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Oxasecoalkylation via Cyclobutanone Intermediates

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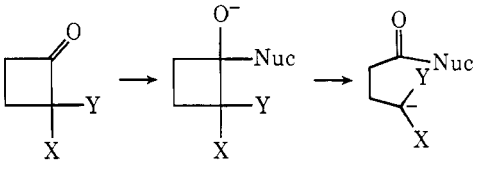
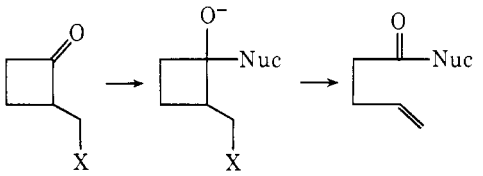
Abstract: [*n*,4]Spiroannelation of α,β-epoxy ketones utilizing diphenylsulfonium cyclopropylides followed by fragmentation constitutes a novel chain extension procedure. The fragmentation has been shown to be stereospecificially anti. From one diastereomer of an epoxycyclobutanone, fragmentation can produce either olefin geometry in the chain-extended product. Conversion of the cyclobutanone to a cyclobutanol prior to fragmentation also allows facile subsequent cleavage to a ketone. An annelation that complements the Robinson "annelation" has been developed based upon this sequence. Utilizing the methyl-substituted ylide and an epoxyperhydroindanone, model studies directed toward steroids have been explored. The sequence is a synthetic equivalent of a carbanion β to a carbonyl group concomitant with regio- and stereocontrolled introduction of a γ,δ double bond.

The potential of small-ring chemistry in organic synthesis depends upon controlled molecular reorganization in the release of the strain energy. One such approach is embodied in the nucleophilically triggered cleavage of cyclobutanones (eq 1).[1,2] Such reactions require the presence of some group(s) at



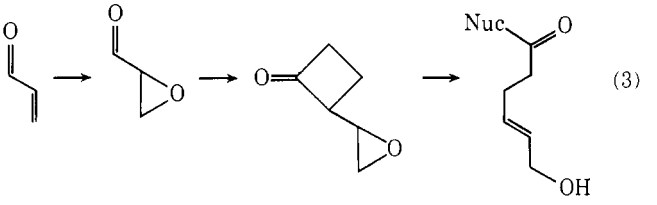
(1)

the α carbon in order to stabilize the incipient carbanion. Previously X and/or Y as halogen,[1a,c,f,h,2e,h] alkyl- or arylthio substituents,[1b,e,g,2i] olefins,[2a-d,g] aromatic rings,[1f,2f] or acyl groups[1d] have proven successful. An alternative envisions placing a potential leaving group β to an incipient carbanion in order to induce a fragmentation (eq 2). Fragmentation re-



(2)

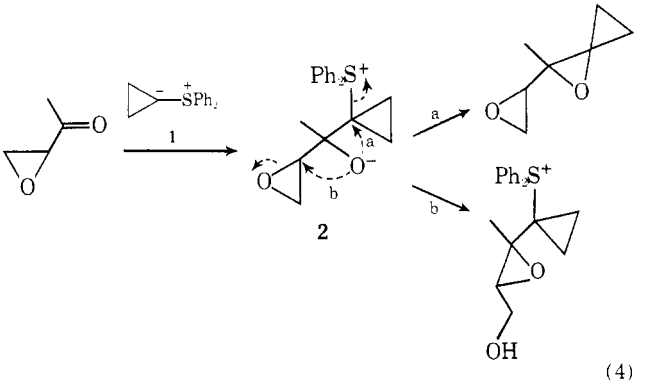
actions have played a major role in organic chemistry.[3] Interest in the above sequence stems from the facility of forming the requisite system by [*n*,4]spiroannelation of carbonyl compounds.[4] A particularly intriguing aspect of this sequence is the ability to elaborate enones via their corresponding α,β-epoxycarbonyl systems as summarized in eq 3. The introduction of cyclic units by initial ring formation followed by ring cleavage has been termed secoalkylation. In this case, since one of the ring atoms is oxygen, it is termed oxasecoalkylation. In



(3)

this paper we wish to report the realization of this approach and the determination of its stereochemistry.[5]

Two major problems concerned us. The first problem was the possibility of a competition in the elimination step of the cyclobutanone annelation utilizing the sulfur ylide **1**. Thus, the



(4)

intermediate **2** could effect epoxide ring opening (path b, eq 4) in competition with the desired sulfide displacement (path a, eq 4). The latter process, an S_N2 displacement at a cyclopropyl carbon, normally is anticipated to be a relatively high activation energy process. The fact that it occurs under such mild conditions with **1** and simple carbonyl partners remains a delightful mystery[6] that is compounded by the fact that the corresponding sulfoxamine ylide does not possess a similar

