which was conducted using a response factor correction of the relative peak areas using internal standards. A 4 ft × $^1/_8$ in. 8% Apiezon L on Chromosorb P column (column C) was used for the analyses of 2,2-dimethyl-1-iodo-5-hexene, 2,2-dimethyl-1-iodohexane, 1-bromo-2,2-dimethyl-5-hexene, 1-bromo-2,2-dimethylhexane, 2,2-dimethyl-5-hexenyl 2-propyl sulfide, 2,2-dimethylhexyl 2-propyl sulfide, and *n*-butyl 2,2-dimethyl-5-hexenyl sulfide with *n*-decane as an internal standard at 95 °C column temperature and 18 psi of nitrogen flow pressure. Column C was also used for the analysis of 1-chloro-2,2-dimethylhexane with *n*-decane as an internal standard at 90 °C column temperature and 18 psi of nitrogen flow pressure. 2,2-Dimethyl-5-hexenyl phenyl sulfide was analyzed with column C with the use of *n*-dodecane as an internal standard at 110 °C column temperature and 40 psi. A 1.5 ft × $^1/_8$ in., 10% SE-30 column (column D) at 115 °C and 18 psi was used for analysis of 2,2-dimethyl-5-hexenyl tosylate and 2,2-dimethylhexyl tosylate with *p*-chlorobenzophenone as an internal standard. A 20 ft. × $^1/_8$ in, 8% Apiezon L on Chromosorb P column (column E) was used for the analysis of 5,5-dimethyl-1-hexene and 1,1,3-trimethylcyclopentane with 1-hexene as an internal standard at a column temperature of 65 °C and 40 psi of nitrogen flow pressure.

The retention time of 2,2-dimethyl-5-hexenyl 2-propyl sulfide and 2,2-dimethylhexyl 2-propyl sulfide were established from spectral data of pure materials isolated by preparative GLC using a 6 ft × $^1/_4$ in, 10% Apiezon L column (column F) with a column temperature of 140 °C and 50 cm^3/min helium flow rate. 2,2-Dimethyl-5-hexenyl 2-propyl sulfide: NMR ($CDCl_3$) 0.91 (s, 6 H), 1.25 (d, 6 H), 1.52–1.85 (m, 4 H), 2.40 (s, 2 H), 2.77 (m, 1 H), 4.73–5.25 (m, 3 H); MS, *m/e* 186 (M^+). Anal. Calcd for $C_{11}H_{22}S$: C, 70.88; H, 11.92. Found: C, 70.96; H, 17.95. 2,2-Dimethylhexyl 2-propyl sulfide: NMR ($CDCl_3$) 0.95 (s, 6 H), 1.25 (d, 6 H), 1.50–2.00 (m, 9 H), 2.42 (s, 2 H); MS, *m/e* 188 (M^+). Anal. Calcd for $C_{11}H_{24}S$: C, 70.12; H, 12.87. Found: C, 70.13; H, 12.88. 2,2-Dimethyl-5-hexenyl phenyl sulfide and *n*-butyl 2,2-dimethyl-5-hexenyl sulfide were also isolated by preparative GLC using column F at 150 °C. 2,2-Dimethyl-5-hexenyl phenyl sulfide: NMR ($CDCl_3$) 0.97 (s, 6 H), 1.27–1.60 (m, 4 H), 2.82 (s, 2 H), 4.77–6.13 (m, 3 H), 7.00–7.50 (m, 5 H); MS, *m/e* 220 (M^+). *n*-Butyl 2,2-dimethyl-5-hexenyl sulfide: NMR ($CDCl_3$) 0.97 (s, 6 H), 0.90–2.60 (m, 13 H), 2.43 (s, 2 H), 4.80–6.00 (m, 3 H); MS, *m/e* 200 (M^+). The retention time of 5,5-dimethyl-1-hexene was established by an authentic sample obtained by preparative GLC of a hydrolyzed sample of the corresponding Grignard reagent: NMR (CCl_4) 0.88 (s, 9 H), 1.05–2.33 (m, 4 H), 4.83–6.25 (m, 3 H); MS, *m/e* 112 (M^+). A sample of 1,1,3-trimethylcyclopentane was purchased from Chemical Samples with 98% purity and used to determine its retention time.

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Reductive, Radical-Induced Cyclizations of 5-Hexenals as a Biomimetic Model of the Chemistry of Secologanin Formation

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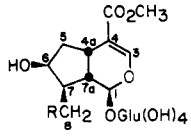
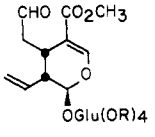
A model reaction for studying the mechanism of the biological conversion of the iridoid loganin (1) to the secoiridoid secologanin (2) is the reductive, radical-induced cyclization of secologanin tetraacetate (4) to loganin tetraacetate. Treatment of 4 with Mg and Me_3SiCl in THF at room temperature gives a mixture of the four possible C-6 and C-7 epimers of loganin tetraacetate in which the natural stereochemistry predominates. This result suggests that the biochemical event, which involves cleavage of the C-6 and C-7 bond of 1 in forming 2, may be a homolytic process that is initiated by formation of a carbon radical at C-8. The scope of the cyclization reaction, which formally occurred in a 5-hexenal moiety in 4, is defined by studies of the cyclization of six other δ,ε-unsaturated aldehydes. The results illustrate a new way for ring annulation through the reductive, radical-induced cyclization of δ,ε-unsaturated aldehydes.

The biosynthesis of many of the monoterpenoid indole alkaloids found in plants uses an amino acid and the cyclopentanomonoterpenoid ("iridoid"), loganin (1), in forming their principal structural framework.[1] Loganin first is converted to the secoiridoid secologanin (2), a key



1, R = H
3, R = OH



2, R = H
4, R = Ac

intermediate which then undergoes a biochemical Pictet–Spengler cyclization with an amino acid. Subsequent biochemical processing converts the secoiridoid moiety into a nine- or ten-carbon portion of the final alkaloid.

The mechanism of cleavage of the C-6/7 bond of 1 when it is converted to 2 is still obscure despite several studies of this process. It is known that cleavage occurs without loss of the hydrogen at positions 5, 6, and 7 of 1 in vivo.[2] This eliminates mechanisms involving oxidation of position 6 to a ketone or substitution at position 7. Battersby, Tietze, and their co-workers[3] have tested 8-hydroxyloganin (3), which was suggested by Battersby et al.[4] to be a likely

† In part.

(1) Cordell, G. A. "Introduction to Alkaloids. A Biogenetic Approach"; Wiley: New York, 1981; pp 810–830.
(2) Battersby, A. R.; Hall, E. S. *Chem. Commun.* **1970**, 194. Battersby, A. R.; Gibson, D. H. *Chem. Commun.* **1971**, 902. Battersby, A. R.; Hutchinson, C. R.; Westcott, N. D.; Larson, R. A. 163rd National Meeting of the American Chemical Society, Boston, MA, **1972**; American Chemical Society: Washington, D.C.; Abstr. ORGN 11. Daddona, P. E.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1974**, *96*, 6806.
(3) Battersby, A. R.; Westcott, N. D.; Glusenkamp, K.-H.; Tietze, L.-F. *Chem. Ber.* **1981**, *114*, 3439.
(4) Battersby, A. R.; Burnett, A. R.; Parsons, P. G. *J. Chem. Soc. C* **1969**, 1187.

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intermediate preceding bond cleavage, and its C-6 epimer as precursors of the indole alkaloids produced by *Catharanthus roseus*. Neither of these two compounds were incorporated into the alkaloids, catharanthine and vindoline, and **3** was not present in a plant that produces **2** from **1**. Consequently, it generally is accepted that no intermediates appear in the cleavage process, but as this has not been examined yet in vitro using a purified enzyme preparation, such intermediates may only have escaped detection.

