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MACROEXPANSION METHODOLOGY

MEDIUM RING SYNTHESIS BASED ON AN EIGHT UNIT RING EXPANSION PROCESS[1]

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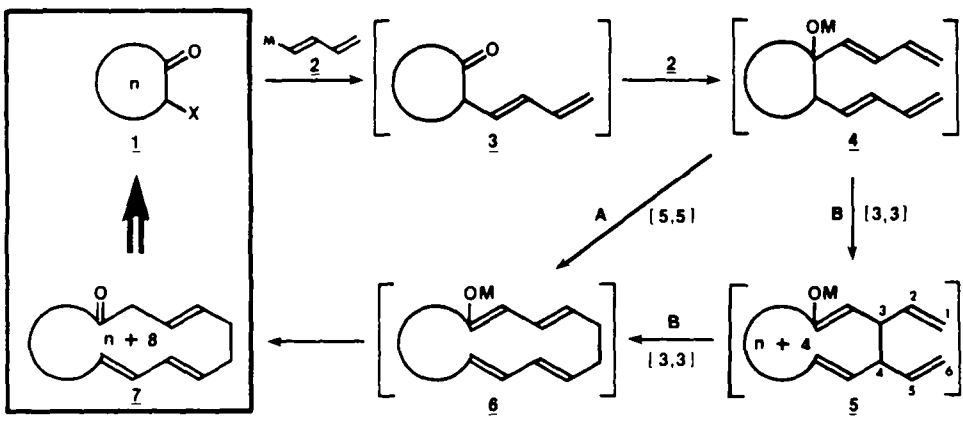
Abstract—Treatment of 1,2-(*E*,*E*)-di(1-buta-1,3-dienyl)cyclohexanol (**21**) with potassium hydride in tetrahydrofuran at room temperature resulted in the facile formation of a 14-membered ring dienolate which on kinetic protonation provided cyclotetradeca-3,5,7-trien-1-one. This novel rearrangement which provides the basis for an efficient, eight unit ring expansion method was also observed when 5,8-dimethyl-5-hydroxy-1,3,7,9-decapentaene (**28**), the acyclic analogue of **21**, was treated with potassium hydride in tetrahydrofuran. Methodology for the preparation of **21** and **28** including the preparation of 1-lithio-1,3-butadiene is also described.

Medium and large ring compounds have been the focus of considerable attention in chemistry for over a century. The early speculation that such systems could "hardly be capable of existence"[4] was unequivocally set aside by Ružička's identification of naturally occurring muscone and civetone as stable 15- and 17-membered ring systems, respectively, and his subsequent success in the synthesis of most of the ring systems between 8 and 32 members.[4] Since that time, research in this area has increased dramatically due to the expanding medicinal, theoretical, and commercial interest in naturally occurring macrocycles and, more recently, non-natural systems such as the crown ethers and annulenes.[5]

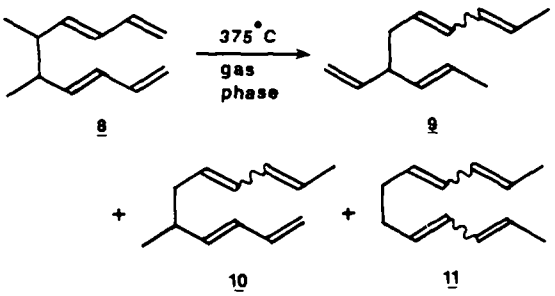
From these studies encompassing now a full half century of innovative thought, acyclic closure, polycyclic fragmentation, and ring expansion have emerged as the fundamental concepts for macrocycle synthesis with each theme offering its unique advantages and disadvantages. Ring expansion methodology, for example, has found considerable service in synthesis although its use has been restricted largely to one operation expansions of, at most, four units.[6] Thus, 9-, 10-, and 11-membered rings can be derived from the pool of readily available 5-, 6-, and 7-membered rings, respectively, through the use of such four unit ring enlargement methods. Currently, however, general methodology for the one operation conversion of the common rings to the rapidly increasing class of macrocycles of twelve or more members, a process which necessarily involves expansions of five or more units,[7] is limited to Story's peroxide decomposition method,[5a] Carlson's photochemical expansion,[8a] olefin metathesis based on [2 + 2]cycloaddition-cycloreversion processes,[8b] and variations of trans-lactamization and trans-lactonization chemistry.[8c]

Our own studies[1,9] in this area have been focused on the design and development of expansion methods which would allow for the one operation conversion of the readily-available common rings to the large rings in a fashion which would provide for the stereo-controlled development of new chiral centers. These objectives were expected to be realized through the strategy depicted in Scheme 1. Thus, based on the previously demonstrated[10] conversion of α-haloketones to 1,2-divinylcycloalkanols, it was expected that the former compounds in the presence of 1-metallobuta-1,3-dienes would be converted to the corresponding 1,2-dibutadienylcycloalkanol salt (**4**). Under the conditions of its generation, this salt was expected to provide the initial expansion product, dienolate **6**, *via* an unprecedented vinylogous oxy-Cope rearrangement (path A)[11] or an equally novel path (B) involving consecutive [3,3]-sigmatropic rearrangements. It is noteworthy in connection



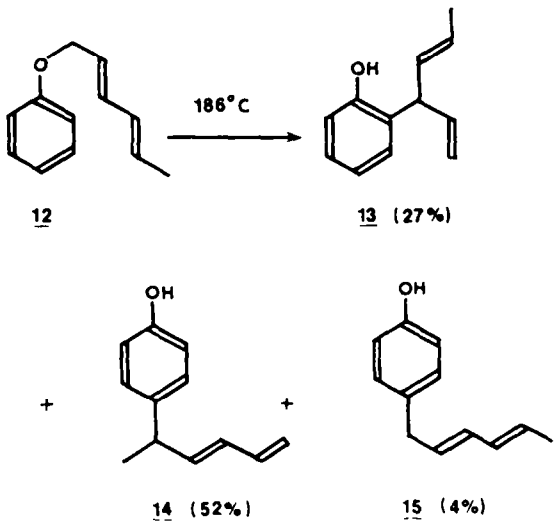
Scheme 1.

with the former possibility that the solution phase thermolysis of tetraene **8**, an all carbon acyclic analogue of **4**, resulted only in its extensive polymerization, as reported by Pettit and Gibson,[11a] whereas its vapor phase isomerization at 375° provided seven products *via* a proposed homolytic cleavage, radical recombination



8 **9** **10** **11**

sequence. These complications were not expected to attend the direct transformation of **4** to **6** if the accelerating effect of the negatively charged oxygen on this potential [5,5]-sigmatropic rearrangement were comparable to that described by Evans *et al.*[12] in their elegant studies on the corresponding [3,3]-sigmatropic rearrangement. However, based on the report by Fráter and Schmid[11b] that the pentadienyl phenyl ether **12** gives products **13**, **14** and **15** arising from competing [3,3]-and



