1.70–1.09 (bm, 4 H). IR ($CHCl_3$): 1738, 1452, 1330 cm^{-1}.

The product obtained above (128.6 mg, 0.29 mmol) was dissolved in 7 mL of absolute methanol and cooled to 0 °C. Anhydrous disodium hydrogen phosphate (500 mg, 3.5 mmol) and granulated 6% sodium amalgam (1.5 g) were consecutively added and the mixture was stirred at 0 °C for 1.5 h. The mixture was decanted into 5 mL of pentane, the residue was washed with pentane, and the combined portions were extracted with saturated aqueous ammonium chloride (3 × 30 mL) and dried over anhydrous magnesium sulfate. The solvent was removed by distillation at atmospheric pressure (Vigreux) with the last traces of solvent removed under vacuum for a short time to give 34.7 mg (75%) of 1-carbomethoxy-3-methylcyclohexane as a clear, colorless oil. Analysis of the product by VPC[10e] and coinjection with an authentic sample of (*Z*)- and (*E*)-1-carbomethoxy-3-methylcyclohexane revealed a *Z*:*E* ratio of approximately 55:45.

Alkylation of Lactone 25 with Bis(benzenesulfonyl)methane. As before, lactone **25** (124 mg, 1.0 mmol) and catalyst **2** (69 mg, 0.0598 mmol) were reacted with bis(benzenesulfonyl)methylsodium, prepared from 592 mg (2.0 mmol) of bis(benzenesulfonyl)methane and 76 mg (1.9 mmol) of sodium hydride in 8 mL of THF, for 6 h at reflux. Purification by preparative TLC (50% ethyl acetate in hexane) gave a mixture of alkylated product, bis(benzenesulfonyl)methane, and lactone **25**. The 270-MHz NMR revealed that the alkylated product was a single isomer as evidenced by the appearance of only one singlet at δ 3.67 assigned to the methyl ester protons, and one doublet (J = 1.8 Hz) at δ 4.60 assigned to the bis(benzenesulfonyl)methine proton.

The material prepared above was dissolved in absolute ethanol and hydrogenated over 5% palladium on barium carbonate as described previously. After filtration and removal of the solvent in vacuo, the residue was dissolved in 10 mL of absolute methanol. Anhydrous disodium hydrogen phosphate (700 mg) and granulated 6% sodium amalgam (1.5 g) were added and the mixture was stirred at 0 °C for 30 min. Analysis of the reaction mixture by VPC[10e] and by comparison to an authentic sample of 1-carbomethoxy-3-methylcyclohexane (85% *Z*, 15% *E*) revealed the presence of only the *Z* isomer.

Acknowledgments. We wish to thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of our programs.

Supplementary Material Available: Preparation of methyl benzenesulfonylacetate, **1a**, **1b**, **4**, and **14** (4 pages). Ordering information is given on any current masthead page.

Cyclization Catalyzed by Palladium(0). Initial Studies and Macrolide Formation

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Abstract: The intramolecular reaction of stabilized anions with allylic acetates catalyzed by Pd(0) complexes proceeds with high regioselectivity. Four-, five-, and six-membered carbocyclic rings have been observed. Extension to macrolide formation revealed selective formation of 16-, 14-, 12-, and 10-membered rings over the allylically related isomers possessing 14-, 12-, 10-, and 8-membered rings, respectively. Most surprising was the obtention of only nine and eight membered ring lactones rather than the alternative seven and six membered ring systems. Palladium-catalyzed cyclization reactions do not appear to possess any ring size preferences, thus making the reaction an excellent approach to the noncommon rings. The various factors that affect intra- vs. intermolecular reaction and regio- and stereochemistry are discussed. In the course of these studies, total syntheses of the naturally occurring macrolides exaltolide, recifeiolide, phoracantholide I, and phoracantholide J were achieved. In such applications, removal of the carbomethoxy and benzenesulfonyl groups to create a methylene group employed tetramethylammonium acetate in HMPA and 6% sodium amalgam in alcohol solvents buffered with disodium acid phosphate or acetic acid.

Introduction

The structural elucidation of civetone and muscone as large-ring ketones by Ruzika[1] in 1926 earmarks the origin of macrocyclic chemistry. The previous prediction that these ring structures would be planar and thus severely destabilized due to overextension of the internal bond angles from tetrahedral geometry (von Baeyer strain theory) was replaced by the conception of large rings as nonplanar, flexible, and virtually strain-free structures. Although significant synthetic and theoretical advances were realized in the ensuing years,[2] it was with the isolation of the first macrolide antibiotic, pikromycin, in 1950[3] that the biological potential and synthetic challenge of macrocycles were genuinely appreciated.

The term "macrocycle" broadly refers to medium- (8–11 atoms) and large- (12 or more) ring compounds. The term "macrolide", originally reserved as a description of the large-ring lactone antibiotics isolated from *Streptomyces* organisms, has gradually come to denote that subset of macrocycles which incorporates a lactone moiety. Current efforts have focused primarily on macrolide synthesis.

Naturally occurring macrolides may be conveniently classified according to structural type,[4] with the polyoxo (e.g., pikromycin,[7] erythromycin[8]), polyene (e.g., amphoterian B,[9] tetrin[10]), ionophoric (e.g., nonactin,[11] boromycin[12]), and the lactam-containing ansa

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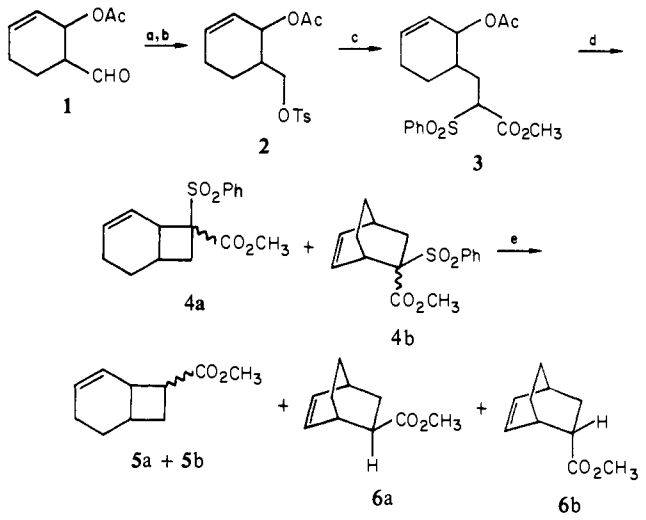
Scheme I. Bicyclo[4.2.0]- and Bicyclo[2.2.20]octene Formation



(a) $NaBH_4$, CH_3OH, 0 °C, 92% crude. (b) TsCl, pyridine, 0 °C, 60% from (a). (c) $PhSO_2CH_2CO_2CH_3$, KH, HMPA, 60–70 °C, 62%. (d) NaH, $(Ph_3P)_4Pd$, THF, reflux, 67%. (e) 6% Na–Hg, Na_2HPO_4, CH_3OH, 0 °C, 92%.

(e.g., maytansine[13]) macrolides being but a few examples from this diverse group.[4-6] Other lactone-containing macrocycles are exemplified by brefeldin A,[14] vermiculine,[15] tricothecane esters,[16] diplodialides,[17] phoracantholides,[18] and zearalenone.[19] Current therapeutic use of some of these compounds and the intensive research into the biological and physiological activities of others clearly attest to their importance. A number of current reviews deal with this subject.[4-6,20-22]

An equally diverse array of large- and especially medium-ring carbocycles has been identified. Among these, the macrocyclic sesquiterpenes[23] (caryophyllanes, humulanes, bazzananes, cyclogermacranes, and germacranes), sesterterpenes (e.g., ophiobolins[23,24]), and diterpenes (e.g., jatrophone,[25] jatrophotrione,[26] and taxus alkaloids[27]) enjoy a wide spectrum of activity. The compounds have been employed as fragrances, exhibited phermonal activity, and been implicated as potentially important antitumor agents.

A general problem associated with the synthesis of macrocyclic natural products has been the efficient construction of medium or large rings, with the methodological approaches broadly categorized into two types: (1) ring expansion or contraction procedures and (2) cyclization of bifunctional acyclic molecules. In the case of macrolides, the latter approach has focused on lactonization reactions.[28] Generation of macrolides by C–C bond formation has been a much rarer approach. A modified Dieckmann procedure employing sodium bis(trimethylsilyl)amide was successfully applied to a synthesis of zearalenone.[29] Intramolecular acylation of an aromatic ring has also been used, both in the case of zealeranone[30] and curvularin.[31,32] Alkylation approaches to macrolides have included a directed aldol cyclization, employing activated zinc and diethylaluminum chloride with α-bromocarboxylate esters,[33] and displacement reactions employing the anions from α-sulfenylated esters or *o*-phenylthiomethylbenzoates with alkyl or allyl halides.[34] Novel approaches involving an intramolecular Diels–Alder reaction[35] or a Claisen rearrangement[36] and an oxidative coupling of an α,ω-diacetylene[37] have also been reported.

At the outset of these investigations, few methods for the construction of medium- or large-ring compounds by carbon–carbon bond formation existed which were sufficiently mild or efficient to allow general entry to the expanding number of complex macrocyclic natural products. This was surprising since the approach appeared attractive from a number of perspectives. The versatility of such a method is immediately obvious since both carbocycles and macrolides would be equally accessible. In regard to macrolide synthesis, a second advantage exists. The preparation of lactones via carbon–carbon bond formation rather than the more conventional lactonization routes potentially provides a greater degree of flexibility in synthetic design. In particular, one may employ a convergent synthetic scheme, thus allowing synthesis of alcohol and acid portions independently which can then be readily condensed, forming the ester linkage prior to ring closure.

The potential for application of palladium-catalyzed allylic alkylations to an intramolecular process appeared particularly exciting. Our earlier investigations revealed the intermolecular reaction to be highly efficient yet mild and chemoselective.[38,39] Successful modification to an intramolecular process would thus provide a cyclization method which may be compatible with relatively sensitive functionality. The rigid conformational requirements imposed by a π-allylpalladium intermediate have been demonstrated to be crucial for assessing reactivity in the intermolecular reaction and may also serve a vital role in the intramolecular reaction. Finally, the high degree of regio- and stereocontrol observed earlier would be of obvious benefit if successfully transferred to an intramolecular process.[40]

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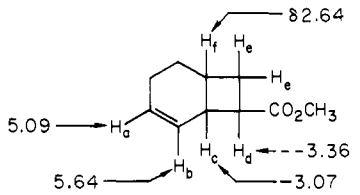
Results

Initial attention focused on allyl acetate **3** (Scheme I), which is available from the Diels–Alder adduct **1**,[41] determined to be 95% *Z* based upon integration of the aldehydic resonances at δ 9.73 (*Z*) and 9.49 (*E*). Reduction of **1** with sodium borohydride and formation of sulfonate ester **2**, followed by nucleophilic displacement with the potassium salt of methyl benzenesulfonylacetate in hexamethylphosphoric triamide, produced the requisite precursor **3**. Use of sodium hydride or other dipolar aprotic solvents (DMF or Me_2SO) for alkylation of **2** was uniformly unsuccessful. The assignment of the *Z* stereochemistry in **3** was based on the unambiguous nature of its synthesis from **1**.

Formation of the anion of **3** with sodium hydride in THF was conducted at elevated temperatures (~60 °C) to ensure complete conversion. Cyclization was then initiated by the addition of tetrakis(triphenylphosphine)palladium(0) (2 mol %) to the mixture with heating at reflux for 4.5 h. After chromatography, a mixture of cyclized products **4a** and **4b** was obtained in 67% yield with the bicyclo[4.2.0]octene derivative (**4a**) predominating. The identical chromatographic properties on silica gel and complexity of the ^1H NMR spectrum for **4a** and **4b** precluded accurate analysis at this stage. For characterization purposes, the mixture of **4a** and **4b** was desulfonylated with buffered 6% sodium amalgam[42] and analyzed by VPC to reveal four separable isomeric products. The two minor isomers (33% combined) were identified as bicyclo[2.2.2]octenes **6a** and **6b** by comparison to authentic samples prepared by the Diels–Alder reaction between 1,3-cyclohexadiene and ethyl acrylate followed by transesterification.[43] The two major isomers (67% combined) were assigned as bicyclo[4.2.0]octenes **5a** and **5b**. The longer retention time isomer

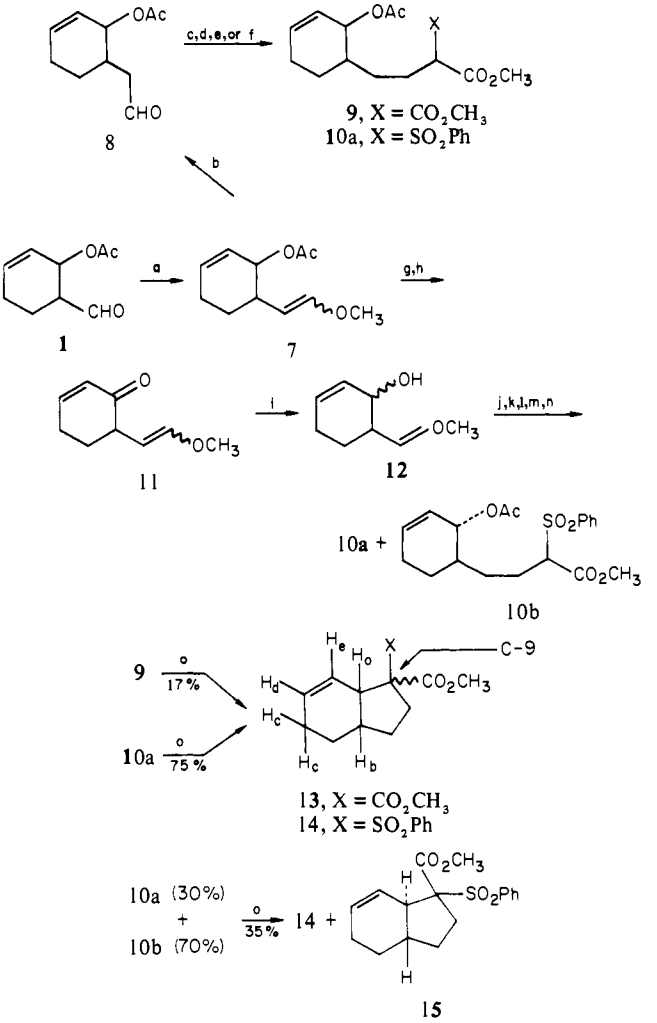


5a

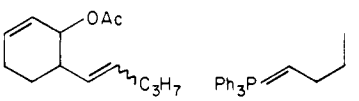
(**5a**) was analyzed at 270 MHz. The contiguous nature of protons a–d could be established through decoupling experiments with J_{ab} = 10, J_{bc} = 4, J_{cd} = 9, and J_{de} = 9 Hz. In particular, irradiation of H_c effects the following perturbations: (1) a sharpening of H_a (d of d of m, *J* = 10, 6 Hz) to a d of d of d (*J* = 10, 5.5, 2.5 Hz), (2) the collapse of H_b (d of m, *J* = 10 Hz) to a broad doublet (*J* = 10 Hz), (3) the collapse of H_d (q, *J* = 9 Hz) to a triplet (*J* = 9 Hz), and (4) a sharpening of the multiplet corresponding to H_f. Isomer **5b**, also isolable by VPC, was contaminated with 18% of structural isomer **6b**. The similarity of the 270-MHz NMR spectrum of **5b** with that of **5a** indicated that this isomer also possessed the bicyclo[4.2.0]octene skeleton. Although **5a** and **5b** are assuredly stereoisomers, the available data do not warrant a stereochemical assignment for each.

Encouraged by the success in cyclization of **3**, we investigated application to the one-carbon homologues **9** and **10** (Scheme II). Homologation of **1** with methoxymethyltriphenylphosphorane (generated with *tert*-butyllithium) produced enol ether **7** in 88% yield. Attempted ylide generation with *n*-butyllithium resulted in isolation of significant quantities of olefin **16**. The requisite phosphorane **17** responsible for this competing reaction was likely generated through displacement of methoxymethide anion by *n*-butyllithium.[44] Acid hydrolysis of the sensitive enol ether with aqueous oxalic acid produced aldehyde **8**, which was converted

Scheme II. Intramolecular Alkylation. Five-Membered-Ring Formation



(a) $CH_3OCH_2PPh_3Cl$, *t*-C_4H_9Li, ether, 0 °C, 88%. (b) Oxalic acid, THF-H_2O, room temperature, 93%. (c) $NaBH_4$, C_2H_5OH, 0 °C, 54%. (d) TsCl, pyridine, 0 °C, 73%. (e) $CH_2(CO_2CH_3)_2$, KH, HMPA, 50–60 °C, 88%. (f) $PhSO_2CH_2CO_2CH_3$, NaH, HMPA, 50 °C, 95%. (g) 20% aq NaOH-THF-C_2H_5OH, room temperature 96% crude. (h) $C_5H_5NH^+$-$ClCrO_3^-$, NaOAc, CH_2Cl_2, room temperature 62%. (i) $LiAlH_4$, ether, 0 °C. (j) Ac_2O, NaH, 60 °C, 66%. (k) Same as (b), 99% crude. (l) Same as (c), 99% crude. (m) Same as (d), 82% crude. (n) Same as (f), 50% from (k). (o) NaH, $(Ph_3P)_4Pd$, THF, reflux.



16 17

to cyclization precursors **9** and **10a** via the same sequence employed for the preparation of **3**. As before, the *Z* orientation was based on the unambiguous method of synthesis. Additionally, a 100-MHz NMR comparison of *Z* isomer **10a** with the subsequently synthesized *E* derivative **10b** (vide infra) indicated isomeric homogeneity.

Cyclization of the sodium anion of **9** in refluxing tetrahydrofuran with 5.4 mol % palladium catalyst afforded a 17% isolated yield of **13**, determined to be homogeneous by NMR and VPC analysis. At 270 MHz, the bicyclo[4.3.0]nonene skeleton was clearly evidenced by the multiplicity of the olefinic resonances at δ 5.73 (d of t of d, *J* = 10.2, 3.6, 2.3 Hz) and 5.40 (d of d of t, *J* = 10.2, 3.6, 2.0 Hz). This indicated the presence of three

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(42) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
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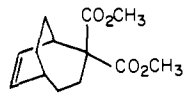
allylic protons, thus eliminating the possibility of regioisomer **18**.[45]



18

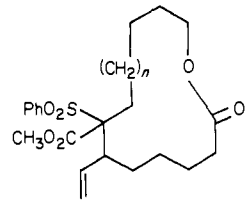
Indeed, irradiation at δ 3.3 (H_a, Scheme II) collapsed the olefin resonances [5.73 (d of t, J = 10.2, 3.7 Hz), and 5.40 (d of t, J = 10.2, 2 Hz)] as expected. Removal of the homoallylic coupling[46] (J_{ac}) by irradiation at δ 1.86 simplified H_a sufficiently to allow extraction of coupling constant data (J_{ab} = 7, J_{ad} = 2.3, J_{ae} = 3.6 Hz), with the magnitude of J_{ab} being more consistent with a Z ring fusion (J_{ax-eq}) than the E stereochemistry (J_{ax-ax}).[46b]

Cyclization of **10a** by slow addition of the derived sodium anion (in tetrahydrofuran) to a refluxing solution of the palladium catalyst provided a 75% yield of **14** as a mixture of two diastereomers (at C-9), as evidenced by the four olefinic resonances [δ 6.27 (bd, J = 10 Hz, 0.25 H), 5.94 (d of d of t, J = 10, 5, 2.5 Hz, 0.25 H), 5.74 (d of m, J = 10 Hz, 0.75 H), and 5.30 (d of d of t, J = 10, 4, 2 Hz, 0.75 H)]. The Z hydrindan structural assignment was based on analogy to **13**, although it was not rigorously proven.

Further investigations, employing a Z-E isomeric mixture of **10**, revealed certain stereochemical limitations in this intramolecular process. A mixture of **10**, enhanced in the E isomer, was synthesized by reduction of enone **11** to give an epimeric mixture of allyl alcohols **12** (70% E, 30% Z) which was converted to **10a** and **10b** as outlined. Cyclization led to a product which differed only slightly from that obtained by cyclization of pure Z isomer **10a**. Two new olefinic resonances at δ 5.50 (d of m, J = 10 Hz) and 5.40 (bd, J = 10 Hz) were tentatively assigned to the E-fused hydrindan **15**, although further substantiative data are lacking. Integration provided a Z:E ratio of 85:15.

Our success in cyclizations to normal rings prompted further exploration and our attention focused on macrolide synthesis. Scheme III outlines the route developed toward 14- and 16-membered macrolides and the conversion of the latter to exaltolide. The preparation of carboxylic acid **22** was accomplished from hydroxy ester **19** (prepared by the method of Brown).[47] Oxidation with pyridinium chlorochromate[48] and Grignard addition followed by hydrolysis afforded hydroxy acid **21**. Acylation with acetic anhydride in pyridine completed the sequence.

The requisite alcohols **24** and **26** could be conveniently prepared from THF and 1,6-hexanediol, respectively. Thus, ether cleavage of THF with hydrogen chloride[49] and tetrahydropyranylation of the resulting chlorohydrin produced chloride **23**. In similar fashion, monoprotection of 1,6-hexanediol with dihydropyran and conversion of the remaining alcohol moiety into its p-toluenesulfonate ester afforded **25**. Treatment of both **23** and **25** with the sodium anion of methyl benzenesulfonylacetate followed by deprotection provided the requisite alcohol portions **24** and **26**. Conversion of **22** to its acid chloride and condensation with the alcohols led to the desired cyclization substrates, which were converted to their anions with sodium hydride in tetrahydrofuran, and the resulting solutions were added via a syringe pump to a refluxing solution of 2–6 mol % palladium(0) catalyst. In this manner, macrolides **29** and **30** (mp 105–106 °C) were obtained in 49 and 69% yields as the sole isolable products after chromatography. Analysis of the crude reaction mixture by NMR confirmed the regioselectivity. The lack of resonance signals in the regions of δ 4.8–5.2 and 5.8–6.2, characteristic of a terminal vinyl group, confirms the absence of regioisomers **31** and **32** which would have resulted from



31, n = 1
32, n = 3

alkylation at the allylically related carbon. The presence of dimeric or higher oligomeric products was not detected in the mass spectra of the chromatographed material. However, the total absence of these products in the reaction mixture could not be conclusively proven since the complex NMR spectra exhibited by material(s) isolated at lower R_f values than those of **29** or **30** could not be adequately interpreted.

Assignment of the olefin stereochemistry in cyclized products **29** and **30**, as well as final verification of overall structure, was based upon 270-MHz NMR analysis and chemical conversion to known derivatives. Thus, the E stereochemistry in tridecanolide **29** was established by observance of a 15-Hz coupling constant for the olefinic protons (δ 5.79 and 5.56). The Z isomer was not observable by ^{1}H NMR but was evidenced by ^{13}C NMR through a number of low-intensity signals. That these signals corresponded to geometrical isomers and not structural isomers was subsequently confirmed by hydrogenation to a homogeneous product. Further characterization by decarbomethoxylation[50] to **33** (mp 110–112.5 °C) and desulfonylation[42] to **35** (mp 25–33 °C) allowed ready establishment of the isomeric ratio. In **35**, integration of two triplets (J = 5 Hz) at δ 4.05 (E isomer) and 4.15 (Z isomer) assigned as the C-13 methylene protons provided an E:Z ratio of 75:25. Further, irradiation at δ 2.0 decoupled the olefinic region of the spectrum sufficiently to permit detection of a resonance at δ 5.26 (d, J = 10.8 Hz) assigned to the Z isomer. Hydrogenation of **35** established the stereoisomeric nature of the two isomers by producing a homogeneous (^{1}H NMR, ^{13}C NMR, TLC) macrolide **37** (mp 24–26 °C) whose melting point was identical with the literature value.[51] In pentadecenolide **30**, the nearly exclusive E geometry was confirmed with the observance of two major olefin resonances at δ 5.56 (d of t, J = 15, 6.5 Hz) and 5.43 (d of t, J = 15, 7 Hz). A minor signal (~5%) at δ 5.29 (d of t, J = 11.5, 7.5 Hz) which collapsed to a doublet (J = 11.5 Hz) upon irradiation at δ 2.80 was tentatively assigned to the Z isomer. Again, subsequent hydrogenation to a homogeneous product indicated that this minor product was not a structural isomer. Decarbomethoxylation to **34** (mp 91.5–92 °C), followed by reduction of the sulfone moiety, gave the waxy solid **36** (mp 46–48 °C). Hydrogenation produced exaltolide (**38**, mp 33–35 °C),[51] the fragrant constituent in angelica root oil.

With a demonstrated ability for macrolide formation (14- and 16-membered rings) via palladium-catalyzed intramolecular allylic alkylation, emphasis shifted toward a more general determination of the scope and limitations of this method. Medium-ring compounds (7- to 12-membered rings) appeared to be attractive targets for a variety of reasons. Current cyclization methods are less effective when applied to medium-ring formation (especially eight- to ten-membered rings) in comparison to the higher homologues. The effect of ring size on the regioselectivity of alkylation could thus be tested and compared with the known ring-size preferences

(45) For NMR spectral data on some bicyclo[3.2.2]nonenes similar to **18**, see: Alfaro, I.; Ashton, W.; Rabone, K. L.; Rogers, N. A. J. *Tetrahedron* **1974**, *30*, 559.

(46) For a discussion of allylic and homoallylic coupling see: (a) Chow, Y. L.; Streith, J.; Taurand, G. *Org. Magn. Reson.* **1973**, *5*, 155. (b) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; p 316.

(47) Yoon, N.-M.; Pak, C.-S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786.