The information obtained from model studies of the C-6/7 bond cleavage has illuminated our thinking about the in vivo mechanism. Two possible mechanisms have been studied wherein the formal oxidation of **1** to **2** occurred by radical or ionic processes. Partridge et al.[5] oxidized the four possible C-6 and C-7 epimers of 1-*O*-methylloganin aglucon with $Pb(OAc)_4$ and observed the formation of a novel tricyclic orthoester (bond formed by insertion of a C-6 oxygen radical into the C-1 C–H bond) and a small amount of 6-dehydrologanin (6-ketologanin), but no cleavage products. Since the same product was formed independently of the C-6 and C-7 configuration, they proposed that the C-6/7 bond had opened to a C-6 aldehyde and a C-7 carbon radical which then reclosed to the C-6 oxygen radical without eliminating a hydrogen atom to form 1-*O*-methylsecologanin aglucon. This mechanism accounted for the lack of stereochemical control with respect to C-6 and C-7 and supported the possibility of a homolytic process for the biochemical analogue even though the desired product was not formed. Tietze's group[6] examined the base-induced fragmentation of derivatives of 1-*O*-methyl-8-hydroxyloganin aglucon and found that the one with the natural configuration at C-6 gave an oxetane by intramolecular ring closure between the C-6 oxygen and C-8, but that the C-6 epimer gave 1-*O*-methylsecologanin aglucon in good yield. This ionic mechanism might have been a precedent for the biochemical analogue, but it is now moot in view of the negative results from the feeding experiments with the two C-6 epimers of **3**.[3]

The difficulty with justifying a homolytic mechanism for cleavage of the C-6/7 bound in **1** is the limitations on the way radicals can be generated at positions 6, 7, or 8. As demonstrated by Partridge et al.[5] a C-6 oxygen radical, which is the easiest to generate, has two fates—further oxidation to a ketone or rearrangement and intramolecular trapping—but the desired bond cleavage is only indirectly demonstrable. A C-7 carbon radical would be the most difficult to prepare and, as for a C-6 carbon radical, would not likely undergo C-6/7 bond cleavage in vitro. A C-8 carbon radical, which is feasible by adaptation of the methods used to synthesize 8-hydroxyloganin, might not undergo C-6/7 bond cleavage in vitro if the stereoelectronic requirements were not met by the natural configuration at positions 6 and 7. Therefore, we sought to overcome these limitations by studying a model of the reverse process, the transformation of **2** to **1**, in which the anticipated carbon radical at C-8 would be trapped rapidly by hydrogen atom donation from the solvent. As illustrated by the results discussed below, this approach provides a good model for the biological event and, from the chemistry used to define the scope of this reaction, illustrates a convenient way to annulate *cis*-fused five-membered rings by reductive, radical-induced cyclization of 5-hexenals.

(5) Partridge, J. J.; Chadha, N. K.; Faber, S.; Uskokovic, M. R. *Synth. Commun.* **1971**, *1*, 233.
(6) Tietze, L.-F. *J. Am. Chem. Soc.* **1974**, *96*, 946. Kinast, G.; Tietze, L.-F. *Chem. Ber.* **1976**, *109*, 3626.

Results

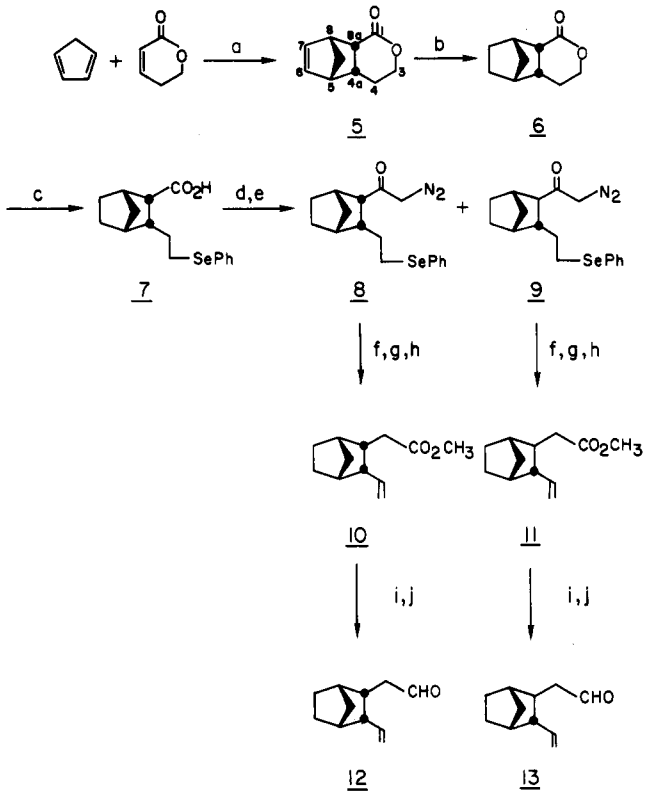
The reductive, radical-induced cyclization of 5-hexenals is not precedented, but the paper of Corey and Pyne,[7] in which they described a method for five-membered ring annulation by free-radical generation from ketones followed by internal addition to a π-bond, prompted us to explore a similar reaction with secologanin tetraacetate (**4**). Optimal conditions for the desired intramolecular cyclization were treatment of **4** with Mg (ca. 20 equiv) and Me_3SiCl (ca. 6 equiv) in THF (1 mM in **4**) at room temperature for 80 h. This gave a mixture of four stereoisomers of loganin tetraacetate in a combined yield of ca. 55% without any other observable products. The major isomer was tetraacetyl-1 (50% of the total) which was identified by acetylation to loganin pentaacetate.[8] The second major isomer was Ac_4-6-*epi*-**1** (35% of the total) which was identified by comparison with an authentic sample of 6-*epi*-loganin tetraacetate prepared from 6-dehydrologanin tetraacetate by reduction with $NaBH_4$.[8] Two minor products were isolated as 15% of the total and tentatively identified as the two other C-6/7 isomers since the mixture of all four products gave only 6-dehydrologanin tetraacetate[8] when oxidized with Jones reagent.

The following experimental variations were tried but found to be less satisfactory than the above. Na or Al in THF with Me_3SiCl gave no reaction; Zn gave a mixture of several unknown products but no loganin tetraacetate. Addition of 2,6-lutidine to the reaction mixture, as in the work of Corey and Pyne, resulted in enol silylation of **4** and the evolution of H_2 from the reaction of 2,6-lutidinium chloride with Mg. Refluxing the reaction mixture promoted the formation of 1,8-octanediol which presumably resulted from the reductive opening of THF to give 4-[(trimethylsilyl)oxy]butyl radical followed by its dimerization. Replacement of THF with other solvents capable of hydrogen atom donation (dioxane, dimethoxyethane, or 1-propanethiol in CH_2Cl_2) did not result in product formation.

The scope of the reductive, radical-induced cyclization reaction, which in **4** formally involves the 5-hexenal portion represented by carbons 6, 5, 4a, 7a, 7, and 8, was defined by studies with six other δ,ϵ-unsaturated aldehydes. To examine the effect of annulation stereochemistry, compounds **12** and **13** were synthesized from cyclopentadiene and 5,6-dihydropyran-2-one as shown in Scheme I. The Lewis acid catalyzed Diels–Alder reaction of the two starting materials gave **5** in 76% yield. Its expected endo configuration at the ring junction carbons was confirmed by analysis of the vicinal coupling constants among the protons at positions 4a, 5, 8, and 8a. Catalytic reduction of **5** to **6** followed by the sequence of transformations we used recently in a synthesis of (−)-1-*O*-methyl sweroside from an analogue of **6**[9] gave the cis and trans isomers[10] **12** and **13** in overall yields of 4% and 6%, respectively. Their relative stereochemistry was assigned from the vicinal coupling constants between the protons at C-4a and C-8a, and the structure of **14**. The cis isomer, **12**, cyclized to the bicyclic cis-fused cyclopentanol **14** (40%) but the trans isomer, **13**, gave only its reduction product **15** (and no

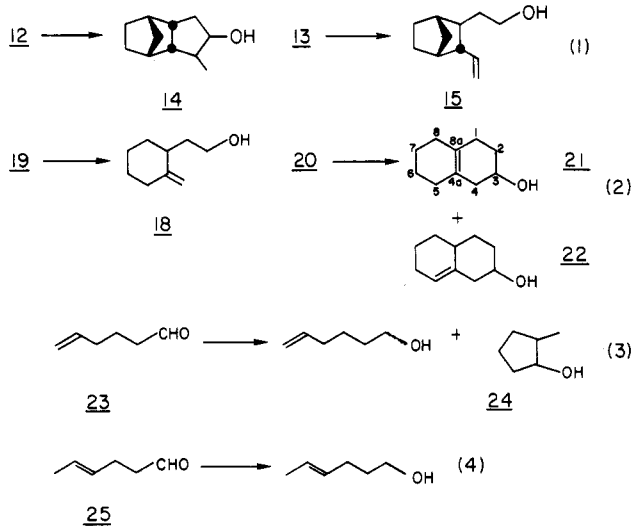
(7) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.
(8) Battersby, A. R.; Hall, E. S.; Southgate, R. *J. Chem. Soc. C* **1969**, 721.
(9) Ikeda, T.; Hutchinson, C. R. *J. Org. Chem.* **1984**, *49*, 2837.
(10) The two diazo ketone isomers, **8** and **9**, but none of the other compounds following **7** in Scheme I, could be separated chromatographically (Experimental Section). We are not certain when racemization of C-8a occurred in this homologation sequence. When the same reaction sequence was used in the analogous case[9] we did not observe racemization of the position alpha to the carbonyl.

