_4) 3080, 2940, 2860, 1722, 1430, 1110 cm^{-1}. Anal. Calcd for $C_{26}H_{34}O_3Si$: C, 73.89; H, 8.11. Found: C, 73.61; H, 8.07.

Hydroxylation of 30. Ketone **30** (125 mg, 0.29 mmol) in 3 mL of acetone was added to a solution of *N*-methylmorpholine *N*-oxide (75.6 mg, 0.56 mmol) and OsO_4 (3.7 mg, 0.014 mmol, 5%) in 1 mL of water. The solution was stirred 1 day at 25 °C and evaporated in vacuo. The solution was acidified with 1 *M* HCl. Excess OsO_4 was reduced with 10 mL of 15% $NaHSO_3$ and NaCl was added to give a saturated solution. The resulting solution was extracted several times with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered through Florisil (5 g), and evaporated to give 122 mg (90%) of pure diol **31**: NMR ($CDCl_3$) δ 7.55 (m, 4), 7.36 (m, 6), 3.66 (t, 2, J = 6 Hz), 3.2–3.9 (m, 5), 2.65 (m, 2), 2.3–3.0 (br s, 2, OH) 2.12 (s, 3), 1.9 (br, 1), 1.6 (m, 2), 0.98 (s, 9); IR (neat) 3450, 2940, 1720, and 1430 cm^{-1}.

Protection of Diol 31. Diol **31** (122 mg, 0.27 mmol), benzene (3 mL), cyclohexanone (0.139 g, 1.4 mmol), anhydrous $CuSO_4$ (263 mg, 1.6 mmol), and *p*-toluenesulfonic acid (2 mg) were stirred for 15 h at 25 °C. The solution was filtered through Celite and washed through with benzene. The filtrate was evaporated to give 216 mg of crude product. Chromatography on Florisil (6:1 pentane–ether) gave 130 mg (92%) of pure **32**, which was identical with an authentic sample by spectroscopic and chromatographic comparison: NMR ($CDCl_3$) δ 7.7 (m,4), 7.4 (m, 6), 4.11 (br, 1), 3.74 (t, 2, J = 6.2 Hz), 3.4–3.9 (m, 4), 2.6 (m, 2), 2.3 (m, 1), 2.17 (s, 3), 1.2–1.9 (m, 12), 1.04 (s, 9); ^{13}C NMR ($CDCl_3$) δ 135.4, 133.6, 129.6, 127.6, 109.5, 75.6, 73.3, 66.7, 61.6, 47.1, 38.0, 35.6, 33.5, 33.3, 26.8, 25.0, 24.0, 23.7, 19.1; ^{13}C NMR (C_6D_6) δ 205.0, 134.6, 130.4, 129.0, 110.0, 76.6, 76.1, 74.3, 67.2, 62.6, 47.5, 39.0, 36.5, 34.6, 34.2, 31.0, 27.5, 25.9, 24.9, 24.6, 19.8; IR ($CHCl_3$) 3005, 2940, 2865, 1720, 1364 cm^{-1}; MS, m/e (relative intensity, %) 538 (3, M + 2), 537 (10, M + 1), 536 (23, M +), 480 (12), 479 (23), 438 (3), 421 (4), 403 (4), 381 (73), 363 (30), 351 (29), 323 (83), 199 (100).

Synthesis of 3,6-Heptadien-1-yl Mandelate (54). A solution of **18** (350 mg, 3.1 mmol), *d*-mandelic acid (517 mg, 3.4 mmol), $CuSO_4$ (2.04 g, 12.7 mmol), and toluenesulfonic acid (2 mg) in 4 mL of benzene was stirred 8 days at 25 °C under N_2. Removal of the solvent gave 737 mg of crude product. Chromatography of 625 mg on silica gel (1:1 pentane–ether) gave 350 mg (56%) of pure **54**: NMR (CCl_4) δ 7.0–7.4 (m, 5), 5.64 (ddt, 1, J = 10, 18, 6 Hz), 5.1–5.4 (m, 2), 5.01 (br s, 1), 4.8–5.1 (m, 2), 4.07 (t, 2, J = 6 Hz), 3.64 (m, 1), 2.62 (t, 2, J = 5 Hz), 2.21 (dt, 2, J = 6, 6 Hz).