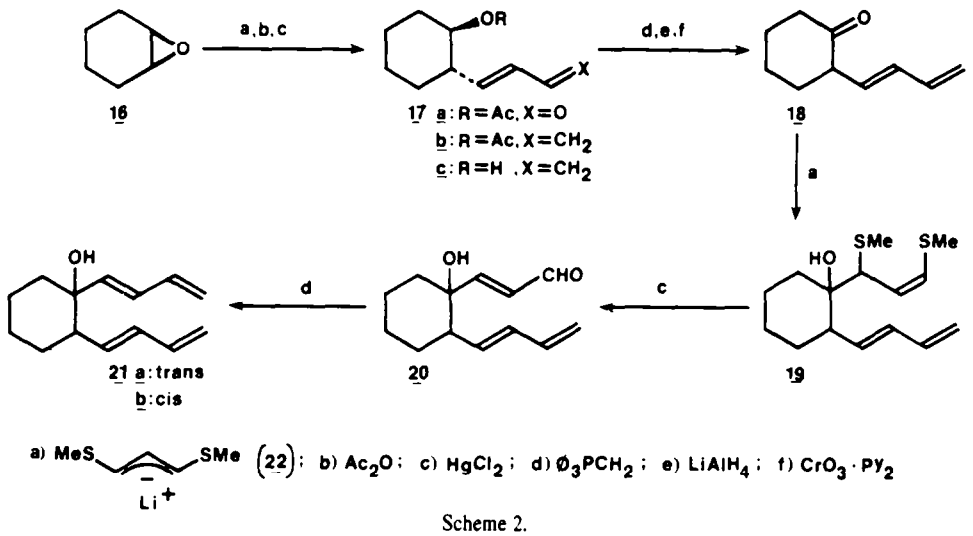
12 **13** (27%) **14** (52%) **15** (4%)

[5,5]-rearrangements, it was also recognized that tetraene **4** could initially provide enolate **5** *via* a charge accelerated [3,3]-sigmatropic rearrangement.[13] If this proved to be the major or exclusive path for rearrangement, then the efficiency of the second [3,3]-sigmatropic rearrangement would determine the success of this macroexpansion method. While rearrangements of divinyl cycloalkadienolates of the type involved in this sequence (e.g. **5**) have not been studied, it was expected that such a process would be facilitated by the vinyl groups on carbons 3 and 4 of the hexa-1,5-diene subunit and, depending on ring size, the strain of the medium ring diene. In regard to the former point, Lutz and Berg[14] have shown that phenyl substituents in the 3 and 4 positions of a hexa-1,5-diene lower the activation energy for Cope rearrangement by *ca.* 10 kcal/mole relative to the parent hexa-1,5-diene rearrangement. Vinyl substitution at positions 3 and 4 of a hexa-1,5-diene would be expected, therefore, to exert a similar effect, although its magnitude is presently unknown. It is noteworthy, however, in this connection that a 3,4-divinyl substituted compound, specifically 4,5-divinyl-octa-2,6-diene, was not observed among the seven products obtained from the above-noted rearrangement of **8**.[11a] The significance of a ring strain effect on the second [3,3]-sigmatropic rearrangement cannot be determined on the basis of existing thermochemical data. Our attempts to estimate ring strain by using molecular mechanics calculations[15] have consistently indicated that such an effect would favor this rearrangement, however, due to the variability of these determinations further analysis of the importance of this effect is deferred at this time. Finally, while its magnitude would be expected to be small, it is noteworthy that the second [3,3]-sigmatropic rearrangement noted above might also be accelerated by a charge effect, interestingly in this case, associated with the enolate subunit.[16] Thus, the expectation that emerges from these considerations is that the rearrangement of **4** *via* either path A or B would lead to the dienolate **6**, the product of an eight unit ring expansion process. Our studies on this concept for macroexpansion are described herein.

RESULTS AND DISCUSSION

Our first investigation[17] of this method terminated five years ago when it was found that butadienyl magnesium bromide (**2**; M=MgBr), a key reagent for the one operation approach outlined above and potentially the most practical butadienyl nucleophile since it is derived from butadiene, bromine, and magnesium, could not be prepared in high yield.[18] However, our growing interest in the theoretical ramifications of the key 10 electron rearrangement and its considerable synthetic potential prompted, more recently, our development of the less direct methodology for the preparation of 1,2-dibutadienylcycloalkanols outlined in Scheme 2. It was of some consolation to recognize that, notwithstanding its length, this sequence could potentially prove useful in the preparation of the more highly substituted butadienyl groups needed for various objectives in natural product synthesis. As outlined, for this approach to the key intermediate, acetoxy aldehyde **17a** was prepared in 81% overall yield from cyclohexene oxide by the method of Corey, Erickson, and Noyori[19] and was converted to **18** in 64% overall yield by a sequence based, in part, on chemistry reported by Carlson and Mardis.[8a] The second butadiene unit was then introduced by essentially the same methodology. Thus, the readily available reagent[19] 1,3-bis-(methylthio)allyllithium (**22**) upon reaction with ketone **18** provided **19** as a mixture of isomers in 90% yield. Mercuric chloride induced hydrolysis of **19** afforded in 56% yield unsaturated aldehyde **20** which upon reaction with methylene triphenylphosphorane gave the long sought alcohol **21** in 77% yield. Overall, this alcohol was obtained in nine steps and in 20% yield from cyclohexene oxide.

The disubstituted olefinic units in **21** are assigned an *E* geometry on the basis of previous studies,[8a,19] the strong IR absorption at 985 cm^{-1} exhibited by **21**[20] and its derivation from α,β-unsaturated aldehydes (see **20** and **17**) with an *E* double bond geometry. The ^{13}C NMR spectrum of **21** exhibits an intense set of 14 carbon signals and a much smaller set of signals with correspondingly similar shifts. Based on peak height analy-

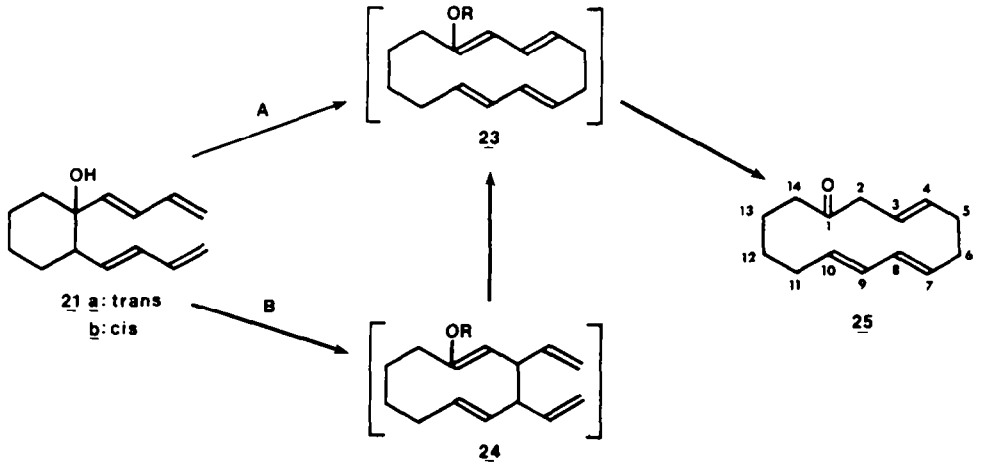


Scheme 2.