Scheme I[a]



[a] a, $EtAlCl_2$; b, H_2/Pd; c, NaSePh; d, $(COCl)_2$; e, CH_2N_2; f, Ag_2O, MeOH; g, O_3; h, heat; i, $LiAlH_4$; j, PCC.

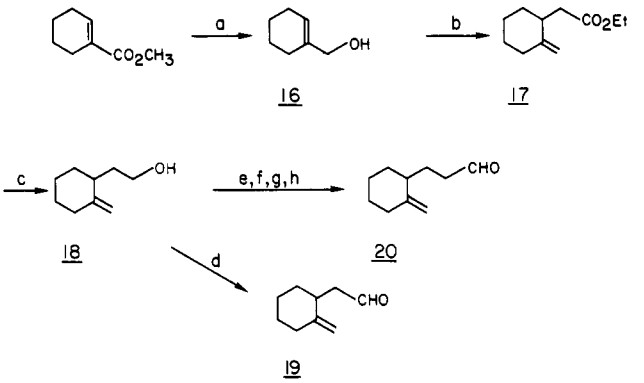
six-membered ring formation product) when treated with Mg and Me_3SiCl in THF at room temperature (eq 1). The



relative stereochemistry of the secondary alcohol and methine carbons in **14** was not assigned but may well be cis following the general trend observed for 1,5-ring closures of 1-substituted 5-hexenyl radicals.[11b]

The effect of double-bond substitution was examined with compounds **19** and **20** which were synthesized as shown in Scheme II. Commercially available methyl 1-cyclohexencarboxylate was reduced to the allyl alcohol, **16**, by AlH_3. Claisen rearrangement of this alcohol using ethyl orthoacetate afforded the ethyl ester **17** which was reduced

Scheme II[a]



[a] a, AlH_3; b, $CH_3C(OEt)_3$, CH_3CH_2COOH, heat; c, $LiAlH_4$; d, PCC; e, CH_3SO_2Cl; f, LiBr; g, 1,3-dithianyl Li; h, $CaCO_3$, MeI, aqueous acetone, heat.

with $LiAlH_4$ to **18**. The latter alcohol was oxidized to the aldehyde **19** or homologated by a four-step reaction sequence to aldehyde **20**. Although the 4-pentenal analog **19** might have formed a five-membered ring, it was not expected to do so based on Beckwith's proposals[11] and Baldwin's rules[12] (a disfavored 5-*endo*-Trig ring closure). Therefore, the formation only of its reduction product, **18**, on treatment with Mg and Me_3SiCl in THF at room temperature was not surprising. The homologue **20** did cyclize giving two six-membered ring products **21** and **22** in a ratio of 3:2 in 60% combined yield (eq 2) plus the deoxygenated form of **21** or its C-4,4a/C-4a,5 double bond isomers in ca. 35% yield. The position of the double bond in **21** was based on analysis of the proton and carbon NMR spectra of its ketonic oxidation product, which were identical with literature values,[19] and in **22** on the results of proton-decoupling experiments which permitted assignment and analysis of the resonances for the protons at C-3, C-4, C-5, and C-6. The configuration of the secondary alcohol was not assigned for either compound.

Finally, we studied the cyclization of 5-hexenal (**23**), which was prepared by Swern oxidation[13] of commercially available 5-hexenol, and *trans*-4-hexenal (**25**), which was made from 3-buten-2-ol and ethyl vinyl ether by Claisen rearrangement in the presence of $Hg(OAc)_2$. 5-Hexenal gave a mixture of its reduction product, 5-hexenol, and 2-methylcyclopentanol, **24** (32% yield), in an ca. 2:1 ratio (eq 3), but *trans*-4-hexenal (**25**) gave only its reduction product, *trans*-4-hexenol (eq 4). Again, **25** was not expected to cyclize according to the rules for intramolecular cyclization of radical intermediates.[11a,12]

Discussion

The mechanism of the cyclization of **4**, **12**, and **20** presumably parallels the proposal made by Corey and Pyne for the reductive, radical-induced cyclization of ketones having δ,ϵ,π-functionality.[7] Mg–Me_3SiCl generates an α-trimethylsilyloxy radical by electron transfer and sily-

(11) (a) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(12) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas R. C. *Ibid.* **1976**, 736.

(13) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(14) Buchi, G.; Carlson, J. A.; Powell, J. E., Jr.; Tietze, L.-F. *J. Am. Chem. Soc.* **1973**, *95*, 540.

(15) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

(16) House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 53.

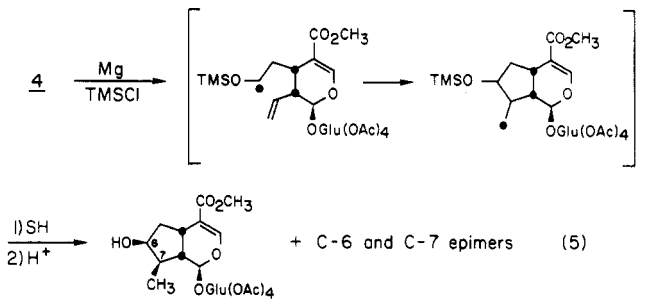
(17) Cresson, P. *Bull. Soc. Chim. Fr.* **1964**, 2629.

(18) Sisti, A.; Burgmaster, J.; Fudim, M. *J. Org. Chem.* **1962**, *27*, 279.

(19) Holland, H. L.; Diakow, P. R. P.; Taylor, G. J. *Can. J. Chem.* **1978**, *56*, 3121.

(20) Rei, M.-H. *J. Org. Chem.* **1978**, *43*, 2173.

lation which adds to the double bond at the δ-position forming a primary carbon radical that rapidly abstracts a hydrogen atom from the solvent. This sequence of events is illustrated for the cyclization of 4 in eq 5. Since the



thermodynamically favorable C-7 configuration of loganin[14] was formed in 85% of the cyclized products, the kinetically-controlled five-membered ring formation was highly stereoselective as generally observed for the intramolecular cyclization of 1-substituted 5-hexenyl radicals.[11b] The arguments cited by Beckwith[11b] suggest that the α-(trimethylsilyl)oxy radical at C-6 will prefer the conformation which places it in the convex face of the molecule as it approaches the similarly aligned C-7/8 vinyl group and adopt the most favorable electrostatic interaction in a dipolar transition state leading to a cis relationship between the C-6 OH and C-7 CH_3 groups of **1**. This again would favor the observed result. We cannot analyze the cases of **12** and **20** in this way since their stereochemistry was not fully assigned.

The overall results show that ring formation takes place only when the cyclization of the intermediate α-(trimethylsilyl)oxy radical is favored by factors in addition to the preferred exo attack[11,12] and formation of five- over six-membered carbocyclic rings.[11,12] Thus in the case of **12** vs. **13** it is expected and observed (eq 1) that the radical intermediate, which leads to the stabler cis-fused hydrindanol analogue, cyclizes and then is trapped to give **14**, whereas the radical intermediate that would form the less stable trans-fused hydrindanol analogue does not cyclize and is reduced to **15**. A route leading to a trans-fused six-membered ring was available to **13**, but not taken, probably because the resulting *trans*-bicyclo[3.3.0]octane substructure would be highly strained. Thus hydrogen atom donation from the solvent could compete exclusively with (reversible) ring closure. In the case of **20** a cyclization route leading to a cis-fused hydrindanol was available, but not observed, due to steric congestion as the α-(trimethylsilyl)oxy radical approached the more substituted end of this double bond. Stork and Baine[15] and others (as cited in ref. 11b) have noted that substitution of the olefin undergoing attack by the radical can reverse the preferred formation of a five-membered ring. In the case of **20** the tertiary carbon radical formed by closure to a six-membered ring intermediate rapidly formed **21** and **22** by loss of a hydrogen atom from C-5 or C-8a. Since deoxygenated products were formed in this cyclization reaction, hydrogen atom loss from C-4 also must have occurred but the product then was reduced by cleavage of its allylic alcohol bond. Finally, in the case of **23** the rate of reduction of the α-(trimethylsilyl)oxy radical must have been competitive with the combined rates of (reversible) ring closure and trapping of the primary carbon radical as noted in related cases.[11b]

The reductive, radical-induced cyclization of 5-hexenals demonstrated by our results defines the scope of this method for ring annulation and extends the observations described by Corey and Pyne.[7] Its value lies in the ready availability of the δ,ε-unsaturated aldehyde intermediates, as illustrated above, and the chemoselectivity since cyclization occurs without noticeable side reactions.