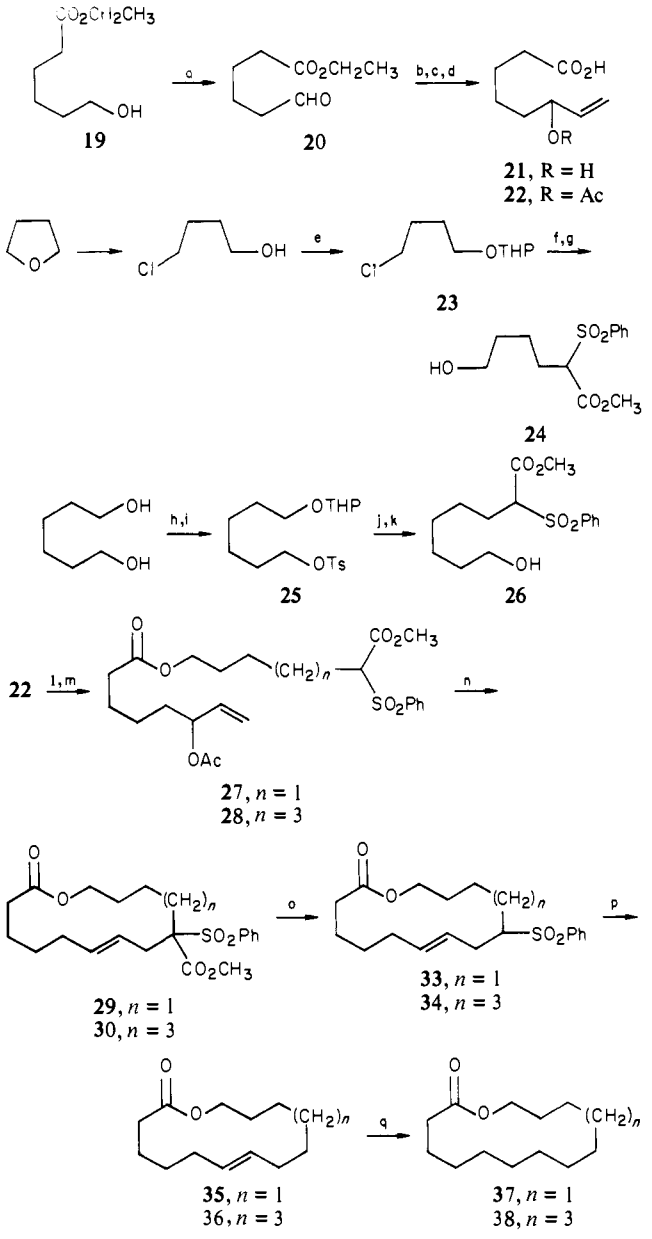
(48) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(49) Starr, D.; Hixon, R. M. "Organic Syntheses", Collect. Vol. II; Wiley: New York, 1943; p 571.

(50) A modification of the procedure of Johnson et al. was employed. Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188. For an excellent discussion of this type of reaction see: Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138. For a review see: McMurry, J. E. *Org. React.* **1977**, *24*, 187.

(51) Ruzicka, L.; Stolle, M. *Helv. Chim. Acta* **1928**, *11*, 1159.

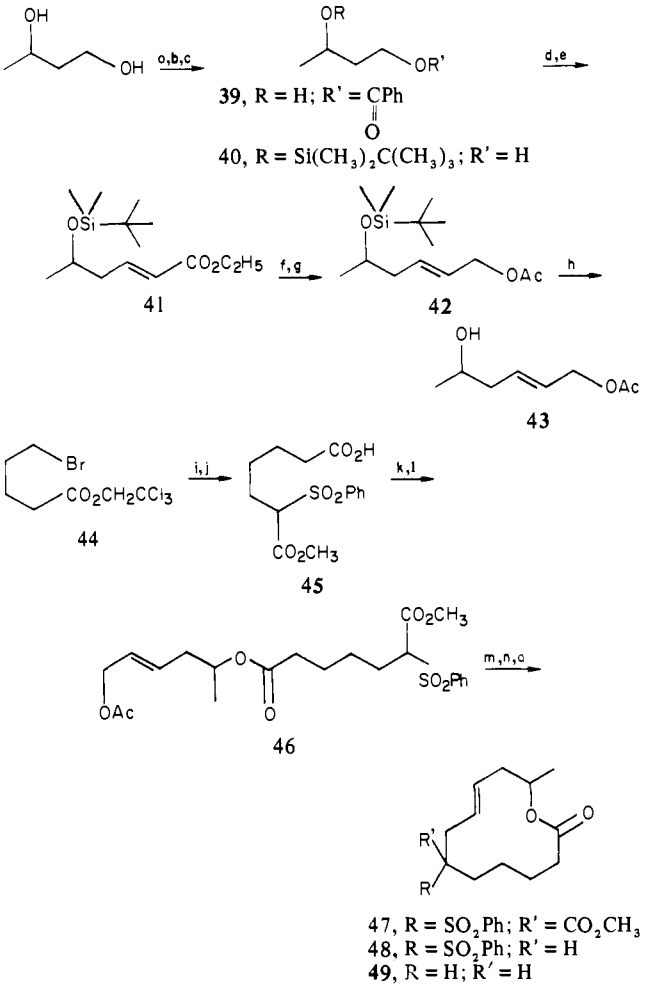
Scheme III. Macrolide Formation. Fourteen- and Sixteen-Membered Rings



(a) $C_5H_5NH^+$-$ClCrO_3^-$, NaOAc, room temperature, 75%. (b) CH_2=$CHMgBr$, THF, 0 °C, 71%. (c) KOH, 50% aq C_2H_5OH, room temperature, 91%. (d) Ac_2O, pyridine, room temperature, 60%. (e) DHP, CH_2Cl_2, TsOH, 0 °C, 83%. (f) $PhSO_2CH_2CO_2CH_3$, NaH, NaI, DMF, 100 °C. (g) AcOH-THF-H_2O, room temperature, 50% from f. (h) Same as e, 38%. (i) TsCl, pyridine, 0 °C, 93%. (j) Same as (f), 60 °C. (k) Same as (g), 69% from (j). (l) $SOCl_2$, ether, reflux. (m) **24** or **26**, $(C_2H_5)_3N$, ether, 50 °C, 84 or 94%. (n) NaH, THF, $(Ph_3P)_4Pd$, reflux, 49% for n = 1, 69% for n = 3. (o) $(CH_3)_4N^+$ OAc^-, HMPA, 90–95 °C, 76% for n = 1, 83% for n = 3. (p) 6% Na-Hg, Na_2HPO_4, THF, C_2H_5OH, −20 °C, 69% for n = 1, 89% for n = 3. (q) H_2, Pd-$BaCO_3$, 2 atm, room temperature, 98% for n = 1, 99% for n = 3.

observed with other cyclization methods. A question unanswered in cyclization studies on substrates **27** and **28** concerns the factors responsible for determining olefin geometry in the cyclized product. Earlier studies in the intermolecular reaction indicated that total or partial retention of original olefin geometry was possible based upon the degree of substitution at the double bond. Comparison of this behavior with the intramolecular variant would be instructive from both a synthetic and mechanistic viewpoint. With these considerations, synthesis of the 12-membered-ring lactone (±)-recifeiolide (**49**), a naturally occurring macrolide isolated from

Scheme IV. Synthesis of (*E*)-11-Hydroxy-8-dodecenoate Lactone [(±)-Recifeiolide]



(a) PhCOCl, pyridine, 0 °C, 91%. (b) $(t\text{-}C_4H_9)(CH_3)_2SiCl$, imidazole, DMF, 0 °C-room temperature, 99%. (c) 20% aq NaOH, THF, CH_3OH, 95%. (d) $C_5H_5NH^+$-$ClCrO_3^-$, NaOAc, room temperature. (e) $(C_2H_5O)_2POCH_2CO_2C_2H_5$, NaH, THF, −78 °C. (f) DIBALH, toluene, 0 °C. (g) CH_3COCl, pyridine, CH_2Cl_2, 0 °C. (h) $HClO_4$, THF-H_2O, room temperature, 53% from (d). (i) $PhSO_2CH_2CO_2CH_3$, NaH, Me_2SO, 50 °C. (j) Zn, DMF, 0 °C, 84% from (i). (k) $SOCl_2$, cat. DMF. (l) **43**, pyridine, ether, 79% from (k). (m) NaH, THF, $(Ph_3P)_4Pd$, Diphos, reflux, 78%. (n) $(CH_3)_4N$ OAc, HMPA, 95–100 °C, 86%. (o) 6% Na-Hg, Na_2HPO_4, THF-C_2H_5OH, −20 °C, 94%.

the fungus *Cephalosporium recifei*,[52] was undertaken.[34a,53]

The synthetic approach is outlined in Scheme IV. Alcohol portion **43** was readily synthesized from 1,3-butanediol. Thus, treatment with benzoyl chloride at 0 °C effected selective acylation of the primary alcohol to give **39**. Silylation with *tert*-butyldimethylsilyl chloride followed by base hydrolysis afforded silyl ether **40**. Oxidation of **40** followed by an Emmons–Wadsworth–Horner condensation[54] afforded α,β-unsaturated ester **41**. The expected *E* stereochemistry was clearly discernible by the magnitude of the coupling constant (J = 15.3 Hz) between the two olefinic

(52) Vesonder, R. F.; Stodola, F. H.; Wickerham, L. J.; Ellis, J. J.; Rohwedder, W. K. *Can. J. Chem.* **1971**, *49*, 2029. Vesonder, R. F.; Stodola, F. H.; Rohwedder, R. W. *Can. J. Biochem.* **1972**, *50*, 363.

(53) Corey, E. J.; Ulrich, P.; Fitzpatrick, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 222. Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755. Narasaka, K.; Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 959. Utimoto, K.; Uchida, K.; Yamaya, M.; Nozaki, H. *Tetrahedron Lett.* **1977**, 3641. Tsuji, J.; Yamakawa, T.; Mandai, T. *Ibid.* **1978**, 565. Yoshida, J.; Tamao, K.; Takahashi, M.; Kumada, M. *Ibid.* **1978**, 2161.

(54) Wadsworth, W. S., Jr. *Org. React.* **1978**, *25*, 73.

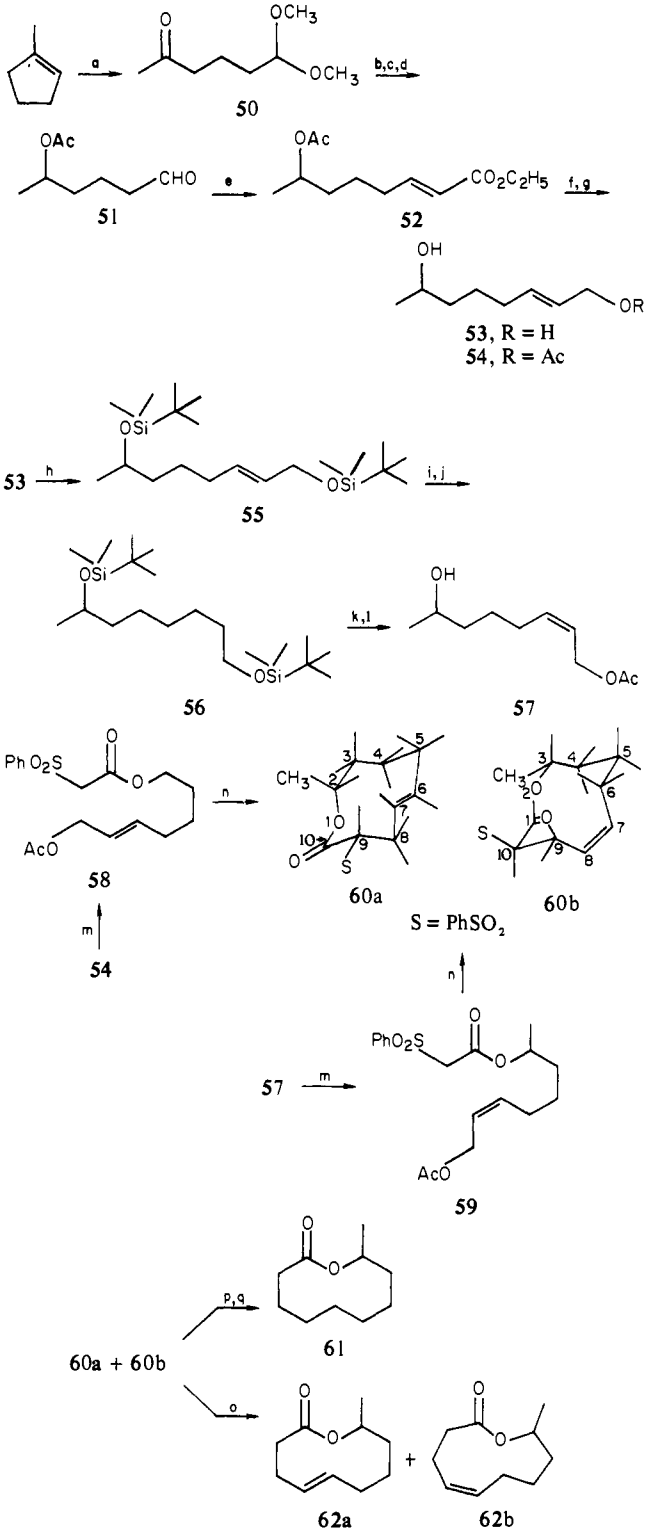
protons in **41**. Ester reduction, followed by acylation, provided acetate **42**, which upon hydrolytic cleavage of the silyl ether with aqueous perchloric acid afforded the requisite alcohol portion **43** in 53% isolated yield from **40**. Again, the *E* stereochemistry was evident by the olefinic resonances at δ 5.77 (d of t of t, J = 15.5, 7, 1 Hz) and 5.59 (d of t of t, J = 15.5, 6.3, 1 Hz). Acid portion **45** was available in two steps from the β,β,β-trichloroethyl ester of 5-bromopentanoic acid, **44**. Alkylation of the sodium salt of methyl benzenesulfonylacetate in hot dimethyl sulfoxide and reductive hydrolysis[55] provided acid **45** in 84% yield. Conversion of **45** to its acid chloride and condensation with alcohol **43** produced the cyclization precursor **46** in 79% yield.

Conversion of **46** to the anion with sodium hydride, and slow addition to a solution of 9 mol % palladium(0) catalyst as described before, produced only the 12-membered-ring lactone **47** (mp 126–129 °C) in 78% yield. Examination of the NMR spectrum at 270 MHz revealed an *E* olefin (J = 15.5 Hz) and the absence of a terminal vinyl group. The absence of oligomeric products in the chromatographed product was demonstrated by mass-spectral analysis. No signals at higher mass than the molecular ion of the monomer were observed. Final proof of structure derives from the successful completion of this synthesis. Thus, decarbomethoxylation to **48** and reductive desulfonylation gave (±)-recifeiolide (**49**), identical by spectroscopic (IR, NMR, MS)[56] and chromatographic (TLC, VPC) criteria with the major constituent of an authentic sample.[56] The authentic sample[56] contained 15% of the *Z* isomer which was observable as a second methyl doublet at δ 1.28 (*E* isomer occurs at δ 1.24). This resonance was completely absent in our synthetic **49**. Thus, exclusive cyclization at the less substituted position of the allyl unit was observed with substrates **27**, **28**, and **46**. Noteworthy is the complete retention of olefin geometry during cyclization of **46**.

To further explore the olefin stereochemistry and the regioselectivity of this cyclization as a function of ring size, a study was initiated directed toward the synthesis of (±)-phoracantholide I and J (**61** and **62b**), two ten-membered-ring lactones isolated from the metasternal secretion of the eucalypt longicorn, *Phoracantha synonyma*.[18,34a,36,57] The isomeric allyl acetates, **54** and **57**, were prepared as outlined in Scheme V. Ozonolysis of 1-methylcyclopentene in the presence of excess methanol and reductive workup with dimethyl sulfide afforded keto acetal **50**. After ketone reduction and acylation of the resulting alcohol, acid hydrolysis of the acetal produced aldehyde **51**[57a] in good yield. The *E* olefin was established by an Emmons–Wadsworth–Horner olefination[54] to give α,β-unsaturated ester **52** in 60% isolated yield starting from 1-methylcyclopentene. Treatment with excess diisobutylaluminum hydride afforded diol **53**, which was selectively acylated at low temperature (−15 °C) with acetic anhydride in pyridine to produce **54** in 69% yield. Analysis at 270 MHz established the *E* stereochemistry (δ 5.77, d of t of t, J = 15.3, 6.3, 1 Hz; 5.56, d of t of t, J = 15.3, 6.3, 1 Hz) in the major isomer. Observance of a low-intensity doublet (J = 6 Hz) at δ 4.62 was assigned to the allylic methylene protons in the *Z* isomer based upon comparison with a subsequently synthesized sample (vide infra). Integration of this resonance with the corresponding resonance of the *E* isomer (δ 4.50, d, J = 6 Hz) indicated an *E*:*Z* ratio of greater than 98:2.

The *Z* isomer, **57**, could be conveniently prepared via the olefin inversion procedure of Vedejs and Fuchs on disilyl ether **55**.[58]

Scheme V. Synthesis of Phoracantholide I and J



(a) O_3, CH_2Cl_2–CH_3OH, −78 °C, CH_3SCH_3. (b) $NaBH_4$, C_2H_5OH, 93% from (a). (c) AcCl, pyridine, CH_2Cl_2, 0 °C. (d) 10% aq HCl, CH_2Cl_2, room temperature, 75% from (c). (e) $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, NaH, THF, −78 to 0 °C, 85%. (f) DIBALH, toluene, 0 °C, 95%. (g) Ac_2O, pyridine, CH_2Cl_2, −15 °C, 69%. (h) t-$C_4H_9Si(CH_3)_2Cl$, imidazole, DMF, room temperature, 86%. (i) MCPBA, CH_2Cl_2–aq $NaHCO_3$, room temperature. (j) $LiPPh_2$, THF, room temperature, CH_3I, 23%. (k) $HClO_4$, THF–H_2O, room temperature, 77%. (l) Same as (g), 85%. (m) $PhSO_2CH_2CO_2H$, **54** or **57**, Ph_3P, $(=NCO_2C_2H_5)_2$, toluene, 87 or 83%. (n) NaH, $(Ph_3P)_4Pd$, Diphos, THF, reflux, 88% from **58**, 80% from **59**. (o) 6% Na–Hg, Na_2HPO_4, C_2H_5OH (abs), −20 °C 87–90%. (p) H_2, 5% Pd–$BaCO_3$, C_2H_5OH(abs), 2 atm, room temperature, 88%. (q) Same as (o), 95%.

(55) Chauvette, R. R.; Pennington, P. A.; Ryan, C. W.; Cooper, R. D. G.; Jose, F. L.; Wright, I. G.; Van Heyningen, E. M.; Huffman, G. W. *J. Org. Chem.* **1971**, *36*, 1259.

(56) An authentic sample was generously supplied by H. Gerlach, ETH, Zurich, and NMR and mass-spectral data by E. J. Corey, Harvard University, Cambridge, Mass.

(57) (a) Ishida, T.; Wada, K. *J. Chem. Soc., Chem. Commun.* **1977**, 337. For an alternative approach to the *tert*-butyldimethylsilyl ether related to **51** see: Luthy, C.; Konstantin, P.; Untch, K. G. *J. Am. Chem. Soc.* **1978**, *100*, 6211. (b) Wakamatsu, T.; Akasaka, K.; Ban, Y. *Tetrahedron Lett.* **1977**, 2755. (c) Tsuji, J.; Mandai, T. *Ibid.* **1978**, 1817. (d) Gerlach, H.; Kunzler, P.; Oertle, K. *Helv. Chim. Acta* **1978**, *61*, 1226. (e) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096.

(58) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822.

Indeed, the *Z* stereochemistry of inverted olefin **56** was clearly discernible at 270 MHz with the observance of olefin resonances at δ 5.52 (d of t of t, J = 11, 6, 1.5 Hz) and 5.42 (d of t of t, J = 11, 7, 1.5 Hz). Hydrolysis of the silyl ether protecting groups and selective acetylation as previously described produced acetate **57**. NMR comparison of this sample with the corresponding *E* isomer **54** by integration of the two allylic methylene doublets at δ 4.50 (*E*) and 4.62 (*Z*) provided a *Z*:*E* ratio of 98:2.

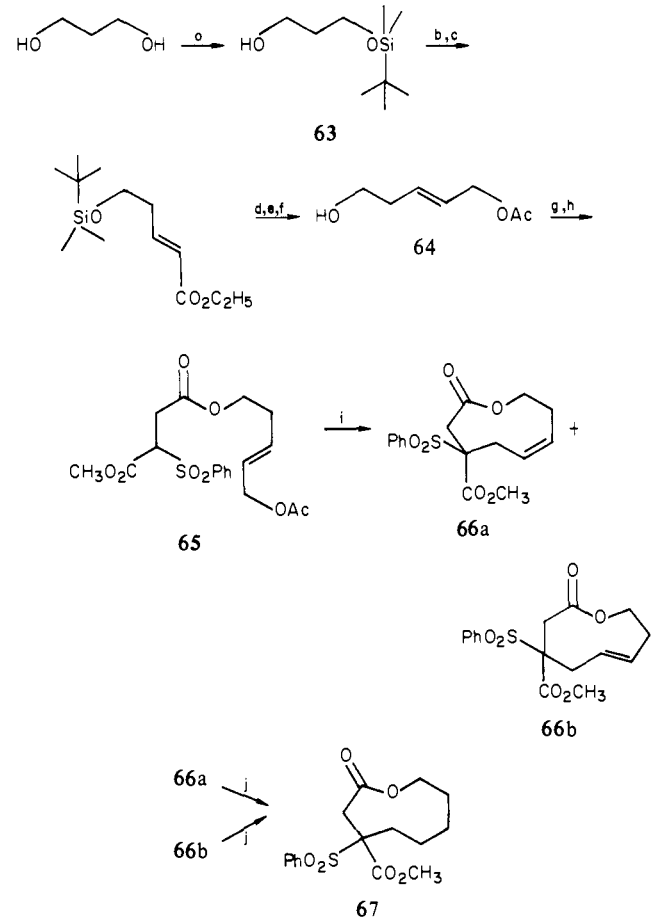
Both hydroxy acetates **54** and **57** were esterified with benzenesulfonylacetic acid by a reverse activation procedure[59] to afford cyclization substrates **58** and **59**. In both cases, slow addition of the corresponding sodium anions to the palladium(0) catalyst in the presence of 1,2-bis(diphenylphosphino)ethane (Diphos) led to an isomeric mixture (*E*, *Z* *R*R**, and *S*R**) of cyclization products **60a** and **60b** in 88% yield. The lack of absorptions at δ 5.5–5.0 for a monosubstituted olefin suggested the absence of eight-membered rings. Desulfonylation removed one site of asymmetry and produced the readily separable (VPC) and analyzable (270-MHz NMR) lactones **62a** and **62b**.

The *Z* isomer, **62b**, was identified as phoracantholide J via mass-spectral and NMR comparison to an authentic sample.[57d,60] The *Z* stereochemistry was readily discerned by the olefinic resonances at 270 MHz (δ 5.46, t of d of d, J = 11, 5.5, 2 Hz; 5.35, t of d, J = 11, 4 Hz). In identical fashion, the *E* stereochemistry in isomer **62a** was also assigned (δ 5.42, d of d of d, J = 15, 9.5, 4.5 Hz; 5.28, d of d of d, J = 15, 10.5, 4 Hz).[61] Substantiation of the stereoisomeric nature of **62a** and **62b** was accomplished by hydrogenation of the olefins to produce a homogeneous product (vide infra). The ratios of **62a**:**62b** were 88:12 from **58** and 65:35 from **59**. Thus, in contrast to the 12-membered-ring case, substantial loss of olefin geometry accompanied these cyclizations. Noteworthy is the higher percentage of *Z* isomer obtained in cyclization of **59** in comparison to the reaction with **58**. This partial retention of original olefin geometry in the intramolecular process is similar to observations made for the intermolecular reaction. Final confirmation of structure arose from catalytic hydrogenation of a mixture of **60a** and **60b** followed by desulfonylation to give (±)-9-hydroxydecanoate lactone **61** (phoracantholide I) as the sole product, whose spectral properties agree with those of an authentic sample.[57d,60]

While palladium-induced cyclization of **58** and **59** produced the ten-membered ring with exclusion of eight-membered-ring products, this ring-size preference would also be anticipated in simple cyclizations. On the other hand, in intramolecular displacements, an approximate rate factor of 10^3 exists in favor of a seven-membered ring compared to a nine-membered ring.[62] Since these reactions can be viewed as displacements with palladium as the leaving group, similar factors should be applicable here. Thus, the regioselectivity might switch in such competition. Substrate **65** tests this idea (Scheme VI).

Beginning with *tert*-butylsilyl ether **63** (obtained from 1,3-propanediol) requisite allyl acetate **64** was prepared in an analogous fashion as described for the preparation of **43** (Scheme IV). The *E* stereochemistry was again elucidated by 270-MHz NMR spectroscopy (δ 5.79, d of t, J = 15.3, 6.6 Hz; 5.65, d of t, J = 15.4, 5.9 Hz), with a minor (5–7%) doublet at δ 4.62 (J = 5.7 Hz) tentatively assigned to the acetate-bearing allylic methylene protons in the *Z* isomer. Condensation of alcohol **64** with bromoacetyl bromide and alkylation with methyl benzenesulfonylacetate in dimethylformamide afforded cyclization substrate **65** in 62% yield. Unexpectedly, cyclization of **65** produced only

Scheme VI. Synthesis of Octan-8-olides



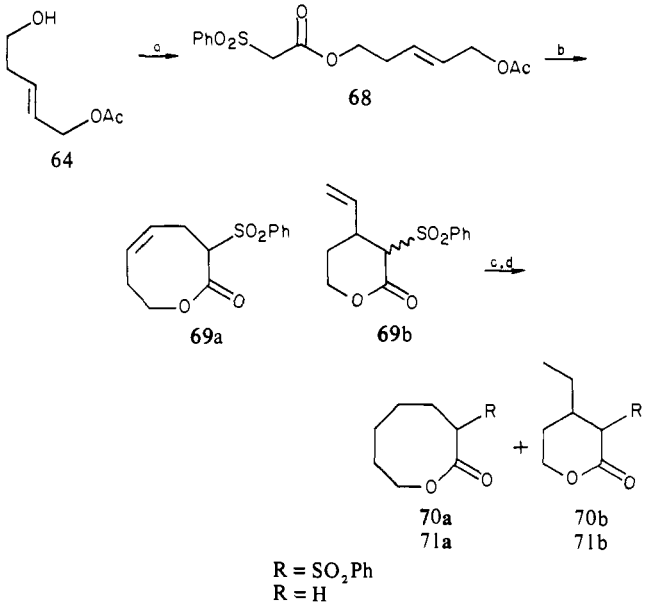
(a) t-$C_4H_9(CH_3)_2SiCl$, imidazole, DMF, −25 to 0 °C, 86%. (b) C_5H_5NH-$ClCrO_3$, NaOAc, CH_2Cl_2, room temperature. (c) $(C_2H_5O)_2POCH_2CO_2C_2H_5$, NaH, THF, −78 °C, room temperature. (d) DIBALH, toluene, 0 °C. (e) AcCl, pyridine, CH_2Cl_2, 0 °C. (f) $HClO_4$, THF–H_2O, room temperature, 39% from (b). (g) $BrCH_2COBr$, pyridine, CH_2Cl_2, 0 °C. (h) NaH, $PhSO_2CH_2CO_2CH_3$, DMF, 0 °C, 62% from (g). (i) NaH, $(Ph_3P)_4Pd$, THF, reflux. (j) H_2, 5% Pd-$BaCO_3$, C_2H_5OH(abs), 2 atm, room temperature, 82% for **66a**, 91% for **66b**.

nine-membered-ring lactones **66a** and **66b** which were separated by TLC (25% ethyl acetate in hexane; **66b** R_f 0.35; **66a** R_f 0.28, mp 125–126 °C). That the two compounds represent double-bond isomers was demonstrated by their catalytic hydrogenation to give the same compound **67**. The singularity of resonances in the 270-MHz ^1H NMR and ^{13}C NMR as well as the mass spectra (no fragments above M^+) was highly indicative of a monomeric structure.