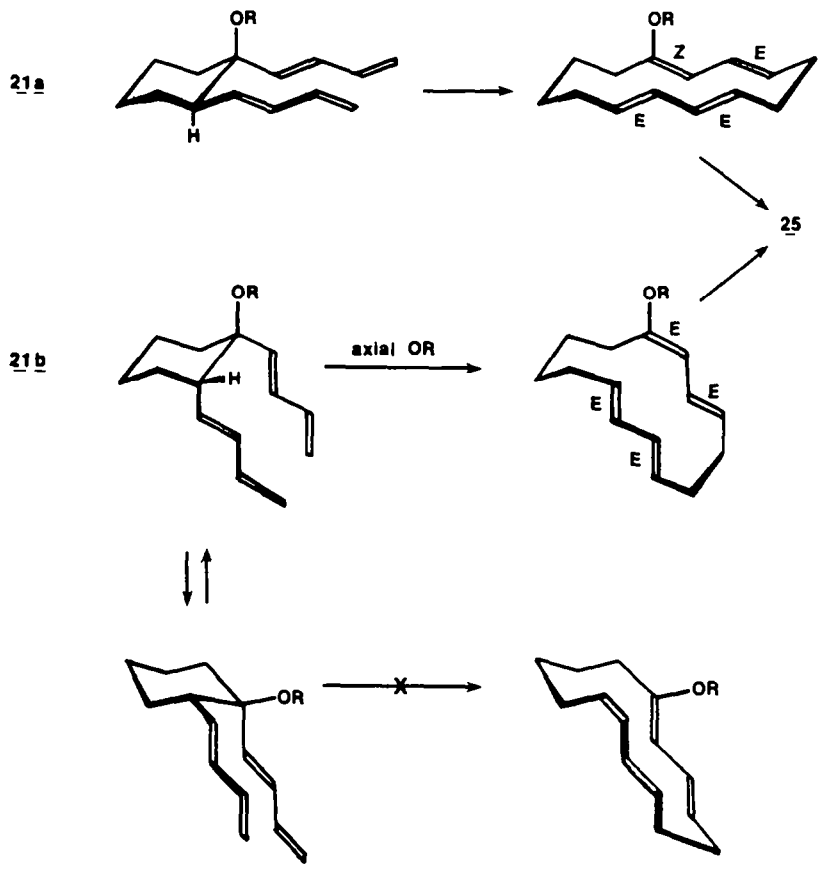
sis these signals are present in the ratio 9:1. Additionally, signals attributable to allylic hydrogens are found in a ratio of 10:1 in the ^{1}H NMR spectrum of **21** recorded at 300 MHz. Their assignment to the *trans*-1,2-dibutadienyl and *cis*-1,2-dibutadienyl isomers of **21**, respectively, is based on the observations[21] that additions of carbon nucleophiles to 2-methylcyclohexanone and 2-vinylcyclohexanone give predominantly the *trans* isomer.

The availability of tetraenol **21** finally set the stage for an investigation of the viability of the aforenoted rearrangement process. Thus, when the starting cyclohexane derivative **21** (a/b > 9; Scheme 3) was treated with potassium hydride (KH) suspended in tetrahydrofuran (THF) at room temperature and the mixture quenched after 1 hr with saturated ammonium chloride solution and submitted to a standard workup procedure, the 14-membered ring trienone **25** was obtained in crystalline form and in an isolated yield of 90%. The ^{13}C NMR spectrum of **25** exhibits only a single set of signals, suggesting that both isomers of tetraenol **21** give only one of several possible isomeric products, a result which is consistent with the involvement of either rearrangement path (Scheme 4). Thus, if path A, involving a [5,5]-sigmatropic shift or its equivalent were involved, isomer **21a** would give *Z,E,E,E* enolate intermediate *via* an all chair transition state whereas isomer **21b** would give the *E,E,E,E* enolate intermediate *via* an all chair transition state in which the negatively charged oxygen is axially oriented with respect to the original 6-membered ring.[22] Kinetic protonation of this *Z,E,E,E* and *E,E,E,E* enolate pair would then give the *E,E,E*-trienone **25**. A similar result would be expected if path B were followed, provided that the preferred transition states are chair-like and that in isomer **21b** the oxygen assumes an axial orientation with respect to the 6-membered ring in the reactive conformation.

The above structural assignment for **25** is further supported by the presence of an absorption at 1705 cm^{-1} in its IR spectrum, assigned to the saturated ketone, and signals at 990 and 975 cm^{-1} consistent with the presence of *E*-substituted olefins.[20] Moreover, the ^{1}H NMR of **25** exhibits five multiplets in the ratio 6:2:2:6:4 corresponding to hydrogens at positions 3,4,7,8,9,10; 2; 14; 5,6,11; and 12,13, respectively. Finally, the 14-membered ring skeleton assigned to **25** was unequivocally



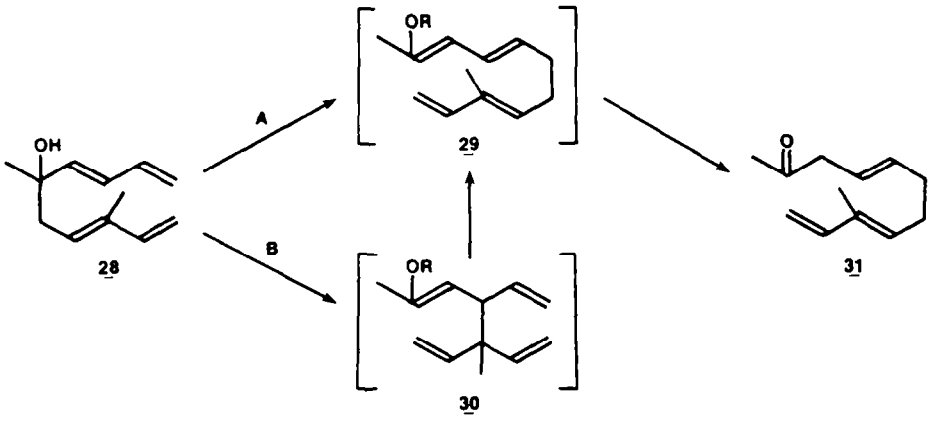
Scheme 3.



Scheme 4.

established by the following transformations. Reduction of **25** with hydrogen and Pd-C catalyst gave in quantitative yield cyclotetradecanone (**26**) whose mp (53–54.5°) was comparable to that (52°, 53°) reported[23a] for independently prepared ketone. A similar correspondence was established for the 2,4-dinitrophenylhydrazone derivative of this ketone (cyclotetradecanone 2,4-DNP: m.p. 117.5–118°; lit. 117–118°[23b]) and cyclotetradecanol (**27**, m.p. 78.5–79.5°; lit. 78.6–79.4°[23c]) obtained by treating ketone **26** in ether with lithium aluminum hydride.