As a model for the biological conversion of loganin to secologanin it justifies the belief that the cleavage of the C-6/7 bond in **1** takes place by a homolytic process. This could involve one-electron oxidation at the C-8 methyl and subsequent reversal of the reaction demonstrated here for the conversion of **4** to loganin tetraacetate. The exact mechanism of the biochemical event, however, will be solved only when it becomes possible to study this process with purified enzyme preparations.

Experimental Section

General Procedures. All compounds and reagents were used as available commercially. Solvents were dried according to standard literature procedures, and rendered peroxide-free by distillation from $LiAlH_4$ or sodium benzophenone ketyl. Organic extracts of reaction mixtures were dried over anhydrous Na_2SO_4 and evaporated to dryness on a rotary evaporator at <37 °C under water aspirator or oil pump vacuum. Melting points are uncorrected. NMR spectra were determined on Varian EM 390, JEOL FXQ 90 or 200, or Bruker-IBM 270 spectrometers. Chemical shifts are given relative to $CHCl_3$ (δ_H 7.26 ppm; δ_C 77.0 ppm) as the internal standard and coupling constants are given in hertz. Mass spectrum were determined on Finnegan 4000 GC/MS or AEI MS 902 spectrometers.

Reductive Cyclization of Secologanin Tetraacetate (4). Mg (400 mg, 16.7 mmol), Me_3SiCl (0.51 mL, 4 mmol), and a catalytic amount of I_2 was added to a solution of secologanin tetraacetate (**4**, 370 mg, 0.66 mmol) in THF (3 mL). The mixture was stirred for 72 hr at room temperature under a N_2 atmosphere and filtered through a pad of Celite, and the residue was rinsed with diethyl ether (50 mL). The combined filtrates were acidified with 2 N HCl (3 mL) and stirred for 10 min, and then the organic layer was washed with brine, saturated aqueous $NaHCO_3$ solution, and brine. This solution was dried and the solvent evaporated to obtain the crude product (315 mg), which was purified by chromatography on silica gel (6 g) with a hexane–EtOAc (1:1) eluant to give an alcohol fraction (165 mg) and recovered starting material (48 mg). Proton and carbon NMR spectral analysis of the alcohol fraction showed two major products in ca. 1:1 ratio. A portion (80 mg) of this fraction was separated by PLC on silica gel in diethyl ether (developed two times) to give two major and one minor alcohol diastereomers. The less polar fraction was loganin tetraacetate (23 mg, 13% yield); the more polar fraction contained 6-*epi*-loganin tetraacetate (17 mg, 10% yield) and a minor compound (2 mg) which were separated by PLC on silica gel in CH_2Cl_2–EtOH (50:1, developed seven times). The exact ratio of the products was determined by HPLC (C-18 Corasil; CH_3CN–CH_3OH–H_2O, 3.5:0.5:6.0; 0.5 mL/min) which showed the three products as peaks at 18.1 min, 22.1 min, and 25.6 min in a ratio, respectively, of 3.8 (loganin tetraacetate):3.2 (6-*epi*-loganin tetraacetate and a minor diastereomer):1 (the minor compound).

Loganin tetraacetate: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.27 (1 H, d, J = 2.7, H-3), 5.21 (1 H, t, J = 9.5), 5:18 (1 H, d, J = 1.7), 5.09 (1 H, t, J = 9.7, H-4′), 4.98 (1 H, dd, J = 9.3, 10.0), 4.85 (1 H, d, J = 9.6), 4.29 (1 H, dd, J = 4.4, 11.8, H-6′), 4.16–4.07 (2 H, m, H-6 and H-6′), 3.75–3.65 (4 H, m + s, the methyl peak at 3.69 and H-5′), 3.03 (1 H, br q, J = 7.5, H-4a) 2.32–1.87 (14 H, m + s, 4 acetyl methyl peaks at 2.09, 2.02, 1.99, and 1.91), 1.86–1.55 (3 H, m), and 1.08 (3 H, d, J = 6.8, H-8) ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 170.7, 170.3, 169.5, 169.2, 167.5, 149.3, 114.2, 96.2, 95.7, 74.6, 72.9, 72.4, 71.0, 68.7, 62.0, 51.3, 45.0, 41.8, 40.5, 30.3, 20.7, 20.3, and 12.5 ppm.

A portion (12 mg) of this loganin tetraacetate was acetylated with dry pyridine (0.3 mL) and acetic anhydride (0.3 mL) at room temperature overnight, the crude residue resulting from solvent evaporation was purified by PLC on silcia gel in hexane–diethyl ether (1:2), and the material recovered from the plates was recrystallized from ethanol to give loganin pentaacetate (6.5 mg) whose melting point and proton and carbon NMR spectral properties were identical with the literature values[8] or those of authentic standards.

6-*epi*-Loganin tetraacetate: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.32 (1 H, d, J = 1.0, H-3), 5.25 (1 H, d, J = 4.2, H-1), 5.22 (1 H, t, J = 9.4, H-3′), 5.09 (1 H, t, J = 9.7, H-4′), 4.99 (1 H, t, J = 9.4, H-2′), 4.85 (1 H, d, J = 8.1, H-1′), 4.33–4.16 (2 H, m, H-6′), 3.82–3.64 (5 H, m + s, the methyl peak at 3.70, H-6 and H-5′), 2.84 (1 H, ddd, J = 7.8, 7.8, 7.8, H-4a), 2.56 (1 H, ddd, J = 7.7, 7.7, 13.9, H-5), 2.10 (3 H, s, Ac), 2.03 (3 H, s, Ac), 2.00 (3 H, s, Ac), and 1.94 (3 H, s, Ac ppm); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 170.3, 169.5, 169.3, 167.5, 149.8, 113.4, 96.7, 95.8, 79.2, 72.9, 72.5, 71.0, 68.6, 61.8, 51.4, 46.2, 43.3, 40.8, 30.1, 20.9, 20.7, 20.4, and 17.0 ppm.

This compound had the same melting point and proton and carbon NMR spectral properties as an authentic standard made by reduction of dehydrologanin tetraacetate with $NaBH_4$ according to the literature procedures.[8]

6-Dehydrologanin Tetraacetate. A portion (32 mg) of the mixture of diastereomers of loganin tetraacetate produced by the reductive cyclization was treated with Jones' reagent in acetone (1 mL) at 0 °C for 5 min. Then the mixture was quenched with 2-propanol (0.5 mL) and extracted with ethyl acetate (3 mL × 5), and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic extract was dried and the solvent removed to give the crude product (30 mg) which was purified by chromatography on silica gel (300 mg) with hexane–EtOAc (1:2) as eluant to give the pure product (24 mg). Recrystalization of this material from ethanol gave 6-dehydrologanin tetraacetate as colorless crystals (9 mg) with mp 146–147 °C (lit.[8] 147–149 °C). When the recrystalization was carried out from EtOAc–hexane (1:6), the melting point of the crystals was 93–94 °C: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.28 (1 H, d, J = 1.4, H-3), 5.44 (1 H, d, J = 2.1, H-1), 5.23 (1 H, t, J = 9.4), 5.10 (1 H, t, J = 9.7), 5.00 (1 H, t, J = 9.2), 4.88 (1 H, d, J = 8.0, H-1′), 4.31 (1 H, dd, J = 4.5, 12.5, H-6′), 4.14 (1 H, dd, J = 2.1, 12.4, H-6′), 3.81–3.66 (4 H, m + s, methyl peak at 3.70), 3.15 (1 H, br t, J = 6.7), 2.64 (1 H, br d, J = 19.0), 2.53 (1 H, dd, J = 7.7, 19.5), 2.12–1.95 (10 H, m + 3s, methyl peaks at 2.09, 2.03, and 2.00), 1.89 (3 H, s, acetyl methyl), and 1.15 (3 H, d, J = 7.1) ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 217.2, 170.6, 170.2, 169.4, 169.1, 166.7, 150.6, 111.2, 96.2, 93.6, 72.6 (2 resonances), 70.8, 68.5, 61.9, 51.5, 45.3, 43.2, 42.2, 26.7, 20.8, 20.7 (2 resonances), 20.2, and 13.4 ppm.