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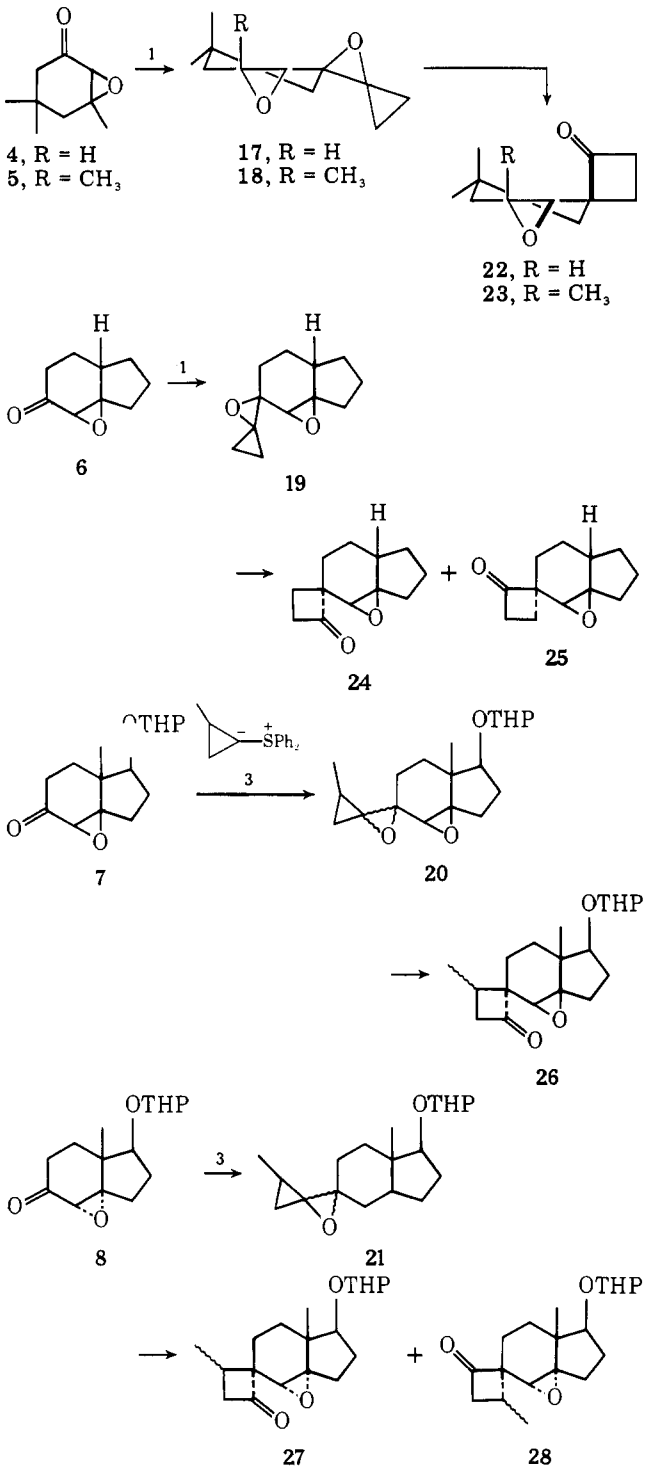
Scheme I. [6,4]Spiroannelation

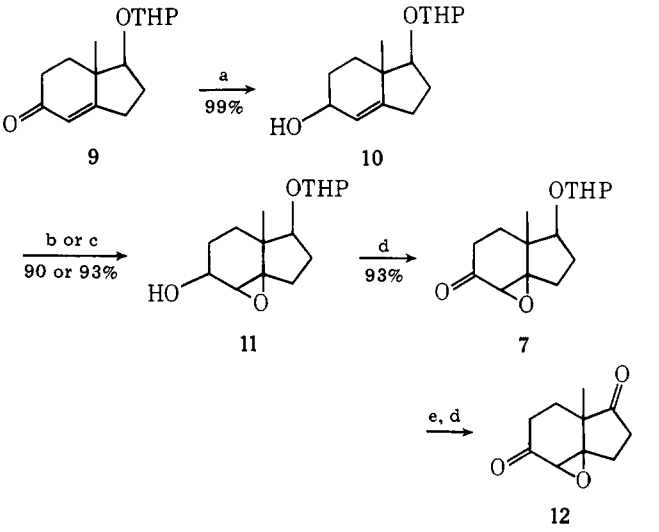


reactivity.[7] The second problem involves the chemospecific rearrangement of the oxaspiropentane in the presence of a reactive epoxide.

Results

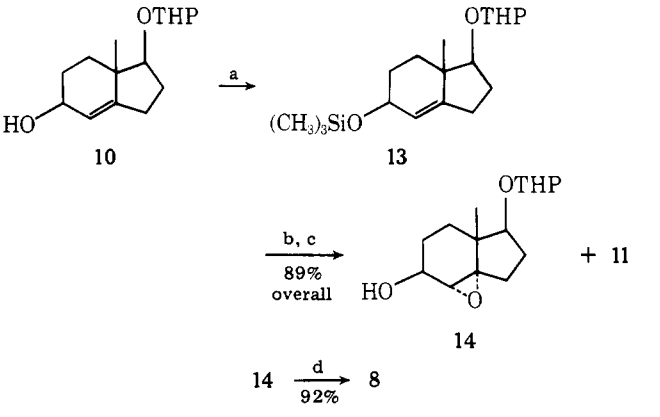
The ketones examined, **4–8** (see Scheme I), were either available (**4** and **5**) or prepared by epoxidation of the enone **6** with basic hydrogen peroxide. In the case of **6**, a single epoxide is formed. The stereochemistry is assigned based upon the known tendency of this method to produce *cis*-epoxides in the Δ^4-octalin-3-one system,[8] the thermodynamic preference for cis over trans ring junctures in perhydroindanones,[9] and the known tendency for similar enones to produce cis ring junctures upon Michael addition.[10] Epoxy ketones **7** and **8** were available

Scheme II. Preparation of Epoxy Ketone 7



a, $LiAlH_4$, ether, reflux; b, MCPBA, ether, 0 °C; c, *t*-C_4H_9OOH, $Mo(CO)_6$, PhH, reflux; d, $CrO_3 \cdot (C_5H_5N)_2$, CH_2Cl_2, room temperature; e, 2:1 HOAc–H_2O, 40 °C.