The successful transformation of **21** to **25** serves to generate a variety of theoretical and synthetic considerations which are now the focus of our expanded investigations. One important consideration bearing on this process pertains, of course, to its mechanism and its generality as a vehicle for macroexpansions of eight units, issues which we felt could be most broadly addressed through an examination of the acyclic system **28** (Scheme 5). In this connection, rearrangement of the salt of **28** *via* a homolytic cleavage-radical recombination mechanism would be expected to lead to a complex



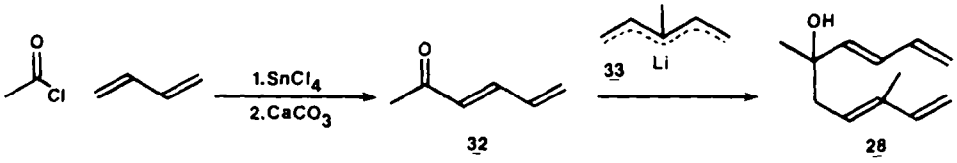
Scheme 5.

mixture of products not unlike that found[11a] in the rearrangement of **8**. Furthermore, since the rearrangement of the salt of **28** would not be influenced by the ring size or strain of starting material, intermediate, or product its study was expected to indicate whether or not this expansion method could be applied to other ring systems. Additionally, if the rearrangement of the salt of **28** were to involve an initial [3,3]-sigmatropic process, further rearrangement of the resulting intermediate might in this case be sufficiently slow to allow for its accumulation and subsequent detection.

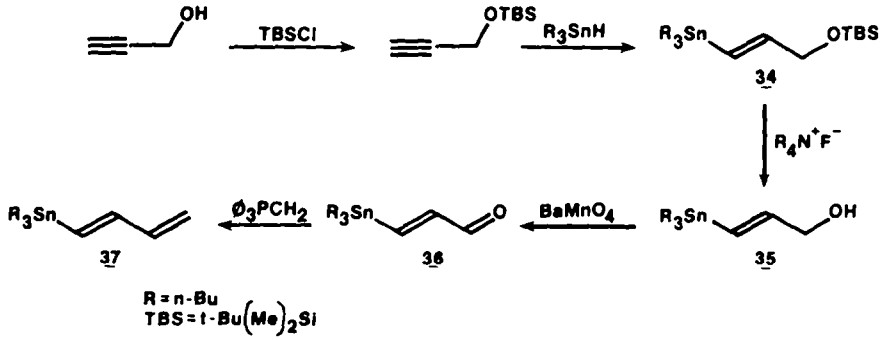
For the purpose of this investigation, **28** was found to be most conveniently prepared according to the sequence outlined in Scheme 6. Thus, dienone **32** was prepared by a procedure patterned after that reported by Nader, Franck, and Weinreb[24] for the preparation of (*E*)-1,3-heptadien-5-one. Reaction of **32** with 3-methylpentadienyllithium (**33**)[25] provided tetraenol **28** which was determined by ^{13}C NMR spectroscopy to be greater than 90% one isomer. When this compound was treated with KH in THF and the reaction quenched after 1 hr and submitted to a standard workup procedure, trienone **31** (>90% one isomer) was obtained in an isolated yield of 78%. Thus, once again, the vinylogous alkoxy-Cope rearrangement proceeded in an efficient, selective, and facile manner. These results substantially discount the involvement of a radical cleavage path proceeding without the involvement of a cage effect. Moreover, if this reaction were to proceed *via* consecutive [3,3]-sigmatropic rearrangements, the second Cope rearrangement, i.e. the rearrangement of **30** to **29**, would have to be remarkably facile. Indeed, the half-life for the rearrangement of the potassium salt of tetraenol **28** is 50.6 ± 7.7 min at 0° and *ca.* 1.8 min at 25°. It is also noteworthy in this connection that the rearrangement of the potassium salt of **21** is equally facile with a half-life of 54.5 ± 4.4 min at 0°. While these data are useful in the design of syntheses based on this method, a definitive analysis of the mechanism(s) for the key rearrangement must await the outcome of further studies in progress.

The successful expansion of **21** to **25** and the potential generality of this method suggested by the correspondingly facile rearrangement of the potassium salt of **28** to **29** clearly call attention to the importance of developing more efficient methods for the preparation of 1,2-di(1-alka-1,3-dienyl) cycloalkanols, the starting materials required in this ring enlargment method. In connecton with this objective, we have recently prepared 1-lithio-1,3-butadiene (**38**), a reagent which provides the basis for a three step alternative to the original nine step route to **21** (Scheme 2). For this preparation (Scheme 7), propargyl alcohol was converted to the alkenyl stannane **34** using a sequence previously developed by Corey and Wollenberg[26] for the preparation of the correponding tetrahydropyranyl protected derivative. Hydrolysis of **34** with tetra-n-butylammonium fluoride provided alcohol **35** which was converted to **37** in a manner similar to that reported by Piers and Morton[27] in their work on related compounds. Reaction of stannane **37** with n-butyllithium in THF at −78° for 15 min provided butadienyllithium (**38**) as evidenced by its reaction with 2-chlorocyclohexanone from which chlorohydrin **39** was isolated in 61% yield (Scheme 8). Importantly, when this chlorohydrin (**39**) was allowed to react with ethylmagnesium bromide in benzene for 5 min at 0° and the resulting solution immersed in a 75° oil bath for 2 min, then cooled with aid of an ice bath and finally quenched with saturated ammonium chloride solution, butadienyl cyclohexanone (**18**) was obtained in 66% isolated yield. Finally, treatment of **18** with butadienyllithium (**38**) derived by using the above-noted procedure provided upon workup the key intermediate **21** in 70% yield. Thus, **21** and presumably related intermediates required for the extension of this novel macroexpansion method can now be derived in three steps from commercially available chloroketones and, consequently, the overall process can now be effected in four steps.

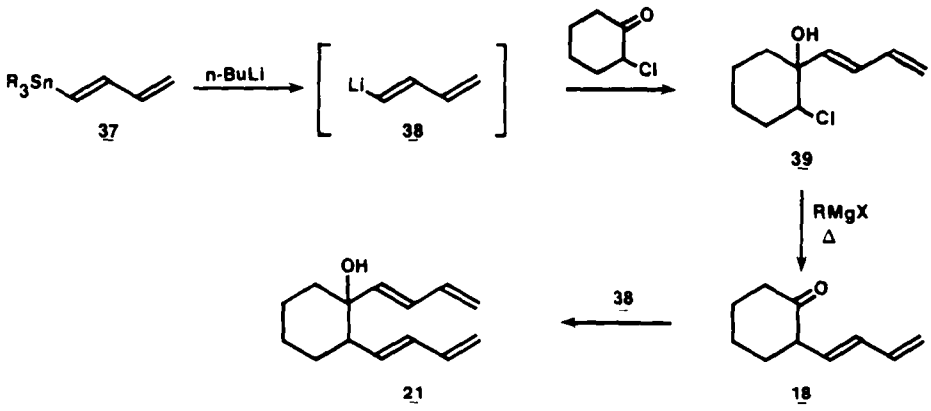
In summary, an 8 unit ring expansion method has been demonstrated in the 4 step transformation of 2-chlorocyclohexanone to the 14-membered ring trienone **25** in-



Scheme 6.



Scheme 7.



Scheme 8.

volving a novel, efficient, and particularly facile rearrangement of the salt of tetraenol **21**. Studies on the mechanism of this rearrangement, the further development of this and conceptually related macroexpansion methods, and their applications are in progress.