5,8-Methano-3,4,4a,5,8,8a-hexahydro-1*H*-2-benzopyran-1-one (5). 5,6-Dihydro-2*H*-pyran-2-one (500 mg, 5.10 mmol) was added to a 25% solution of $EtAlCl_2$ in methylene chloride (2.78 mL, 5.10 mmol) at −50 °C and the reaction was stirred at 0 °C for 30 min under a N_2 atmosphere. This mixture was cooled to −70 °C, cyclopentadiene (0.5 mL, 6.1 mmol) in toluene (1 mL) was added dropwise, and then the reaction mixture was warmed to 0 °C and stirred for 16 h. The cold mixture then was carefully treated with 6 *N* HCl (2 mL) and extracted with EtOAc (10 mL × 5). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and evaporated to give the crude product (670 mg). Chromatography of this material on silica gel (15 g) with a hexane–EtOAc (3:1) eluant gave pure product, **5**, (626 mg, 76% yield): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.29 (1 H, dd, J = 2.9, 5.6, vinyl H), 6.06 (1 H, dd, J = 3.0, 5.6, vinyl H), 4.21 (1 H, ddd, J = 2.7, 3.8, 11.0, CH_2O), 4.19 (1 H, ddd, J = 1.6, 11.0, 11.0, CH_2O), 3.33 (1 H, br s), 2.92 (1 H, ddd, J = 3.6, 3.6, 6.4), 2.75–2.63 (2 H, m), 1.93 (1 H, br dd, J = 7.0, 14.1), 1.53 (1 H, ddd, J = 1.8, 1.8, 8.6), 1.36 (1 H, br d, J = 8.6), and 1.15 (1 H, ddd, J = 3.9, 12.2, 12.2, 14.2) ppm; (C_6D_6) δ 6.35 (1 H, dd, J = 3.0, 5.6, H-7), 5.72 (1 H, dd, J = 3.0, 5.6, H-6), 3.64 (1 H, ddd, J = 2.5, 3.5, 10.4, H-3), 3.40 (1 H, ddd, J = 1.5, 10.4, 12.4, H-3), 3.29–3.22 (1 H, m, H-8), 2.44–2.37 (1 H, m, H-5), 2.33 (1 H, dd, J = 4.0, 10.5, H-8a), 1.87 (1 H, dddd, J = 3.4, 6.9, 10.4, 11.6, H-4a), 1.27 (1 H, ddd, J = 1.8, 1.8, 8.3, H-9), 1.15 (1 H, br dd, J = 7.0, 13.9, H-4), 0.89 (1 H, br d, J = 8.3, H-9), and 0.68 (1 H, ddd, J = 3.7, 12.2, 13.8, H-4) ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 174.1, 138.2, 135.1, 67.7, 48.3, 45.8 (2 resonances), 43.6, 39.0, and 28.0 ppm; IR ($CHCl_3$) ν 3010, 2900, 2821, 1766, 1658, 1478, 1434, 1370, 1305, 1225, 1193, 1171, 1132, 1077, 1039, 1010, 995, 976, 945, 917, 897, 700, and 656 cm^{-1}; MS, m/z (% relative abundance) 164 (M^+, 0.5), 149 (0.6), 136 (0.4), 118 (0.8), 81 (5), 79 (5), 77 (6), and 66 (100); HRMS calcd for $C_{10}H_{14}O_2$ 164.0837, found 164.0825.

5,8-Methano-3,4,4a,5,6,7,8,8a-octahydro-1*H*-2-benzopyran-1-one (6). The lactone **5** (620 mg, 3.78 mmol) in ethyl acetate (10 mL) was reduced with H_2 over 5% Pd/C (60 mg) at room temperature for 2 h. Filtration and evaporation of the solvent gave the desired product, **6**, (612 mg, 98% yield): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 4.37 (1 H, ddd, J = 3.0, 3.6, 10.5, CH_2O), 4.07 (1 H, ddd, J = 2.8, 10.5, 10.5, CH_2O), 2.90–2.57 (2 H, m), 2.57–2.00 (2 H, m), and 1.95–1.15 (6 H, m) ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 174.0, 67.8, 44.5, 40.2, 40.0, 38.8, 37.5, 24.9, 22.4, and 22.3 ppm; IR ($CHCl_3$) δ 2950, 2878, 1720, 1475, 1455, 1438, 1387, 1330, 1317, 1308, 1288, 1269, 1257, 1241, 1187, 1168, 1157, 1075, 1051, 1016, 1001, 971, 956, 910, 891, and 835 cm^{-1}; MS, m/z (% relative abundance) 166 (M^+, 0.2%), 138 (7), 133 (3), 122 (11), 107 (17), 105 (13), 99 (21), 94 (33), 91 (30), 79 (65), 67 (71), 55 (26), 53 (29), and 41 (100); HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.1001.

2-[(Diazomethylene)carbonyl]-3-[2-(phenylseleno)-ethyl]bicyclo[2.2.1]heptane (8 and 9). $NaBH_4$ (476 mg, 12.6 mmol) was added to a solution of diphenyl diselenide (1.97 g, 6.3 mmol) in degassed DMF (5 ml) at room temperature, and then the mixture was heated to 120 °C under a N_2 atmosphere. The lactone (**6**, 1.94 g, 12 mmol) in DMF (3 mL) was added to this solution, and the mixture was stirred at 120 °C for 6 h under nitrogen. Most of the solvent was removed under aspirator vacuum at 70 °C, and then 10 mL of 2 N HCl was added to the resulting viscous material. This mixture was extracted with ethyl acetate (30 mL × 3), the combined extracts were washed with water and dried, and the solvent was evaporated. The residue was dissolved in a 3 N solution of NaOH in MeOH–H_2O (2:1, 50 mL), the solution was washed with hexane (30 mL × 5), and then the aqueous layer was acidified with 2 N HCl to pH 2. This solution was extracted with ethyl acetate (30 mL × 5), the combined extracts were washed with brine and dried, and the solvent was evaporated to give the crude acid product, **7**, (2.19 g). Without purification, the solution of this acid (2.09, 6.45 mmol) in dry benzene (20 mL) was mixed with $(COCl)_2$ (0.73 mL, 8.4 mmol) and stirred for 1 h at room temperature. The reaction mixture then was evaporated to dryness, dissolved in dry diethyl ether (100 mL), and added dropwise to CH_2N_2 (ca. 2g, excess) in diethyl ether (200 mL) at room temperature during a period of 20 min. The resulting mixture was stirred for 30 min and then the solvent and excess CH_2N_2 were removed by evaporation. Chromatography of the resulting residue on silica gel (100 g) with CH_2Cl_2 as eluant gave two compounds: the less polar compound, **8**, (725 mg, 18%) and the more polar compound, **9**, (683 mg, 17%).

Cis isomer (8): ^{1}H NMR ($CDCl_3$, 270 MHz), δ 7.52–7.38 (2 H, m, phenyl *H*), 7.31–7.13 (3 H, m, phenyl *H*), 5.16 (1 H, s, $COCHN_2$), 2.95–2.72 (2 H, m), 2.72–2.57 (1 H, m), 2.39 (1 H, s), 2.28–2.13 (2 H, m), 2.13–1.78 (3 H, m), 1.67–1.54 (1 H, m), 1.42 (2 H, s), and 1.40–1.23 (2 H, m) ppm.

Trans isomer (9): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.52–7.38 (2 H, m, phenyl H), 7.32–7.17 (3 H, m), 5.18 (1 H, br s, $COCHN_2$), 2.96–2.69 (2 H, m), 2.36 (1 H, br s), 2.28 (1 H, d, J = 4.0), 2.22 (1 H, s), 1.82–1.52 (5 H, m), and 1.49–1.06 (4 H, m) ppm.