Scheme III. Preparation of Epoxy Ketone 8

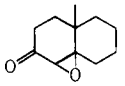
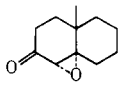
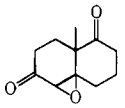
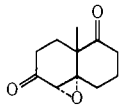


a, $(CH_3)_3SiCl$, imidazole, DMF, 0 °C; b, MCPBA, ether, 0 °C; c, C_2H_5OH, H_2O, 50 °C; d, $CrO_3 \cdot (C_5H_5N)_2$, CH_2Cl_2, room temperature.

as outlined in Schemes II and III, respectively.[11] Direct epoxidation (basic hydrogen peroxide or peracid) of enone **9** failed. Reduction followed by either peracid or transition metal catalyzed epoxidation of **10** gave a single epoxide **11** whose stereochemistry derives from the known directing effect of the allylic hydroxyl group in such reactions[12,13] and the known stereochemistry of ketone reduction.[14] Oxidation with Collins reagent produces **7**. The overall transformation of enone **9** to keto epoxide **7** could routinely be carried out in 85% overall yield without purification at intermediate stages. Further characertization was achieved by conversion to the dione **12**, mp 141–142 °C.

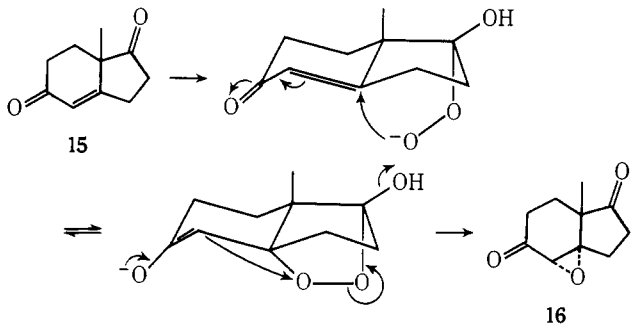
The alternative epoxide **8** was available due to preferential (~2:1) attack of an epoxidizing agent on the less hindered α face of **13**. Attempts to improve the ratio of α:β attack by increasing the bulk of the hydroxyl protecting group or decreasing the bulk of the peracid failed. Routinely, epoxy alcohol **14** was available in about 60% isolated yield and the minor product **11**, identical with the previously prepared sample, was isolated in about 25% yield. Conversion of the hydroxyl group to a ketone completed the sequence.

Table I. NMR Shifts for Keto Epoxides

compd	epoxide methine	angular methyl
7	2.90	1.15
8	3.23	1.02
12	3.23	1.32
16	3.60	1.16
	2.78[a]	1.15[a]
	2.85[a]	1.11[a]
	2.87[b]	*c*
	3.10	1.37

[a] Reference 15. [b] Reference 8b. [c] Not reported in ref 8b.

In the course of these studies, it was discovered that direct base-catalyzed epoxidation of dione **15** led to the trans-fused product **16,** mp 74–76 °C, exclusively. This unusual stereochemistry is thought to arise by an unusual neighboring group participation as depicted. As we previously pointed out, the Wieland–Mischler ketone also undergoes a similar epoxidation with the same stereochemical outcome.[11] The same diketone



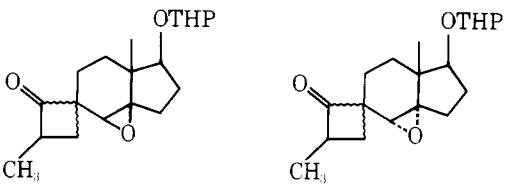
15 16

16 arises by oxidation of the diol corresponding to **14.** Thus, the epimeric nature of the two series (i.e., **7** vs. **8**) is confirmed. With the two series in hand and with stereochemistry firmly established, it can be seen that the proton NMR shifts for the epoxide methine and angular methyl groups do allow stereochemical assignment. As summarized in Table I, for the trans-fused series the epoxide methine protons come at lower field and the angular methyl group protons come at higher field than the corresponding cis-fused series. The same result is true for the decalin systems which are also included in Table I.

Addition of the parent ylide **1** to ketones **4** and **5** gave apparently single oxaspiropentanes. One broadened doublet for the epoxide methine at δ 2.75 and two sharp singlets for the methyl groups at δ 0.98 and 1.05 for **17** and a broadened singlet for the epoxide methine at δ 2.60 and three sharp methyl singlets at δ 0.98, 1.02, and 1.30 for **18** indicate the stereohomogeneity of both oxaspiropentanes. The latter, **18,** crystallized upon distillation to form a low-melting solid, mp 24–25 °C. The relative stereochemistry is simply assigned based upon anticipated pseudoequatorial attack.[1,16] The diepoxide **19** was a mixture of two isomers as determined by the presence of two epoxide methines at δ 2.80 (86.5%) and 2.87 (13.5%). The major isomer is assumed to derive from β attack of the ylide.