EXPERIMENTAL

M.ps were obtained by using a Thomas–Hoover capillary m.p. apparatus and are uncorrected. B.ps are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. UV spectra were determined by using a Perkin–Elmer 599a spectrophotometer and MeOH as solvent. Absorption maxima are reported in nanometers in the form λ_{max} (log ϵ). IR spectra were obtained on a Perkin–Elmer model 137 spectrophotometer and are reported in cm^{-1}. NMR spectra were recorded on a Varian HFT-80 (80 MHz) or a Brucker WM-300 (300 MHz) instrument; chemical shifts are reported in ppm downfield (δ) from TMS. CMR spectra were recorded on a Varian XL-100-15 (25.1 MHz) instrument; chemical shifts are reported in ppm downfield from TMS. Mass spectra were determined on an AEI MS-9 or a Kratos MS-50L, both double focussing instruments, at an ionizing voltage of 70 eV and 8 kV accelerating voltage. Column chromatography was conducted at medium pressure with the indicated solvent system.[29]

For experiments requiring dry solvents, ether and THF were distilled from sodium benzophenone ketyl. Benzene was azetropically distilled. Diisopropylamine and pyridine were distilled from calcium hydride. All reactions requiring anhydrous conditions were conducted under a positive pressure of nitrogen or argon.

1 - *Acetoxy* - trans - 2 - (E) - (1 - *buta* - 1,3 - *dienyl*)*cyclohexane* (**17b**). To a 0° suspension of methyltriphenylphosphonium bromide (19.1 g, 53.5 mmol) in 250 ml of THF was added n-BuLi in hexane (21.3 ml, 46.7 mol, 2.19M). The soln was warmed to room temp for 3 hr, cooled to −30°, and a soln of **17a**[19] (9.16 g, 46.7 mmol) in 28 ml THF was added dropwise over 30 min. After the addition was complete, the soln was stirred at −30° for 20 min, and then warmed to room temp for 30 min. 100 ml each of water and pentane were added to the mixture, and the aqueous phase was extracted with pentane. The combined organic extracts were washed with sat NaCl aq, dried (Na_2SO_4), and concentrated *in vacuo* to a small volume. Dilution of the resulting residue with pentane, filtration, and removal of the solvent *in vacuo* gave an orange oil which was purified by column chromatography (silica gel, 4 × 14 cm, 15% ether in hexane) to give 7.35 g (81%) of the title compound. IR (CCl_4): 1735, 1650, 1600, 1440, 1365, 1235, 1030, 1005, 950, 905 cm^{-1}. NMR ($CDCl_3$): δ 6.5–4.8 (m, 5H), 4.6 (m, 1H), 2.0 (s, 3H), 2.3–1.0 (m, 9H). UV_{max} 224 nm (4.43). The mass spectum of **17b** was in accord with the assigned structure. (Found: 194.13050; Calc. for $C_{12}H_{18}O_2$: 194.13067).

2-trans-(E)-(1-*Buta*-1,3-*dienyl*)*cyclohexanol* (**17c**). To a 0° suspension of LAH (300 mg, 7.9 mmol) in 20 ml ether was added dropwise **17b** (792 mg, 4.08 mmol) in 5 ml ether. After 1 hr, EtOAc was added and the reaction was subjected to a standard workup.[30] Column chromatography of the oil (silica gel, 2 × 8 cm, 30% ether in hexane) gave 578 mg (93%) of the title compound. IR (CCl_4): 3450, 1650, 1600, 1440, 1055, 1030, 1005, 955, 935, 905, 870 cm^{-1}. NMR ($CDCl_3$): δ 6.6–4.9 (m, 5H), 3.25 (m, 1H) 2.5–0.8 (m, 10H). UV_{max} 224 nm (4.44). Mass spectrum of **17c** was in accord with the assigned structure. (Found; 152.11986; Calc. for $C_{10}H_{16}O$: 152.12011; (Anal. $C_{10}H_{16}O$) C, H).

2-(E)-(1-*Buta*-1,3-*dienyl*)*cyclohexanone* (**18**). To a room temp soln of pyridine (15.7 ml, 194 mmol) in 240 ml CH_2Cl_2 was added CrO_3 (9.7 g, 97 mmol) and the mixture stirred for 15 min. Alcohol **17c** (2.46 g, 16.2 mmol) in 10 ml CH_2Cl_2 was added and the mixture stirred for 20 min. The resultant soln was decanted and the black residue rinsed twice with ether. The organic soln was washed twice with 5% NaOH aq and with 5% HCl aq, once with sat NaCl aq, dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography of the oil (silica gel, 3 × 8 cm, 20% ether in hexane) gave 2.06 g (85%) of the title compound. IR (CCl_4): 1705, 1650, 1600, 1440, 1125, 1005, 950, 900 cm^{-1}. NMR ($CDCl_3$): δ 6.6–4.9 (m, 5H), 3.1 (m, 1H), 2.7–1.25 (m, 8H). UV_{max} 223 nm (4.35). Mass spectrum of **18** was in accord with the assigned structure. (Found: 150.10441; Calc. for $C_{10}H_{14}O$: 150.10446).

1 - (1,3 - *Bis*(*methylthio*)*prop* - 2 - *enyl* - 2 - (1 - *buta* - 1,3 - *dienyl*) *cyclohexanol* (**19**). To a −78° soln of 1,3 - bis(methylthio) - 2-methoxypropane[19] (3.09 g, 18.6 mmol) and diisopropylamine (5.52 ml, 39.4 mmol) in 60 ml THF was added n-BuLi in hexane (17.5 ml, 38.3 mmol, 2.19M). The cooling bath was removed and the soln was allowed to warm to room temp over 100 min. The deep burgundy soln was then cooled to −78° and **18** (2.06 g, 13.7 mmol) in 7 ml THF was added dropwise. After 15 min, the cooling bath was removed, the soln allowed to warm for 15 min and sat NH_4Cl aq added. The aqueous phase was extracted with CH_2Cl_2, the combined extracts dried (Na_2SO_4) and the solvent removed *in vacuo*. Column chromatography of the red oil (silica gel, 3 × 15 cm, 20% ether in hexane) gave 3.5 g (90%) of the title compound as a mixture of isomers. IR (CCl_4): 3500, 1650, 1600, 1440, 1430, 1420, 1005, 975, 960, 945, 900 cm^{-1}. NMR ($CDCl_3$): δ 6.75–4.8 (m, 7H), 3.9–3.0 (4d, 1H, J = 10–10.8 Hz), 2.8–1.0 (m, 16H). Mass spectrum of **19** was in accord with the assigned structure. (Found: 284.12694; Calc. for $C_{15}H_{24}OS_2$; 284.12685; Anal. ($C_{15}H_{24}OS_2$) C, H).

2-(E)-(1-*Buta*-1,3-*dienyl*)-1-(E)-(3-*prop*-2-*en*-1-*al*)*cyclohexanol* (**20**). To a 0° soln of **19** (1.47 g, 5.17 mmol) in 100 ml acetonitrile:water (4:1) was added $CaCO_3$ (2.95 g, 29.5 mmol) followed by mercuric chloride (5.62 g, 20.7 mmol). The cooling bath was removed and the suspension stirred at room temp for 40 min. The suspension was filtered through celite with ether, the organic phase washed four times with sat NaCl aq, dried (K_2CO_3), and the solvent removed *in vacuo* to give an oil which on column chromatography (silica gel, 3 × 14 cm, 25% ether in hexane) gave 593 mg (56%) of the title compound. IR (CCl_4): 3500, 1695, 1645,

1600, 1120, 1005, 990, 980, 960, 905 cm^{-1}. NMR ($CDCl_3$): δ 9.6 (d, 1H, J = 7.5 Hz), 7.1–4.9 (m, 7H), 2.7–1.0 (m, 10H). UV_{max} 218 nm (4.59). The mass spectrum of **20** was in accord with the assigned structure. (Found: 206.13063) Calc. for $C_{13}H_{18}O_2$: 206.13067; Anal. ($C_{13}H_{18}O_2$) C, H).