Further structural and stereochemical assignment of **66a** and **66b** was facilitated by NMR spectroscopy. At 270 MHz (ambient probe temperature), cyclization product **66b** is clearly observed as a mixture of two diastereomers; this dissymmetry arising from the chirality at C-3 and the *E* olefin in a medium ring has been previously observed and is a consequence of restricted rotation of the plane of the sp^2-hybridized bonds due to incurrence of ring strain and severe nonbonded interactions of the olefinic hydrogen atoms with other ring substituents.[63,64] Cope found that the energy of activation for the racemization of (*E*)-cyclononene was 20 ±

(59) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.
(60) The mass-spectral data were supplied by B. P. Moore, CSIRO, Division of Entomology, Canberra, Australia.
(61) A sample of the *E* isomer was sent to Dr. B. P. Moore, CSIRO, who informed us that it is absent from the metasternal secretion.
(62) (a) Galli, C.; Illuminati, G.; Mandolini, L. *J. Am. Chem. Soc.* **1973**, *95*, 8374. (b) Illuminati, G.; Mandolini, L.; Masci, B. *Ibid.* **1974**, *96*, 1422. (c) *J. Org. Chem.* **1974**, *39*, 2598. (d) Galli, C.; Mandolini, L. *Gazz. Chim. Ital.* **1975**, *105*, 367. (e) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1975**, *97*, 4960. (f) Galli, C.; Mandolini, L. *J. Chem. Soc., Perkin Trans. 2* **1977**, 443. (g) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591.
(63) Cope, A. C.; Banholzer, K.; Keller, H.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644. Cope, A. C.; Fordice, M. W. *Ibid.* **1967**, *89*, 6187.
(64) For other examples of this phenomenon see: (a) Binsch, G.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 5157. (b) Whitesides, G. M.; Pawson, B. A.; Cope, A. C. *Ibid.* **1968**, *90*, 639. Reese, C. B.; Shaw, A. *Chem. Commun.* **1970**, 1367. Vedejs, E.; Arco, M. J.; Renga, J. M. *Tetrahedron Lett.* **1978**, 523. Loozen, H. J. J.; de Haan, J. W.; Back, H. M. *J. Org. Chem.* **1977**, *42*, 418.

Scheme VII. Synthesis of Heptan-7-olides

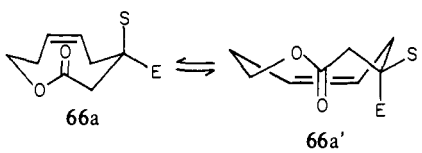


(a) $PhSO_2CH_2CO_2H$, Ph_3P, $C_2H_5O_2CN{=}NCO_2C_2H_5$, toluene, 51%. (b) NaH, $(Ph_3P)_4Pd$, Diphos, THF, reflux, 73%. (c) H_2, 5% Pd-$BaCO_3$, C_2H_5OH(abs), 98%. (d) 6% Na-Hg, HOAc, C_2H_5OH, −20 °C, 52%.

2 kcal mol^{-1}, and estimated the half-life for this process as 6 s at 30 °C.[63] Thus, although the equilibration of diastereomers would be expected to occur rapidly at room temperature, this interconversion rate is slow enough on the NMR time scale to allow the spectra of the distinct diastereomers to be recorded. Indeed, the observance of four olefinic resonances at δ 5.48 (d of d of d, J = 15.8, 10, 5.9 Hz), 5.41 (d of d of d, J = 15.8, 10.4, 5.3 Hz), 5.23 (d of d of d, J = 15.8, 10.3, 4.3 Hz), and 5.12 (d of d of d, J = 15.8, 11.2, 3.5 Hz) confirmed the presence of both the nine-membered ring and *E* olefin.

The NMR spectrum of **66a** also exhibited a temperature dependency. At ambient probe temperature the sample was near coalescence, but upon warming to 76 °C a time-averaged spectrum was obtained in which the *Z* olefin geometry could be deduced by the two olefinic resonances at δ 5.63 (d of t, J = 11, 8.6 Hz) and 5.38 (d of t of t, J = 11, 8.3, 1 Hz). Cooling to −43 °C retarded conformational interconversion sufficiently to permit observance of two conformers (methyl ester resonances at δ 3.81 and 3.77) in an approximate ratio of 7:3. A high barrier for conformational interconversion is not uncommon for rigid, highly nonplanar cycloalkanes.[65] For instance, the barrier for ring inversion for 1,1,4,4-tetramethylcyclononane is ≃20 kcal/mol[66] and for (*Z*,*Z*,*Z*)-1,4,7-cyclononatriene is 15.5 kcal/mol.[67] By analogy to the restricted rotation observed for isomer **66b**, hindered rotation about a transoid ester may account for the relatively slow rate of conformational interconversion.[68]

A remarkable influence on both the yield and stereoselectivity in cyclization of **65** was incurred through addition of Diphos (equimolar with palladium). An improvement in the overall yield (from 29 to 60) and a variation in the ratio of **66a**:**66b** from 76:24 (without Diphos) to 91:9 (with Diphos) were noted. Subsequent work (vide infra) further substantiated this observation as a general trend.



Scheme VII illustrates a more severe test for cyclization preferences since six-membered-ring formation is kinetically favored by an approximate factor of 10^4 over an eight-membered ring.[62] Treatment of **68** under the usual cyclization conditions (in the presence of Diphos) gave hepten-7-olide **69a** (mp 87.5–89 °C) as the vastly major product with only a trace (6% by NMR integration) of the six-membered lactone **69b**. The latter was detected in the product mixture by NMR signals for the monosubstituted olefin at δ 5.21 (d of m, J = 10.3 Hz) and 5.18 (d of m, J = 17.1 Hz). The *Z* olefin geometry in **69a** was apparent at 270 MHz (δ 5.88, d of t of d, J = 11, 7.8, 1.2 Hz; 5.71, d of d of d of d, J = 11, 9.3, 7.4, 1.4 Hz). No evidence for dimeric products was observed by mass-spectral analysis of **69** or **71**. The overall yield of **69a** and **69b** was 73%. This shocking preference for cyclization to the eight-membered ring was confirmed by correlating **69** (NMR, IR, VPC) with the parent heptanolide **71a**, an authentic sample of which was independently synthesized by Baeyer–Villiger rearrangement of cycloheptanone.[69] Observance of a small triplet (~7%) at δ 0.98 (J = 7.5 Hz) upon hydrogenation of **69** confirmed the presence of an ethyl group for regioisomer **70b**. The lability of the eight-membered-ring lactone[68] made desulfonylation rather tricky until the discovery that buffering the reaction medium with acetic acid alleviated this problem.

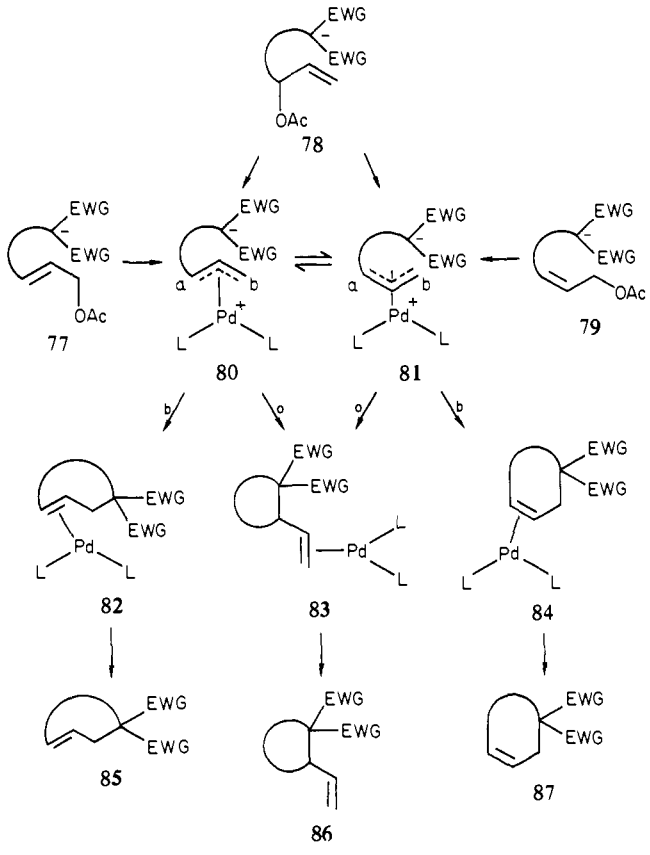
Discussion

The reaction of bifunctional substrates with palladium(0) catalysts raises the questions of (1) inter- vs. intramolecular reactions, (2) regiochemistry, and (3) olefin stereochemistry. In all the cyclizations, i.e., forming normal rings of 5 or 6 members, medium rings of 8–12 members, or large rings of over 12 members, advantages accrued to performing the reaction by the slow addition of the substrate to a solution of the catalyst to give a final concentration of approximately 0.05 M in substrate. Since the reaction seems to proceed at a rate comparable to the rate of addition, these conditions may be comparable to high-dilution conditions. The insensitivity with respect to optimal mode of addition and yield as a function of ring size suggests that the underlying factors determining the intra- vs. intermolecularity of the reaction are *independent* of ring size. For this reason, these palladium-based methods have special advantages over more traditional reactions which show a marked dependence of efficiency of reaction to mode of addition and ring size.[70] The well-documented and characteristic minimum in ring closures to medium rings[2,62,71] is absent in these palladium reactions.

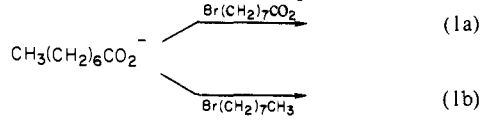
Even assuming that pseudo-high-dilution conditions may be operating, the absence of dimeric products in the cyclizations to macrolides, especially in the medium ring size range, is noteworthy. In these latter cases, lactonization methods carried out under similar conditions do produce dimers rather than monomers.[72]

(65) Anet, F. A. L.; Anet, R. In "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; p 543.
(66) Borgen, G.; Dale, J. *Chem. Commun.* **1970**, 1105.
(67) Untch, K. G.; Kurland, R. J. *J. Am. Chem. Soc.* **1963**, *85*, 346.
(68) Huisgen, R.; Ott, H. *Tetrahedron* **1959**, *6*, 253.
(69) Huisgen, R.; Ott, H. *Angew. Chem.* **1958**, *70*, 312. Friess, S. L.; Frankenburg, P. E. *J. Am. Chem. Soc.* **1952**, *74*, 2679.
(70) Reductive couplings show an insensitivity of yield to ring size. For acyloin reaction, see: Prelog, V.; Frenkiel, L.; Kobelt, M.; Barman, P. *Helv. Chim. Acta* **1947**, *30*, 1741. Stoll, M.; Hulstkamp, J. *Ibid.* **1947**, *30*, 1815. Stoll, M.; Rouvé, A. *Ibid.* **1947**, *30*, 1822. Stoll, M.; Commarmont, M. *Ibid.* **1948**, *31*, 1077. Mathuri, H. H.; Bhattacharyya, S. C. *J. Chem. Soc.* **1963**, 114. Tsuji, J.; Mandai, T. *Tetrahedron Lett.* **1977**, 3285. For a modified pinacol type, see: McMurry, J. E.; Kess, K. L. *J. Org. Chem.* **1977**, *42*, 2655. McMurry, J. E.; Fleming, M. P.; Kess, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255. Baumstark, A. L.; McCloskey, C. J.; Witt, K. E. *J. Org. Chem.* **1978**, *43*, 3609.
(71) (a) Belinkii, L. I. *Russ. Chem. Rev. (Engl. Transl.)* **1964**, *33*, 551. (b) Sicher, J. *Prog. Stereochem.* **1962**, *3*, 202. (c) Eliel, E. L; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley: New York, 1965.
(72) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. Mukaiyama, T.; Unsui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455. Vorbruggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 876.

Scheme VIII. Mechanistic Rationale for Cyclizations



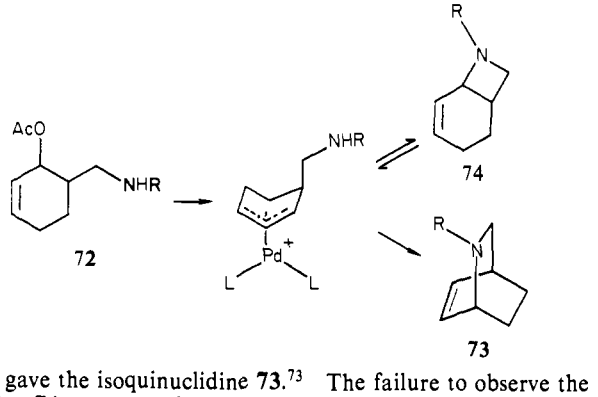
The electrostatic field developed by the negatively charged nucleophile, which may inhibit intermolecular attack by Coulombic repulsion of other negatively charged nucleophiles, and the absence of an electrophilic part until activated by palladium, which is present in low concentration resulting in a pseudo-high-dilution effect, may combine to favor intra- vs. intermolecular reactions. In intermolecular reactions, some charge effects have been noted as in the 3.5 rate differential between eq 1a and 1b.[62f]



(1a)

(1b)

The major question is that of regiochemistry. The cyclization of **3** may be contrasted to that of the nitrogen analogue **72**, which



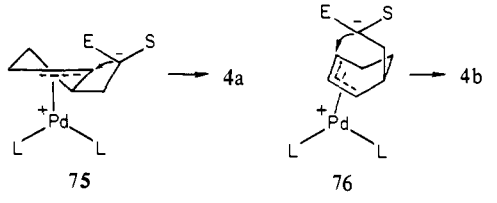
only gave the isoquinuclidine **73**.[73] The failure to observe the azetine **74** may stem from the feasibility of the amine to serve as a leaving group in these Pd(0) reactions.[74] If such were true, azetine would be expected to isomerize to the thermodynamically more stable isoquinuclidine. Since carbon is *not* a leaving group,

(73) Trost, B. M.; Genet, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 8516.
(74) Cf. Wiger, G. R.; Rettig, M. F. *J. Am. Chem. Soc.* **1976**, *98*, 4168.

Table I. Relative Rates of Cyclization by Displacement Reactions[62e,g]

ring size	rel rate	rel rate
6	2.6×10^4	1.8×10^4
7	97.3	3.4×10^4
8	1.0	1.0
9	1.12	0.16
10	3.35	0.14
12	10.6	
14	41.9	
16	52.0	

the ratio of **4a** to **4b** represents a kinetic selectivity. Conformational considerations suggest that cyclization of **75** with the bulky



group pseudoequatorial on a half-chair ring should be kinetically preferred over that via **76** with the bulky group pseudoaxial on a twist-boat ring.

The regiochemistry is most astounding in the cyclizations to medium and large rings. Scheme VIII outlines the sequence.[38,39] By virtue of the intermediacy of a cationic π-allylpalladium complex, two options exist for ring closure (path a or b). The nature of this intermediate and the consequent factors affecting regiochemistry are quite dissimilar to those found in other transition metal induced cyclizations. For example, in the cyclization of bis allyl halides with nickel(0) complexes, the intermediacy of a bis(π-allyl)nickel(0) complex in which both reactive ends are held proximal by chelation decidedly influences the reactivity profile of this complex.[75-78] In contrast, palladium-catalyzed allylic alkylations more typically resemble a classical S_N2 displacement–nucleophilic attack on the π-allyl moiety with the metal serving as a leaving group.

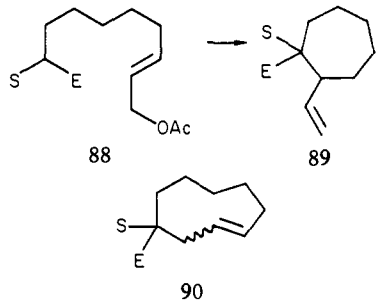
Considering this analogy to the classical displacement reaction, the regiochemical preferences might be expected to reflect the normal kinetic preferences in such intramolecular alkylation. Alternatively, we must also consider the various factors that are important in the intermolecular allylic alkylation which include (1) nature of the nucleophile, (2) nature of the substitution on the π-allyl unit, and (3) nature of the ligands on palladium.[38,39]

Recent investigations by Illuminati et al. on the lactonization of ω-bromoalkanoate anions and on the cyclic ether formation of *o*-(ω-bromoalkyl)phenolates, as summarized in Table I, reveal that in formation of a 16- vs. a 14-membered ring or 14- vs. 12-membered ring, a slight kinetic preference for the larger ring is expected.[62e,g] Combined with the preference for attack at a primary vs. secondary carbon on the π-allyl unit (in the intermolecular reaction ~9:1 ratio for primary vs. secondary carbon of a π-allyl unit with the anion from methyl benzenesulfonyl-

(75) Corey, E. J.; Hamanaka, E. *J. Am. Chem. Soc.* **1964**, *86*, 1641. Corey, E. J.; Semmelhack, M. F. *Tetrahedron Lett.* **1966**, 6237. Corey, E. J.; Wat, E. K. W. *J. Am. Chem. Soc.* **1967**, *89*, 2757. Corey, E. J.; Hamanaka, E. *Ibid.* **1967**, *89*, 2758. Corey, E. J.; Helquist, P. *Tetrahedron Lett.* **1975**, 4091.
(76) Baker, R.; Copeland, A. H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2497. *Tetrahedron Lett.* **1976**, 4535. Baker, R.; Bevan, P. C.; Cookson, R. C.; Copeland, A. H.; Gribble, A. D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 480.
(77) Fischli, A.; Branca, Q.; Daly, J. *Helv. Chim. Acta* **1976**, *59*, 2443. Branca, Q.; Fischli, A. *Ibid.* **1977**, *60*, 925. Dauben, W. G.; Beasley, G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. *J. Am. Chem. Soc.* **1975**, *97*, 4973. Crombie, L.; Kneen, G.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1976**, 66.
(78) For a review see: Semmelhack, M. F. *Org. React.* **1972**, *19*, 115.

acetate[38]), formation of the larger ring for **27** and **28** is not unexpected, although the total lack of detection of the alternative product (**31** or **32**) is somewhat surprising. A similar argument can be put forth for expecting 12-membered-ring formation to dominate over 10- in the case of **46** and 10-membered-ring formation over 8- in the cases of **58** and **59**.

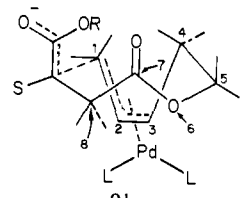
However, formation of a seven-membered ring is kinetically preferred over that of a nine-membered ring by about a factor of 10^2–10^3. The exclusive formation of the octan-8-olide **66** from **65** is thus quite surprising. It becomes even more surprising if it is realized that cyclization occurs predominantly through an "anti" intermediate analogous to **81** (Scheme VIII) which is less stable than the syn complex corresponding to **80**.[79] To the extent that the nonbonded repulsions present in **81** that destabilize it relative to **80** are reflected in the transition state for cyclization, we might have expected an increased preference for cyclization via **80**. Further, the strain associated with placing an *E* olefin in a nine-membered ring[80] might be expected to enhance the propensity of seven-membered-ring formation from **80** and thus from **65**. These factors lead to a prediction of cyclization to form seven-membered rings—in opposition to experimental observations. In the competition between six- and eight-membered rings, the $>10^4$ preference for cyclization to a six-membered ring plus a set of arguments similar to the above lead to a prediction of six-membered-ring formation in the case of **68**. The contrary observation is truly astounding. That such expectations are not unjustified, we have shown that cyclization of the all-carbon analogue of **65**, *i.e.*, **88**, does indeed produce the seven-membered-ring product **89** rather than the isomeric nine-membered-ring product **90**.[40c,81]



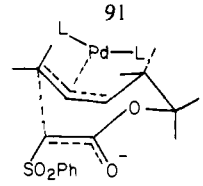
88 89

90

Conformational considerations suggest that the transition states leading to medium rings in the cases of **65** and **68** may not be as bad as in the all-carbon case. In the ring-shaped transition state **91** leading to **66a**, the nonbonded repulsions between substituents at C-1, C-4, and C-7 are diminished owing to the trigonal C-7 carbon atom (eq 2).[82] The presence of a heteroatom and the increased C–C(O)–O bond angle may also serve to decrease the destabilization associated with medium-ring formation by relief of torsional strain and bond-angle deformation. This same type of relief is present in cyclization of **92** (eq 3).[82,83] Here, five of the eight ring atoms are sp^2 hybridized in the transition state, with a sixth ring substituent being a heteroatom. Ample precedent

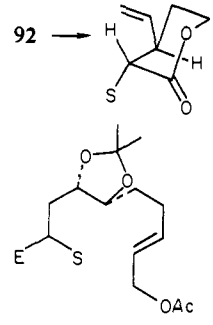


91 → 66a (2)



92 → 69a (3)

exists for facilitation of cyclization reactions by replacement of one or more methylene groups in the carbon chain by heteroatom or trigonal groups.[84] While such considerations rationalize why such ring closures may not be so unfavorable, they do not explain why they should be really preferred. For example, ring closure from the same conformation illustrated in eq 3 at the allylically related carbon atom would produce a stable, chair δ-valerolactone (eq 4).



93 (4)

Besides the kinetic preference for attack at the primary position and the enhancement afforded by the presence of heteroatoms or trigonal atoms, a third factor contributing to medium-ring formation has been postulated by Illuminati, and considers the preferred conformation of the ester in assessing the reactivity picture in lactone formation.[62a] In this view, if the ester can adopt the more stable trans conformation during the transition state, then the cyclization rate should be enhanced. A transoid ester conformation is preferred over a cisoid one by up to 2 kcal/mol and the activation energy for conformational interconversion from transoid to cisoid is about 5 kcal/mol.[68,69,85] Accordingly, ring closure to eight- or nine-membered lactones may show accelerated rates in comparison to the all-carbon analogues and may be preferred over closure to six or seven since such an ester conformation is geometrically precluded in these rings. This simplistic assumption is not borne out by experiment in a carbocyclic series. Cyclization of **93** where the chains are held transoid does not lead to nine-membered-ring formation; only seven-membered-ring product was obtained.[81]

What role, if any, does the transition metal play in determining the regiochemistry? Since the nucleophile approaches the π-allyl unit on the face opposite the metal, it is not as obvious how the

(79) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642.

(80) Cope, A. C.; Moore, P. T.; Moore, W. R. *J. Am. Chem. Soc.* **1959**, *81*, 3153.

(81) (a) Verhoeven, T. R.; Martina, D., unpublished observations in these laboratories. (b) Verhoeven, T. R. Ph.D. Thesis, University of Wisconsin—Madison, 1979.

(82) Dunitz, J. D. *Pure Appl. Chem.* **1971**, *25*, 495. In "Perspectives in Structural Chemistry"; Dunitz, J. D., Ibers, J. A., Eds.; Wiley: New York, 1968; Vol. II, p 1. Dale, J. *Pure Appl. Chem.* **1971**, *25*, 465. Anet, F. A. L. In "Conformational Analysis, Scope and Present Limitations"; Chiurdoglu, G., Ed.; Academic Press: New York, 1971; p 15. Anet, F. A. L. *Top. Curr. Chem.* **1974**, 169.

(83) Anet, F. A. L.; Degen, P. J. *Tetrahedron Lett.* **1972**, 3613. Anet, F. A. L.; Yavari, I. *J. Am. Chem. Soc.* **1977**, *99*, 6986. Anet, F. A. L.; Degen, P. J.; Krane, J. *Ibid.* **1976**, *98*, 2059. Anet, F. A. L.; Korerski, L. *Ibid.* **1973**, *95*, 3407. Anet, F. A. L.; Degen, P. J.; Yavari, I. *J. Org. Chem.* **1978**, *43*, 3021. Dale, J.; Ekeland, T.; Krane, J. *J. Am. Chem. Soc.* **1972**, *94*, 1389.

(84) Stoll, M.; Rouvē, A. *Helv. Chim. Acta* **1934**, *17*, 1283. Hill, J. W.; Corothers, W. H. *J. Am. Chem. Soc.* **1933**, *55*, 5031. Ziegler, K.; Holl, H. *Justus Liebigs Ann. Chem.* **1937**, *528*, 143. Leonard, N. J.; Fox, R. C.; Oki, M. *J. Am. Chem. Soc.* **1954**, *76*, 5708. Lutringhaus, A.; Prinzbach, H. *Justus Liebigs Ann. Chem.* **1959**, *624*, 79. Criegee, R.; Schnorrenberg, W.; Becke, J. *Ibid.* **1949**, *565*, 7. Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518.

(85) Bailey, J.; Walker, S.; North, A. M. *J. Mol. Struct.* **1970**, *6*, 53. George, W. O.; Hassid, D. V.; Maddems, W. F. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1798.

Table II. Thermodynamic Data for the $E \rightleftarrows Z$ Cycloalkene Equilibrium in Acetic Acid at 80 °C

ring size	Z:E	ring size	Z:E
8	v large	10	16.2:1
9	298:1	12	1:1.9

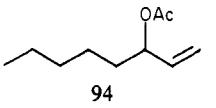
metal may steer the reaction in contrast to the nickel coupling reactions. Returning to Scheme VIII, conversion of **80** to **82** or **84** vs. **83** involves the formation of a disubstituted olefin–palladium(0) complex vs. a monosubstituted olefin–palladium(0) complex. Electronically and sterically, the latter are preferred.[86] Thus, to the extent that the transition state reflects ligand bonding,[87] preferential formation of **83** would be expected—in contrast to our observations. In the all-carbon system, such factors appear to play a role in determining regiochemistry.[81] In the macrolide reactions, the advantageous effect of Diphos on the yield of the larger rings may be ascribed in part to such a phenomenon. A rationale of this yield enhancement may likely derive from the decreased steric bulk of Diphos with respect to triphenylphosphine. Measurements of ligand cone angles, a useful means for correlating the steric requirements of ligands, reveals a large difference in size (Ph_3P, θ = 145°; $Ph_2PCH_2CH_2PPh_2$, θ = 125°).[88] The smaller ligand can minimize the steric destabilization associated with the more highly substituted olefin–palladium(0) complex.