Chemospecific rearrangement of the oxaspiropentane proceeded without complications in the cases of **17** and **18** utilizing aqueous fluoboric acid. For **18,** rearrangement also succeeded with 25 mol % anhydrous lithium perchlorate in acetonitrile although it was quite slow (4 days). Again, a single cyclobutanone was isolated as determined by TLC and the cleanliness of the proton NMR [**22,** δ 2.97 (epoxide methine) and 0.91 (methyl groups); **23,** δ 2.84 (epoxide methine), 0.91 (two methyl groups), and 1.28 (one methyl group)]. Furthermore, **23** was sharp melting, mp 35.5–36.0 °C. Stereochemistry is assigned based upon analogy to other cyclobutanone annelations.[1,16] Rearrangement of **19** under the same conditions led to decomposition of both epoxides. Use of 10 mol % oxalic acid in acetonitrile at 37 °C did lead to selective rearrangement. Following the reaction by disappearance of the pseudosinglet for the cyclopropyl hydrogens in the NMR spectrum at δ 0.95 indicated a half-life of 11 min for the rearrangement. The complexity of the NMR spectrum of the cyclobutanone did not permit an evaluation of the isomeric ratio. Based upon the very high stereospecificity of the rearrangement, we assume that the ratio of **24**:**25** resembles that of the oxaspiropentane mixture, i.e., ~87:13. The oxalic acid conditions ultimately proved to be the most general for this chemoselective rearrangement. Because of our interest in the possible application of this method for the synthesis of 14α- and 14β-hydroxy steroids, we examined [6,4]spiroannelation of the methyl-substituted ylide **3**[6a] with epoxy ketones **7** and **8.** The stereochemistry of such adducts is complicated by the fact that a mixture of *E* and *Z* sulfonium salts is employed as a precursor to the ylide **3,** giving rise to a mixture epimeric at the cyclopropyl carbon bearing the methyl group. In the case of **20,** two epoxide methine protons were discernible at δ 2.62 and 2.54, clearly indicating that at least two isomers, if not more, are present. Refrigeration of the crude oil did cause precipitation of white crystals, mp 108–110 °C; however, these were still an isomeric mixture. For **21,** the complexity of the NMR spectrum precluded a definitive determination of stereochemistry.

Rearrangement of **20** and **21** is clouded by the question of regiochemistry. We have previously established that the carbon bearing the methyl group undergoes preferential migration leading to **26** from **20** and **27** + **28** from **21** rather than **29** or



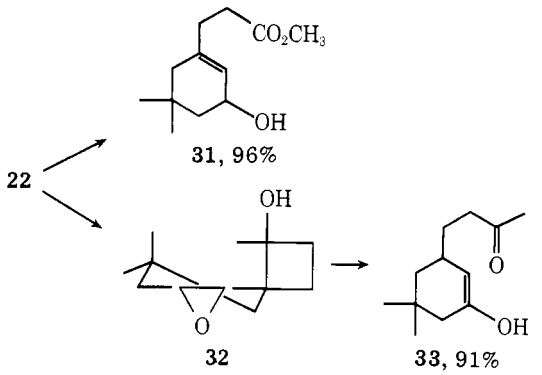
29 30

30.[16] Such a selectivity is anticipated on electronic grounds (i.e., the carbon best able to stabilize a positive charge migrates preferentially) and by analogy to solvolytic opening of cyclopropylcarbinols to homoallylic alcohols.[17] Subsequent transformations confirm this anticipation and we consider only the products involving ring expansion by migration of the secondary over the primary carbon, i.e., **26–28.**

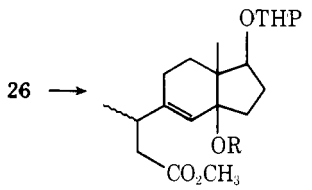
In the case of **26,** the NMR spectrum is remarkably clean, showing essentially a single bridgehead methyl group at δ 0.92 and a single cyclobutyl methyl group as a doublet (J = 7 Hz) at δ 1.20. Based upon least hindered attack of the ylide on the ketone and stereospecific rearrangement, the major product should have the stereochemistry depicted in **26.** Rearrangement of **21** led to two easily separable cyclobutanones in 68 and 12% yields, respectively. The NMR spectra of these two compounds indicate that they are still epimeric mixtures. The fact that they fragment to the same product (as an epimeric mixture) indicates that they are not isomeric with respect to the position of the methyl group. This fact plus the large difference in chromatographic behavior suggests that they differ as to the stereochemistry at the spiro center. By analogy,[1,16]

the major isomer is expected to be **27** and the minor isomer **28.**

In the conformation of epoxycyclobutanone **22** depicted, the cyclobutyl and epoxy bonds emboldened bear an approximate trans-diaxial relationship. Conversion of the carbonyl group into a good electron source (i.e., a carbalkoxide group) by addition of nucleophiles should initiate fragmentation accompanied by release of 54 kcal/mol, the combined strain energies of cyclobutyl and epoxide rings.[18] Thus, allowing a methanolic solution of sodium methoxide and epoxycyclobutanone **22** to stand at room temperature resulted in nearly quantitative isolation of hydroxy ester **31.** Methyllithium addition to **22** in ether at −78 °C followed by addition of water, initially at −78 °C and subsequently at 25 °C, resulted in direct isolation of **33.** Alternatively, the cyclobutanol **32** is isolated if the reaction mixture is worked up immediately after quenching with water. Treating the cyclobutanol **32** with