1,2-(E,E)-*Di*(1-*buta*-1,3-*dienyl*)*cyclohexanol* (**21**). To a 0° suspension of methyltriphenylphosphonium bromide (1.9 g, 5.3 mmol) in 25 ml THF was added n-BuLi in hexane (2.21 ml, 4.8 mmol, 2.19M). The cooling bath was removed, the soln stirred at room temp for 3 hr, and then cooled to −30°. Alcohol **20** (498.5 mg, 2.42 mmol) in 6 ml THF was added dropwise to give a light yellow suspension. After the addition was complete, the suspension was stirred at −30° for 45 min, then warmed to room temp for 45 min. Pentane and NH_4Cl aq were added, and the aqueous phase extracted with pentane. The combined extracts were filtered and the solvent was removed *in vacuo*. Column chromatography of the orange oil (silica gel, 2.5 × 10 cm, 12% ether in hexane) gave 378 mg (77%) of the title compound. IR (CCl_4): 3600, 1650, 1600, 1005, 985, 955, 905 cm^{-1}. NMR ($CDCl_3$): δ 6.75–4.8 (m, 10H), 2.5 and 2.3 (m, 1H, ratio 1:10), 1.9–1.2 (m, 9H). UV_{max} 220 nm (4.65). Mass spectrum of **21** was in accord with the assigned structure. (Found: 204.15117. Calc. for $C_{14}H_{20}O$: 204.15141). Anal. ($C_{14}H_{20}O$) C,H. CMR ($CDCl_3$): δ 141.8, 137.3, 136.7, 135.0, 132.4, 128.4, 116.5, 115.7, 73.1, 47.9, 38.0, 26.6, 25.3, 21.2.

Cyclotetradeca-3,5,7-*trien*-1-*one* (**25**). To a 0° suspension of potassium hydride (404 mg, 2.2 mmol, 22% in mineral oil) in 20 ml of THF was added dropwise a soln of **21** (174.6 mg, 0.855 mmol) in 4 ml THF. When the addition was complete, the soln was stirred at 0° for 5 min, the cooling bath was removed, and the soln allowed to warm to room temp for 1 hr. The soln was then recooled to 0°, sat NH_4Cl aq added, and the aqueous phase extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. Column chromatography (silica gel, 1 × 14 cm, 7% ether in hexane) gave 157.4 mg (90%) of the title compound as a faint yellow solid. Recrystallization of this sample from cold pentane gave colorless needles, m.p. 50.5–51.5°. IR (CCl_4): 1705, 1650, 1440, 1430, 1100, 990, 975 cm^{-1}. NMR ($CDCl_3$): δ 6.2–4.75 (m, 6H), 3.1–2.75 (bd, 2H), 2.7–2.3 (m, 2H), 2.3–1.8 (m, 6H), 1.75–1.25 (m, 4H). UV_{max} 233 nm (4.32). Mass spectrum of **25** was in accord with the assigned structure. (Found: 204.15126. Calc. for $C_{14}H_{20}O$: 204.1541. Anal. ($C_{14}H_{20}O$) C, H. CMR ($CDCl_3$): δ 209.3, 134.2, 133.3 (2C), 131.2, 130.7, 125.4, 48.3, 42.6, 34.3, 32.7, 31.6, 26.4, 22.1.

Half-life determination for **21** → **25**. Alcohol **21** (48 mg, 0.23 mmol) and biphenyl (internal standard, 11.3 mg, 0.07 mmole) in 2 ml THF were cooled to 0° and transferred to a flask containing excess KH free from mineral oil. The mixture was maintained at 0° with the aid of an ice bath.

Aliquots of the mixture were removed at intervals, quenched with NH_4Cl aq, dried (Na_2SO_4), and the resulting sample analyzed by GC (20-ft × 0.125-in. 3% SE-30, column temp 160°, flame ionization detection) to yield the following information:

RXN. time (min)	% **21** remaining	half life (min)
0	100	—
30	71	60.9
60	45	51.9
120	21	52.5
180	8	50.1
270	4	57.1

Cyclotetradecanone. A room temp mixture of **25** (97.3 mg, 0.476 mmol) and 5% Pd-C (30 mg) in 10 ml EtOAc was flushed first with H_2 and then maintained under one atmosphere of H_2 for 2 hr. Filtration of the mixture through celite with ether and concentration *in vacuo* gave 114.9 mg of colorless crystals which on column chromatography (silica gel, 0.5 × 5 cm, 5% ether in pentane) gave 99.8 mg (99.6%) of colorless crystals. Recrystallization of this sample from cold pentane gave fine needles m.p. 53–54.5° (sealed capillary, lit. 52°, 53°).[23a] IR (CCl_4): 2900, 2840, 1705, 1455, 1440, 1360 cm^{-1}. NMR ($CDCl_3$): δ 2.45 (t, 4H, J = 6 Hz), 2.2–1.2 (m, 22H). The mass spectrum was in accord with the assigned structure. (Found: 210.19824. Calc. for $C_{14}H_{26}O$ 210.19838) A 2,4-DNP[30b]-derivative was obtained as yellow/orange crystals, m.p. 117.5–118° (lit.[23b] 117–118°).

Cyclotetradecanol. To a 0° suspension of LAH (5.5 mg, 0.14 mmol) in 0.5 ml ether was added cyclotetradecanone (7.6 mg, 0.036 mmol) in 1 ml ether and the soln stirred for 40 min. Standard workup gave 6.1 mg (79%) of a colorless solid, which on recrystallization from pentane gave colorless granular crystals m.p. 78.5–79.5° (lit.[25c] 78.6–79.4°).

(E),5-*Hexadien*-2-*one* (**32**). A mixture of anhyd $SnCl_4$ (134.4 g, 60 ml, 0.516 mol) and 400 ml CH_2Cl_2 was cooled to −42° under N_2. A mixture of acetyl chloride (40.5 g, 37 ml, 0.516 mol) and 300 ml CH_2Cl_2 was added and the combined mixture stirred at −42°. Butadiene was slowly bubbled through the soln for 1 hr and the mixture stirred an additional 0.5 hr at −42°. The mixture was allowed to warm to −10° over 1 hr and was poured slowly over ice containing 150 ml 0.1 N HCl. The layers were separated and the organic layer washed with 300 ml water followed by 300 ml brine. The organic layer was dried ($MgSO_4$) and solvent was removed at reduced pressure. A mixture of anhyd $CaCO_3$ (60 g, 0.60 mol) and 100 ml toluene was added to the residue and the combined mixture stirred under N_2 at an oil bath temp of 85° for 33 hr. Toluene was removed at reduced pressure. Distillation of the resulting oil yielded 5.23 g of **32** contaminated with a trace of toluene: b.p. 40–47° (10 mm).[33] Flash chromatography on 6 in × 50 mm silica using a 3:1 hexane–ether mixture as eluant provided 4.30 g (9%) of the title compound as a pale, yellow liquid; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H), 5.45–7.13 (m, 5H), ; IR (film) 1675, 1630, 1600 cm^{-1}.