Preparation of 10 and 11. The cis diazo ketone **8** (725 mg, 2.10 mmol), was treated with methanol in the presence of freshly prepared Ag_2O under reflux for 20 min. Filtration of the mixture through a pad of Celite and evaporation of the filtrate gave the crude methyl ester product (710 mg). This was dissolved in CH_2Cl_2 (40 mL) and treated with a slight excess of O_3 at −78 °C for 30 min. The solvent was evaporated and the resulting residue was dissolved in $CHCl_3$ (50 mL), pyridine (0.2 mL) was added, and the mixture was refluxed for 1 h. Evaporation of the solvent gave the crude product which was purified by chromatography on silica gel (5 g) with hexane and then hexane–EtOAc (20:1) as eluants to give **10** (287 mg, 71% yield): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.86–5.68 (1 H, m, vinyl H), 5.06–5.01 and 4.98–4.93 (2 H, m, vinyl H), 3.59 (3 H, s, $COOCH_3$), 2.59 (1 H, ddd, J = 3.6, 11.0, 11.0, allyl H), 2.50–2.13 (5 H, m), and 1.55–1.32 (6 H, m) ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 173.7, 137.5, 117.1, 51.1, 45.9, 43.3, 40.9, 39.9, 38.8, 32.8, 22.8 and 22.3 ppm; IR ($CHCl_3$) ν 3036, 3010, 3000, 2950, 2879, 1723, 1667, 1633, 1477, 1453, 1433, 1420, 1375, 1325, 1305, 1292, 1281, 1269, 1170, 995, 912, and 651 cm^{-1}; MS, m/z (% relative abundance) 194 (0.7%, M^+), 166 (28), 138 (8), 134 (9), 120 (18), 106 (26), 93 (30), 92 (30), 91 (38), 79 (60), 67 (92), 59 (35), 55 (23), 53 (30), and 41 (100); HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1322.

By the same procedure, **9** (683 mg, 1.97 mmol) was converted to the corresponding methyl ester (670 mg), which then was

oxidized and eliminated to 11 (315 mg, 82% yield): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.87–5.70 (1 H, m, vinyl H), 5.03–4.88 (2 H, m, vinyl H), 3.62 (3 H, s, $COOCH_3$), 2.31–2.05 (3 H, m, including 4 peaks at 2.24, 2.21, 2.19, and 2.18), 2.04–1.93 (2 H, m), 1.66–1.31 (5 H, m), and 1.31–1.14 (2 H, m) ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHZ) δ 173.1, 139.9, 114.6, 52.5, 51.2, 44.3, 42.7, 42.1, 40.1, 36.8, 30.1, and 22.2 ppm; IR ($CHCl_3$) ν 3036, 3000, 2945, 2935, 1725, 1635, 1475, 1452, 1435, 991, and 911 cm^{-1}; MS m/z (% relative abundance) 194 (1.5, M^+), 166 (42), 134 (11), 120 (21), 106 (41), 93 (38), 92 (59), 91 (46), 79 (65), 67 (98), 59 (39), 55 (25), 53 (33), and 41 (100); HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1313.

2-[*cis*-3-Vinylbicyclo[2.2.1]hept-2-yl]ethanal (12). A solution of **10** (137 mg, 0.71 mmol) in THF (1.5 mL) was added to $LiAlH_4$ (40 mg, 1.05 mmol) at 0 °C and stirred for 30 min. Diethyl ether (3 mL), ice (2 g), and then 2 *N* HCl (2 mL) were added to the reaction mixture, then the aqueous layer was extracted with diethyl ether (2 mL × 5), and the combined extracts were washed with brine, saturated aqueous $NaHCO_3$, and brine. The organic solution was dried and evaporated to give the crude product which was purified by chromatography on silica gel (3 g) with hexane–EtOAc (5:1) as eluant to give 2-(hydroxyethyl)-3-vinylbicyclo-[2.2.1]heptane (65 mg, 55%): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.85 (1 H, ddd, 10.1, 10.9, 15.9, vinyl H), 4.98 (1 H, br d, J = 10.98 vinyl H), 4.97 (1 H, br d, J = 17.0, vinyl H), 3.57–3.44 (2 H, m, CH_2O), 2.49 (1 H, ddd, J = 10.1, 10.1, 2.0, allyl H), 2.41 (1 H, s, OH), 2.11 (2 H, br s), 2.00–1.87 (1 H, m), and 1.65–1.20 (8 H, m) ppm; MS, m/z (% relative abundance) 166 (0.3, M^+), 151 (1), 149 (1), 148 (1), 138 (9), 110 (14), 107 (24), 105 (16), 91 (32), 79 (68), 67 (74), 55 (26), 53 (27), and 41 (100).

PCC (284 mg, 1.3 mmol) was added to a solution of the alcohol (110 mg, 0.66 mmol) in CH_2Cl_2 (2 mL) and the mixture stirred at room temperature for 2 h. The mixture was poured into diethyl ether (10 mL) and filtered through Florisil (1 g) which then was eluted with Et_2O–CH_2Cl_2 (5:1), and the combined filtrates were evaporated. The crude residue was chromatographed on a silica gel column (2 g) with a hexane–EtOAc (20:1) eluant to give pure **12** (79 mg, 73% yield): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.69 (1 H, s, CHO), 5.78 (1 H, ddd, J = 16.3, 10.0, 10.0), 4.96 (1 H, br, d, J = 10), 4.95 (1 H, br d, J = 16.8), 2.69–2.38 (3 H, m), 2.37–2.09 (3 H, m), and 1.67–1.16 (6 H, m) ppm; IR (film) ν 3080, 2940, 2880, 2800, 2710, 1630, 1480, 1420, 1408, 1385, 1370, 1320, 1302, 1290, 1279, 1242, 1170, 1120, 1030, and 908 cm^{-1}; MS, m/z (% relative abundance) 164 (22%, M^+), 136 (49), 120 (52), 107 (34), 93 (43), 92 (48), 91 (44), 79 (70), and 67 (100); HRMS calcd for $C_{11}H_{16}O$ 164.1202, found 164.1200.

2-[*trans*-3-Vinylbicyclo[2.2.1]hept-2-yl]ethanal (13). By the same procedure, **11** (98 mg, 0.5 mmol) was reduced to the trans alcohol product (65 mg, 77% yield): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.81 (1 H, ddd, J = 7.7, 10.2, 17.4), 5.01 (1 H, br d, J = 17.1), 4.95 (1 H, br d, 10.3), 3.58 (2 H, t, J = 6.8), 2.15 (1 H, br s), 2.05–1.96 (1 H, m, allyl H), 1.97 (1 H, s, OH), 1.93 (1 H, d, J = 3.5), and 1.67–1.05 (9 H, m) ppm; MS, m/z (% relative abundance) 166 (10, M^+), 151 (0.3), 149 (0.5), 148 (0.4), 138 (15), 122 (25), 107 (33), 105 (14), 94 (52), 91 (50), and 79 (100).

This alcohol (104 mg, 0.62 mmol) was oxidized to the trans aldehyde, **13** (73 mg, 70% yield), by the method used in the preparation of **12**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.66 (1 H, s, CHO), 5.77 (1 H, ddd, J = 17.5, 8.0, 8.0, vinyl-H), 5.02–4.87 (2 H, m, vinyl H), 2.36–2.22 (2 H, m), 2.16 (1 H, s), 2.06–1.86 (2 H, m), and 1.69–1.03 (7 H, m); IR (film) ν 3080, 2940, 2880, 2810, 2710, 1710, 1637, 1485, 1455, 1412, 1390, 1370, 1350, 1250, 1210, 1175, 1145, 1030, and 908 cm^{-1}; MS, m/z (% relative abundance), 164 (8% M^+), 136 (14), 120 (30), 93 (45), 92 (55), 91 (48), 79 (50), and 67 (100); HRMS calcd for $C_{11}H_{16}O$ 164.1202, found 164.1204.