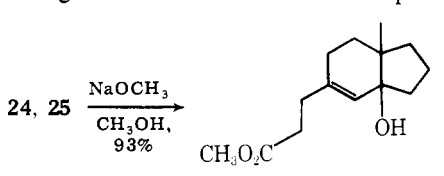
methanolic sodium methoxide fragments **32** smoothly to the same hydroxy ketone **33.** Similarly, epoxycyclobutanone **26**



34a, R = H
b, R = $(CH_3)_3Si$

also underwent smooth cleavage to **34a** in methanolic sodium methoxide at room temperature. The cleavage product was further characterized as its trimethylsilyl ester **34b.** Both products showed two singlets for the angular methyl group (**34a,** δ 0.88 and 0.95; **34b,** δ 0.76 and 0.79) and one or two doublets for the secondary methyl group (**34a,** δ 1.04 and 1.11; **34b,** δ 1.00)—suggestive of the two epimers at the secondary methyl group.

The cases of the pairs of spiro isomers, **24, 25** and **27, 28,** are most interesting since a trans elimination is not possible in one



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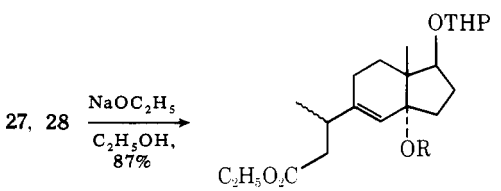


36a, R = H
b, R = $(CH_3)_3Si$

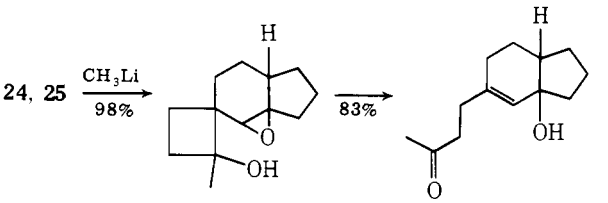
Table II. NMR Data for Epoxycyclobutanones **40a** and **40b**

	40a		40b	
Position	^1H NMR[a]	^{13}C NMR[b]	^1H NMR[a]	^{13}C NMR[b]
1		208.7 (s)		210.4 (s)
2		63.7 (s)		63.9 (s)
3a	2.33[c]	22.7 (t)	1.93[j]	18.6 (t)
3b	1.84[d]		1.57[j]	
4a	2.94[e]	43.0 (t)	2.95[k]	43.0 (t)
4b	3.03[f]		3.03[k]	
5	2.99[g]	54.1 (d)	3.08[l]	52.1 (d)
6a	2.75[h]	44.8 (t)	2.80[m]	43.3 (t)
6b	2.80[i]		2.52[n]	
7	1.30	18.2 (q)	1.28	18.0 (q)

[a] Spectrum taken at 270 MHz in $CDCl_3$ with chemical shifts given in δ. [b] Spectrum taken at 15.1 MHz with chemical shifts given in δ. [c] ddd, J = 11.5, 10.8, 6.3 Hz. [d] ddd, J = 11.5, 9.8, 7.5 Hz. [e] B part of ABMX, J = 18.2, 9.8, 6.3 Hz. [f] A part of ABMX, J = 18.2, 10.8, 7.5 Hz. [g] dd, J = 4.1, 2.8 Hz. [h] dd, J = 4.7, 4.1 Hz. [i] dd, J = 4.7, 2.8 Hz. [j] ddd, J = 11.4, 9.7, 7.5 Hz. [k] A or B part of ABMX, J = 17.1, 9.7, 7.5 Hz. [l] dd, J = 4.0, 2.6 Hz. [m] br t, J = 4.3 Hz. [n] dd, J = 4.7, 2.6 Hz.

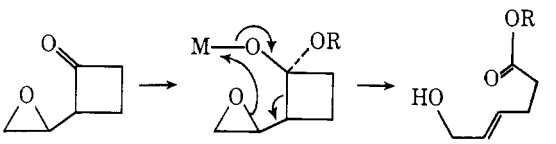
of the two isomers. Again, fragmentation was smooth in all cases. The lability of **36a** led us to incorporate a silylation step in the workup and allowed isolation of **36b** in 81% overall yield. Utilizing the NMR criterion, hydroxy ester **35** is homogeneous. Silyloxy ester **36b** was a mixture of two compounds in the ratio of ~5:2 as determined by two vinyl protons at δ 5.50 and 5.07; unfortunately, the doublets for the secondary methyl group were coincident with the signals for the methyl group of the ethyl ester.