Synthesis of the Mandelate corresponding to 24 (55). Reaction of **54** (316 mg, 1.35 mmol), paraformaldehyde (121 mg, 4.0 mmol), and $EtAlCl_2$ (1.2 mL, 3.54 M in CH_2Cl_2, 4.2 mmol) in CH_2Cl_2 (2 mL) and CH_3NO_2 (2.5 mL) for 12 h at 0 °C gave 540 mg of crude product. Medium-pressure chromatography of 506 mg on silica gel (1:1 pentane–ether) gave 127 mg (33%) of **55** as a ca. 1:1 mixture of diastereomers: ^{13}C NMR ($CDCl_3$) δ 173.6, 138.4, 130.37, and 130.33, 128.8, 128.5, 128.4, 128.2, 128.1, 126.5, 74.23 and 74.18, 73.0, 67.37 and 67.32, 64.0, 60.0, 37.0, 32.2, 31.4.

Reaction of 3,5-heptadien-1-ol (9a) with formaldehyde was carried out by the general method described above. The crude product was evaporatively distilled (65 °C, 0.05 torr) and the distillate was analyzed by GC. The results are shown in Table II.

The data for the unidentified compound follow: NMR ($CDCl_3$) δ 5.91–5.34 (m, 2), 4.0–3.4 (m, 5), 2.13 (m, 2), 1.72 (d, 3, J = 5.6 Hz); GC (A, 170 °C) t_R = 28.1 min.

Reaction of 3,5-heptadien-1-yl acetate (9e) (150 mg, 1.0 mmol), paraformaldehyde (60 mg, 2.0 mmol), and Me_2AlCl (0.53 mL, 1.9 M in hexane, 1.0 mmol) in 5 mL of 1:1 CH_2Cl_2–CH_3NO_2 for 24 h gave 143 mg of crude product. Evaporative distillation of 102 mg (50 °C, 0.05 torr) gave 65 mg (51%), which was shown by GC (A, 140 °C) to consist of **9e** (6%), **10e** (37%, t_R = 36.6 min), and **11e** (46%, t_R = 39.9 min). Hydrolysis of 39 mg of the distillate with 70 mg of K_2CO_3 in 0.5 mL of MeOH gave 25 mg of a mixture which was shown by GC (A, 170 °C) to consist of **9a** (6%), **10a** (37%), **11a** (46%), and the unidentified compound (7%). The data for **10e** and **11e** follow: NMR ($CDCl_3$) δ 5.95–5.30 (m, 2), 4.35–4.00 (m, 3), 3.95–3.40 (m, 2), 2.5–2.0 (m, 1), 2.03 (s, 3), 1.98–1.60 (m, 2), 1.21 (d, 3, J = 6 Hz, **11e**), 1.03 (d, 3, J = 7 Hz, **10e**).

Reaction of 1,4-pentadiene (340 mg, 5.0 mmol), paraformaldehyde (900 mg, 30 mmol), and Me_2AlCl (31 mL, 1.1 M in heptane, 35 mmol) in 15 mL of CH_2Cl_2 for 1 h at 0–25 °C gave 0.50 g of crude product. Chromatography of 284 mg on silica gel (2:1 hexane–ethyl acetate) gave 29 mg of a mixture containing some 3,5-hexadien-1-ol, 155 mg (37%) of **36**, and 114 mg of a fraction containing aromatic materials that appears to result from toluene present as an impurity in the Me_2AlCl solution.

The data for **36** follow: NMR ($CDCl_3$) δ 5.75 (m, 2), 4.35 (m, 1), 4.2–3.5 (m, 2), 3.80 (t, 2, J = 7 Hz), 2.90 (s, 1, OH), 2.6–1.9 (m, 2), 1.78 (dt, 2, J = 6, 6 Hz); IR (neat) 3430, 3045, and 1082 cm^{-1}; GC (A, 170 °C) t_R = 13.6 min. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.78; H, 9.54.