Reductive Cyclization of 12. Mg (165 mg, 6.9 mmol) and Me_3SiCl (260 μL, 2.0 mmol) were added to a solution of **12** (60.9 mg, 0.36 mmol) in THF (2.5 mL) and the mixture stirred at room temperature for 80 h. HCl (2 N) was carefully added to the mixture until the magnesium was dissolved, and the mixture was stirred at room temperature for 5 min and then extracted with diethyl ether (2 mL × 5). The extract was washed with brine, saturated aqueous $NaHCO_3$ solution, and brine. Drying and evaporation of the solvent gave the crude product (70 mg). Chromatography on silica gel (1.5 g) with a hexane–EtOAc (5:1) eluant gave **14** (10 mg, 14% yield) and recovered starting material (35 mg, 57% yield): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.65 (1 H, ddd, J = 6.2, 8.6, 9.6, CHO), 2.21–2.07 (3 H, m), 1.87–1.66 (3 H, m, including OH at 1.73), 1.65–1.20 (8 H, m), and 0.99 (3 H, d, J = 6.4) ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 82.3, 50.3, 43.2, 41.0, 40.3, 39.8, 38.7, 34.1, 23.6, 22.2, and 17.1 ppm; MS, m/z (% relative abundance) 166 (M^+, 0.2%), 165 (0.1), 148 (5), 137 (3), 133 (9), 122 (9), 119 (9), 107 (21, 97 (22), 94 (23), 93 (32), 91 (24), 87 (32), 85 (100), 81 (64), 79 (52), and 67 (63); HRMS calcd for $C_{11}H_{18}O$ 166.1358, found 166.1336.

1-(Hydroxymethyl)cyclohexene (16). A solution of methyl cyclohexanoate (2.8 g, 20 mmol) in THF (20 mL) was added to a 3 M solution of AlH_3 in THF (40 mL) which was made in situ by the addition of $LiAlH_4$ to a solution of $AlCl_3$ in THF at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 5 min and then cooled to 0 °C. Slow addition of ice (5 g) to this mixture followed by filtration and evaporation of the solvent gave the crude product (**24**, 2.7 g): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.66 (1 H, br s, vinyl H), 3.94 (2 H, br s, CH_2O), 2.42–1.83 (5 H, m), and 1.83–1.30 (4 H, m) ppm; MS, m/z (% relative abundance) 112 (M^+, 26), 95 (19), 94 (23), 81 (81), 79 (91), 67 (33), 57 (25), 55 (65), 53 (44), and 41 (100).

2-(2-Methylenecyclohexyl)ethan-1-ol (18). Ethyl orthoacetate (13.5 mL, 74 mmol) and propionic acid (0.05 mL, catalyst) were added to a solution of **16** (1.66 g, 14.8 mmol) in xylene (50 mL) at room temperature, and then the reaction mixture was stirred under reflux for 12 h. Ethanol (40 mL) was added to the mixture and the solvents were azeotropically removed. This process was repeated three times. The crude product (**17**) was treated with $LiAlH_4$ in THF–Et_2O (1:1) at 0 °C for 5 min, and the reaction was cooled to 0 °C, mixed with ice (5 g), filtered, and evaporated to give the crude product (1.43 g). Chromatography of this material on silica gel (30 g) eluted with hexane–EtOAc (5:1) gave pure **18** (1.01 g, 49% yield): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 4.67 (1 H, br s, vinyl H), 4.53 (1 H, br s, vinyl H), 3.63 (2 H, t, J = 7, CH_2O), and 2.40–1.00 (12 H, m) ppm; MS, m/z (% relative abundance) 140 (M^+, 2.5), 122 (7), 109 (18), 107 (19), 96 (35), 95 (20), 94 (17), 93 (36), 91 (14), 81 (60), 79 (46), 67 (78), 55 (53), 53 (38), and 41 (100).

2-(2-Methylenecyclohexyl)ethanal (19). The alcohol **18** (0.98 g, 7 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of PCC (3.02 g, 14 mmol) and NaOAc (287 mg, 3.5 mmol) in CH_2Cl_2 (40 mL) at room temperature. The reaction proceeded exothermically; therefore, the magnetically stirred mixture was cooled to 15 °C (bath temperature) and then allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was poured into diethyl ether (300 mL) and combined with CH_2Cl_2 (20 mL × 5) rinses of the reaction flask, and the combined solution was filtered through Florisil (5 g) which was then eluted with diethyl ether–CH_2Cl_2 (5:1, 500 mL). Evaporation of the combined filtrates gave the crude product (712 mg). Chromatography on this material on silica gel (15 g) eluted with hexane–EtOAc (20:1) gave the pure **19** (420 mg, 42% yield). ^{1}H NMR ($CDCl_3$, 90 MHz) δ 9.75 (1 H, t, J = 1.5, CHO), 4.70 (1 H, br s, vinyl H), 4.50 (1 H, br s, vinyl H), 2.80–2.00 (4 H, m), and 2.00–1.00 (7 H, m) ppm; IR ($CHCl_3$) ν 2927, 2855, 2720, 1718, 1642, 1445, and 895 cm^{-1}; MS, m/z (% relative abundance) 138 (M^+, 2), 120 (12), 109 (42), 96 (30), 95 (36), 94 (45), 91 (21), 81 (74), 79 (60), 67 (100), 55 (56), 53 (35), and 41 (93).

3-(2-Methylenecyclohexyl)propanal (20). Mesyl chloride (0.67 mL, 8.7 mmol) was added to a solution of **18** (1.1 g, 7.2 mmol) and triethylamine (1.2 mL, 8.7 mmol) in CH_2Cl_2 (40 mL) at 0 °C and the mixture stirred for 30 min. Then the mixture was washed with brine, dried over Na_2SO_4, and evaporated to give the crude product. Without purification, this mesylate was dissolved in acetone (20 mL), LiBr (1.82 g, 21 mmol) was added, and the mixture was refluxed for 4 h. After being cooled to room temperature, the reaction mixture was mixed with water (5 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL × 3), and the combined extracts were washed with brine, dried, and evaporated to give the crude bromide (1.1 g). Chromatography of this material on silica gel (20 g) eluted with hexane–EtOAc (20:1) gave the pure 1-bromo-2-(2-methylenecyclohexyl)ethane (870 mg, 59% yield): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 4.53 (1 H, br s, vinyl H), 4.63 (1 H, br, s, vinyl H), 3.33 (2 H, t, J = 6), 2.30–1.80 (4 H, m), and 1.80–1.10 (7 H, m) ppm.

A solution of the bromide (870 mg, 4.28 mmol) in THF (3 mL) was added to a solution of 1,3-dithianyllithium (4.28 mmol) in

THF (3 mL) at −78 °C under a N_2 atmosphere. The reaction mixture was allowed to stir at −20 °C for 12 h, then water (2 mL) was added, and the mixture was extracted with ethyl acetate (5 mL × 3). The combined extracts were washed with brine, dried, and evaporated to give the crude dithiane (920 mg). Chromatography on silica gel (20 g) eluted with hexane–EtOAc (20:1) gave the pure 1-(1,3-dithiacyclohexyl)-2-(2-methylenecyclohexyl)ethane (715 mg, 69% yield): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 4.52 (2 H, br s, vinyl H), 3.68 (1 H, t, J = 6.8, SCHRS), 3.08–2.68 (5 H, m), and 2.12–1.30 (14 H, m) ppm.

$CaCO_3$ (2.5 g, 25 mmol) and then MeI (3.1 mL, 50 mmol) were added to a solution of the dithiane (620 mg, 2.52 mmol) in 80% acetone (50 mL), and the mixture was heated under reflux for 2 h. The reaction mixture then was poured into water (20 mL) and extracted with EtOAc (40 mL × 4). The combined extracts were washed with brine, dried, and evaporated to give the crude product (220 mg). Chromatography on this material on silica gel (10 g) eluted with hexane–EtOAc (25:1) gave the pure **20** (183 mg, 47% yield): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.75 (1 H, t, J = 1.5, CHO), 4.63 (1 H, br s, vinyl H), 4.51 (1 H, br s, vinyl H), 2.38–2.26 (2 H, m), 2.16–2.03 (1 H, m), 2.02–1.76 (3 H, m), and 1.60–1.13 (7 H, m) ppm; MS, m/z (% relative abundance) 152 (M^+, 3%), 135 (8), 134 (10), 119 (10), 108 (33), 95 (37), 93 (55), 91 (26), 81 (42), 79 (45), 67 (92), 55 (57), 53 (36), and 41 (100).