The fragmentation of the cyclobutanols also did not appear to require the trans orientation. Thus, the mixture of epoxycyclobutanones **24** and **25** adds methyllithium and subsequently undergoes fragmentation to hydroxy ketone **37.**



37

Stereochemical Course. Grob fragmentations generally show a stringent requirement for a planar trans elimination.[3] The observation that, in sterically rigid systems, both a cis and trans elimination occurred led us to investigate the stereochemical preferred mode of fragmentation in an unconstrained system. We were especially intrigued by the possibility of a very favorable cis-syn cleavage as a result of an internal acid catalyst for facilitating the opening of the epoxide as in eq 5.

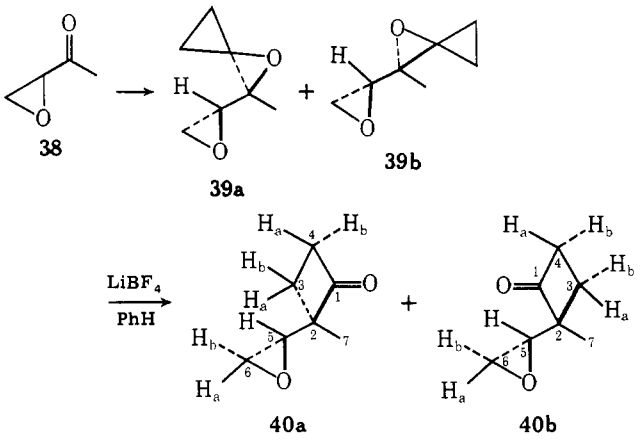


(5)

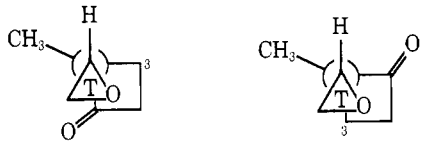
M = H or Lewis acid

Reaction of epoxy ketone **38** with ylide **1** led to a 4:3 mixture of the oxaspiropentanes, **39a** and **39b.** The mixture was chemoselectively rearranged utilizing lithium fluoroborate in benzene to give the two epoxycyclobutanones **40a** and **40b** in about the same ratio. The other acid catalysts decomposed the oxaspiropentanes. The two isomers were separated by preparative VPC. Table II summarizes the proton and carbon-13 NMR data for the epoxycyclobutanones. We have previously shown that the shift for C(3) is sensitive to the steric arrangement of the cyclobutanone.[19] Considering the best con-

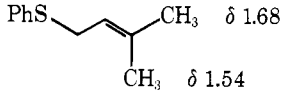
formations of **40a** and **40b**, as represented by **41a** and **41b**, respectively, the shielding by the expoxide ring[20] would be expected to more greatly affect **40b** than **40a** as observed. The higher field proton shifts for those at C(3) in **40b** also agree with this interpretation.[21]



More rigorous proof of stereochemistry was required for mechanistic interpretation. For this purpose, acyclic geometry



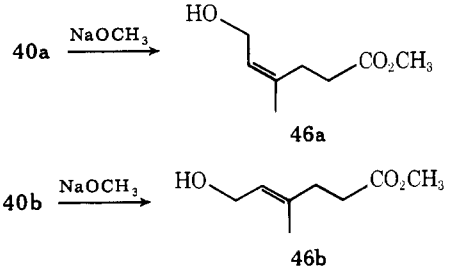
was converted to olefin geometry as outlined in Scheme IV. Baeyer-Villiger oxidation produced epoxy lactones **42a** and **42b** with retention of configuration at the center which migrated.[16,22] Vicinal glycols were created by nucleophilic opening of the epoxides at the primary carbon to avoid disturbing the asymmetric centers at C(5) and reduction of the lactones to the triols **43a** and **43b**. Thermal cis-syn vicinal dehydroxylation via an intermediate 2-dimethylamino-1,3-dioxolane utilizing the method of Eastwood et al.[23] produces the olefins **44a** and **44b** with concomitant acetylation of the primary hydroxyl groups. It is known that the methyl groups in an *E* olefin absorb at higher field than those in the *Z* olefin[24]—a fact confirmed in the model compound **45**.[25] The