Reaction of 3,5-hexadien-1-ol (33) (200 mg, 2 mmol), paraformaldehyde (100 mg, 3 mmol), and Me_2AlCl (1.1 mL, 1.9 M in hexane, 2 mmol) in 10 mL of CH_2Cl_2 for 24 h gave 221 mg of crude product. Evaporative distillation of 134 mg (60 °C, 0.05 torr) gave 122 mg (68%) of clear oil, which was shown by GC analysis to be 88% **36**.

Reaction of 3,5-hexadienoic acid (34) (560 mg, 5.0 mmol), paraformaldehyde (240 mg, 8.0 mmol), and Me_2AlCl (9.1 mL, 1.1 M in hexane, 10 mmol) in 15 mL of CH_2Cl_2 for 30 min gave 600 mg of crude products. Chromatography of 500 mg on silica gel (1:1 hexane–ethyl acetate) gave 210 mg (45%) of recovered **34** and 210 mg (35%) of **37**, mp 72–75 °C.

Recrystallization from diisopropyl ether gave pure **37**[8d]: mp 75–76 °C; NMR ($CDCl_3$) δ 10.99 (s, 1), 5.92 (dddd, 1, $J_{3,4}$ = 10.3 Hz, $J_{2,3}$ = 4.4 Hz, $J_{3,5\beta}$ = $J_{3,5\alpha}$ = 2.2 Hz, H_3), 5.64 (ddd, 1, $J_{3,4}$ = 10.3 Hz, $J_{2,4}$ = 1.6 Hz, $J_{4,5\alpha}$ = 3.5 Hz, H_4), 4.55 (m, 1), 3.99 (ddd, 1, $J_{6\alpha,6\beta}$ = 11.2, $J_{5,6\alpha}$ = 5.5, 3.4 Hz, $H_{6\alpha}$), 3.69 (ddd, 1, $J_{6\alpha,6\beta}$ = 11.2 Hz, $J_{5,6\beta}$ = 4.4, 8.6 Hz, $H_{6\beta}$), 2.60 (dd, 1, $J_{2,\beta}$ = 7.5 Hz, $J_{\beta,\beta'}$ = 15.4 Hz, H_β), 2.52 (dd, 1, $J_{2,\beta}$ = 6.2 Hz, $J_{\beta,\beta'}$ = 15.4 Hz, $H_{\beta'}$), 2.5–1.8 (m, 2); IR (neat) 3700–2300, 3042, 1705, 1091, 705 cm^{-1}. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.24; H, 7.11.

Reaction of ethyl 3,5-hexadienoate (35) (420 mg, 3.0 mmol), paraformaldehyde (140 mg, 4.5 mmol), and $EtAlCl_2$ (6.0 mL, 1.5 M in heptane, 9.0 mmol) in 15 mL of CH_2Cl_2 for 10 min at 0 °C gave 0.58 g of crude product. Chromatography of 430 mg on silica gel (4:1 hexane–ether) gave 240 mg (63%) of **38**: NMR ($CDCl_3$) δ 5.92 (m, 1), 5.64 (m, 1), 4.53 (m, 1), 4.24 (q, 2, J = 7 Hz), 4.10–3.55 (m, 2), 2.57 (dd, 1, J = 6.3, 15.5 Hz), 2.49 (dd, 1, J = 7.8, 15.5 Hz), 2.4–1.8 (m, 2), 1.27 (t, 3, J = 7 Hz); IR (neat) 3030, 1733, 1160 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found C, 63.27; H, 8.27.

Reaction of *trans*-1,3-pentadiene (70 mg, 1.0 mmol), nonanal (140 mg, 1.0 mmol), and $Me_3Al_2Cl_3$ (0.53 mL, 0.95 M in hexane, 0.5 mmol, 1.0 mmol of Lewis acid) in 5 mL of CH_2Cl_2 for 10 min at 25 °C followed by normal workup and evaporative distillation (70 °C, 0.05 torr) gave 170 mg of a colorless oil, which was shown by GC analysis (A, 140 °C) to consist of nonanal (2%, t_R = 5.1 min), 2-decanol (11%, t_R = 17.3 min), **39** (67%, t_R = 21.4 min), and **40** (18%, t_R = 29.0 min). Pure samples were obtained by preparative GC.