The same steric effect may be involved to explain the role of ligand in facilitating the intramolecular reaction. The rate of the initial oxidative addition is highly dependent upon the favorability for complexation of the metal species with the allyl acetate. Consequently, the steric environment of both the metal ligands and olefin may have an inhibitory effect by destabilizing such complexation. Since reaction appears to proceed at a rate comparable to the rate of addition, any decrease in the rate of reaction which is not compensated for by a decrease in the substrate addition rate would increase the concentration of unreacted substrate with a corresponding increase in probability for intermolecular processes to intervene. The observance of up to 25% of dimeric products in cyclizations with triphenylphosphine as the only ligand by Nozaki, Yamamoto, et al.,[89] may be conveniently explained in this manner. While we did not observe dimeric products in any of our cases, the increase in yield of simple cyclization may reflect decreased competition from a decomposition pathway of an intermolecular nature.

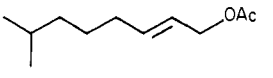
In contrast to most cyclization methods, this palladium-based method does not appear to have a strong intrinsic preference for any particular ring sizes. The regiochemical outcome rests on the close interplay of several small effects—the nature of the nucleophile, of the π-allyl unit, of the ligands on palladium, and of the chain conformation. Presently, the question of the relative importance of these sometimes competing factors remains clouded. None appears overwhelming. Nevertheless, for macrolide formation, a consistent trend for exclusive cyclization at the less substituted atom of the π-allyl unit, producing the larger ring, is established.

Two factors contribute to olefin stereochemistry in the cyclized product: (1) the kinetic stability of the intermediate π-allylpallaldium isomer and (2) the thermodynamic stability of the π-allyl isomer and incipient olefin. The kinetic stability of π-allylpalladium complexes has been previously discussed in connection with the intermolecular reaction and a similar behavior is exhibited in the intramolecular process.[38,39] In the reaction of **46**, cyclization is faster than syn–anti interconversion leading to complete retention of olefin stereochemistry; however, in formation of ten-membered rings, i.e., cyclization of **58** and **59**, the rates of the two processes become more competitive.

Thermodynamically, a high preference exists for substituents to occupy the syn position. For instance, with only a proton attached at the central carbon atom, the steric interactions are such that only 5–6% of the anti isomer is observed in 1-substituted or 1,3-disubstituted π-allylpalladium complexes.[79] Thus in the absence of competing effects, the *E* isomer should be formed quite selectively. The variation of olefin isomer stability with ring size introduces a second variable. Table II summarizes the equilibrium ratios of *Z* and *E* isomers for a series of cycloalkenes.[80] The *Z* stereochemistry becomes less favorable and the *E* isomer becomes more stable in the region of 10- to 11-membered rings. The exact crossover point may vary considerably, depending upon other structural features. With larger rings (>12 members) the magnitude of the preference for the *E* isomer becomes similar to open-chain analogues.[71c,90] Thus, like the intermolecular reaction, a high preference for the *E* stereochemistry is exhibited in formation of pentadecenolide **30** (>95% *E*), tridecenolide **29** (75% *E*), and dodecenolide **47** (100% *E*). Exclusive formation of the *E* isomer in **47** is likely due to the kinetic preference afforded by employing the *E* olefin geometry in the acyclic precursor **46**. Comparison of the *E*:*Z* ratios obtained upon alkylation of **94** and **95** reveals a similarity.[81] In **94** a 90:10 ratio was obtained, whereas alkylation of **95** produced a 97:3 ratio.



94



95

At the other extreme, the heptenolide **69a** forms only in the *Z* olefin configuration. Octenolide **66** exhibits a *Z*:*E* ratio ranging between 11:1 and 3:1. Further, the nonenolide products **62** actually show a preference for the *E* isomer. It thus appears that the crossover point from *Z* to *E* olefin stability occurs at smaller ring sizes (~nine to ten members) with lactones than with the corresponding carbocycles. For example, the preferred conformation of the lactone moiety in 7-octanolide is transoid.[68,69]

The merits of this methodology are obvious. The ability to form a variety of macrolides by carbon–carbon bond formation provides a useful and potentially preferred complement to currently popular lactonization methods. Indeed, the fact that the exploration of ring-size effects could be easily accomplished within the framework of total synthesis of the naturally occurring macrolides exaltolide, recifeiolide, phoracantholide I, and phoracantholide J illustrates the facility of synthetic design using this principle. Unlike esterification reactions, this intramolecular alkylation process is not restricted to lactones, and may be readily applied to the construction of carbocyclic systems as well.[81] Since stable, readily manipulated allyl acetates and relatively acidic active methylene compounds are employed, the compatibility of this method with a number of sensitive functionalities is likely. This facet further illustrates the unique mediating ability afforded by palladium in activating and directing the reactivity of otherwise nonreactive substrates. In contrast, the recently described intramolecular displacements of already activated allyl halides with less stabilized anions (α-sulfenylated esters or benzyl phenyl sulfones) do not possess this trait and consequently may likely experience limited success in applications to complex, sensitive molecules.

The demonstrated ability to form both large and medium rings with equal facility is quite exciting from both a synthetic and theoretical perspective. The unexpectedly large change which seemingly minor modifications in structure can effect on ring-closure preferences emphasizes the need for more extensive investigations. While ascribing the unique directive effects entirely to palladium would be in error, its crucial role in contributing to the rigidity of the transition-state conformation and influencing the site of nucleophilic attack cannot be denied. This becomes especially apparent by the successful cyclizations to eight- and nine-membered lactones. Hence, the results obtained herein

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provide yet further illustration of the exciting advances to be realized through the merger of transition-metal and organic reactivities.

Experimental Section

General. All reactions were run under a positive pressure of dry nitrogen. Infrared spectra were determined on a Perkin-Elmer 267 spectrophotometer and are reported in cm^{-1}. ^1H NMR spectra were determined in the indicated solvent on a Jeolco MH-100 (100 MHz) or a Bruker WH270 (270 MHz) instrument. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Coupling constants are reported in hertz. ^{13}C NMR spectra were determined in the indicated solvent on a Jeolco FX-60 (60 MHz) instrument with chemical shifts reported downfield relative to tetramethylsilane. Mass spectra were obtained at an ionizing current of 98 mA and an ionizing voltage of 70 eV. Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Boiling points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, Mich. VPC analyses were obtained with a Varian Aerograph Model 90P. For reactions requiring slow additions, a Sage syringe pump Model 352 was employed. Thin layer or preparative layer plates (1.5 mm) were made of E. Merck AG Darmstadt silica gel PF-254 or Brinkmann silica gel P/UV-254 no. 66 and activated by drying at 120 °C for 2 h. Eluting solvents are indicated in the text, with composition given as volume percent. Removal of the material from silica gel was accomplished by successive washings with ether or ethyl acetate. The term LC is used for high-pressure liquid chromatography and refers to the use of a standard 2.5 (i.d.) × 100 cm column with a precolumn filter of 1.5 (i.d.) × 25 cm dimensions, both of which were packed with 32–63 μm Woelm silica gel and preequilibrated with the indicated solvent mixture. The system utilized a single-stage constant flow pump at an approximate flow rate of 20 mL/min.

For reactions requiring dry solvents, tetrahydrofuran, 1,2-dimethoxyethane, ethyl ether, toluene, and benzene were distilled from sodium benzophenone ketyl. Hexane, pentane, pyridine, dichloromethane, hexamethylphosphoric triamide, diethylamine, cyclohexylisopropylamine, dimethylformamide, and dimethyl sulfoxide were distilled from calcium hydride. Thionyl chloride was purified by distillation from triphenyl phosphite. Sodium hydride was employed as a 55–63% dispersion in mineral oil and weights are recorded for the dispersion. All palladium(0) catalysts were transferred under an inert atmosphere. Glassware for experiments requiring anhydrous conditions was dried by a flame under a stream of nitrogen.

Purity of Products. Unless otherwise noted, purity was verified by chromatographic means (TLC and/or VPC) in the solvent and/or column condition specified in each case. Spectral data and, in many instances, combustion analysis further confirmed the purity.

Preparation of Methyl (*Z*)-2-Benzenesulfonyl-3-(2′-acetoxy-3′-cyclohexen-1′-yl)propanoate (3). Sodium borohydride (1.52 g, 40.2 mmol) was added in portions over 30 min to a cooled (0 °C) solution of (*Z*)-2-acetoxy-1-formyl-3-cyclohexene[94] (4.12 g, 24.5 mmol) in 15 mL of anhydrous methanol. After the addition was completed, 10% aqueous hydrochloric acid (7 mL) was carefully added and the mixture then neutralized with solid sodium bicarbonate. The mixture was concentrated on a rotary evaporator, poured into a separatory funnel containing 50 mL of saturated aqueous sodium chloride, extracted with chloroform (4 × 50 mL), and dried over anhydrous sodium sulfate and the solvent removed in vacuo to give 3.79 g (92%) of impure (*Z*)-2-acetoxy-1-(hydroxymethyl)-3-cyclohexene as a colorless oil which was employed without further purification. The olefinic region of the 100-MHz NMR (δ 6.0–5.52) integrated to 3.3 protons in comparison to the C-2 methine (δ 5.19), indicating the product to be approximately 60% pure.

The alcohol prepared above (3.79 g) was dissolved in 40 mL of pyridine and cooled to 0 °C. *p*-Toluenesulfonyl chloride (6.18 g, 32.4 mmol) was added in portions and the mixture stored at 0 °C for 2 days. The mixture was poured into 300 mL of an ice–water mixture, vigorously agitated to induce solidification, and filtered. The solid was washed with a total of 200 mL of cold water and dried under vacuum at room temperature overnight to give 4.68 g of a white powder which was employed without further purification. Recrystallization of a sample from pentane–ethanol gave white platelets, mp 80.5–81.5 °C. The spectral properties of *cis*-2-acetoxy-1-(4′-toluenesulfonyloxymethyl)-3-cyclohexene follow. NMR (100 MHz, $CDCl_3$): δ 7.87 (d, J = 8 Hz, 2 H), 7.42 (d, J = 8 Hz, 2 H), 5.97 (m, 2 H), 5.26 (m, 1 H), 4.08 (m, 2 H), 2.48 (s, 3 H), 2.13 (m, 2 H), 1.95 (s, 3 H), 1.63 (m, 2 H). IR (CCl_4): 3020, 2920, 1750, 1595, 1370, 1230, 1045, 1010, 960 cm^{-1}.

A solution of methyl benzenesulfonylacetate (2.45 g, 11.4 mmol) in 2 mL of hexamethylphosphoric triamide was added over 10 min to a slurry of pentane-washed potassium hydride (458.8 mg, 11.5 mmol) in 10 mL of hexamethylphosphoric triamide and stirred for an additional 15 min. The tosylate (2.48 g, 7.65 mmol) was added in one portion and the mixture was heated at 60–70 °C for 6 h. Upon cooling, the reaction mixture was partitioned between ether (50 mL) and water (50 mL), the aqueous layer was extracted with ether (3 × 50 mL), the combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to give a yellow oil. Initial purification by dry column chromatography on silica gel (150 g, 25% ethyl acetate in hexane) provided 2.48 g of a clear oil (R_f 0.3–0.4) as a mixture of alkylated product and methyl benzenesulfonylacetate. Preparative TLC (14% ethyl acetate in chloroform) gave 1.51 g (51% of alkylated product) as a clear oil plus a second fraction contaminated with methyl benzenesulfonylacetate. The contaminated fraction was rechromatographed (25% ethyl acetate in hexane containing 1% ethanol, three elutions), giving 301 mg of alkylated product for a combined yield of 62%. NMR (100 MHz, $CDCl_3$): δ 7.92 (bd, J = 7.5 Hz, 2 H), 7.67 (m, 3 H), 5.90 (bm, 2 H), 5.16 (bm, 1 H), 4.16 (m, 1 H), 3.66 (s, 3 H), 2.00 (bm, 7 H) containing 2.02 and 1.99 (two singlets), 1.60 (m, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.6, 170.3, 166.2, 137.5, 137.1, 134.3, 134.2, 133.2, 132.5, 129.1, 124.5, 124.0, 68.8, 68.3, 67.8, 65.9, 42.9, 35.3, 28.0, 27.7, 25.2, 24.6, 24.2, 22.8, 20.9. IR (CCl_4): 1742, 1448, 1370, 1331 cm^{-1}. Calcd for $C_{16}H_{19}O_5S$ (M − C_2H_3O): 323.0953. Found: 323.0953.

Cyclization of 3. Acetate **3** (518.2 mg, 1.42 mmol) dissolved in 4 mL of THF was added in one portion to a slurry of sodium hydride (62 mg, 1.42 mmol) and heated to 60 °C for 25 min to give a clear yellow solution. Tetrakis(triphenylphosphine)palladium(0) (34.0 mg, 0.029 mmol) was added and the mixture heated at reflux for 4.5 h. The cloudy yellow mixture was cooled, poured into 20 mL of water, extracted with ether (4 × 20 mL), dried over anhydrous magnesium sulfate, and filtered, and the solvent removed in vacuo to give 511.8 mg of a light brown oil. Purification by preparative TLC (25% ethyl acetate in hexane containing 2% ethanol) gave 307.4 mg (67%) of cyclized products as a clear, light yellow oil assigned as a mixture of **4a** and **4b**. The ratio of products could not accurately be determined by 100-MHz NMR. NMR (100 MHz, $CDCl_3$): δ 7.88 (m, 2 H), 7.62 (m, 3 H), 6.3–5.6 (bm, 2 H), 3.6 (4 H) containing 3.63, 3.59, and 3.49 (three singlets), 3.1–2.4 (bm, 4 H), 2.0 (m, 1 H), 1.6–1.1 (m, 2 H). IR (CCl_4): 1732, 1448, 1432, 1322 cm^{-1}. Calcd for $C_{16}H_{18}O_4S$: 306.0926. Found: 306.0915.

Desulfonylation of 4a and 4b. A mixture of **4a** and **4b** (302.1 mg, 0.987 mmol) and anhydrous disodium hydrogen phosphate (500 mg, 3.52 mmol) in 10 mL of anhydrous methanol was cooled to 0 °C. Granulated 6% sodium amalgam (1.5 g) was added in one portion and the mixture stirred for 30 min. The mixture was decanted, diluted with 50 mL of pentane, washed with saturated aqueous ammonium chloride (2 × 15 mL), water (15 mL), and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo at room temperature gave 151 mg (92%) of desulfonylated products as a clear, colorless oil. Analysis by VPC (20% DC-710 on Chromosorb W, 60/80 mesh, 3.66 m × 0.64 cm, t = 155 °C) revealed four isolable products with retention times of 16.9, 15.1, 14.5, and 12.4 min. Two fractions were identified as methyl *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylate (retention time = 14.5 min) and methyl *exo*-bicyclo-[2.2.2]oct-5-ene-2-carboxylate (retention time = 12.4 min) by coninjection and 270-MHz NMR comparison with authentic samples.[43] The other two fractions were identified by 270-MHz NMR as the syn and anti isomers of methyl bicyclo[4.2.0]oct-7-ene-2-carboxylate (retention times = 15.1 and 16.9 min). The isolated fractions with retention times of 14.5 and 15.1 min were not homogeneous and were contaminated with approximately 5–18% of each other. Integration of the four peaks indicated a ratio of bicyclo[2.2.2]octene:bicyclo[4.2.0]octene of 1:2. The spectral data for each isolated fraction follow. **5a** (retention time = 16.9 min): NMR (270 MHz, $CDCl_3$) δ 5.94 (d of d of m, J = 10, 6 Hz, 1 H), 5.64 (d of bt, J = 10, 3 Hz, 1 H), 3.64 (s, 3 H), 3.36 (bq, J = 9 Hz, 1 H), 3.07 (m, 1 H), 2.64 (m, 1 H), 2.23–1.93 (bm, 4 H), 1.55 (m, 1 H), 1.38 (m, 1 H). Irradiation at δ 5.64 collapses the resonances at δ 5.94 (bm) and 3.07 (bt, J = 8 Hz). Irradiation at δ 3.36 sharpens the multiplets at δ 3.07 and 2.23–1.93. Irradiation at δ 3.07 collapses the resonances at δ 5.94 (d of d of d, J = 10, 5.5, 2.5 Hz), 5.64 (bd, J = 10 Hz), and 3.36 (bt, J = 9 Hz) and sharpens the multiplets at δ 2.64 and 2.23–1.93. Irradiation at δ 2.64 collapses the resonances at δ 1.38 (d of d of d, J = 14, 11, 6 Hz) and sharpens the resonances at δ 3.07, 2.23–1.93, and 1.55. Irradiation at δ 2.12 collapses the resonances at δ 5.94 (d, J = 10 Hz), 5.64 (d of d, J = 10, 4 Hz), 1.55 (d of d, J = 14, 2 Hz), and 1.38 (d of bd, J = 14, 3 Hz) and sharpens the resonances at δ 3.36, 3.07, and 2.64. Irradiation at δ 1.99 collapses the resonances at δ 5.94 (d, J = 10 Hz), 5.64 (bd, J = 10 Hz), and 3.36 (t, J = 9 Hz) and sharpens the resonances at δ 3.07, 2.64, 1.55, and 1.38. IR (CCl_4): 1745, 1438 cm^{-1}. Calcd for $C_{10}H_{14}O_2$: 166.0994. Found: 166.0990.

5b (retention time = 15.1 min): NMR (270 MHz, $CDCl_3$) δ 5.88 (bd of t, J = 10, 4 Hz, 1 H), 4.76 (d of m, J = 10 Hz, 1 H), 3.69 (s, 3 H), 2.94 (m, 1 H), 2.84 (m, 1 H), 2.60 (m, 1 H), 2.28 (m, 1 H), 2.12–1.88 (bm, 3 H), 1.69 (m, 1 H), 1.54 (m, 1 H); IR (CCl_4) 1440 cm^{-1}. Calcd for $C_{10}H_{14}O_2$: 166.0994. Found: 166.0988.

Preparation of (*Z*)-2-Acetoxy-1-(2′-methoxyethen-1′-yl)-3-cyclohexene (7). (Methoxymethyl)triphenylphosphonium chloride (7.9 g, 23.1 mmol) which had been dried under vacuum (100 °C, 0.1 mm) was suspended in 40 mL of ether and cooled to 0 °C. A hexane solution of *tert*-butyllithium (2.3 M, 10 mL, 23 mmol) was added over 15 min and the resulting dark red mixture warmed to room temperature and stirred for an additional 15 min. After recooling to 0 °C, a solution of *cis*-2-acetoxy-1-formyl-3-cyclohexene in 20 mL of ether was slowly added over 10 min and the mixture then stirred for 30 min. The reaction mixture was partitioned between ether and aqueous ammonium chloride, and the aqueous layer separated and extracted with ether (4 × 50 mL). The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo to give an oily solid which was resuspended in 200 mL of pentane at 0 °C and filtered, and the solvent was removed in vacuo to give a yellow oil. Purification via Kugelrohr distillation (70–80 °C, 0.1 mm) gave 2.63 g (88%) of the title compound as a clear, colorless liquid. NMR (100 MHz, $CDCl_3$): δ 6.36 (d, J = 13 Hz, 0.6 H), 5.89 (bm, 2.4 H), 5.17 (m, 1 H), 4.05 (d of d, J = 13, 9 Hz, 0.6 H), 4.25 (d of d, J = 9.5, 7 Hz, 0.4 H), 3.59 and 3.52 (two singlets, 3 H), 2.93 (m, 0.4 H), 2.53–1.3 (bm, 7.6 H) containing 2.03 (s). IR (CCl_4): 1730, 1642, 1448, 1369 cm^{-1}. Calcd for $C_{11}H_{16}O_3$: 196.1099. Found: 196.1106.

Preparation of (*Z*)-(2′-Acetoxy-3′-cyclohexen-1′-yl)acetaldehyde (8). (*Z*)-2-Acetoxy-1-(2′-methoxyethen-1′-yl)-3-cyclohexene (1.10 g, 5.6 mmol) was dissolved in 12 mL of THF and 4 mL of water. Oxalic acid (1.0 g, 1.04 mmol) was added and the mixture vigorously stirred at room temperature for 36 h. The mixture was neutralized with saturated aqueous sodium bicarbonate, extracted with ether (80 mL), and dried over anhydrous magnesium sulfate and the solvent removed in vacuo to give 946 mg of a clear oil which was used without further purification. NMR (100 MHz, $CDCl_3$): δ 9.84 (m, 1 H), 6.01 (d of t, J = 10, 3.5 Hz, 1 H), 5.78 (d of m, J = 10 Hz, 1 H), 5.27 (m, 1 H), 2.71–1.98 (bm, 8 H) containing 2.01 (s), 1.69 (m, 2 H). IR (CCl_4): 2715, 1735, 1368 cm^{-1}. Calcd for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0939.

Preparation of Methyl *cis*-2-Carbomethoxy-4-(2′-acetoxy-3′-cyclohexen-1′-yl)butanoate (9). The experimental procedure closely paralleled that for the preparation of **3**. Thus, the details for this case appear as supplementary material.

Preparation of Methyl (*Z*)-2-Benzenesulfonyl-4-(2′-acetoxy-3′-cyclohexen-1′-yl)butanoate (10a). Sodium hydride (200 mg, 5 mmol) was added to a solution of methyl benzenesulfonylacetate (800 mg, 3.73 mmol) in 3 mL of HMPA and stirred at room temperature for 30 min. A solution of (*Z*)-1-(2′-acetoxy-3′-cyclohexen-1′-yl)-2-(4′-toluenesulfonyloxy)ethane in 2 mL of HMPA and sodium iodide (150 mg) were added, and the mixture was heated at 50 °C for 4 h. Upon cooling, the reaction mixture was partitioned between ether and saturated aqueous ammonium chloride and extracted with ether (4 × 20 mL), the organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residue was purified by preparative TLC (25% ethyl acetate in hexane, three elutions) to give 688 mg (95%) of the title compound as a clear, colorless oil (R_f 0.6). NMR (100 MHz, $CDCl_3$): δ 7.89 (bd, J = 7.5 Hz, 2 H), 7.66 (m, 3 H), 5.83 (m, 2 H), 5.09 (m, 1 H), 3.94 (m, 1 H), 3.63 (s, 3 H), 2.20–1.8 (m, 7 H) containing 1.97 (s), 1.8–1.10 (bm, 5 H). ^{13}C NMR ($CDCl_3$): δ 170.0, 166.1, 137.5, 137.4, 134.1, 132.7, 129.1, 129.0, 124.8, 70.9, 70.7, 68.4, 67.7, 52.6, 37.0, 36.8, 28.5, 28.0, 25.2, 24.9, 24.3, 23.5, 23.1, 20.9, 20.7. IR (CCl_4): 2065, 3030, 2930, 2860, 2830, 1740, 1445, 1432, 1368, 1330, 1235, 1150, 1082. Mass spectrum *m/e* (%): 380 (0.2), 360 (1), 337 (1), 164 (4), 150 (4), 141 (11), 123 (6), 121 (55), 119 (99), 117 (100), 91 (8), 85 (9), 84 (34), 83 (13), 82 (51), 77 (44).

Preparation of a *Z*–*E* Mixture of Methyl 2-Benzenesulfonyl-4-(2′-acetoxy-3′-cyclohexen-1′-yl)butanoate (10a + 10b) from Allyl Acetate 7. The experimental procedures to go from **7** to **12** follow standard conditions and those to go from **12** to **10a + 10b** closely parallel those for preparation of pure **10a**. Thus, the details for these procedures appear as supplementary material.

Cyclization of 9. Sodium hydride (31.5 mg, 0.787 mmol) was added in one portion to a solution of the title compound (260 mg, 0.873 mmol) in 15 mL of THF and heated at 50–55 °C for 30 min to give a clear, yellow solution. After dilution with 6.5 mL of THF, tetrakis(triphenylphosphine)palladium(0) (54.3 mg, 0.047 mmol) was added and the mixture heated at reflux for 7 h. After cooling, the brown mixture was partitioned between ether and water and extracted with a total of 70 mL of ether, the organic portion dried over anhydrous magnesium sulfate, and the solvent removed in vacuo to give a brown oil. Purification by preparative TLC (25% ethyl acetate in hexane) gave 33.8 mg (17%) of (*Z*)-9,9-bis(carbomethoxy)bicyclo[4.3.0]non-2-ene as a clear oil (R_f 0.7). Analysis by 270-MHz NMR and VPC (10% XE-60 on Chromosorb W, 60/80 mesh, 2.44 m × 0.64 cm, t = 145–150 °C, retention time = 7 min) provided evidence for only one isomer. NMR (270 MHz, $CDCl_3$): δ 5.73 (d of t of d, J = 10.2, 3.6, 2.3 Hz, 1 H), 5.40 (d of d of t, J = 10.2, 3.6, 2.0 Hz, 1 H), 3.72 (s, 3 H), 3.67 (s, 3 H), 3.30 (m, 1 H), 2.51 (d of t, J = 13.5, 8.4 Hz, 1 H), 2.37 (m, 1 H), 2.05–1.87 (bm, 3 H), 1.78 (m, 1 H), 1.61 (m, 2 H), 1.46 (m, 1 H). Irradiation at δ 3.3 collapses resonances at δ 5.73 (d of t, J = 10.2, 3.7 Hz) and 5.40 (d of t, J = 10.2, 2 Hz). Irradiation at δ 2.5 sharpens the pattern at δ 3.3 but resonances at δ 5.73 and 5.40 remain unchanged. Irradiation at δ 1.86 collapses resonances at δ 5.73 (d of d, J = 10.2, 2 Hz) and 5.40 (d of d, J = 10.2, 3.6 Hz). IR (CCl_4): 1732, 1430, 1260 cm^{-1}. Calcd for $C_{13}H_{18}O_4$: 238.1205. Found: 238.1208.