5,8-*Dimethyl*-1,3(E),7(E *and* Z),9-*decatetraen*-5-*ol* (**28**). A mixture of 3-methyl-1,4-pentadiene (3.185 g, 0.039 mol) and 8 ml dry THF was stirred under N_2 and cooled to −78°. n-BuLi (9.2 ml, 0.022 mol) in hexane was added dropwise by syringe, and the soln allowed to warm to room temp over 1 hr. The dark orange soln was stirred at room temp for 1 hr and was cooled to −50°. A mixture of **32** (1.715 g, 0.018 mol) and 8 ml dry THF was added, dropwise by syringe, and the soln stirred for 1.5 hr at −50° to −30°. The soln was allowed to warm to room temp and was quenched with 10 ml water. The layers were separated and the aqueous layer was extracted with ether (3 × 25 ml). The combined organic layers were dried ($MgSO_4$) and solvent was removed at reduced pressure. Flash chromatography on 6 in × 90 mm silica using 4:1 hexane–ether mixture as eluant provided 1.136 g (36%) of the title compound as a colorless liquid (>90% one isomer[34]). R_f = 0.35; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.58 (s, 1H), 1.77 (br, s, 3H), 2.43 (d, J = 7.7 Hz, 2H), 4.1–6.59 (m, 9H); ^{13}C NMR (CD_3OD) δ 12.2, 27.6, 42.4, 73.8, 111.2, 116.8, 129.1, 129.5, 137.2, 138.2, 141.9, 142.9 with minor intensities sppearing at δ 30.8, 41.4, and 112.5; IR (film) 3400, 2980, 1645, 1610, 1360, 1010, 990, 900 cm^{-1}; mass spectrum, *m/e* (%) 152 (18), 98 (100), 97 (82), 79 (50), 67 (47). (Found: C, 80.56; H, 10.16. Calc. for $C_{12}H_{18}O$: C, 80.84; H, 10.18).

9-*Methyl*-4(E),8(E *and* Z),10-*undecatrien*-2-*one* (**31**). A mixture of KH (0.139 g, 22.9% in mineral oil, 0.80 mmol) and 5 ml dry THF was stirred under N_2 at room temp. To this mixture, a soln of **28** (0.074 g, 0.41 mmol) and 5 ml dry THF was added, at once, by syringe. The soln was stirred for 1 hr at room temp and 10 ml sat $(NH_4)_2SO_4$ aq was slowly added. The layers were separated and the aqueous layer extracted with ether (3 × 25 ml). The combined organic layers were dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was submitted to preparative tlc (silica) using a mixture of 2:1 hexane–ether as eluant. The product was isolated by CH_2Cl_2 extraction and solvent removal under reduced pressure to provide 0.057 g (78%) of the title compound (>90% one isomer[35]) as a clear, colorless liquid; ^1H NMR ($CDCl_3$) 1.74 (br s, 3H), 2.13 (s, 3H), 2.16 (br s,

4H), 3.10 (br d, 2H), 4.86–6.55 (m, 6H); IR (film) 2900, 1720, 1640, 1610, 1440, 1350, 1160, 990, 970, 895 cm^{-1}; mass spectrum, *m/e* (%) 178 (3), 150 (6), 135 (9), 120 (12), 108 (16), 93 (19), 81 (100); High resolution mass spectrum, molecular ion at *m/e* 178.13561 (calc. for $C_{12}H_{18}O$, 178.13576).

Half-life determination for **28**→**31**. Half-lives for conversion of **28** to **31** were determined at 25° and 0° by allowing tetraenol **28** to react with KH in dry THF for a given amount of time (1 and 2 min at 25°; 30 and 45 min at 0°) before quenching with water, and monitoring the disappearance of **28** by NMR. This was accomplished by comparing integration of the methylene proton peaks of **28** (δ 2.46, d) with that of the methylene proton peak of a known amount of acenaphthene (δ 3.42, s) added after the mixture was quenched. Each experiment was carried out twice to allow an average half-life to be calculated at each temp. A typical experiment is provided below:

A mixture of KH (0.056 g, 22.9% in mineral oil, 0.324 mmol) and 10 ml dry THF was placed under N_2 at room temp (25°). The THF and dissolved mineral oil were removed by syringe and 10 ml fresh, dry THF was added. The mixture was stirred at 25°. Added at once, by syringe, was **28** (0.029 g, 0.162 mmol) in 3 ml dry THF and the soln stirred for exactly 2 min. At this time the mixture was quickly quenched with 5 ml water. The mixture was transferred to a separatory funnel to which was added acenaphthene (0.025 g, 0.162 mmol) dissolved in ether. The layers were separated and the organic layer was dried ($MgSO_4$). Solvent was removed at reduced pressure to provide the NMR sample ($CDCl_3$). Integration indicated the presence of 47% of the original starting material. Half-lives determined in this fashion are: 25°:$t_{1/2}$ = 1.8 ± 0.1 mins; 0°:$t_{1/2}$ = 50.6 ± 7.6 min.

(3-*t-Butyldimethylsiloxy*-1-*propenyl*)*tri-n-butylstannane*[26] (**34**). To a 0° soln of t-butyldimethylsilyl chloride (31.8 g, 211 mmol), Et_3N (23.5 g, 230 mmol), and 4-dimethylamino pyridine (103 mg, 0.83 mmol) in 65 ml CH_2Cl_2 was added dropwise propargyl alcohol (10.6 g, 192 mmol) in 15 ml CH_2Cl. The cooling bath was removed and the mixture stirred at room temp for 21 hr. 175 ml water was added and the aqueous phase extracted with CH_2Cl. The combined organic extracts were washed with water and sat. NaCl aq and dried ($MgSO_4$). The solvent was distilled at atmospheric pressure and the remaining yellow oil distilled (52–54°/15 torr) to give 30.3 g (93%) of t-butyldimethylsilylpropargyl ether as a colorless oil. IR (neat): 3350, 1480, 1370, 1255, 1100 cm^{-1}. NMR ($CDCl_3$): δ 4.31 (d, 2H, J = 2.4 Hz), 2.37 (t, 1H, J = 2.4 Hz), 0.91 (s, 9H), 0.13 (s, 6H).

A mixture of poly-methyl hydrogen siloxane (16.8 g), bis tri-n-butyltinoxide (77.8 g, 124 mmol), t-butyldimethylsilylpropargyl ether (30.1 g, 177 mmol), and 2,2'-azobis(2-methylpropionitrile) (AIBN, 180 mg, 1.1 mmol) under a N_2 was heated at 80–85° for 2 hr, cooled, and then fractionally distilled through a 5 cm Vigreux column (121–124°/0.008 torr) to give 53.5 g (66%) of the title compound. IR (neat): 1610, 1460, 1370, 1360, 1250, 1090 cm^{-1}. NMR ($CDCl_3$): δ 6.13–6.10 (m, 2H), 4.20 (d, 2H, J = 2.5 Hz), 1.53–0.80 (m, 27H), 0.92 (s, 9H), 0.01 (s, 6H).