The data for **39** follow: NMR ($CDCl_3$) δ 5.64–5.60 (m, 2), 4.20 (m, 1), 3.50 (m, 1), 1.90 (m, 2), 1.28 (m, 14), 1.22 (d, 3, J= 6.5 Hz), 0.88 (t, 3, J = 7 Hz); IR (neat) 3035, 1652, 1085, 670 cm^{-1}; MS, m/e 210 (M^+), 195, 152, 97, 95, 71, 69, 68; mol wt calcd for $C_{14}H_{26}O$ 210.1984, found 210.1988.

The data for **40** follow: NMR ($CDCl_3$) δ 5.72 (m, 2), 4.35 (m, 1), 3.62 (m, 1), 1.96 (m, 2), 1.28 (m, 14), 1.24 (d, 3, J = 7 Hz), 0.89 (t, 3, J = 7 Hz); IR (neat) 3040, 1078, 707 cm^{-1}.

A similar reaction using Me_2AlCl (0.53 mL, 1.9 M in hexane, 1.0 mmol) for 1 h at 25 °C gave, after distillation (70 °C, 0.05 torr), 190 mg which was shown by GC analysis to consist of 2-decanol

(47%), **39** (40%), and **40** (11%).

In similar compounds H_2 and H_6 also absorb downfield in the trans isomer.[34]

Reaction of 3,5-hexadien-1-ol (33) (20 mg, 0.2 mmol), paraldehyde (9 mg, 0.25 mmol), and Me_2AlCl (0.11 mL, 1.9 M in hexane, 0.2 mmol) in 1 mL of CH_2Cl_2 for 24 h gave 25 mg of crude product. Evaporative distillation of 21 mg (65 °C, 0.025 torr) gave 20 mg of a colorless oil which was shown by GC to consist of **41** (32%) and **42** (38%). Pure samples were obtained by preparative GC.

The data for **41** follow: NMR ($CDCl_3$) δ 5.83 (m, 1), 5.58 (ddd, 1, J = 10.5, 2, 2 Hz), 4.41 (m, 1), 3.83 (m, 1, $J_{\alpha,\alpha'}$ = 12 Hz), 3.77 (m, 1, $J_{\alpha,\alpha'}$ = 2 Hz), 3.71 (ddq, 1, J = 5.0, 8.5, 6.3 Hz, H_6), 2.85 (s, 1, OH), 2.02–1.66 (m, 4), 1.23 (d, 3, J = 6.3 Hz); IR (CCl_4) 3520, 3030, 1068, 733 cm^{-1}; GC (B, 120 °C) t_R = 12.8 min.

The data for **42** follow: NMR ($CDCl_3$) δ 5.80 (m, 1), 5.64 (dddd, 1, J = 10.3, 3, 1.5, 1.5 Hz), 4.39 (br d, 1, $J_{2,\beta}$ = 10.3 Hz, H_2), 3.89 (ddq, 1, J = 8.3, 3.8, 6.3 Hz, H_6), 3.80 (dd, 2, J = 5, 9 Hz), 2.85 (s, 1, OH), 2.05 (dddd, 1, J = 17.3, 3.8, 5, 1.5 Hz, H_5), 1.93 (m, 1, $J_{\beta,\beta'}$ = 14.5 Hz, H_β), 1.87 (m, 1, $H_{5'}$), 1.62 (m, 1, $J_{\beta,\beta'}$ = 14.5 Hz, $H_{\beta'}$), 1.20 (d, 3, J = 6.3 Hz); IR (CCl_4) 3470, 3030, 1651, and 705 cm^{-1}; GC (B, 120 °C) t_R = 19.0 min.

Reaction of ethyl 2-methyl-3,5-hexadienoate (44) (770 mg, 80% **44**, 20% **52**, 5.0 mmol), paraformaldehyde (230 mg, 7.5 mmol), and $EtAlCl_2$ (10 mL, 1.5 M in heptane, 15 mmol) in 25 mL of CH_2Cl_2 for 10 min at 0 °C gave 1.00 g of crude product. Medium-pressure chromatography of 800 mg on silica gel (4:1 hexane–ether) gave 89 mg (9%) of ethyl α,α'-dimethyl-2*H*-5,6-dihydropyran-2-acetate (**56**) and 430 mg (47%) of a 2.2:1 mixture of **46** and **48** as determined by GC analysis.