Cyclization of Methyl 2-Benzenesulfonyl-4-(2′-acetoxy-3′-cyclohexen-1′-yl)butanoate (10a). Sodium hydride (36.4 mg, 0.91 mmol) was added to a solution of the title compound (339 mg, 0.892 mmol) in 2 mL of THF and stirred at room temperature for 30 min, then at 45 °C for 30 min. The resulting clear, yellow solution was diluted to a total volume of 6 mL with THF and added via a syringe pump at a rate of 4 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (17.3 mg, 0.015 mmol) in 4 mL of THF. After the addition, refluxing was continued for 3 h. Upon cooling, the mixture was partitioned between ether and saturated aqueous ammonium chloride and extracted with ether (3 × 30 mL), the organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. Purification of the dark residual oil by preparative TLC (30% ethyl acetate in hexane) gave 215 mg (75%) of **14**. Analysis by 270-MHz NMR revealed the product to be a mixture of two diastereomers. The olefinic resonances at δ 6.27 and 5.94 were assigned to one diastereomer, and the resonances at 5.74 and 5.30 to the second. Integration gave a ratio of 1:3, respectively. The isomers were assigned as a diastereomeric mixture about C-9. NMR (270 MHz, $CDCl_3$): δ 7.93 (d of m, J = 7.5 Hz, 1.5 H), 7.78 (d of m, J = 7.5 Hz, 0.5 H), 7.63 (m, 1 H), 7.54 (t of m, J = 7.5 Hz, 2 H), 6.27 (bd, J = 10 Hz, 0.25 H), 5.94 (d of m, J = 10 Hz, 0.25 H), 5.74 (d of m, J = 10 Hz, 0.75 H), 5.30 (d of m, J = 10 Hz, 0.75 H), 3.59 and 3.54 (two singlets, 3 H), 3.44 and 3.31 (two multiplets, 1 H), 2.77–2.36 (m, 3 H), 2.22–1.85 (m, 3 H), 1.77–1.50 (m, 2 H), 1.46–1.26 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 168.0, 137.8, 133.7, 130.4, 130.1, 129.1, 128.5, 124.4, 83.3, 52.2, 44.9, 37.9, 30.5, 29.9, 24.1, 23.0, with minor resonances at 129.6, 82.3, 53.0, 46.4, 35.5, 25.9, 20.5. IR (CCl_4): 1735, 1445, 1432, 1315, 1141 cm^{-1}. Calcd for $C_{17}H_{20}O_4S$: 320.1082. Found: 320.1085.

Cyclization of a *Z*–*E* Mixture of Methyl 2-Benzenesulfonyl-4-(2′-acetoxy-3′-cyclohexen-1′-yl)butanoate (10a and 10b). Sodium hydride (28 mg, 0.7 mmol) was added to a solution of the title compounds (*Z*:*E*, 30:70) (192.7 mg, 0.507 mmol) in 1 mL of THF and the mixture heated at 50 °C for 15 min, then recooled to room temperature. The resulting slurry was diluted to a total volume of 4 mL with THF and added via a syringe pump at a rate of 1.5 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (29.7 mg, 0.026 mmol) in 3 mL of THF. The needle used for the addition was fitted at the top with a small glass-wool plug to remove unreacted sodium hydride. After 15 h at reflux, the reaction mixture was cooled and purified in the same manner as described for the previous experiment to give 58 mg (35%) of a clear, colorless oil. Analysis of the product mixture by 270-MHz NMR revealed the product to be nearly identical with that obtained from the cyclization of the pure *Z* isomer with the exception of two new olefinic resonances at δ 5.50 (d of m, J = 10 Hz) and 5.40 (bd, J = 10 Hz) as well as a singlet at δ 3.62. These signals were assigned to **15**. Integration of the olefinic region led to a *Z*:*E* ratio of 85:15.

Preparation of Ethyl 5-Formylpentanoate (20). Pyridinium chlorochromate (28.3 g, 131.2 mmol) and anhydrous sodium acetate (2.965 g, 36.2 mmol) were suspended in 160 mL of methylene chloride and a solution of ethyl 6-hydroxyhexanoate[47] (12.07 g, 75.43 mmol) in 30 mL of methylene chloride was added in a steady stream. The mixture was stirred at room temperature for 1 h. Anhydrous ether (250 mL) was added with vigorous stirring and the mixture filtered through a column containing 85 g of Florisil and 5 g of silica gel. The remaining black residue was rinsed with ether (2 × 100 mL) and filtered through the column. Removal of the solvent in vacuo (ice-water bath) gave a yellow liquid which was purified by distillation through a 160-cm Vigreux column (50 °C, 0.02 mm) to give 8.99 g (75%) of **20**. NMR (100 MHz, $CDCl_3$): δ 9.78 (t, J = 2 Hz, 1 H), 4.12 (q, J = 7 Hz, 2 H), 2.6–2.25 (bm, 4 H), 1.64 (m, 4 H), 1.12 (t, J = 7 Hz, 3 H). IR (CCl_4): 2720, 1740, 1485, 1470, 1455, 1425, 1400, 1380, 1360, 1310 cm^{-1}. Calcd for $C_8H_{14}O_3$: 158.0943. Found: 158.0946.

Preparation of Ethyl 6-Hydroxy-7-octenoate. A freshly prepared 1 M solution of vinylmagnesium bromide[91,92] in tetrahydrofuran (56 mL, 56 mmol) was slowly added over 1 h to a cooled (0 °C) solution of ethyl

5-formylpentanoate (8.80 g, 55.7 mmol) in 30 mL of THF. Immediately after the addition, TLC analysis indicated complete consumption of the starting material and saturated aqueous ammonium chloride (100 mL) was added. The layers were separated, and the aqueous portion was extracted with ether (4 × 70 mL). The combined organic portions were dried over anhydrous magnesium sulfate and the solvent was concentrated in vacuo. The residual yellow oil was purified by dry column chromatography (400 g) eluting with 20% ethyl acetate in hexane to give 7.31 g (71%) of the title compound. NMR (100 MHz, $CDCl_3$): δ 5.82 (d of d of d, J = 17, 10, 6.5 Hz, 1 H), 5.14 (d of m, J = 17 Hz, 1 H), 5.02 (d of m, J = 10 Hz, 1 H), 4.10 (bq, J = 7 Hz, 3 H), 2.7 (bs, 1 H), 2.28 (bt, J = 6 Hz, 2 H), 1.8–1.2 (bm, 6 H), 1.06 (t, J = 8 Hz, 3 H). IR (CCl_4): 3640, 3520, 1740, 1480, 1470, 1450, 1375, 1305 cm^{-1}. Mass spectrum m/e (%): 169 (1), 141 (7), 130 (27), 129 (8), 123 (7), 113 (6), 112 (27), 111 (11), 102 (7), 101 (100), 97 (15), 95 (22), 88 (8), 85 (12), 84 (16), 83 (18), 81 (26), 80 (13), 73 (51), 69 (8), 67 (15), 60 (11), 57 (69), 56 (15), 55 (59).

Preparation of 6-Hydroxy-7-octenoic Acid (21) and 6-Acetoxy-7-octenoic Acid (22). Potassium hydroxide (3.0 g, 53.6 mmol) was added to a solution containing ethyl 6-hydroxy-7-octenoate (7.30 g, 39.2 mmol) in 50 mL of 50% aqueous ethanol and stirred at room temperature for 2.5 h. The resulting homogeneous solution was cooled (0 °C) and acidified with concentrated hydrochloric acid. After concentration on a rotary evaporator, the residue was partitioned between saturated aqueous sodium chloride (50 mL) and ether (50 mL) and extracted with a total of 300 mL of ether. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo, giving 5.70 g (91%) of **21** as a clear, yellow oil which was used without further purification. This oil was dissolved in 25 mL of acetic anhydride followed by the addition of 15 mL of pyridine and the mixture stirred at room temperature overnight. The mixture was diluted with 250 mL of ether, washed with cold (0 °C) 10% aqueous hydrochloric acid (4 × 50 mL), and dried over anhydrous sodium sulfate. Filtration and removal of the solvent in vacuo gave a yellow oil which was subjected to Kugelrohr distillation (70 °C, 1 mm) to remove the remaining acetic anhydride. The brown pot residue was purified by column chromatography on Florisil (60–100 mesh, 100 g), eluting with chloroform (1 L) and 50% ether in chloroform (1 L) to give 4.72 g (60%) of **22**. **21**: NMR (100 MHz, $CDCl_3$) δ 7.29 (bs, 2 H), 5.90 (d of d of d, J = 16, 10, 6 Hz, 1 H), 5.24 (d of m, J = 16 Hz, 1 H), 5.12 (d of m, J = 10 Hz, 1 H), 4.14 (m, 1 H), 2.36 (m, 2 H), 1.6 (bm, 6 H); IR (CCl_4) 3600–2500, 1710, 1410, 1258 cm^{-1}. Calcd for $C_8H_{14}O_3$: 158.0943. Found: 158.0951. **22**: NMR (100 MHz, $CDCl_3$) δ 10.82 (bs, 1 H), 5.78 (d of d of d, J = 16.5, 9.8, 6.0 Hz, 1 H), 5.14 (bm, 3 H), 2.34 (m, 2 H), 2.00 (s, 3 H), 1.6 (bm, 6 H); IR (CCl_4) 3300–2500, 1755, 1725, 1420, 1380, 1285, 1235 cm^{-1}. Calcd for $C_{10}H_{16}O_4$: 200.1049. Found: 200.1044.

Preparation of 1-Chloro-4-(tetrahydropyranyloxy)butane (23). A mixture of 4-chlorobutanol[49] (10.07 g, 92.8 mmol) and dihydropyran (12.1 g, 144 mmol) in 150 mL of methylene chloride was cooled to 0 °C and 100 mg of *p*-toluenesulfonic acid added. The solution was stirred at 0 °C for 1.5 h, then at room temperature for 30 min. After dilution with 250 mL of ether, the reaction mixture was washed with a saturated aqueous sodium bicarbonate solution (2 × 50 mL), dried over magnesium sulfate, and concentrated in vacuo and the resulting yellow oil distilled at reduced pressure. After a small forerun (70–86 °C, 1.4 mm), 14.82 g (83%) of **23** was collected as a clear, colorless oil (87 °C, 1.4 mm). NMR (100 MHz, $CDCl_3$): δ 4.53 (bs, 1 H), 3.91–3.26 (bm, 6 H), 2.0–144 (bm, 10 H). IR (CCl_4): 1460, 1448, 1360, 1205, 1140, 1125 cm^{-1}. Calcd for $C_9H_{17}ClO_2$: 192.0917. Found: 192.0924.

Preparation of Methyl 2-Benzenesulfonyl-6-hydroxyhexanoate (24). A solution of **23** (5.01 g, 26.09 mmol) and sodium iodide (1.0 g, 6.67 mmol) in 5 mL of dimethylformamide was stirred at 80 °C for 30 min. In a separate vessel, a solution of methyl benzenesulfonylacetate (7.207 g, 33.65 mmol) in 15 mL of DMF was slowly added to a slurry of sodium hydride (1.392 g, 33.06 mmol) in 20 mL of DMF. The resulting clear solution was added to the former in one portion, then heated at 100 °C for 2.5 h. The reaction mixture was cooled, diluted with water, and extracted with ether (4 × 50 mL). The combined organic portions were extracted with water (50 mL) and dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The resulting yellow oil was dissolved in a THF–acetic acid–water mixture (50:100:50 mL) and stirred at room temperature for 48 h. After careful neutralization with solid sodium bicarbonate and dilution with water, the reaction mixture was extracted with ether (5 × 100 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting yellow oil was purified by LC (column length = 100 cm, inside diameter = 2.5 cm) eluting with 50% ethyl acetate in hexane to give 3.73 g (50%) of **24**. NMR (100 MHz, $CDCl_3$): δ 7.95 (d of d, J = 7.5, 2 Hz, 2 H), 7.68 (m, 3 H), 4.07 (d of d, J = 8, 7 Hz, 1 H), 3.67 (s, 3 H), 3.58 (t, J = 6 Hz, 2 H), 3.18 (bs, 1 H), 2.03 (m, 2 H), 1.49 (bm, 4 H). IR (CCl_4): 3610, 3500 cm^{-1} (b). Calcd for $C_{13}H_{18}O_5S$: 286.0875. Found: 286.0877.

Preparation of Methyl 2-Benzenesulfonyl-8-hydroxyoctanoate (26) from 1,6-Hexanediol. The conversion of the diol to **25** follows standard procedures and the conversion of **25** to **26** closely parallels the preparation of **24**. For this reason, the detailed procedures for all of these transformations appear as supplementary material.

Preparation of Methyl (1′-Benzenesulfonyl-1′-carbomethoxypentan-5′-yl)-6-acetoxy-7-octenoate (27). A solution of 6-acetoxy-7-octenoic acid (1.031 g, 5.155 mmol) in 5 mL of ether and 2 mL of thionyl chloride was refluxed for 4 h. Upon cooling, the solvent was carefully removed under reduced pressure (oil pump, 5 mm) with heating to 30 °C. The resulting tan-colored oil was redissolved in 3 mL of methylene chloride and cooled to 0 °C. A solution of **24** (2.064 g, 7.22 mmol) in 2 mL of pyridine and 2 mL of methylene chloride was slowly added and the mixture refluxed for 2 h. The reaction mixture was diluted with ether (150 mL), washed with 10% aqueous hydrochloric acid (2 × 20 mL), saturated aqueous sodium bicarbonate (2 × 20 mL), and saturated aqueous sodium chloride (20 mL), and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo to give a yellow oil which was purified by preparative TLC, eluting with 50% ethyl acetate in hexane, gave 2.037 g (84%) of **27**. NMR (100 MHz, $CDCl_3$): δ 7.90 (d of d, J = 7, 2 Hz, 2 H), 7.68 (m, 3 H), 5.82 (d of d of d, J = 16, 10, 6 Hz, 1 H), 5.23 (m, 3 H), 4.05 (m, 3 H), 3.68 (s, 3 H), 2.30 (m, 2 H), 2.06 (s, 3 H), 2.08–1.20 (bm, 12 H). ^{13}C NMR ($CDCl_3$): 172.5, 169.3, 165.6, 136.8, 136.0, 133.7, 128.7, 128.5, 116.0, 73.7, 70.1, 63.0, 52.2, 33.4, 33.3, 27.5, 25.8, 24.1, 23.0, 20.6. IR (CCl_4): 1750, 1460, 1370, 1330, 1310, 1235, 1148, 1082 cm^{-1}. Calcd for $C_{23}H_{32}O_8S$: 468.1830. Found: 468.1824.

Preparation of Methyl (1′-Benzenesulfonyl-1′-carbomethoxyheptan-7′-yl)-6-acetoxy-7-octenoate (28). 6-Acetoxy-7-octenoic acid (1.00 g, 5.00 mmol) was dissolved in 5 mL of ether and freshly distilled thionyl chloride (2.0 mL, 27.7 mmol) was slowly added. The mixture was refluxed for 3 h and cooled, and the solvent removed in vacuo (oil pump). The vacuum was released under nitrogen and the resulting yellow oil redissolved in 3 mL of ether. A solution of **26** (2.4 g, 7.6 mmol) in 2 mL of triethylamine and 5 mL of ether was added in one portion and the mixture heated at 40 °C for 5 h. The reaction mixture was diluted with water and extracted with a total of 100 mL of ether. The combined organic portions were back-extracted with 10% aqueous hydrochloric acid and saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC, eluting with 40% ethyl acetate in hexane to give 2.348 g (94%) of **28**. NMR (100 MHz, $CDCl_3$): δ 7.91 (d of d, J = 7, 4 Hz, 2 H), 7.67 (m, 3 H), 5.79 (d of d of d, J = 17.5, 10.5, 6 Hz, 1 H), 5.29–5.07 (m, 3 H), 4.02 (bm, 3 H), 3.63 (s, 3 H), 2.28 (m, 2 H), 2.03 (s, 3 H), 2.0–1.3 (bm, 16 H). IR (CCl_4): 1750, 1460, 1445, 1385, 1348, 1325, 1255, 1220, 1175, 1110, 1045 cm^{-1}. Calcd for $C_{25}H_{36}O_8S$: 496.2131. Found: 496.2130.

Cyclization of 27. Sodium hydride (40.9 mg, 1.02 mmol) was added to a solution of **27** (420 mg, 0.897 mmol) in 2 mL of THF and stirred at room temperature for 30 min. The resulting clear, yellow solution was diluted to a total volume of 9.5 mL with THF and added via a syringe pump at a rate of 1.0 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (28.6 mg, 0.0247 mmol) in 15 mL of THF. The needle used for the addition was fitted with a small glass-wool plug. After the addition, refluxing was continued for 2.5 h. The cloudy, yellow mixture was cooled, the solvent removed in vacuo, and the residue purified by preparative TLC (25% ethyl acetate in hexane, two elutions) to give 181.5 mg (49%) of **29**. Analysis of the crude reaction mixture by NMR indicated the absence of a terminal vinyl moiety by the lack of resonance signals between δ 5.24 and 4.8. NMR (100 MHz, $CDCl_3$): δ 7.85 (d of d, J = 7, 2 Hz, 2 H), 7.55 (m, 3 H), 5.79 (d of t, J = 15, 6.5 Hz, 1 H), 5.56 (d of t, J = 15, 7 Hz, 1 H), 4.09 (m, 2 H), 3.67 (s, 3 H, shoulder at 3.62), 2.87 (m, 2 H), 2.35 (m, 2 H), 2.01–1.28 (bm, 12 H). ^{13}C NMR ($CDCl_3$): δ 172.6, 168.0, 136.2, 135.3, 134.0, 129.9, 128.6, 124.3, 75.7, 62.8, 52.7, 35.1, 33.4, 30.9, 29.8, 29.5, 28.8, 23.1, 19.8. Analysis of the ^{13}C NMR spectrum indicated low-intensity resonance signals at δ 133, 122, 76, 63, 34, 28, 27, 24.5, and 21, which were assigned to (*Z*)-9-benzenesulfonyl-9-carbomethoxy-13-hydroxy-6-tridecenoic lactone. IR (CCl_4): 1730, 1445, 1322, 1308, 1230, 1145, 1322, 1308, 1240, 1145, 1080 cm^{-1}. Calcd for $C_{21}H_{28}O_6S$: 408.1607. Found: 408.1611.

Preparation of 33. Lactone **29** (200 mg, 0.490 mmol) and tetramethylammonium acetate (592 mg, 4.45 mmol) in 2 mL of hexamethylphosphoric triamide were heated at 90–95 °C for 6 h. The reaction mixture was partitioned between 30 mL of water and ether and extracted with ether (5 × 20 mL). The combined organic portions were

(91) Seyferth, D. In ref 49, Collect. Vol. IV, 1963; p 258.
(92) Diaper, D. G. M. *Can. J. Chem.* **1966**, *44*, 2819.

back-extracted with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC, eluting with 25% ethyl acetate in hexane (two elutions) to give 129.1 mg (76%) of **30** as a white solid. A sample was recrystallized from hexane–benzene to give white needles, mp 110–112.5 °C. NMR (270 MHz, $CDCl_3$): δ 7.91 (bd, J = 7.5 Hz, 2 H), 7.67 (bt, J = 7.5 Hz, 1 H), 7.56 (bt, J = 7.5 Hz, 2 H), 5.70 (d of t, J = 15.5, 6.8 Hz, 1 H), 5.31 (d of t, J =15.5, 6.8 Hz, 1 H), 4.03 (t, J = 5 Hz, 2 H), 3.02 (m, 1 H), 2.63 (m, 1 H), 2.31 (m, 3 H), 2.00 (m, 2 H), 1.69 (bm, 7 H), 1.35 (bm, 3 H). IR (CCl_4): 1730, 1445, 1320, 1305, 1245, 1148, 1085, 1065, 1020 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_4S$: C, 65.09; H, 7.48; S, 9.15; mol wt, 350.1552. Found: C, 65.08; H, 7.46; S, 9.06; mol wt, 350.1549.

Preparation of 13-Hydroxy-6-tridecenoate Lactone (35). Lactone **33** (90 mg, 0.257 mmol) was dissolved in 2.5 mL of THF. Absolute ethanol (2.0 mL) and anhydrous disodium hydrogen phosphate (143 mg, 1.0 mmol) were added and the mixture was cooled to −20 °C. Granulated 6% sodium amalgam (342 mg, 0.89 mmol) was added and the mixture stirred for 1 h, at which time additional amounts of disodium hydrogen phosphate (70 mg, 0.5 mmol) and sodium amalgam (200 mg, 0.52 mmol) were added. After the mixture was stirred for an additional 1 h, additional sodium amalgam (100 mg, 0.26 mmol) was added and the mixture stirred for 30 min. The reaction mixture was filtered through a glass-wool plug, diluted with saturated aqueous ammonium chloride, extracted with ether (40 mL), and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave a fragrant oil (83 mg). Purification by preparative TLC, eluting with 20% ethyl acetate, gave 37.5 mg (69%) of **35** as a waxy solid (R_f 0.51), which melted slowly upon heating to 35 °C. Analysis of the product with 270-MHz NMR revealed two triplets at δ 4.15 and 4.05 which were assigned to the Z and E isomers and which integrated in a ratio of 25:75, respectively. Irradiation at δ 2.00 collapsed the signal at δ 5.29 into two sets of resonances at δ 5.29 (d, J = 15 Hz) and 5.26 (d, J = 10.8 Hz) which were assigned to the E and Z isomers, respectively. NMR (270 MHz, $CDCl_3$): δ 5.46 (d of t, J = 15, 7.5 Hz, 1 H), 5.29 (d of t, J = 15, 7.5 Hz, 1 H), 4.15 (t, J = 5 Hz, 0.5 H), 4.05 (t, J = 5 Hz, 1.5 H), 2.38 and 2.31 (2 t, J = 6 Hz, 2 H), 2.03 (m, 4 H), 1.67 (m, 4 H), 1.38 (m, 8 H). IR (CCl_4): 1730, 1445, 1248 cm^{-1}. Calcd for $C_{13}H_{22}O_2$: 210.1620. Found: 210.1620.

Preparation of 13-Tridecanolide (37). Lactone **35** (30.4 mg, 0.144 mmol) and 5% palladium on barium carbonate in 10 mL of absolute ethanol were shaken under 2 atm of hydrogen for 2 h at room temperature. The reaction mixture was filtered through Celite, the vessel was rinsed with ethyl acetate, and the combined solvent portions were removed in vacuo, giving 30.1 mg (98%) of **37** as a colorless, thick oil. A sample was distilled (30 °C, 0.05 mm), giving a waxy, white solid, mp 24–26 °C (lit.[51] 25–26 °C). NMR (100 MHz, $CDCl_3$): δ 4.15 (bt, J = 6 Hz, 2 H), 2.36 (bt, J = 6 Hz, 2 H), 1.64–1.36 (bm, 20 H). ^{13}C NMR ($CDCl_3$): δ 173.7, 63.3, 34.4, 27.7, 26.3, 26.1, 25.9, 25.8, 24.9, 24.7, 24.2, 23.8, 22.9. IR (CCl_4): 1737, 1465, 1450, 1390, 1350, 1245, 1215 cm^{-1}. Calcd for $C_{13}H_{24}O_2$: 212.1776. Found: 212.1775.

Cyclization of Methyl (1′-Benzenesulfonyl-1′-carbomethoxyheptan-5′-yl)-6-acetoxy-7-octenoate (28). Sodium hydride (51 mg, 1.275 mmol) was added to a solution of **28** (524.2 mg, 1.056 mmol) dissolved in 2 mL of THF and heated to 45 °C for 10 min, then cooled and stirred at room temperature for 30 min. The resulting yellow mixture was diluted to a total volume of 13.0 mL with THF and added via a syringe pump at a rate of 1.5 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (42.4 mg, 0.0367 mmol) in 15 mL of THF. The needle used for the addition was equipped with a small glass-wool plug. After the addition, refluxing was continued for 4 h. The reaction mixture was cooled, partitioned between saturated aqueous ammonium chloride and ether, extracted with a total of 75 mL of ether, and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave a yellow oil (626 mg) which was purified by preparative TLC (25% ethyl acetate in hexane, two elutions) to give 319.4 mg (69%) of lactone **30** as a clear oil (R_f 0.3) which solidified on standing. Recrystallization of a sample from cyclohexane–ethanol gave prisms, mp 105–106 °C. Analysis of the crude reaction product by 100-MHz NMR indicated the absence of a terminal vinyl function by the lack of resonance signals between δ 5.8 and 6.2. Analysis of the chromatographed product by 270-MHz NMR indicated a small signal at δ 5.29 (d of t, J = 11.5, 7.5 Hz) which was assigned as one of the olefinic protons in the Z isomer. Irradiation at δ 2.80 collapsed this resonance to a doublet (J = 11.5 Hz). Estimation by peak height afforded an E:Z ratio of approximately 95:5. NMR (270 MHz, $CDCl_3$): δ 7.82 (d of m, J = 7.5 Hz, 2 H), 7.67 (t of t, J = 7.5, 1.5 Hz, 1 H), 7.55 (t of m, J = 7.5 Hz, 2 H), 5.56 (d of t, J = 15, 6.5 Hz, 1 H), 5.43 (d of t, J = 15, 7 Hz, 1 H), 5.29 (d of t, J = 11.5, 7.5 Hz, <5%), 4.11 (m, 2 H), 3.64 (s, 3 H), 2.88 (d of d, J = 15, 6.5 Hz, 1 H), 2.72 (d of d, J = 15, 7 Hz, 1 H), 2.32 (t, J = 7 Hz, 2 H), 2.04 (bm, 4 H), 1.62–1.36 (bm, 12 H). Irradiation at δ 2.04 collapses δ 5.56 (d, J = 15 Hz). Irradiation at δ 2.80 collapses δ 5.43 (d, J = 15 Hz) and 5.29 (d, J = 11.5 Hz). ^{13}C NMR ($CDCl_3$): δ 173.6, 168.3, 136.5, 135.3, 134.0, 130.1, 128.6, 123.7, 75.8, 63.4, 52.7, 35.4, 34.0, 32.5, 29.8, 29.1, 28.5, 27.5, 25.5, 23.7. IR (CCl_4): 1735, 1470, 1460, 1341, 1327, 1255 cm^{-1}. Anal. Calcd for $C_{23}H_{32}O_6S$: C, 63.26; H, 7.39; S, 7.35; mol wt, 436.1919. Found: C, 63.41; H, 7.45; S, 7.21; mol wt, 436.1916.