Tri-n-butyl-1-*propen*-3-*ol stannane* (**35**). To a 0° soln of **34** (11.3 g, 24.5 mmol) in 100 ml THF was added a soln of tetra-n-butylammonium fluoride in THF (49 ml, 1M, 49 mmol). The cooling bath was removed and the soln stirred at room temp for 2.5 hr. Water was added and the aqueous phase extracted with CH_2Cl_2. The combined organic extracts were washed with sat NaCl aq, dried ($MgSO_4$), and the solvent removed *in vacuo*. Distillation of the residue through a 5 cm Vigreux column gave 8.11 g (95%) of the title compound as a colorless oil. IR (neat): 3350, 1600, 1165, 990, 960 cm^{-1}. NMR ($CDCl_3$): δ 6.20–6.14 (m, 2H), 4.21–4.14 (M, 2H), 1.75–1.07 (m, 18H), 0.97–0.80 (m, 10H). (Found: 291.07718. Calc. for $C_{11}H_{23}OSn^{32}$: 291.07707).

(E)-(*Prop*-1-*en*-3-*al*)*tri-n-butylstannane* (**36**). The alcohol **35** (19.0 g, 54.7 mmol) was added to a mechanically stirred suspension of barium manganate[31] (140 g, 541 mmol) in 1.91 CH_2Cl_2 at room temp and stirred for 12 hr. As the reaction was judged to be incomplete (tlc), additional barium manganate (14.5 g, 56 mmol) was added and the suspension stirred for another 4 hr. Filtration of the mixture through celite, drying (K_2CO_3) of the organic phase and removal of the solvent *in vacuo* provided 17.3 g (92%) of the title compound as a faint-yellow oil. IR (neat): 2820, 2720, 1690, 1460 cm^{-1}. NMR ($CDCl_3$): δ 9.41 (d, 1H, J = 7.5 Hz), 7.78 (d, 1H, J = 19.1 Hz), 6.60 (dd, 1H, J = 7.5, 19.1 Hz), 1.61–0.77 (m, 27H). UV_{max} 217 nm (3.99). (Found: 289.06174; Calc. for $C_{11}H_{21}OSn^{32}$: 289.06143. Anal. ($C_{15}H_{30}OSn$): C, H, Sn).

1-*Buta*-1,3-*dienyl*-*tri-n-butylstannane* (**37**). To a 0° suspension of methyltriphenylphosphonium bromide (19.58 g, 54.8 mmol) in 250 ml THF was added n-BuLi in hexane (21.9 ml, 2.39M, 52.3 mmol). The cooling bath was removed and the mixture stirred at room temp for 2 hr. The resulting soln was cooled to 0°, and **36** (17.20 g, 49.8 mmol) in 50 ml THF was added dropwise. After the addition was complete, the soln was allowed to warm to room temp for 2 hr. Sat NH_4Cl aq was added and the aqueous phase was extracted with hexane. The combined organic extracts were washed with sat NaCl aq, dried ($MgSO_4$), and the solvent removed *in vacuo*. Filtration of the resulting residue through silica gel with hexane gave 14.82 g (87%) of the title compound as a yellow oil. IR (neat): 3100, 1620, 1560 cm^{-1}. NMR ($CDCl_3$): δ 7.0–5.75 (m, 3H), 5.3–4.8 (m, 2H), 1.7–0.5 (m, 27H). UV_{max} 233 nm (4.37). (Found: 287.08202. Calc. for $C_{12}H_{23}Sn^{32}$: 287.08216). Anal. ($C_{16}H_{32}Sn$)): C, H. CMR ($CDCl_3$): δ 147.5, 140.2, 134.7, 115.7, 29.1, 27.3, 13.6, 9.6. Distillation gave **37** as a colorless oil b.p. 99–102°/0.006 mm.

1-(1-*Buta*-1,3-*dienyl*)-2-*chlorocyclohexanol* (**39**). To a −78° soln of **37** (2.02 g, 5.87 mmol) in 30 ml THF was added dropwise n-BuLi in hexane (3.76 ml, 1.49M, 5.61 mmol) and the soln stirred for 10 min. 2-Chlorocyclohexanone (780 mg, 5.34 mmol) in 5 ml THF was added dropwise over several minutes and then the mixture was removed from the cooling bath for 30 min. Sat NH_4Cl aq was added and the aqueous layer extracted with ether. The combined organic extracts were washed with sat NaCl aq, dried ($MgSO_4$), and the solvent removed *in vacuo* to give 3.05 g crude material. Column chromatography (silica gel, 0.5 × 7 cm, 5% ether in hexane) was performed on 1.50 g of the crude material to yield 305 mg (61%) of the title compound. IR (neat): 3600, 3100, 1600, 1000, 960, 910, 740 cm^{-1}. NMR ($CDCl_3$): δ 6.6–5.6 (m, 3H), 5.3–5.0 (m, 2H), 3.98 (dd, 1H), 2.3–1.2 (m, 9H).

2-(E)-(1-*Buta*-1,3-*dienyl*)*cyclohexanone* (**18**) (*from chlorohydrin* **39**). To a 0° mixture of EtMgBr in ether (0.21 ml, 2.9M, 0.61 mmol) and 13 ml benzene was added dropwise **39** (113.7 mg, 0.61 mmol) in 4 ml benzene to give a slightly turbid soln. After stirring for 5 min at 0°, the soln was transferred to a preheated 75° oil bath for 2 min at which time a large quantity of salt had precipitated. The soln was then recooled to 0° and sat NH_4Cl aq added. The aqueous layer was extracted with ether, and the combined extracts washed with sat NaCl aq, dried ($MgSO_4$), and the solvent removed *in vacuo*. Column chromatography of the resulting oil (silica gel, 2 × 12 cm, CH_2Cl_2) gave 60.1 mg (66%) of the title compound whose structure was confirmed by comparison with a sample of **18** obtained by oxidation of **17c**.

1,2-(E,E)-*di*(1-buta-1,3-dienyl)cyclohexanol (**21**) (*from* 1-*lithio*-1,3-*butadiene addition to* **18**). To a −78° soln of **37** (396 mg, 1.15 mmol) in 16 ml THF was added dropwise n-BuLi in hexane (0.46 ml, 2.39M, 1.10 mmol). The resulting soln was stirred for 15 min, and **18** (103 mg, 0.69 mmol) in 1 ml THF was added dropwise. After 30 min, NH_4Cl aq was added and the aqueous phase extracted with ether. The combined ether extracts were washed with sat NaCl aq, dried (K_2CO_3), and the solvent removed *in vacuo*. Column chromatography (silica gel, 1.5 × 10 cm, 40% CH_2Cl in hexane) gave 98 mg (78%) of **21** as a clear, colorless oil whose structure was established by comparison with a sample of **21** obtained from aldehyde **20**.

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[35]This product ratio was most conveniently analyzed by GC (10-ft × 0.25-in 3% SE-30 on Anakrom 45, column temp 130°, thermal conductivity detector) which showed **31** to be a mixture of two isomers in a ratio of approximately 91:9.