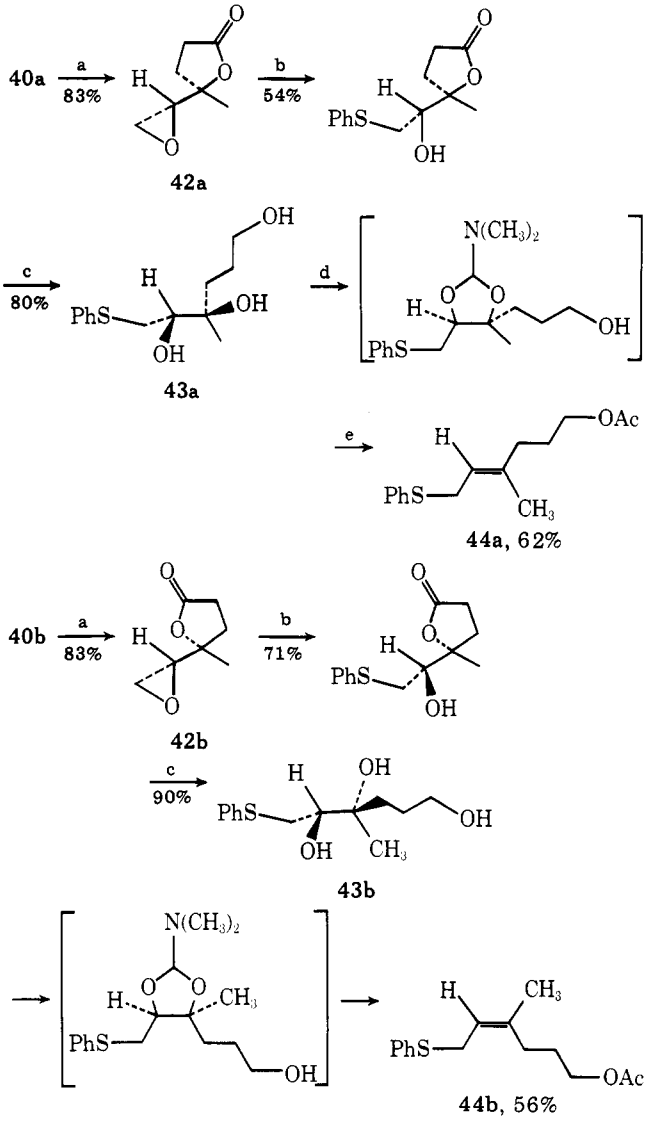
45

appearance of the methyl groups at δ 1.59 and 1.75 in **44a** and **44b**, respectively, confirms their assignment as the *E* and *Z* isomers as depicted.

Fragmentation of **40a** with methanolic sodium methoxide leads cleanly to a single olefin; similarly, **40b** produces a single olefin under identical conditions. Assignment of the *Z* and *E* configuration to **46a** and **46b**, respectively, derives from the relative chemical shifts for the vinyl methyl groups at δ 1.71 and 1.67, respectively. Confirmation of these assignments derives from Eu(dpm)$_3$-induced shifts. Europium salts complex



Scheme IV. Stereochemical Determination of Epoxycyclobutanones 40a and 40b



a, MCPBA, CH_2Cl_2, $NaHCO_3$, reflux; b, PhSNa, CH_3OH, room temperature; c, $LiAlH_4$, THF, reflux; d, $(CH_3)_2NCH(OCH_3)_2$, 60–80 °C, neat; e, Ac_2O, 130 °C.

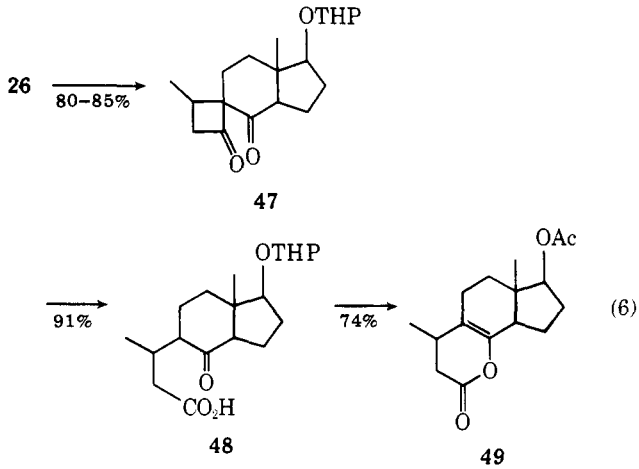
more strongly with a hydroxyl group than a carbonyl group.[26] Thus, the greater shift for the vinyl methyl group in **46b** (from δ 1.67 to 2.11) compared to **46a** (from δ 1.71 to 1.87) upon addition of 5 mol % Eu(dpm)$_3$ indicates the closer proximity of this methyl group to the hydroxyl group in **46b**.

Although the fragmentation is stereospecifically anti under the above reaction conditions, the attractiveness of the chelated intermediate for a syn fragmentation suggested the possibility that we might be able to reverse the stereospecificity of the reaction by choosing reaction conditions which favor such chelation. Fragmentation of **40a** with methanolic magnesium methoxide (a stronger Lewis acid) produced a 3:1 mixture of **46a** and **46b** and with a THF solution of magnesium methoxide a 1:1 mixture of these isomers. On the other hand, **40b** produced a 1:3 mixture of **46a** and **46b** with methanolic magnesium methoxide and a 1:1 mixture of these isomers in a THF solution of this base.

It is attractive to conclude that the ratios of isomers reflect a mixed mechanism between the concerted anti and concerted syn fragmentations. Unfortunately, the possibility that a carbonium ion mechanism accounts for the olefin of inverted stereochemistry cannot be rigorously excluded. The formation of such a large amount of the thermodynamically less stable