Preparation of (*E*)-9-Benzenesulfonyl-15-hydroxy-6-pentadecenoate Lactone (34). Lactone **30** (274.3 mg, 0.629 mmol) and tetramethylammonium acetate (730 mg, 5.49 mmol) in 2.2 mL of HMPA were heated at 90 °C for 10 h, at which time an additional amount of tetramethylammonium acetate (100 mg, 0.75 mmol) was added and heated for 1 h. The reaction mixture was cooled, partitioned between water (30 mL) and ether, extracted with a total of 70 mL of ether, and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave a yellow oil which was purified by preparative TLC (33% ethyl acetate in hexane) to give 210.7 mg (82.5%) of lactone **34** as a white solid. Recrystallization of a sample from a hexane–benzene mixture gave white crystals, mp 91.5–92 °C. NMR (100 MHz, $CDCl_3$): δ 7.97 (d of d, J = 7.5, 2 Hz, 2 H), 7.67 (m, 3 H), 5.45 (m, 2 H), 4.17 (m, 2 H), 3.01 (m, 1 H), 2.69–1.99 (bm, 6 H), 1.91–1.37 (bm, 14 H). IR (CCl_4): 1735, 1455, 1442, 1315, 1305, 1145, 1080, 965 cm^{-1}. Calcd for $C_{21}H_{30}O_4S$: 378.1865. Found: 378.1869.

Preparation of (*E*)-6-Pentadecen-15-olide (36). Lactone **34** (196.5 mg, 0.519 mmol) was dissolved in a mixture of 4 mL of dry THF and 4 mL of absolute ethanol and cooled to −20 °C. Anhydrous disodium hydrogen phosphate (295 mg, 2.08 mmol) followed by granulated 6% sodium amalgam (700 mg, 1.82 mmol) was added and stirred for 1 h. An additional amount of disodium hydrogen phosphate (250 mg, 1.76 mmol) and 6% sodium amalgam (700 mg, 1.82 mmol) was added and stirred for another 1.5 h. The reaction mixture was filtered, diluted with saturated aqueous ammonium chloride, and extracted with a total of 50 mL of ether. The organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo and the resulting gummy solid (133 mg) was purified by preparative TLC (33% ethyl acetate in hexane) to give 110.4 mg (89%) of lactone **36** as a white solid (R_f 0.8), mp 46–48 °C. The product appeared homogeneous by 270-MHz NMR, ^{13}C NMR, and VPC (10% XE-60 at 160 °C and 10% DC-710 at 175 °C) analysis. NMR (270 MHz, $CDCl_3$): δ 5.29 (m, 2 H), 4.11 (m, 2 H), 2.27 (bt, J = 7.5 Hz, 2 H), 2.03 (m, 4 H), 1.61 (bm, 16 H). ^{13}C NMR ($CDCl_3$): δ 173.7, 131.6, 130.4, 63.8, 35.5, 32.2, 28.7, 28.3, 28.1, 27.6, 26.3, 25.2, 24.2. Calcd for $C_{15}H_{26}O_2$: 238.1933. Found: 238.1933.

Preparation of 15-Pentadecanolide (Exaltolide, 38). A mixture of lactone **36** (92 mg, 0.386 mmol) and 5% palladium on barium carbonate (105 mg) was shaken under 2 atm of hydrogen for 3 h at room temperature. The mixture was filtered through Celite and the reaction vessel rinsed with ethyl acetate. The combined solvent portions were removed in vacuo to give 92.0 mg (99%) of **38** as a clear oil that solidified upon standing. Sublimation (20 °C, 0.05–0.03 mm) afforded a waxy, white solid, mp 33–35 °C (lit.[51] 32 °C). NMR (100 MHz, $CDCl_3$): δ 4.14 (bt, J = 6 Hz, 2 H), 2.33 (bt, J = 7 Hz, 2 H), 1.63–1.35 (bm, 24 H). ^{13}C NMR ($CDCl_3$): δ 173.7, 63.8, 34.4, 28.5, 27.8, 27.2, 27.0, 26.7, 26.4, 26.1, 25.9, 25.2, 24.9. IR (CCl_4): 1738, 1465, 1350, 1350 cm^{-1}. Calcd for $C_{15}H_{28}O_2$: 240.2089. Found: 240.2091.

Preparation of 6-Benzenesulfonyl-6-carbomethoxyhexanoic Acid (45). 5-Bromopentanoic acid (6.06 g, 33.48 mmol) in 12 mL of freshly distilled thionyl chloride was stirred at room temperature for 45 min, then at 45 °C for 2 h. The solvent was removed under reduced pressure and the residual yellow oil cooled to 0 °C. A freshly prepared solution of 2,2,2-trichloroethanol (6.013 g, 40.24 mmol) in 5 mL of methylene chloride and 5 mL of pyridine was added in one portion and the mixture stirred at room temperature for 1 h. After dilution with ether (175 mL), the mixture was washed successively with 10% aqueous hydrochloric acid (3 × 15 mL) and saturated aqueous sodium bicarbonate (15 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo gave 10.85 g of a yellow oil. Kugelrohr distillation (50 °C, 0.2 mm) removed all excess 2,2,2-trichloroethanol, leaving 9.48 g (91%) of 2′,2′,2′-trichloroethyl 5-bromopentanoate (**44**) as a yellow liquid, which was employed without further purification. NMR (100 MHz, $CDCl_3$): δ 4.79 (s, 2 H), 3.47 (bt, J = 6 Hz, 2 H), 2.54 (bt, J = 7 Hz, 2 H), 1.92 (m, 4 H).

A solution of methyl benzenesulfonylacetate (10.53 g, 49.21 mmol) in 10 mL of Me_2SO was slowly added to a cooled (0 °C) slurry of sodium hydride (1.94 g, 48.5 mmol) in 40 mL of Me_2SO. After the addition, stirring was continued for 1 h at room temperature, giving a clear, yellow solution. A solution of **44** (9.48 g, 30.37 mmol) in 10 mL of Me_2SO was added in one portion and the mixture heated at 50 °C for 3 h. Upon cooling, the reaction mixture was diluted with ether (300 mL), washed with water (5 × 20 mL), and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residual brown oil was purified

by dry column chromatography on silica gel (350 g, 25% ethyl acetate in hexane). This gave 10.53 g of 2′,2′,2′-trichloroethyl 6-benzenesulfonyl-6-carbomethoxyhexanoate (R_f 0.27–0.40) as a clear oil plus a second fraction (R_f 0.24–0.27) containing methyl benzenesulfonylacetate and product. Preparative TLC (30% ethyl acetate in hexane, two elutions) of this gave 617 mg of the trichloroethyl ester of the title compound for a combined yield of 11.147 g (82%). NMR (100 MHz, $CDCl_3$): δ 7.88 (m, 2 H), 7.64 (m, 3 H), 4.74 (s, 2 H), 3.96 (d of d, J = 6, 8 Hz, 1 H), 3.64 (s, 3 H), 2.40 (m, 2 H), 2.00 (m, 2 H), 1.84–1.20 (bm, 4 H). IR (CCl_4): 1750, 1445, 1435, 1372, 1330, 1310, 1265 cm^{-1}. Mass spectrum m/e (%): 384 (1), 382 (5), 380 (5), 305 (6), 303 (7), 299 (25), 298 (6), 297 (18), 289 (7), 287 (7), 273 (22), 271 (23), 265 (50), 255 (22), 214 (27), 163 (15), 155 (63), 141 (93), 127 (67), 123 (75), 113 (58), 95 (51), 85 (58), 77 (64), 71 (59), 59 (34).

Zinc dust (11.3 g, 172.8 mmol) was added in one portion to a cooled (0 °C) solution containing 2′,2′,2′-trichloroethyl 5-benzenesulfonyl-5-carbomethoxypentanoate (11.17 g, 25.07 mmol) in 51 mL of DMF and 20 mL of glacial acetic acid. After stirring at 0 °C for 45 min, the reaction mixture was diluted with 300 mL of ethyl acetate, washed with 10% aqueous hydrochloric acid (2 × 40 mL), and water (6 × 50 mL), and dried over anhydrous sodium sulfate. After removal of the solvent in vacuo, the residual dark oil was purified by dry column chromatography on silica gel (150 g, 50% ethyl acetate in hexane) to give 5.553 g (70.5%) of **45**. NMR (100 MHz, $CDCl_3$): δ 11.93 (bs, 1 H), 7.91 (m, 2 H), 7.66 (m, 3 H), 4.01 (d of d, J = 9, 7 Hz, 1 H), 3.66 (s, 3 H), 2.36 (bt, J = 7 Hz, 2 H), 2.02 (m, 2 H), 1.8–1.2 (bm, 4 H). IR (CCl_4): 3600–2500 (b), 1740, 1710, 1450, 1435, 1412, 1328, 1312 cm^{-1}. Calcd for $C_{14}H_{18}O_6S$: 314.0824. Found: 314.0827.

Preparation of 3-Hydroxybutan-1-yl Benzoate (39). Benzoyl chloride (30 mL, 0.258 mol), dissolved in 40 mL of methylene chloride, was added dropwise over 3.5 h to a cooled (0 °C) solution containing 1,3-butanediol (34.1 g, 0.378 mol) in 280 mL of methylene chloride and 90 mL of pyridine. After stirring for an additional 25 h at 0 °C, the reaction mixture was diluted with ether (700 mL), washed successively with 10% aqueous hydrochloric acid (6 × 50 mL) and saturated aqueous sodium bicarbonate (50 mL), and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent in vacuo, the cloudy oil was purified by dry column chromatography on silica gel (three columns, each containing 175 g), eluting with 25% ethyl acetate in hexane, to give 45.61 g (91%) of **39**. NMR (100 MHz, $CDCl_3$): δ 8.04 (d of d, J = 8, 2 Hz, 2 H), 7.47 (m, 3 H), 4.50 (m, 2 H), 4.03 (sextet, J = 6 Hz, 1 H), 3.43 (s, 1 H), 1.91 (q, J = 7 Hz, 2 H), 1.29 (d, J = 7 Hz, 3 H). IR (CCl_4): 3645, 3540 (b), 1730, 1455, 1385, 1320 cm^{-1}. Calcd for $C_{11}H_{14}O_3$: 194.0943. Found: 194.0914.

Preparation of 3-(*tert*-Butyldimethylsiloxy)butanol (40). A solution containing **39** (10.15 g, 57.02 mmol) and imidazole (8.42 g, 123.8 mmol) in 24 mL of dry DMF was cooled to 0 °C and *tert*-butyldimethylsilyl chloride (8.58 g, 57.0 mmol) was added in portions over 15 min. After an additional 20 min at 0 °C, the mixture was allowed to stir at room temperature for 8 h. After dilution with 300 mL of pentane, the mixture was washed with water (5 × 50 mL) and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave 16.61 g (99%) of 3-(*tert*-butyldimethylsiloxy)butan-1-yl benzoate. The product was homogeneous by NMR and TLC analysis and was used without further purification. NMR (100 MHz, CCl_4): δ 8.04 (d of d, J = 7, 2 Hz, 2 H), 7.44 (m, 3 H), 4.39 (t, J = 7 Hz, 2 H), 4.06 (sextet, J = 7 Hz, 1 H), 1.87 (m, 2 H), 1.24 (d, J = 7 Hz, 3 H), 0.94 (s, 9 H), 0.09 (s, 6 H). IR (CCl_4): 1730, 1475, 1468, 1455, 1380, 1368, 1320 cm^{-1}. Mass spectrum m/e (%): 252 (10), 215 (51) (M − C_4H_9), 180 (10), 179 (34), 159 (14), 106 (41), 105 (100), 77 (3), 73 (8).

A 20% aqueous sodium hydroxide solution (20 mL) was added to a solution containing 3-(*tert*-butyldimethylsiloxy)butan-1-yl benzoate (16.61 g, 53.9 mmol) in 50 mL of THF and 10 mL of methanol. After vigorous stirring at room temperature for 36 h, the mixture was diluted with 300 mL of pentane, washed successively with 10% aqueous sodium hydroxide (2 × 20 mL), water (20 mL), and saturated aqueous ammonium chloride (20 mL), and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave a clear liquid which upon Kugelrohr distillation (45–50 °C, 0.08 mm) afforded 10.43 g (95%) of **40**. NMR (100 MHz, CCl_4): δ 3.94 (sextet, J = 6 Hz, 1 H), 3.54 (bt, J = 6 Hz, 2 H), 3.07 (bs, 1 H), 1.54 (m, 2 H), 1.07 (d, J = 7 Hz, 3 H), 0.79 (s, 9 H), −0.03 (s, 6 H). IR (CCl_4): 3645, 3540 (b), 2960, 2935, 2885, 2860, 1470, 1462, 1375, 1360 cm^{-1}. Mass spectrum m/e (%): 189 (1), 161 (2), 159 (5), 146 (30), 119 (75), 105 (4), 101 (5), 77 (96), 76 (12), 75 (100), 73 (23), 55 (7). Calcd for $C_{10}H_{24}SiO_2$: 204.1545. Found: 204.1541.

Preparation of Ethyl (*E*)-5-(*tert*-Butyldimethylsiloxy)-2-hexenoate (41). Pyridinium chlorochromate (13.12 g, 60.94 mmol) was added in two portions to a cooled (0 °C) solution of **40** (6.0 g, 29.4 mmol) in 120 mL of methylene chloride containing anhydrous sodium acetate (1.98 g, 24.2 mmol). The mixture was allowed to warm to room temperature and stirred for 1.5 h. Anhydrous ether (300 mL) was added and vigorously stirred for 5 min, then filtered through a short column containing silica gel and Florisil. The reaction vessel and column were rinsed with a total of 300 mL of ether and the combined portions washed with 10% aqueous sodium hydroxide and saturated aqueous sodium chloride and dried over magnesium sulfate. The product was concentrated to 15 mL by distillation (Widmer column) to give 3-(*tert*-butyldimethylsiloxy)butanal as a yellow solution in ether. This was used immediately without further purification.

To a cooled (0 °C) slurry of sodium hydride (1.70 g, 42.5 mmol) in 60 mL of tetrahydrofuran was added triethyl phosphonoacetate (8.60 mL, 43.3 mmol) over 20 min. After an additional 40 min, the resulting clear, yellow solution was cooled to −78 °C and the freshly prepared 3-(*tert*-butyldimethylsiloxy)butanal in 15 mL of ether was added over 30 min. The mixture was allowed to slowly warm to 0 °C and stirred at this temperature for another 30 min. After partitioning between ether and saturated aqueous ammonium chloride and removal of the aqueous layer, the organic phase was washed with water (4 × 20 mL) and saturated aqueous sodium chloride (20 mL) and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave 5.61 g (70%) of crude **41** as a yellow liquid which was used without further purification. A sample of this was purified via VPC (10% DC-710 on Chromosorb W, 60/80 mesh, 2.46 m × 0.64 cm, t = 150 °C) for spectral characterization. NMR (270 MHz, $CDCl_3$): δ 6.95 (d of t, J = 15.3, 7.5 Hz, 1 H), 5.82 (d of t, J = 15.5, 1.5 Hz, 1 H), 4.18 (q, J = 7.2 Hz, 2 H), 3.92 (sextet, J = 6 Hz, 1 H), 2.32 (m, 2 H), 1.28 (t, 6.9 Hz, 3 H), 1.16 (d, J = 6.1 Hz, 3 H), 0.88 (s, 9 H), 0.05, 0.04 (two singlets, 6 H). IR (CCl_4): 1735, 1665, 1480, 1470, 1455, 1390, 1380, 1370, 1320 cm^{-1}. Calcd for $C_{14}H_{28}O_3Si$: 272.1808. Found: 272.1084.

Preparation of (*E*)-5-(*tert*-Butyldimethylsiloxy)-2-hexen-1-ol. Ester **41** (5.61 g, 20.6 mmol) was dissolved in 20 mL of dry toluene and cooled to 0 °C. Diisobutylaluminum hydride (1.41 M in hexane, 38 mL, 53.6 mmol) was slowly added and stirring continued for 30 min. Absolute ethanol (1.5 mL) was carefully added, followed by saturated aqueous sodium sulfate (2 mL), and the mixture vigorously stirred at 0 °C for 10 min. Upon dilution with 100 mL of ether and continued stirring, a thick gel formed. Anhydrous sodium sulfate (20 g) was added and the mixture stirred for 2 h. After filtration, the gelatinous solid was washed with ether and the portions were removed in vacuo to give 3.89 g (88%) of the title compound as a clear oil which was used without further purification. A sample was purified via VPC (10% DC-710 on Chromosorb W, 60/80 mesh, 2.46 m × 0.64 cm, t = 150 °C) for spectral characterization. NMR (270 MHz, $CDCl_3$): δ 5.68 (m, 2 H), 4.10 (bd, J = 4.8 Hz, 2 H), 3.38 (sextet, J = 6.3 Hz, 1 H), 2.17 (m, 2 H), 1.50 (bs, 1 H), 1.13 (d, J = 6.3 Hz, 3 H), 0.88 (s, 9 H), 0.05, 0.04 (two singlets, 6 H). IR (CCl_4): 3630, 3490 (b), 1478, 1470, 1375, 1360 cm^{-1}. Calcd for $C_{12}H_{26}O_2Si$: 230.1702. Found: 230.1697.

Preparation of (*E*)-1-Acetoxy-2-hexen-5-ol (43). Acetyl chloride (5 mL, 70 mmol) was added dropwise to a cooled (0 °C) solution of 5-(*tert*-butyldimethylsiloxy)-2-hexen-1-ol (3.89 g, 18.18 mmol) in 25 mL of methylene chloride and 10 mL of pyridine. After the white slurry was stirred for 30 min, the mixture was diluted with 100 mL of ether, washed successively with 10% aqueous hydrochloric acid (3 × 15 mL) and saturated aqueous sodium bicarbonate (2 × 15 mL), and dried over anhydrous magnesium sulfate. After filtration, removal of the solvent in vacuo gave 4.48 g (91%) of (*E*)-1-acetoxy-5-(*tert*-butyldimethylsiloxy)-2-hexene as a clear oil which was used without further purification. A sample was purified by VPC (10% DC-710 on Chromosorb W, 60/80 mesh, 2.46 m × 0.64 cm, t = 150 °C). The silyl ether was dissolved in 30 mL of tetrahydrofuran, 20 mL of water, and 10 drops of 60% aqueous perchloric acid. The two-phase mixture was vigorously stirred at room temperature for 8 h. After dilution with 100 mL of ether, the reaction mixture was washed with saturated aqueous sodium bicarbonate (20 mL) and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave an oil that was purified by column chromatography on silica gel (100 g), eluting with hexane (100 mL), 20% ethyl acetate in hexane (300 mL), and 50% ethyl acetate in hexane (300 mL) to give 2.482 g (95%) of the title compound as a clear, colorless oil. The overall yield, starting from 3-(*tert*-butyldimethylsiloxy)-1-butanol, was 53%. **42**: NMR (270 MHz, $CDCl_3$) δ 5.77 (d of t, J = 15.5, 7, 1 Hz, 1 H), 5.59 (d of t of t, J = 15.5, 6.3, 1 Hz, 1 H), 4.51 (d of d, J = 6.3, 1 Hz, 2 H), 3.83 (sextet, J = 5.9 Hz, 1 H), 2.05 (s, 3 H), 2.18 (m, 2 H), 1.13 (d, J = 6.1 Hz, 3 H), 0.88 (s, 9 H), 0.04 and 0.03 (two singlets, 6 H); IR (CCl_4) 1750, 1475, 1468, 1450, 1375, 1360 cm^{-1}; mass spectrum m/e (%) 215 (0.13) (M − C_4H_9), 171 (1), 161 (21), 160 (14), 159 (78), 155 (5), 143 (5), 119 (12), 118 (25), 117 (100), 115 (26), 103 (21), 101 (14), 81 (80), 77 (11), 75 (86), 73 (92). **43**: NMR (270 MHz, $CDCl_3$) δ 5.79 (d of t, J = 15.4, 7 Hz, 1 H), 5.65 (d of t, J = 15.4, 6.1 Hz, 1 H), 4.53 (d, J = 6.1 Hz, 2 H), 3.85 (sextet, J = 6 Hz, 1 H), 3.56 (s, 1 H),

2.22 (t, J = 6 Hz, 2 H), 2.07 (s, 3 H), 1.18 (d, J = 6 Hz, 3 H); IR (CCl_4) 3630, 3500, 1735, 1440, 1375, 1360, 1260, 1225 cm^{-1}. Calcd for $C_8H_{14}O_3$: 158.0943. Found: 158.0944.

Preparation of (*E*)-1′-Acetoxy-2′-hexen-5′-yl 6-Benzenesulfonyl-6-carbomethoxyhexanoate (46). Acid **45** (1.512 g, 4.81 mmol) was dissolved in 6 mL of freshly distilled thionyl chloride and DMF (20 μL) was added. After the mixture was heated at 40–45 °C for 4 h, the solvent was removed at reduced pressure (oil pump, 5 mm) with heating (40 °C). The vacuum was released under nitrogen and the tan-colored residue cooled to 0 °C. A solution containing alcohol **43** (616.5 mg, 3.90 mmol) in 2 mL of pyridine and 2 mL of ether was added in one portion with vigorous stirring. After heating at reflux for 30 min, the mixture was cooled, diluted with 200 mL of ether, washed with 10% aqueous hydrochloric acid (3 × 20 mL) and saturated aqueous sodium bicarbonate (20 mL), and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave a yellow oil which was purified by preparative TLC (30% ethyl acetate in hexane) to give 1.403 g (79%) of the title compound as a clear, colorless oil (R_f 0.21). NMR (270 MHz, $CDCl_3$): δ 7.86 (d of m, J = 7 Hz, 2 H), 7.70 (t of t, J = 7.5, 1.5 Hz, 1 H), 7.59 (t of m, J = 8 Hz, 2 H), 5.65 (m, 2 H), 4.92 (sextet, J = 6.3 Hz, 1 H), 4.50 (d, J = 5 Hz, 2 H), 3.95 (d of d, J = 10.5, 4.5 Hz, 1 H), 3.66 (s, 3 H), 2.29 (m, 4 H), 2.06 (s, 3 H), 2.02 (m, 2 H), 1.61 (m, 2 H), 1.35 (m, 2 H), 1.19 (d, J = 6.1 Hz, 3 H). IR (CCl_4): 1735, 1448, 1435, 1330, 1310, 1230 cm^{-1}. Calcd for $C_{22}H_{30}O_8S$: 454.1661. Found: 454.1655.

Cyclization of (*E*)-1′-Acetoxy-2′-hexen-5′-yl 6-Benzenesulfonyl-6-carbomethoxyhexanoate (46). Substrate **46** (440.1 mg, 0.969 mmol), which had been thoroughly dried under vacuum, was dissolved in 2 mL of THF and cooled to 0 °C. Sodium hydride (40.3 mg, 1.05 mmol) was added in one portion and the mixture maintained at 0 °C for 30 min, then at room temperature for 15 min to give a colorless solution. After dilution to a total volume of 11.5 mL with THF, the solution was transferred to a gas-tight syringe which was fitted with a 30-cm needle. A small piece of glass wool was fitted into the top of the syringe needle. This solution was added via a syringe pump at a rate of 4 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (60.6 mg, 0.053 mmol) and 1,2-bis(diphenylphosphino)ethane (41.0 mg, 0.103 mmol) in 11 mL of THF. After addition, TLC analysis indicated complete absence of starting material. The cloudy, yellow mixture was cooled and filtered, and the solid residue rinsed with ether. The solvent was removed in vacuo and purified by preparative TLC (30% ethyl acetate in hexane) to give 298.8 mg (78%) of lactone **47** as a white solid (R_f 0.25). Analysis of the product by 270-MHz NMR revealed two sets of doublets at δ 1.27 and 1.23 which were assigned as the diastereomeric methyl protons and which integrated in a ratio of 1:1.5, respectively. Recrystallization from absolute ethanol and hexane gave white crystals, mp 126–129.5 °C. NMR (270 MHz, $CDCl_3$): δ 7.79 (t of m, J = 6.2 Hz, 2 H), 7.67 (m, 1 H), 7.56 (m, 2 H), 5.58 (d of d of d of d, J = 15.5, 10.5, 2.0, 1.5 Hz, 0.4 H), 5.51 (d of d of d of d, J = 15, 11, 3, 2 Hz, 0.6 H), 5.37 (d of d of d of c, J = 15.5, 10.5, 4, 2 Hz, 0.4 H), 5.27–5.07 (m, 1.6 H), 3.62 (s, 3 H), 3.03 (m, 1 H), 2.80 (d of d, J = 13.6, 10.8 Hz, 0.6 H), 2.55 (d of d, J = 16.1, 10.8 Hz, 0.4 H), 2.62–1.68 (m, 8 H), 1.43 (bm, 2 H), 1.27 (d, J = 6.5 Hz, 1.2 H), 1.23 (d, J = 6.5 Hz, 1.8 H). IR (CCl_4): 1722, 1447, 1365, 1325, 1310, 1270, 1250, 1225 cm^{-1}. Anal. Calcd for $C_{20}H_{18}O_6S$: C, 60.89; H, 6.64; S, 8.13. Found: C, 60.83; H, 6.56; S, 8.09.

Preparation of (*E*)-6-Benzenesulfonyl-11-hydroxy-8-dodecenoate Lactone (48). Tetramethylammonium acetate (438 mg, 3.29 mmol) and lactone **47** (143.6 mg, 0.364 mmol) were heated in 2 mL of HMPA at 95–100 °C for 3 h. Since monitoring the reaction by TLC analysis proved difficult, an additional amount of tetramethylammonium acetate (201.4 mg, 1.51 mmol) was added and heating continued for 3 h to ensure complete reaction. Upon cooling, the reaction mixture was partitioned between hexane and water and extracted with a total of 120 mL of hexane. The combined organic extracts were washed with water (2 × 15 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo, giving 141 mg of a yellow solid. Purification by preparative TLC eluting with 30% ethyl acetate in hexane gave 104.9 mg (86%) of lactone **48** as a white foam (R_f 0.43). Analysis of the product by NMR revealed two sets of doublets at δ 1.26 and 1.20 assigned as the diastereomeric methyl protons whose peak heights indicated a ratio of 1:1.7, respectively. NMR (270 MHz, $CDCl_3$): δ 7.85 (t of m, J = 7.5 Hz, 2 H), 7.65 (t of m, J = 7.5 Hz, 1 H), 7.53 (t of m, J = 7.5 Hz, 2 H), 5.60 (m, 0.37 H), 5.46–5.01 (m, 2.63 H), 3.05 (m, 1 H), 2.68 (m, 1 H), 2.41–2.07 (m, 6 H), 2.07–1.77 (m, 1 H), 1.75–1.31 (m, 4 H), 1.26 and 1.20 (two doublets, J = 7.5 Hz, 3 H). IR (CCl_4): 1730, 1478, 1448, 1380, 1365, 1320, 1307 cm^{-1}. Calcd for $C_{18}H_{24}O_4S$: 336.1395. Found: 336.1399.