Reductive Cyclization of 20. Mg metal (100 mg, 4.2 mmol), trimethylsilyl chloride (0.2 mL, 1.6 mmol), and a catalytic amount of I_2 were added to a solution of **20** (76 mg, 0.5 mmol) in THF (2 mL) and the reaction mixture was stirred at room temperature under a N_2 atmosphere for 60 h. The mixture was diluted with diethyl ether (10 mL) and filtered, and the residue was rinsed with diethyl ether (10 mL). The combined filtrates were acidified with 1 N HCl and vigorously stirred for 5 min. Then the aqueous layer was extracted with diethyl ether (5 mL), and the combined organic layers were washed with brine, saturated aqueous $NaHCO_3$, and brine, and then dried and evaporated to give the crude product (68 mg). Chromatography of this material on silica gel eluted with hexane–EtOAc (10:1) gave three products, **21** (27 mg, 36% yield), **22** (18 mg, 24% yield), and deoxygenated **21** or its double-bond isomers (40% yield), plus recovered **20** (5 mg, 5%).

Compound 21: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.85–4.00 (1 H, m) and 1.0–2.5 (14 H, m) ppm; MS, m/z (% relative abundance) 152(M^+, 51), 136(28), 135(64), 134(64), 133(39), 119(57), and 93(100).

Compound 22: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.53–5.43 (1 H, m, vinyl-H), 4.09–3.97 (1 H, m, CH(OH)), 2.35–2.12 (2 H, m), and 2.08–1.13 (12 H, m); ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 136.4, 124.3, 67.3, 42.9, 37.3, 32.6, 30.9, 29.0, 25.9, and 21.4 ppm; MS, m/z (% relative abundance) 152(M^+, 20), 134(33), 119(34), 108(40), and 91(100).

The mass spectrum of the crude deoxygenated compounds exhibited a molecular ion at m/z of 134/136 and the NMR spectrum contained a small amount of vinylic proton resonances, but they were not further characterized.

Oxidation of the Alcohol 21. The Swern oxidation reagent was made from oxalyl chloride (0.06 mL, 0.67 mmol) and Me_2SO (0.1 mL, 1.4 mmol) in CH_2Cl_2 (0.3 mL) at −60 to −50 °C. Alcohol **21** (40 mg) dissolved in CH_2Cl_2 (0.3 mL) was added, the mixture was stirred at −50 °C for 10 min, and then Et_3N (0.39 mL, 2.8 mmol) was added and the reaction stirred for 5 min at −40 °C. The reaction mixture was partitioned between diethyl ether (5 mL) and 0.5 N HCl (5 mL) and the organic layer washed with brine. After evaporation of the solvents, the crude product was immediately chromatographed on silica gel eluted with hexane–EtOAc (10:1) to give 25 mg of the ketone corresponding to **21**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.72 (s, 2 H), 2.54–2.20 (m, 4 H), 2.10–1.80 (m, 4 H), and 1.75–1.50 (m, 4 H) ppm; IR[16] and ^{13}C NMR[19] data were identical with the literature values; MS, m/z (% relative abundance) 150 (49, M^+), 108 (60), and 93 (100).

Preparation of 5-Hexenal (23). The Swern reagent was prepared from dimethyl sulfoxide (1.56 mL, 22 mmol) and oxalyl chloride (0.96 mL, 11 mmol) in CH_2Cl_2 (30 mL) at −78 °C. This mixture was stirred at −60 °C for 2 min and then a solution of 5-hexen-1-ol (1 g, 10 mmol) in CH_2Cl_2 (10 mL) was added. After 20 min triethylamine (7 mL, 50 mmol) was added and the reaction mixture stirred for 5 min at −60 °C and then at room temperature for 30 min. Water (50 mL) was added to the mixture and the aqueous layer extracted with additional CH_2Cl_2 (50 mL). The combined organic layers were washed with brine (100 mL) and dried, and the filtered solution was concentrated and distilled to give **23** (340 mg, 35% yield, bp 117.5–118 °C; lit.[17] 118.0–118.5 °C): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.76 (1 H, t, J = 1.6, H-1), 5.76, (1 H, ddt, J = 16.9, 10.2, 6.6, H-5), 5.07–4.96 (2 H, m, H-6), 2.44 (2 H, dt, J = 1.6, 7.3, H-2), 2.09 (2 H, br q, J = 6.8, H-4), and 1.73 (2 H, quintet, J = 7.1, H-3) ppm; IR ($CHCl_3$) ν 3070, 2950–2820, 1717, 1638, 1457, 1437, 1344, 1120, 990, and 911 cm^{-1}; MS, m/z (% relative abundance) 98 (M^+, 17), 85 (19), 81 (58), 69 (21), 57 (62), 55 (61), 54 (61), 43 (58), and 41 (100).

Reductive Cyclization of 23. Mg (1.32 g, 55 mmol), Me_3SiCl (1.84 mL, 14 mmol), and then a catalytic amount of I_2 were added to a solution of **23** (216 mg, 2.2 mmol) in THF (2 mL) at room temperature. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 56 h, diethyl ether (20 mL) was added, and the mixture was filtered through a Celite pad. The filtrate was acidified with 1 N HCl (1 mL), stirred for 5 min, and then washed with saturated aqueous $NaHCO_3$ solution and brine, and dried. After filtration, the solution was evaporated and the crude products were treated with benzoyl chloride (0.5 mL) in pyridine (1 mL) for 3 h at 0 °C to room temperature. Water (0.5 mL) was added to the mixture, which then was stirred at room temperature for 1 hr and extracted with diethyl ether (3 mL × 5). The combined organic extracts were washed with 1 N HCl, saturated aqueous $NaHCO_3$ solution, and brine and dried, and the filtered solution was evaporated to dryness. The resulting residue was purified by PLC on silica gel in hexane–EtOAc (8:1) to give the monobenzoates of the two products (140 mg, 32%), **24** and the reduction product, in a ratio of 1:2 as determined by comparison of the integrals between CH_2OBz and $CHCH_3$ in the proton NMR spectrum. After hydrolysis of its monobenzoate, the NMR data for **24** agreeded completely with the literature values for a mixture of *cis*- and *trans*-2-methylcyclopentanol.[20]

Preparation of 4-Hexenal (25). A solution of 3-butene-2-ol (5 g) in methyl vinyl ether (50 mL) containing a catalytic amount of mercuric acetate were placed in a sealed tube and warmed at 30 °C for 12 h. Distillation of the reaction mixture gave pure 4-methyl-3-oxahexa-1,5-diene (1.6 g). This ether was heated in a sealed tube at 80 °C for 3 h to effect the Claisen rearrangement followed by distillation of the reaction give the pure product (0.65 g): bp 127.0–128.0 °C (lit.[18] 128–129 °C).

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Registry No. Ac_4-1, 76703-84-9; Ac_4-6-*epi*-1, 20586-08-7; Ac_5-1, 20586-11-2; **4**, 27856-66-2; **5**, 99128-18-4; **6**, 99128-19-5; **7**, 99128-20-8; **8**, 99212-15-4; **9**, 99128-21-9; **10**, 99128-22-0; **11**, 99211-42-4; **12**, 99128-24-2; **12**-ol, 99128-23-1; **13**, 99211-44-6; **13**-ol, 99211-43-5; **14**, 99128-25-3; **16**, 4845-04-9; **17**, 53544-45-9; **18**, 53544-46-0; **19**, 3991-38-6; **20**, 99128-28-6; **21**, 5689-10-1; **21**-one, 13837-12-2; **22**, 91056-00-7; **23**, 764-59-0; **24** (monobenzoate), 70051-73-9; *cis*-**24**, 25144-05-2; *trans*-**24**, 25144-04-1; **25**, 25166-87-4; 6-dehydrologanin tetraacetate, 20586-14-5; 5,6-dihydro-2*H*-pyran-2-one, 3393-45-1; cyclopentadiene, 542-92-7; diphenyl diselenide, 1666-13-3; methyl cyclohexanoate, 4630-82-4; ethyl orthoacetate, 78-39-7; 1-bromo-2-(2-methylenecyclohexyl)ethane, 99128-26-4; 1,3-dithianyllithium, 36049-90-8; 1-(1,3-dithiacyclohexyl)-2-(2-methylenecyclohexyl)ethane, 99128-27-5; 5-hexen-1-ol, 821-41-0; 5-hexenyl benzoate, 41795-26-0; 3-buten-2-ol, 598-32-3; methyl vinyl ether, 107-25-5; 4-methyl-3-oxahexa-1,5-diene, 3917-16-6.