The data for **56** follow: NMR ($CDCl_3$) δ 5.92 (m, 1), 5.58 (br d, 1, J = 10 Hz), 4.28 (m, 1), 4.13 (q, 2, J = 6.9 Hz), 4.2–3.9 (m, 1), 3.61 (ddd, 1, J = 3.6, 11.4, 11.4 Hz), 2.5–2.0 (m, 1), 2.0–1.5 (m, 1), 1.24 (t, 3, J = 6.9 Hz), 1.17 (s, 3), 1.11 (s, 3); ^{13}C NMR ($CDCl_3$) δ 176.5, 127.0, 126.4, 78.5, 64.1, 60.4, 46.4, 25.2, 20.6, 20.3, 14.1; IR (neat) 3016, 1721, 1384, 1365, 1084 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.43; H, 8.98.

The data for **46** and **48** follow: NMR ($CDCl_3$) δ 6.10–5.50 (m, 2), 4.5–3.5 (m, 3), 4.17 (q, 2, J = 7 Hz), 2.67 (dq, 1, J = 7, 7 Hz, **46**), 2.65–1.70 (m, 2 + 1 (**48**)), 1.26 (t, 3, J = 7 Hz), 1.18 (d, 3, J = 7 Hz, **48**), 1.13 (d, 3, J = 7.5 Hz, **46**); GC (B, 100 °C) **46** t_R = 39.5 min, **48** t_R = 36.5 min. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.92; H, 8.72.

Reaction of 2-methyl-3,5-hexadien-1-ol (14a) (110 mg, 1 mmol), paraformaldehyde (60 mg, 2 mmol), and Me_2AlCl (0.89 mL, 1.9 M in hexane, 1.7 mmol) in 5 mL of 1:1 CH_2Cl_2–CH_3NO_2 for 24 h at 25 °C gave 118 mg of crude product. Evaporative distillation of 84 mg (50 °C, 0.01 torr) gave 68 mg of a 2.8:1.0 mixture of **15a** and **16a** as a colorless oil as determined by NMR analysis.

A similar reaction with 1 equiv of Me_2AlCl gave a comparable yield of a 3.0:1.0 mixture of **15a** and **16a**.

Reaction of 2-methyl-3,5-hexadienoic acid (250 mg, 2.0 mmol, 90% **43**, 10% **51**), paraformaldehyde (90 mg, 3 mmol), and Me_2AlCl (3.6 mL of 1.14 M in hexane, 4.0 mmol) in 10 mL of CH_2Cl_2 for 1 h at 25 °C gave 292 mg of crude product. Since the free acids could not be purified, this mixture was esterified as described below and analyzed by GC, which indicated a 48% yield of a 2.2:1.0 mixture of **46** and **48** and a 28% yield of **44**.

The data for **45** and **47** determined from the hydrolysis of pure **46** and **48**, follow: NMR ($CDCl_3$) δ (**45**) 6.02–5.89 (m, 1), 5.72 (ddd, 1, J = 10.5, 2, 2 Hz, H_3), 4.33 (m, 1, $W_{1/2}$ = 14 Hz, H_2), 4.06–3.96 (m, 1), 3.77–3.63 (m, 2), 2.89 (dq, 1, J = 7, 7Hz, H_α), 2.41 (m, 1), 2.05–1.86 (m, 1), 1.21 (d, 3, J = 7 Hz), (**47**) 5.62 (dddd, 1, J = 10.5, 1, 1, 1 Hz, H_3), 4.46 (m, 1, $W_{1/2}$ = 10 Hz, H_2), 2.53 (dq, 1, J = 5,7 Hz, H_α), 1.20 (d, 3, J = 7 Hz) all other absorptions are the same as for **45**; IR (CCl_4) 3400–2400, 1710, 1654 cm^{-1}.