Preparation of (*E*)-11-Hydroxy-8-dodecenoate Lactone (Recifeiolide, 49). Lactone **48** (101.1 mg, 0.297 mmol) dissolved in a mixture of absolute ethanol (2.5 mL) and dry THF (2.5 mL) was cooled to −20 °C. Anhydrous disodium hydrogen phosphate (200 mg, 1.40 mmol) was added and after 10 min granulated 6% sodium amalgam (490 mg, 1.27 g-atoms) was added. After 45 min TLC analysis indicated remaining starting material, and additional disodium hydrogen phosphate (150 mg, 1.04 mmol) and 6% sodium amalgam were added and stirred for 30 min. After dilution with ether (15 mL) the reaction mixture was filtered and the solid residue rinsed with ether. The combined organic portions were washed with saturated aqueous ammonium chloride (2 × 10 mL) and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo (at 10 °C) gave 55 mg (94%) of pure recifeiolide as a fragrant, colorless oil. The synthetic product was identical with an authentic sample[56] of recifeiolide (E:Z mixture, 88:12) by NMR (270 MHz), IR, mass spectral, and VPC (15% Carbowax 2M on Chromosorb W, 60/80 mesh, 3.66 m × 0.32 cm, t = 165 °C) comparison. Analysis of the E:Z ratio in the authentic sample by NMR revealed two sets of doublets at δ 1.28 and 1.24 corresponding to the methyl groups of the Z and E isomers, respectively. The doublet at δ 1.28 (Z isomer) was completely absent in our synthetic sample. NMR (270 MHz, $CDCl_3$): δ 5.29 (m, 2 H), 5.17 (m, 1 H), 2.45-1.76 (bm, 6 H), 1.67–1.17 (bm, 8 H), 1.24 (d, J = 6.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$): 173.2, 133.4, 127.1, 68.5, 41.1, 33.0, 30.4, 25.1, 24.8, 24.3, 23.4, 20.6. Calcd for $C_{12}H_{20}H_2$: 196.1463. Found: 196.1466.

Preparation of 1,1-Dimethoxy-5-hexanol. A solution of 1-methylcyclopentene[92] (8.30 g, 101.2 mmol) in 50 mL of methanol and 50 mL of methylene chloride was divided into five equal portions and cooled to −78 °C. Ozone was bubbled through each solution to a blue end point. After the reaction mixtures were purged with oxygen, dimethyl sulfide (4 mL to each flask) was added, the temperature raised to room temperature, and the mixture stirred for 3 h. The combined portions were concentrated by distillation at atmospheric pressure to remove methylene chloride and dimethyl sulfide, then under reduced pressure (water aspirator) at 25 °C to remove methanol. Absolute ethanol (80 mL) was added and the solution cooled to 0 °C. Sodium borohydride (2.35 g, 62.3 mmol) was added in portions over 10 min and stirred for 30 min. The solution was concentrated in vacuo and aqueous ammonium chloride carefully added to the cloudy, white residue. The mixture was extracted with ether (5 × 50 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 15.32 g (93%) of 1,1-dimethoxy-5-hexanol as a clear, colorless oil. The crude product was homogeneous by TLC (33% ethyl acetate in hexane, R_f 0.2). A sample purified by preparative TLC (33% ethyl acetate in hexane, R_f 0.25) was identical by NMR with the crude material. NMR (100 MHz, $CDCl_3$): δ 4.37 (bt, J = 6 Hz, 1 H), 3.80 (m, 1 H), 3.32 (s, 6 H), 2.57 (bs, 1 H), 1.52 (bm, 6 H), 1.10 (d, J = 6 Hz, 3 H). IR (CCl_4): 3680, 3625, 3460, 1415, 1385, 1375 cm^{-1}. Mass spectrum m/e (%): 129 (1), 99 (13), 98 (26), 97 (3), 83 (23), 81 (15), 77 (17), 70 (35), 69 (28), 61 (62), 58 (92), 57 (55), 55 (91), 54 (10), 53 (20), 45 (16), 42 (100).

Preparation of 5-Acetoxyhexanal (51). Acetyl chloride (8.5 mL, 119.5 mmol), dissolved in 50 mL of methylene chloride, was added over 1 h to a cooled (0 °C) solution of 1,1-dimethoxy-5-hexanol (15.32 g, 94.56 mmol) in 50 mL of methylene chloride and 20 mL of pyridine. After 30 min, the mixture was warmed to room temperature for an additional 1.5 h. The white slurry was shaken with 10% aqueous hydrochloric acid (3 × 50 mL) over 1.5 h to complete hydrolysis of the acetal. The organic portion was washed with saturated aqueous sodium bicarbonate (2 × 50 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 11.2 g (75%) of **51** as a clear, slightly yellow liquid. The crude product was homogeneous by TLC (50% ethyl acetate in hexane, R_f 0.7) but possessed an unassigned resonance at δ 3.30 in the NMR (100 MHz, $CDCl_3$): δ 9.78 (bs, 1 H), 4.91 (m, 1 H), 2.26 (m, 2 H), 2.00 (s, 3 H), 1.60 (bm, 4 H), 1.21 (d, J = 7 Hz, 3 H). IR (CCl_4): 2710, 1745, 1370, 1240 cm^{-1}. Mass spectrum m/e (%): 157 (0.2), 130 (3), 129 (2), 116 (7), 115 (30), 114 (5), 113 (7), 102 (6), 101 (18), 99 (22), 98 (59), 97 (21), 88 (10), 87 (47), 86 (60), 83 (44), 81 (27), 80 (33), 75 (50), 71 (50), 70 (74), 69 (62), 61 (44), 58 (44), 57 (35), 56 (24), 54 (28), 43 (100). Calcd for $C_8H_{14}O_3$: 158.0943. Found: 158.0944.

Preparation of (*E*)-1-Acetoxy-2-octen-7-ol (54) from 51. The procedures closely paralleled those for the preparation of **43** and thus the details appear as supplementary material. Analysis of **54** by 270-MHz NMR revealed two doublets (J = 6 Hz) at δ 4.50 and 4.62 which were assigned to the allylic methylene protons of the E and Z isomers, respectively. Integration gave an E:Z ratio of greater than 98.2. NMR (270 MHz, $CDCl_3$): δ 5.77 (d of t of t, J = 15.3, 6.3, 1 Hz, 1 H), 5.56 (d of t of t, J = 15.3, 6.3, 1 Hz, 1 H), 4.50 (d of d, J = 6.3, 1 Hz, 2 H), 3.78 (sextet, J = 6 Hz, 1 H), 2.55 (bs, 1 H), 2.10 (m, 2 H), 2.06 (s, 3 H), 1.46 (m, 4 H), 1.18 (d, J = 6.1 Hz, 3 H). IR (CCl_4): 3620, 3480 (b), 1750, 1458, 1375, 1360, 1228 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74; mol wt, 186.1256. Found: C, 64.46; H, 9.62; mol wt, 186.1253.

Preparation of (*E*)-1-Acetoxy-2-octen-7-yl Benzenesulfonylacetate (58). Diethyl azodicarboxylate (871 mg, 5.0 mmol) in 1 mL of toluene was added over 10 min to a cooled (0 °C) mixture of benzenesulfonylacetic acid (1.072 g, 5.36 mmol), monoacetate **54** (755.6 mg, 4.062 mmol), and triphenylphosphine (1.31 g, 5.0 mmol) in 5 mL of toluene. After 30 min, the cloudy, white mixture was warmed and stirred at room temperature for 2 h. After dilution with ether, the mixture was washed with saturated aqueous sodium bicarbonate and water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the solid residue purified by preparative TLC (50% ethyl acetate in hexane) to give 1.300 g (87%) of the title compound as a clear, colorless oil (R_f 0.3). NMR (270 MHz, $CDCl_3$): δ 7.95 (d of m, J = 7.5 Hz, 2 H), 7.69 (t of t, J = 7.5, 1.5 Hz, 1 H), 7.58 (t of m, J = 7.5 Hz, 2 H), 5.71 (d of t of t, J = 15.5, 6.5, 1 Hz, 1 H), 5.55 (d of t of t, J = 15.5, 6.5, 1 Hz, 1 H), 4.88 (sextet, J = 6 Hz, 1 H), 4.50 (d of d, J = 6, 1 Hz, 2 H), 4.12 (s, 2 H), 2.05 (s, 3 H), 2.03 (m, 2 H), 1.42 (m, 4 H), 1.15 (d, J = 6.5 Hz, 3 H). IR (CCl_4): 1740, 1450, 1380, 1340, 1280, 1230, 1160, 1088, 1028 cm^{-1}. Calcd for $C_{18}H_{24}O_6S$: 368.1294. Found: 368.1289.

Preparation of (*Z*)-1,7-Bis(*tert*-butyldimethylsiloxy)-2-octene (56). *tert*-Butyldimethylsilyl chloride (2.86 g, 19.0 mmol) was added to a cooled (0 °C) solution of diol **53** (1.24 g, 8.61 mmol) and imidazole (2.31 g, 33.9 mmol) in 5 mL of DMF. After stirring at room temperature for 8 h, the cloudy mixture was diluted with 150 mL of pentane, washed with water (4 × 20 mL), and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give 2.77 g (86%) of **55** which was employed without further purification. NMR (100 MHz, $CDCl_3$): δ 5.61 (m, 2 H), 4.16 (bd, J = 5 Hz, 2 H), 3.84 (m, 1 H), 2.08 (m, 2 H), 1.46 (m, 4 H), 1.16 (d, J = 6 Hz, 3 H), 0.92 (s, 18 H), 0.08 and 0.06 (two singlets, 12 H). IR (CCl_4): 1474, 1470, 1372, 1360, 1252, 1182, 1052, 1002 cm^{-1}.

m-Chloroperbenzoic acid (85% technical, 1.74 g, 8.57 mmol) was slowly added to a vigorously stirred mixture of silyl ether **55** (2.77 g, 7.45 mmol) in 50 mL of methylene chloride and 16.5 mL of aqueous sodium bicarbonate (0.5 M).[93] After 4 h, the aqueous layer was separated and the organic portion washed successively with 10% aqueous sodium hydroxide (2 × 20 mL), water (20 mL), and saturated sodium chloride (20 mL) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the resulting clear oil dissolved in 3 mL of dry THF. A 1 M solution of lithium diphenylphosphide (10 mL, 10.0 mmol) in THF was prepared according to the method of Vedejs and Fuchs[58] and added over 10 min. After 8 h at room temperature, methyl iodide (1.25 mL, 20 mmol) was added and stirred for 30 min. The mixture was diluted with ether, washed with water, and dried over magnesium sulfate. The solvent was removed in vacuo and purified by preparative TLC (14% ethyl acetate in hexane) to give 648.4 mg (23%) of **56**. NMR (270 MHz, $CDCl_3$): δ 5.52 (d of t of t, J = 11, 6, 1.5 Hz, 1 H), 5.42 (d of t of t, J = 11, 7, 1.5 Hz, 1 H), 4.23 (d of d, J = 6, 1 Hz, 2 H), 3.78 (m, 1 H), 2.03 (m, 2 H), 1.40 (m, 4 H), 1.11 (d, J = 6.3 Hz, 3 H), 0.908 and 0.889 (two singlets, 18 H), 0.076 and 0.046 (two singlets, 12 H). Irradiation at δ 2.03 collapses resonances at δ 5.52 (d of t, J = 11, 6 Hz) and 5.42 (d, J = 11 Hz). Irradiation at δ 4.22 collapses the resonance at δ 5.52 (d, J = 11 Hz) and 5.42 (d of t, J = 11, 7 Hz). IR (CCl_4): 1475, 1468, 1255, 1130 cm^{-1}. Calcd for $C_{20}H_{44}O_2Si_2$: 372.2880. Found: 372.2868.

Preparation of (*Z*)-2-Octene-1,7-diol. A solution of silyl ether **56** (630 mg, 1.69 mmol) in 5 mL of THF and 4 mL of water containing 4 drops of 60% aqueous perchloric acid was stirred at room temperature for 8 h. The mixture was diluted with 10 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 30 mL). The combined organic portions were dried over anhydrous sodium sulfate and the solvent was removed in vacuo. The crude oil was purified by preparative TLC (50% ethyl acetate in hexane containing 5% chloroform) to give 187.3 mg (77%) of (*Z*)-2-octene-1,7-diol as a clear, colorless oil. A sample was prepared for analysis by distillation (90 °C, 0.02 mm). NMR (270 MHz, $CDCl_3$): δ 5.60 (d of t, J = 11, 6.3 Hz, 1 H), 5.51 (d of t, J = 11, 7.3 Hz, 1 H), 4.15 (d, J = 6 Hz, 2 H), 3.77 (m, 1 H), 2.99 (bs, 2 H), 2.09 (m, 2 H), 1.44 (m, 4 H), 1.17 (d, J = 6 Hz, 3 H). IR (film): 3440, 1660, 1465, 1375 cm^{-1}. Anal. Calcd for $C_8H_{16}O_2$: C, 66.61; H, 11.19; mol wt, 144.1150. Found: C, 66.60; H, 11.18; mol wt, 144.1148.

Preparation of (*Z*)-1-Acetoxy-2-octen-7-ol (57). Acetic anhydride (120 μL, 1.27 mmol) was slowly added to a cooled (−78 °C) solution of (*Z*)-2-octene-1,7-diol (170 mg, 1.18 mmol) in 350 μL of pyridine and 1 mL of methylene chloride and stored at −14 °C for 48 h. After dilution with 50 mL of ether, the mixture was washed with 10% aqueous hydrochloric acid (15 mL) and saturated aqueous sodium bicarbonate (10 mL) and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the resulting oil purified by preparative TLC (33% ethyl acetate in hexane) to give 154.7 mg of monoacetate **57** as a clear, colorless oil (R_f 0.2–0.3) and 29.5 mg of recovered (*Z*)-2-octene-1,7-diol (R_f 0.05–0.1). The yield based on unrecovered starting material was 85%. Analysis by 270-MHz ^1H NMR indicated two doublets (J = 6 Hz) at δ 4.62 and 4.50 which were assigned to the allylic methylene protons of *Z* and *E* isomers, respectively. Integration gave a ratio of *Z*:*E* of greater than 98:2. NMR (270 MHz, $CDCl_3$): δ 5.65 (d of t of t, J = 11, 7.3, 1.5 Hz, 1 H), 5.53 (d of t of t, J = 11, 6.8, 1.5 Hz, 1 H), 4.62 (d, J = 6.5 Hz, 2 H), 3.78 (m, 1 H), 2.27 (bs, 1 H), 2.13 (m, 2 H), 2.06 (s, 3 H), 1.45 (m, 4 H), 1.18 (d, J = 6.3 Hz, 3 H). IR (CCl_4): 3630, 3500, 1750, 1460, 1370, 1230 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74; mol wt, 186.1256. Found: C, 64.36; H, 9.77; mol wt, 186.1255.

Preparation of (*Z*)-1-Acetoxy-2-octen-7-yl Benzenesulfonylacetate (59). Diethyl azodicarboxylate (174 mg, 1.00 mmol) in 1 mL of toluene was added at room temperature to a mixture of benzenesulfonylacetic acid (278 mg, 1.39 mmol), monoacetate **57** (150 mg, 0.806 mmol), and triphenylphosphine (262 mg, 1.00 mmol) in 1 mL of toluene. After 2 h, the cloudy, white mixture was diluted with ether, washed with saturated aqueous sodium bicarbonate and water, and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the solid residue purified by preparative TLC (50% ethyl acetate in hexane) to give 246.8 mg (83%) of the title compound as a clear, colorless oil (R_f 0.3). NMR (270 MHz, $CDCl_3$): δ 7.95 (d of m, J = 7.5 Hz, 2 H), 7.70 (t of t, J = 7.5, 1.5 Hz, 1 H), 7.58 (t of m, J = 7.5 Hz, 2 H), 5.57 (m, 2 H), 4.89 (sextet, J = 6.5 Hz, 1 H), 4.60 (d, J = 5.5 Hz, 2 H), 4.11 (s, 2 H), 2.07 (m, 2 H), 2.05 (s, 3 H), 1.43 (bm, 4 H), 1.15 (d, J = 6.5 Hz, 3 H). IR (CCl_4): 1750, 1452, 1370, 1340, 1272, 1228 cm^{-1}. Calcd for $C_{18}H_{24}O_6S$: 368.1294. Found: 368.1292.

Cyclization of (*E*)-1-Acetoxy-2-octen-7-yl Benzenesulfonylacetate (54). Sodium hydride (62 mg, 1.63 mmol) was added to a cooled (0 °C) solution of the title compound (574 mg, 1.56 mmol) in 2 mL of THF. The mixture was stirred at 0 °C for 15 min, then at room temperature for 30 min. The resulting clear, yellow solution was diluted to a total volume of 17 mL with THF and added via a syringe pump at a rate of 5.6 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (117 mg, 0.101 mmol) and 1,2-bis(diphenylphosphino)ethane (76.2 mg, 0.191 mmol) in 16 mL of THF. The needle used for the addition was fitted with a small glass-wool plug. Upon completion of the addition, TLC analysis indicated complete consumption of starting material. The mixture was cooled, filtered through a small pad of silica gel, and rinsed with ether. The combined organic portions were concentrated in vacuo and the resulting yellow oil was purified via preparative TLC (40% ethyl acetate in hexane) to give 420.8 mg (87.6%) of **60** (*E* and *Z*) as a clear, colorless oil, R_f 0.45. Analysis of the mixture by 270-MHz NMR revealed three methyl doublets at δ 1.20, 1.16, and 1.12 (J = 6.7 Hz for each), indicating the presence of at least three diastereomers. Measurement of the peak heights indicated an approximate ratio of 2:1:7. Two multiplets at δ 5.07 and 4.87, which integrated for a total of one proton, were assigned as the C-9 methine. Integration indicated a relative ratio of 1:4, respectively. NMR (270 MHz, $CDCl_3$): δ 7.85 and 7.78 (two broad doublets, J = 7.5 Hz, 2 H), 7.55 (bt, J = 7.5 Hz, 1 H), 7.44 (bt, J = 7.5 Hz, 2 H), 5.35 (bm, 2 H), 5.07 (m, 0.2 H), 4.87 (m, 0.8 H), 4.17 (m) and 3.92 (d of d, J = 13, 4.2 Hz, 1 H), 3.09–2.80 (bm, 1 H), 2.57–2.3 (bm, 1 H), 2.16 (bm, 1 H), 1.82 (bm, 3 H), 1.42 (bm, 2 H), 1.20, 1.16, and 1.12 (three doublets, J = 6.7 Hz, 3 H). IR (CCl_4): 1740, 1448, 1327, 1310 cm^{-1}. Calcd for $C_{16}H_{20}O_4S$: 308.1083. Found: 308.1071.

Cyclization of (*Z*)-1-Acetoxy-2-octen-7-yl Benzenesulfonylacetate (59). Sodium hydride (30 mg, 0.75 mmol) was added to a cooled (0 °C) solution of the title compound (240 mg, 0.652 mmol) in 2 mL of THF. The mixture was stirred at 0 °C for 15 min, then at room temperature for 30 min. The resulting light yellow solution was diluted to a total volume of 8 mL with THF and added via a syringe pump at a rate of 4 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (52.2 mg, 0.0452 mmol) and 1,2-bis(diphenylphosphino)ethane (34.1 mg, 0.0856 mmol) in 8 mL of THF. The needle used for the addition was fitted with a small glass-wool plug. Upon completion of the addition, TLC analysis indicated complete consumption of starting material. The mixture was cooled, filtered through a small pad of silica gel, and rinsed with ether. The combined organic portions were concentrated in vacuo and the resulting yellow oil was purified via preparative TLC (40% ethyl acetate in hexane) to give 159.3 mg (80%) of lactone **60** as a clear, colorless oil, R_f 0.40. Except for the relative ratio of diastereomers, the product was identical with that prepared via cyclization of the *E* isomer. Analysis by 270-MHz NMR revealed three methyl doublets at δ 1.20, 1.16, and 1.12 (J = 6.7 Hz for each) and indicated the presence of at least three diastereomers. Measurement of the peak heights indicated

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an approximate ratio of 40:7:53, respectively. Two multiplets at δ 5.07 and 4.87, which integrated for a total of 1 proton, were assigned as the C-9 methine. Integration indicated a relative ratio of 4:6, respectively.

Preparation of Lactone 62. Lactone **60** (160.1 mg, 0.519 mmol) (prepared from (*E*)-1-acetoxy-2-octen-7-yl benzenesulfonylacetate) and anhydrous disodium hydrogen phosphate (323 mg, 2.27 mmol) in 5 mL of absolute ethanol was cooled to −20 °C. Granulated 6% sodium amalgam (940 and 300 mg, 3.23 mmol) was added in two portions and stirred for 45 min. The reaction mixture was filtered, diluted with 50 mL of pentane, washed successively with saturated aqueous ammonium chloride (15 mL), water, and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation through a Vigreux column with the last traces of solvent removed in vacuo to give 76.1 mg (87%) of lactone **62** (*E* and *Z*) as a volatile, clear, colorless liquid. Analysis of the product by 270-MHz NMR indicated a mixture of two diastereomers. Methyl doublets at δ 1.26 (*J* = 6.8 Hz) and 1.18 (*J* = 6.4 Hz) were assigned to the *Z* and *E* isomers, respectively, and integrated to give a ratio of 18:82. Assignment of the isomer resonances was made by comparison of the original product mixture to pure *Z* and *E* isomers obtained from preparative VPC (20% DC-710 on Chromosorb W, 60/80 mesh, 3.55 m × 0.64 cm, *t* = 170 °C). The ratio of *Z* (retention time = 8.5 min) and *E* (retention time = 7.0 min) determined by VPC analysis (peak height × width at $^1/_2$ height) was 15:85, respectively. The *Z* isomer was identical via mass-spectral comparison with an authentic sample[60] and was in close agreement with published NMR data.[51] **62a**: NMR (270 MHz, $CDCl_3$) 5.42 (d of d of d, *J* = 15, 9.5, 4.5 Hz, 1 H), 5.28 (d of d of d, *J* = 15, 10.5, 4 Hz, 1 H), 4.82 (m, 1 H), 2.39–2.22 (bm, 4 H), 1.96–1.70 (bm, 3 H), 1.58–1.40 (bm, 3 H), 1.18 (d, *J* = 6.4 Hz, 3 H) (irradiation at δ 2.31 collapsed the resonance at δ 5.47 (d, *J* = 15 Hz)); IR (CCl_4) 1740, 1455, 1445, 1358, 1330 cm^{-1}. Calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1146. **62b**: NMR (270 MHz, $CDCl_3$) δ 5.46 (t of d of d, *J* = 11, 5.5, 2 Hz, 1 H), 5.35 (t of d, *J* = 11, 4 Hz, 1 H), 5.09 (m, 1 H), 2.73 (bm, 2 H), 2.52 (d of d of d, *J* = 14.2, 4.5, 4 Hz, 1 H), 2.22 (d of d of d, *J* = 17, 13, 4.5 Hz, 1 H), 1.91 (bm, 4 H), 1.39 (bm, 2 H), 1.26 (d, *J* = 6.8 Hz, 3 H); IR (CCl_4) 1742, 1455, 1360, 1327 cm^{-1}. Calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1143.

In a similar procedure, lactones **60** (150.0 mg, 0.487 mmol) (prepared from **59**) were desulfonylated with anhydrous disodium hydrogen phosphate (325 mg, 2.28 mmol) and granulated 6% sodium amalgam (960 mg, 2.50 mmol) in 4 mL of absolute ethanol. This gave 73.9 mg (90%) of 9-hydroxy-4-decenoate lactones. Analysis of the reaction mixture by both 270-MHz NMR and VPC as described for the previous experiment indicated a *Z*:*E* ratio of 35:65.

Preparation of 2-Benzenesulfonyl-9-hydroxydecanoate Lactone. Lactones **60** (277.3 mg, 0.90 mmol) and 5% palladium on barium carbonate in 6 mL of absolute ethanol were shaken at room temperature under 2 atm of hydrogen for 3 h. The mixture was filtered through a small pad of Celite and rinsed with ethyl acetate. The solvent was removed in vacuo. The yellow oil was purified by preparative TLC (40% ethyl acetate in hexane) to give 246.6 mg (88%) of the title compound as a white solid. Recrystallization of a sample from absolute ethanol gave white needles, mp 144–149 °C. Analysis by 270-MHz NMR revealed two resonances at δ 3.97 (d of d, *J* = 10.5, 4 Hz) and 3.81 (d of d, *J* = 12.3, 3 Hz). These signals were assigned as the C-1 methine proton for each diastereomer and integrated in a ratio of 1:4, respectively. NMR (270 MHz, $CDCl_3$): δ 7.93 (d of m, *J* = 8 Hz, 0.4 H), 7.84 (d of m, *J* = 8 Hz, 1.6 H), 7.65 (m, 1 H), 7.53 (bt, *J* = 8 Hz, 2 H), 4.97 (m, 1 H), 3.97 (d of d, *J* = 10.5, 4 Hz, 0.2 H), 3.81 (d of d, *J* = 12.3, 3 Hz, 0.8 H), 2.28 (m, 1 H), 2.12 (m, 1 H), 1.93 (m, 1 H), 1.70 (m, 1 H), 1.60–1.44 (bm, 6 H), 1.22 (d, *J* = 6.5 Hz), and 1.20 (d, *J* = 6.0 Hz, 3 H), 1.14 (m, 1 H), 0.89 (m, 1 H). IR (CCl_4): 1735, 1475, 1452, 1330, 1310 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.32; mol wt, 310.1239. Found: C, 61.89; H, 7.17; S, 10.36; mol wt, 310.1240.

Preparation of 9-Hydroxydecanoate Lactone (61). A solution of 2-benzenesulfonyl-9-hydroxydecanoate lactone (195 mg, 0.629 mmol) was dissolved in 5 mL of THF and 6 mL of absolute ethanol and cooled to −20 °C. Anhydrous disodium hydrogen phosphate (350 mg, 2.46 mmol) and granulated 6% sodium amalgam (950 mg, 2.48 mmol) were added and the mixture was stirred for 1.5 h. After filtration, the mixture was diluted with pentane, washed successively with saturated aqueous ammonium chloride (2 × 10 mL) and water (2 × 10 mL), and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give 101.6 mg (95%) of lactone **61** as a colorless, volatile oil. The compound was identical via mass-spectral comparison with an authentic sample[60] and had NMR data in close agreement with published NMR data.[57] NMR (270 MHz, $CDCl_3$): δ 5.00 (m, 1 H), 2.48 (d of d of d, *J* = 15.5, 6.5, 3 Hz, 1 H), 2.17 (m, 1 H), 1.98 (m, 2 H), 1.75 (m, 1 H), 1.47 (m, 8 H), 1.27 (d, *J* = 6.5 Hz, 3 H), 1.24 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 173.6, 72.4, 35.0, 31.4, 26.9, 24.2, 24.0, 23.3, 20.6, 19.3. IR (CCl_4): 1735, 1471, 1450, 1362, 1353, 1330 cm^{-1}. Calcd for $C_{10}H_{18}O_2$: 170.1307. Found: 170.1305.

Preparation of 3-(*tert*-Butyldimethylsiloxy)-1-propanol (63). *tert*-Butyldimethylsilyl chloride (15.99 g, 106.22 mmol) was added in portions to a cooled (−25 °C) solution of 1,3-propanediol (19.38 g, 254.6 mmol) and imidazole (15.03 g, 221 mmol) in 60 mL of DMF. After 1 h, the mixture was warmed to 0 °C and stirred for 4 h. The reaction mixture was diluted with 300 mL of pentane, washed with water (6 × 60 mL), and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave 17.49 g (86%) of **63**. A sample was purified by preparative VPC (10% DC-710 on Chromosorb W, 60/80 mesh, *t* = 145 °C) for analysis purposes. NMR (100 MHz, CCl_4): δ 3.68 (m, 4 H), 3.38 (b, 1 H), 1.65 (m, 2 H), 0.86 (s, 9 H), 0.00 and −0.02 (s, 6 H). IR (CCl_4): 3640, 3535, 1472, 1468, 1255 cm^{-1}. Anal. Calcd for $C_9H_{22}O_2Si$: C, 56.79; H, 11.65. Found: C, 56.82; H, 11.65.

Preparation of (*E*)-1-Acetoxy-2-penten-5-ol (64) from 63. The procedures closely paralleled those for the preparation of **43** and thus the detailed descriptions appear as supplementary material. **64**: NMR (270 MHz, $CDCl_3$) δ 5.79 (d of t, *J* = 15.3, 6.6 Hz, 1 H), 5.65 (d of t, *J* = 15.4, 5.9 Hz, 1 H), 4.52 (d, *J* = 5.9 Hz, 2 H), 3.66 (t, *J* = 6.6 Hz, 2 H), 3.28 (bs, 1 H), 2.32 (bq, *J* = 6.4–6.9 Hz, 2 H), 2.06 (s, 3 H); IR (CCl_4) 3655, 3500 (b), 1758, 1450, 1385, 1367, 1230 cm^{-1}. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.26; H, 8.54.

Preparation of (*E*)-1′-Acetoxy-2′-penten-5′-yl 3-Benzenesulfonyl-3-carbomethoxypropanoate (65). Bromoacetyl bromide (650 μL, 7.46 mmol) was added over 5 min to a cooled (0 °C) solution of alcohol **64** (754.2 mg, 5.23 mmol) and pyridine (1.3 mL, 16.0 mmol) in 10 mL of methylene chloride. After 15 min, the mixture was diluted with 60 mL of ether, washed successively with 10% hydrochloric acid (2 × 15 mL) and saturated aqueous sodium bicarbonate (2 × 15 mL), and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give 1.314 g (95%) of (*E*)-1-acetoxy-2-penten-5-yl bromoacetate as a clear, yellow oil. This was dissolved in 5 mL of dimethylformamide and added to a cooled (0 °C) solution of the sodium enolate derived from methyl phenylsulfonylacetate (1.629 g, 7.61 mmol) and sodium hydride (259.6 mg, 6.81 mmol) in 5 mL of DMF. After stirring at 0 °C for 40 min, the mixture was diluted with 80 mL of ether, washed with water (4 × 20 mL), and dried over anhydrous magnesium sulfate and the solvent removed in vacuo. The resulting yellow oil was purified by preparative TLC (hexane–chloroform–acetone mixture, v/v, 4:4:0.75) to give, after two elutions, 1.299 g of the title compound as a clear liquid. The overall yield for the two steps was 62%. Analysis of the product by 270-MHz NMR revealed minor resonances at δ 4.62 and 2.04, which were assigned as the C-1′ methylene and acetate methyl protons of the *Z* isomer. Comparison of these signals to the corresponding resonances of the *E* isomer (δ 4.51 and 2.06) via peak height measurement indicated an approximate ratio of 93:7. NMR (270 MHz, $CDCl_3$): δ 7.87 (d of m, *J* = 7.5 Hz, 2 H), 7.73 (t of t, *J* = 7.4, 1.3 Hz, 1 H), 7.60 (t of m, *J* = 7.5 Hz, 2 H), 5.67 (m, 2 H), 4.60 (bd, *J* = 6.5 Hz, *Z* isomer), 4.51 (bd, *J* = 4.4 Hz, 2 H), 4.45 (d of d, *J* = 9, 6.3 Hz, 1 H), 4.13 (m, 2 H), 3.66 (s, 3 H), 3.12 (m, 2 H), 2.37 (bq, *J* = 6.5 Hz, 2 H), 2.06 (*E* isomer) and 2.04 (*Z* isomer) (two singlets, 3 H). IR (CCl_4): 1755, 1455, 1440, 1410, 1380, 1360, 1330, 1310 cm^{-1}. Calcd for $C_{18}H_{22}O_8S$: 398.1035. Found: 398.1028.

Cyclization of (*E*)-1′-Acetoxy-2′-penten-5′-yl 3-Benzenesulfonyl-3-carbomethoxypropanoate in the Absence of Added Ligand. Sodium hydride (49 mg, 1.28 mmol) was added to a cooled (0 °C) solution of the title compound (431.1 mg, 1.083 mmol) in 2 mL of THF. After 15 min, the mixture was warmed to room temperature and stirred for 15 min. The resulting cloudy, yellow mixture was diluted to a total volume of 14 mL with THF. This was added via a syringe pump at a rate of 1.5 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (119 mg, 0.103 mmol) in 14 mL of THF. The needle used for the addition was fitted with a small glass-wool filter. After the addition was completed, the cloudy mixture was refluxed for 30 min, then filtered through sintered glass and rinsed with ether. The solvent was removed in vacuo and the resulting dark oil was purified by preparative TLC (25% ethyl acetate in hexane, two elutions) to give 80.2 mg (22%) of lactone **66a** as a white solid (R_f 0.25) and 26.3 mg (7%) of lactone **66b** as a clear oil (R_f 0.34). Recrystallization of the *Z* isomer from an ether–ethanol mixture gave white needles, mp 125–126 °C. The *Z* isomer was determined via variable-temperature 270-MHz NMR to be a mixture of two conformers which were near the coalescence point at ambient temperature. The *E* isomer was determined to be a mixture of two conformers at ambient temperature. **66a**: NMR (270 MHz, $CDCl_3$, probe temperature 22 °C) δ 7.81 (d of m, *J* = 7.5 Hz, 2 H), 7.72 (t of t, *J* = 7.5, 1 Hz, 1 H), 7.59 (t of m, *J* = 7.5 Hz, 2 H), 5.70 (bq, *J* = 10 Hz, 1 H), 5.46 (bm, 1 H), 4.48 (b, 1 H), 4.07 (b, 1 H), 3.78 (s, 3 H), 3.15 (bm, 4 H), 2.42 (b, 1 H), 2.26 (b, 1 H); NMR (270 MHz, C_6D_6, probe temperature 22 °C) δ 7.65 (d of m, *J* = 7.5 Hz, 2 H), 6.93 (t of t, *J* =

7.4, 1 Hz, 1 H), 6.83 (t of m, J = 7.5 Hz, 2 H), 5.81 (bm, 1 H), 5.37 (bm, 1 H), 4.13 (b, 1 H), 3.39 (bm, 5 H), 3.20 (s, 3 H), 1.79 (b, 1 H), 1.57 (b, 1 H); NMR (270 MHz, $CDCl_3$, probe temperature −43 °C) δ 7.79 (m, 3 H), 7.62 (bt, J = 7 Hz, 2 H), 5.79 (bm, 1.3 H), 5.70 (bt of d, J = 10, 4 Hz, 0.7 H), 4.79 (bm, 0.3 H), 4.67 (bt, J = 10–11 Hz, 0.7 H), 4.07 (bm, 0.3 H), 3.91 (bd, J = 10–11 Hz, 3.81 and 3.77 (two singlets, 3 H), 3.18 (bm, 3 H), 2.97 (m, 1 H), 2.61 (m, 1 H), 2.16 (m, 1 H); NMR (270 MHz, C_6D_6, probe temperature 76 °C) δ 7.68 (d of m, J = 8 Hz, 2 H), 7.02 (t of t, J = 7.5, 1.3 Hz, 1 H), 6.92 (t of m, J = 7.5 Hz, 2 H), 5.63 (d of t, J = 11, 8.6 Hz, 1 H), 5.38 (d of t of t, J = 11, 8.3, 1 Hz, 1 H), 4.14 (m, 1 H), 3.65 (m, 1 H), 3.42 (d, J = 13.4 Hz, 1 H), 3.29 (d, J = 13.4 Hz, 1 H), 3.27 (s, 3 H), 3.324 (m, 2 H), 1.87 (m, 1 H), 1.72 (m, 1 H); IR (CCl_4) 1760, 1745, 1470, 1455, 1440, 1355, 1330, 1310, 1280, 1260, 1240, 1215, 1200, 1190, 1175, 1150, 1120, 1080, 1660 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_6S$: C, 56.80; H, 5.36; S, 9.47; mol wt, 338.0824. Found: C, 56.78; H, 5.34; S, 9.47; mol wt, 338.0821. **66b**: NMR (270 MHz, $CDCl_3$) δ 7.81 (d of m, J = 7.5 Hz, 2 H), 7.71 (t of t, J = 7.4, 1.3 Hz, 1 H), 7.58 (t of m, J = 7.5 Hz, 2 H), [5.48 (d of d of d, J = 15.8, 10, 5.9 Hz), 5.41 (d of d of d, J = 15.8, 10.4, 5.3 Hz), 5.23 (d of d of d, J = 15.8, 10.3, 4.5 Hz), 5.12 (d of d of d, J = 15.8, 11.2, 3.5 Hz), 2 H], 4.65–4.56 (m, 1 H), 4.01 (m, 1 H), 3.76 and 3.75 (two singlets, 3 H), 3.27 (bm, 2.5 H), 2.90 (d, J = 11 Hz, 0.5 H), 2.75–2.64 (m, 1 H) containing 2.71 (d, J = 11 Hz), 2.35–2.18 (m, 2 H). Irradiation at δ 3.25 collapses resonances at δ 5.41 (d, J = 15.8 Hz), 5.12 (d of d, J = 15.8, 11 Hz), 2.90, and 2.75–2.64 but does not affect resonances at δ 5.48 and 5.23. Irradiation at δ 2.72 collapses resonances at δ 5.12 (d of d, J = 15.8, 4 Hz) and 3.25. Irradiation at δ 2.33 collapses resonances at δ 5.48 (d, J = 15.8 Hz) and 5.23 (d of d, J = 15.8, 5 Hz). IR (CCl_4): 1745, 1465, 1455, 1365, 1330, 1310, 1270, 1225, 1155, 1085, 1045 cm^{-1}. Calcd for $C_{16}H_{18}O_6S$: 338.0824. Found: 338.0814.

Cyclization of (*E*)-1′-Acetoxy-2′-penten-5′-yl 3-Benzenesulfonyl-3-carbomethoxypropanoate in the Presence of 1,2-Bis(diphenylphosphino)ethane. Sodium hydride (38.1 mg, 1.00 mmol) was added to a cooled (0 °C) solution of **65** (365.1 mg, 0.917 mmol) in 2 mL of THF. After 30 min, the resulting clear, yellow solution was diluted to a total volume of 14 mL with THF. This was added via a syringe pump at a rate of 1.5 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (121.3 mg, 0.105 mmol) and 1,2-bis(diphenylphosphino)ethane (44.1 mg, 0.118 mmol) in 8 mL of THF. The needle used for the addition was fitted with a small glass-wool filter. After the addition was completed, the cloudy, yellow mixture was cooled, filtered, and rinsed with ether. The solvent was removed in vacuo and the resulting yellow oil was purified by preparative TLC (25% ethyl acetate in hexane, two elutions) to give 168.8 mg (54.5%) of lactone **66a** as a white solid (R_f 0.28) and 16.4 mg (5.3%) of lactone **66b** as a colorless oil (R_f 0.35). Analysis via 270-MHz NMR and IR revealed both isomers to be identical with those prepared in the previous experiment.

Hydrogenation of 3-Benzenesulfonyl-3-carbomethoxy-8-hydroxy-5-octenoate Lactone. Lactone **66a** (74.3 mg, 0.219 mmol) and 5% palladium on barium carbonate (200 mg) in 5 mL of absolute ethanol was shaken under 2 atm of hydrogen for 2 h. The mixture was filtered through Celite and rinsed with ethyl acetate and the solvent removed in vacuo. The residue was purified by preparative TLC (50% ethyl acetate in hexane) to give 61.1 (82%) of lactone **67** as a clear oil (R_f 0.35). NMR (270 MHz, $CDCl_3$): δ 7.79 (d of m, J = 7.5 Hz, 2 H), 7.71 (t of t, J = 7.5, 1.3 Hz, 1 H), 7.57 (t of m, J = 7.5 Hz, 2 H), 4.56 (d of d of d, J = 11, 7.5, 3.5 Hz, 1 H), 4.01 (d of d of d, J = 11, 6.5, 4.1 Hz, 1 H), 3.71 (s, 3 H), 3.19 (d of d, J = 12.1, 1 Hz, 1 H), 3.08 (d, J = 12.1 Hz, 1 H), 2.51 (d of d of d of d, J = 14, 10, 7.5, 1 Hz, 1 H), 2.18 (d of d of d, J = 14, 6.8, 2.8 Hz, 1 H), 1.92–1.58 (bm, 4 H), 1.45 (m, 1 H), 0.96 (m, 1 H). Irradiation of the signal at δ 2.51 collapses the resonance at δ 3.19 (d, J = 12.1 Hz). ^{13}C NMR ($CDCl_3$): δ 169.2, 166.9, 135.3, 134.5, 130.4, 128.9, 75.2, 65.6, 53.2, 35.8, 27.5, 25.8, 25.4, 23.3. IR (CCl_4): 1750, 1450, 1370, 1358 cm^{-1}. Calcd for $C_{16}H_{20}O_6S$: 340.0981. Found: 340.0974.

In an identical fashion, lactone **66b** (21 mg, 0.062 mmol) was hydrogenated using 5% palladium on barium carbonate (200 mg) in 5 mL of absolute ethanol to give 19 mg (91%) of a compound which was identical by TLC, 270-MHz NMR, and IR analysis with that prepared from the Z isomer.

Preparation of (*E*)-1-Acetoxy-2-penten-5-yl Benzenesulfonylacetate (68). A mixture of benzenesulfonylacetic acid (606.3 mg, 3.03 mmol), (*E*)-1-acetoxy-2-penten-5-ol (312.3 mg, 2.17 mmol), and triphenylphosphine (780.7 mg, 2.98 mmol) suspended in 2 mL of toluene was cooled to 0 °C. A solution of diethyl azodicarboxylate (520 mg, 2.98 mmol) in 1 mL of toluene was slowly added over 10 min. After 30 min, the mixture was warmed to room temperature and stirred for an additional 2 h. The cloudy, white mixture was diluted with ether, washed successively with saturated aqueous sodium bicarbonate and water, and dried over anhydrous magnesium sulfate and the solvent removed in vacuo. Purification by preparative TLC (33% ethyl acetate in hexane, two elutions) gave 360.4 mg (51%) of the title compound. NMR (270 MHz, $CDCl_3$): δ 7.91 (d of m, J = 7.5 Hz, 2 H), 7.66 (t of m, J = 7.5 Hz, 1 H), 7.55 (t of m, J = 7.5 Hz, 2 H), 5.60 (m, 2 H), 4.49 (bd, J = 6 Hz, 2 H), 4.12 (m, 4 H) containing 4.13 (s), 2.31 (m, 2 H), 2.06 (s, 3 H). IR (CCl_4): 1755, 1452, 1342, 1228, 1162, 1085 cm^{-1}. Calcd for $C_{15}H_{18}O_6S$: 326.0824. Found: 326.0821.

Cyclization of 68. Sodium hydride (42.1 mg, 1.11 mmol) was added in one portion to a cooled (0 °C) solution of the title compound (360 mg, 1.10 mmol) in 2 mL of THF. The mixture was stirred at 0 °C for 15 min, then at room temperature for 30 min. The resulting clear, yellow solution was diluted to a total volume of 12 mL with THF and added via a syringe pump at a rate of 5 mL/h to a refluxing solution of tetrakis(triphenylphosphine)palladium(0) (63.5 mg, 0.055 mmol) and 1,2-bis(diphenylphosphino)ethane (43.8 mg, 0.110 mmol) in 10 mL of THF. The needle used for the addition was fitted with a small glass-wool plug. Upon completion of the addition, the cloudy, yellow mixture was cooled, filtered through a small pad of silica gel, and rinsed with ether. The combined organic portions were concentrated in vacuo. The resulting yellow oil was purified via preparative TLC (40% ethyl acetate in hexane) to give 193.4 mg (73%) of **69a** with a trace of **69b** as a white solid. Recrystallization from absolute ethanol gave short, white needles, mp 87.5–89 °C, of pure **69a**. Analysis of the chromatographed product mixture by 270-MHz NMR indicated two signals at δ 5.88 and 5.71 assigned as the two olefinic protons of **69a**. Two minor signals at δ 5.21 and 5.18 were assigned as the two terminal vinyl protons of **69b**. Integration of these signals indicated a ratio of 94:6, respectively. A partial NMR of 2-benzenesulfonyl-5-hydroxy-3-vinylpentanoate lactone follows (270 MHz, $CDCl_3$): δ 5.21 (d of m, J = 10.3 Hz, 1 H), 5.18 (d of m, J = 17.1 Hz, 1 H), 4.58 (d of d of d, J = 11.3, 9.5, 3 Hz, 1 H), 4.42 (unresolved shoulder), 4.02 (d, J = 4.5 Hz, 1 H), 3.66 (m, 1 H), 2.34 (m, 1 H), 1.81 (m, 1 H). (*Z*)-2-Benzenesulfonyl-4-hepten-7-olide (**69a**): NMR (270 MHz, $CDCl_3$) δ 7.96 (d of m, J = 8 Hz, 2 H), 7.69 (t of t, J = 7.5, 1.5 Hz, 1 H), 7.58 (t of m, J = 8 Hz, 2 H), 5.88 (d of t of d, J = 11, 7.8, 1.2 Hz, 1 H), 5.71 (d of d of d of d of d, J = 11, 9.3, 7.4, 1.5 Hz, 1 H), 4.38 (t of d, J = 10.5, 2 Hz, 1 H), 4.36 (d of t, J = 10.5, 4 Hz, 1 H), 4.07 (d of d, J = 10.7, 4.6 Hz, 1 H), 3.19 (d of d of d of d, J = 12.5, 10.5, 9.5, 1 Hz, 1 H), 2.68 (d of d of d, J = 12.5, 7.5, 4.8 Hz, 1 H), 2.61 (m, 1 H), 2.17 (d of d of d of d of d, J = 14.4, 8.2, 3.6, 2.1 Hz, 1 H). IR (CCl_4): 1762, 1467, 1452, 1358, 1340, 1331, 1250, 1188, 1155, 1085, 1040 cm^{-1}. Calcd for $C_{13}H_{14}O_4S$: 266.0613. Found: 266.0607.

Preparation of 70a and 70b. A 94:6 mixture of **69a** and **69b** (103 mg, 0.387 mmol) was dissolved in 4 mL of absolute ethanol; 5% palladium on barium carbonate (175 mg) was added and the mixture was hydrogenated at 2 atm of H_2 at room temperature. The mixture was filtered through a small Celite plug and rinsed with ethyl acetate. The combined solvent portions were removed in vacuo and the clear oil was purified by preparative TLC (33% ethyl acetate in hexane) to give 98.2 mg (98%) of the title compounds (R_f 0.3). Analysis of the product mixture by 270-MHz NMR indicated a resonance at δ 4.09 (d of d, J = 11.2, 5.5 Hz) assigned as the C-2 methine of **70a**. A smaller resonance at δ 3.85 (d, J = 4.3 Hz) was assigned as the C-2 methine proton of **70b**. Integration of these two signals indicated a relative ratio of 93:7, respectively. A partial NMR of **70b** follows (270 MHz, $CDCl_3$): δ 7.86 (d, J = 8 Hz, 2 H), 4.60 (m, 1 H), 3.85 (d, J = 4.3 Hz, 1 H), 2.87 (m, 1 H), 0.98 (t, J = 7.5 Hz, 3 H), unassigned broad singlet at δ 3.04 (>0.5 H). **70a**: NMR (270 MHz, $CDCl_3$) δ 7.93 (bd, J = 8 Hz, 2 H), 7.65 (t of m, J = 8 Hz, 1 H), 7.54 (t of m, J = 8 Hz, 2 H), 4.36 (m, 2 H), 4.09 (d of d, J = 11.2, 5.5 Hz, 1 H), 2.39 (m, 1 H), 2.13 (bq, J = 12.5 Hz, 1 H), 1.75 (bm, 4 H), 1.45 (bm, 2 H); IR (CCl_4) 1745, 1446, 1322, 1232, 1098, 1078, 1042 cm^{-1}. Calcd for $C_{13}H_{16}O_4S$: 268.0769. Found: 268.0769.

Desulfonylation of 70a and 70b. The mixture of lactones (168.3 mg, 0.627 mmol) was dissolved in 8 mL of absolute ethanol and cooled to −20 °C. Glacial acetic acid (500 μL, 8.74 mmol) was added followed by granulated 6% sodium amalgam (1.5 g, 3.75 mmol) and the mixture stirred for 2.5 h. The neutral reaction mixture was diluted with pentane and filtered through glass wool to remove the remaining pieces of sodium amalgam. The solvent was washed successively with water, saturated aqueous sodium bicarbonate, and saturated aqueous ammonium chloride and the solvent removed by distillation through a glass-packed column. The last traces of solvent were removed under vacuum for a short time to give 42 mg (52%) of a clear, colorless oil. Comparison of this product with an authentic sample of 7-heptanolide by 270-MHz NMR and VPC (20% DC-710 on Chromosorb W, 60/80 mesh, 3.66 m × 0.64 cm, t = 175 °C) confirmed the presence of the eight-member-ring lactone (retention time = 6.6 min) as the major product. A second product (retention time = 5.5 min) was observed and assigned as 3-ethyl-5-hydroxypentanoate lactone. Integration gave a ratio of eight-:six-member-ring lactones of 93:7. The products were collected together by preparative VPC. Analysis by 270-MHz NMR revealed a resonance at

δ 4.35 (AA′ of AA′XX′) assigned to the C-7 methylene protons of **71a**. A triplet at δ 4.15 (J = 6.4 Hz) was assigned to the C-5 methylene protons of 3-ethyl-5-hydroxypentanoate lactone. Integration gave a ratio of 92:8, respectively.

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Supplementary Material Available: Preparation of **9**, **11**, a *Z*–*E* mixture of 2-acetoxy-1-(2′-methoxyethen-1′-yl)-3-cyclohexene, **10a**, **10b**, 6-tetrahydropyranyloxy-1 hexanol, **26**, **52**, **53**, **54**, ethyl (*E*)-5-(*tert*-butyldimethylsiloxy)-2-pentenoate, and **64** (14 pages). Ordering information is given on any current masthead page.

Mechanism of the Ozonolysis of Ethylene in the Liquid Phase

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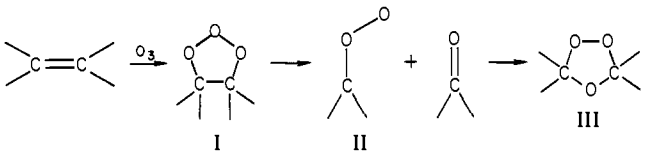
Abstract: The ozonolysis of ethylene to ethylene ozonide was studied in a variety of solvents. The cross-ozonide yields, aldehyde-insertion yields, secondary kinetic isotope effects, and reaction stereochemistry were evaluated by using mass spectroscopy and microwave spectroscopy to follow isotopic labels. Yields of ozonide are high and can be maximized with polar solvents and low temperatures. Cross-ozonide and aldehyde-insertion yields increase with solvent polarity. They reach essentially the statistically expected limits at moderate values of solvent dielectric constants. Inverse secondary deuterium isotope ratios were observed for ethylene upon reaction with ozone and for formaldehyde incorporation in the final ozonide. Stereolabeled ethylene-*1,2-d*$_2$ yields a 1:1 mixture of *cis*- and *trans*-ozonides. These results correlate well with the Criegee mechanistic description for ozonolysis in solvents.

Introduction

The production of ozonides in solvents can be described by the three-step Criegee mechanism.[1] Recent modifications have incorporated stereochemistry considerations (for example, syn and anti forms for II) in order to extend the proposal to substituted alkenes where stereo effects are observed from alkene to ozonide configuration.[2-4] These revisions also viewed the three reaction steps as concerted, symmetry-allowed 1,3-cycloadditions or reversions.



I II III

However, there have been results for some alkenes which do not readily incorporate into the Criegee scheme and its stereo revisions. One category of experiments involves solvent effects. For example, the amount of ozonide produced from di-*tert*-butylethylene decreases in polar solvents or when the concentration of an added aldehyde is increased.[5] In a study of the decomposition behavior of the primary ozonide of *trans*-3-hexene in CF_2Cl_2 and $(C_2H_5)_2O$, the amount of aldehyde produced and the stage at which it was observed varied considerably for the two solvents.[6] Such solvent variations led Criegee to raise the question whether they can be correlated with any solvent parameters.[1] The results for di-*tert*-butylethylene have led to speculation[5] that steps 2 and 3 in the Criegee proposal may be nonconcerted under some conditions. Nonconcerted pathways for steps 2 and 3 have also been recently proposed on the basis of a theoretical analysis.[7]

Another category of data troublesome for the revised Criegee proposals involves some stereochemistry results. For example, there are variations in the cis/trans yields of III as solvent and olefin concentrations are changed.[8,9] Some of these effects have been explained by variations in the equilibration of the syn and anti zwitterion forms of II,[3] although a recent theoretical analysis questions this approach.[10]

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