Conversion of 46 and 48 to 15a and 16a and to 45 and 47. The 2.2:1 mixture of **46** and **48** (92 mg, 0.50 mmol) was reduced with 38 mg of $LiAlH_4$ in 2 mL of ether at reflux for 10 h. Normal workup gave 45 mg (63%) of a 2.1:1 mixture of 15a and 16a as determined by 270-MHz NMR analysis.

Hydrolysis of a 2.2:1.0 mixture of **46** and **48** (67 mg, 0.36 mmol) with 35 mg of NaOH in 2 mL of 95% EtOH for 5 h at 25 °C gave 22 mg (39%) of a 1.0:1.3 mixture of **45** and **47** as determined by 270 MHz NMR analysis. Epimerization was shown to have occurred by conversion of 8 mg of this mixture to a 1.0:1.3 mixture of **46** and **48**, as determined by GC analysis, by treatment with 0.1 mL of a 1 M triethyloxonium tetrafluoroborate in CH_2Cl_2 and 20 μL of diisopropylethylamine[35] in 0.5 mL of CH_2Cl_2.

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Registry No. (±)-**1**, 80558-54-9; **8a**, 86611-10-1; **9a**, 37944-01-7; (3*Z*)-**9a**, 86742-51-0; **9e**, 86611-08-7; (3*Z*)-**9e**, 86611-09-8; **10a**, 81980-10-1; **10e**, 86611-25-8; **11a**, 86611-14-5; **11e**, 86611-26-9; **12a**, 5903-36-6; **13a**, 86611-37-2; (*E*)-**14a**, 86611-07-6; **15a**, 86611-12-3; **16a**, 86611-13-4; **17**, 592-42-7; (*E*)-**18**, 80502-28-9; (*Z*)-**18**, 80502-29-0; (*E*)-**19**, 72161-20-7; (*Z*)-**19**, 86645-63-8; (±)-**24**, 80502-33-6; (±)-**25**, 86611-15-6; (±)-**26**, 86611-16-7; (±)-**27**, 80514-57-4; (±)-**28** (isomer 1), 86611-17-8; (±)-**28** (isomer 2), 86611-18-9; (±)-**29** (isomer 1), 86611-19-0; (±)-**29** (isomer 2), 86611-20-3; (±)-**30**, 80502-35-8; (±)-**31**, 86611-21-4; (±)-**32**, 80558-55-0; (*E*)-**33**, 73670-87-8; (*E*)-**34**, 32775-95-4; (*E*)-**35**, 74054-58-3; **36**, 86611-27-0; **37**, 83600-40-2; **38**, 86611-28-1; **39**, 86632-06-6; **40**, 86611-29-2; **41**, 86611-30-5; **42**, 86611-31-6; (*E*)-**43**, 86611-04-3; (*E*)-**44**, 86611-05-4; **45**, 86611-35-0; **46**, 86611-33-8; **47**, 86611-36-1; **48**, 86611-34-9; (*E*)-**50**, 86632-05-5; (*E*)-**51**, 60221-75-2; (*E*)-**52**, 86611-06-5; **53**, 86611-11-2; **54**, 86611-22-5; **55** (isomer 1), 86611-23-6; **55** (isomer 2), 86611-24-7; **56**, 86611-32-7; (±)-pseudomonic acid C, 80558-56-1; sorbic acid, 110-44-1; ethyl sorbate, 5941-48-0; (3-hydroxypropyl)triphenylphosphonium bromide, 51860-45-8; crotonaldehyde, 4170-30-3; (*E*)-1,4-hexadiene, 7319-00-8; cyclohexanone, 108-94-1; *d*-mandelic acid, 17199-29-0; 1,4-pentadiene, 591-93-5; *trans*-1,3-pentadiene, 2004-70-8; nonanal, 124-19-6; formaldehyde, 50-00-0.

(34) Tavernier, D.; Anteumis, M.; Hosten, N. *Bull. Soc. Chim. Belg.* **1976**, *85*, 151.

(35) Raber, D. J.; Gariano, P., Jr., Brod, A. O.; Gariano, A.; Guida, W. C.; Guida, A. R.; Herbst, M. D. *J. Org. Chem.* **1979**, *44*, 1149.