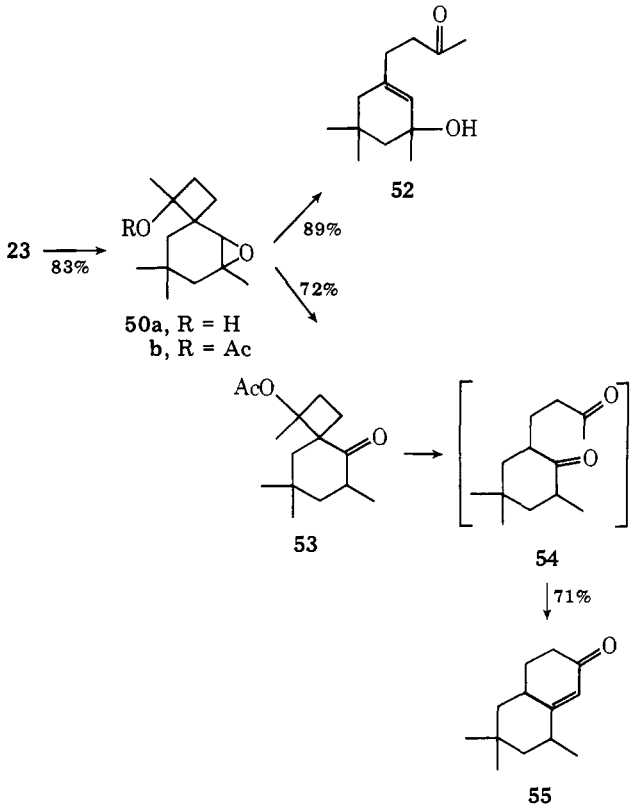
Z isomer from **40b** as well as the absence of any detectable amounts of solvolysis products can be taken to support the idea that both olefins arise from concerted processes.

Alternate Secoalkylation Approach. The epoxycyclobutanones can be rearranged prior to ring cleavage, leading to a different oxidation pattern in the product compared to the direct nucleophilically triggered fragmentation. Selective epoxide rearrangement of **26** to ketocyclobutanone **47** was achieved in 80–85% yield when limited to lower conversions with lithium fluoroborate in hot toluene (see eq 6). A retro-

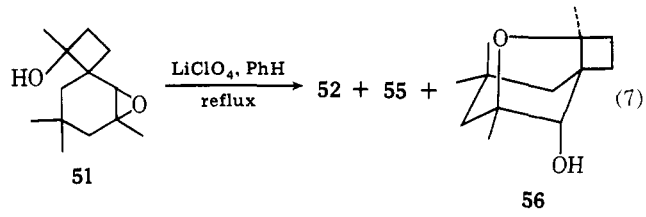


Claisen reaction proceeded smoothly upon treating a THF solution of **47** with aqueous potassium hydroxide at room temperature. The keto acid **48** was directly converted to its enol lactone under conditions in which the THP derivative was cleaved and the freed alcohol was converted to its acetate.

Derivatization of the cyclobutanones prior to epoxide rearrangement proved to be even more facile. Epoxycyclobutanone **23** undergoes addition of methyllithium and in situ acetylation to give acetate epoxide **50.** Fragmentation of **50**



occurs smoothly in a protonic medium to give **52.** Protection of the tertiary hydroxyl group of the alcohol related to **50** (i.e., **51**) was required to avoid side reactions during the course of



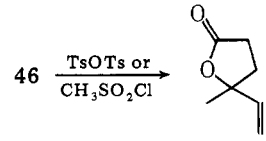
51 56

the epoxide rearrangement outlined in eq 7. The formation of **52** as the major product indicates the feasibility of an acid-catalyzed version of the fragmentation reaction. The formation of bicyclic enone **55** is quite interesting since it is the product anticipated from the desired mode of cleavage. The tentative assignment of structure **56** for one of the products rests upon the IR spectrum, which indicates the presence of a hydroxyl group and the absence of a carbonyl group, and the NMR spectrum, which shows a methine singlet at δ 3.38 for >CHOH and singlets for four methyl groups at δ 1.11, 1.19 (two methyl groups), and 1.29.

Protection of the alcohol by in situ acetylation of the initial methyllithium addition product allowed smooth rearrangment of **50b** to the ketoacetate **53** with 10 mol % of anhydrous lithium perchlorate in refluxing benzene. Sodium ethoxide in 1:2 ethanol–benzene at reflux effected fragmentation, presumably to diketone **5,** and in situ aldol ring closure to give enone **55** as a crystalline solid.

Application to a Pheromone Synthesis. This fragmentation reaction produces in the simple cases an olefin with two chemically different functional groups at either end to allow selective modification as in the synthesis of acylic terpenes. To illustrate this point, the fragmentation product **46** from epoxycyclobutanone **40** was converted to the dimethyl ester of a Monarch butterfly pheromone.[27,28]

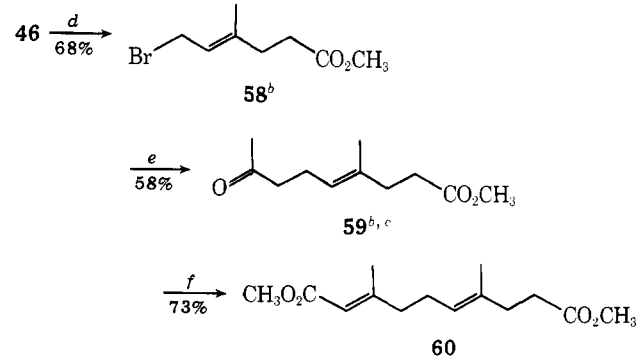
Attempted formation of the mesylate [CH_3SO_2Cl, CH_2Cl_2, $(C_2H_5)_3N$, 0 °C] or tosylate (TsOTs, collidine, benzene, 25 °C) only gave the lactone **57** which was identified by com-



57

parison to an authentic sample.[29] On the other hand, the desired bromide **58** was available utilizing phosphorus tribromide as outlined in Scheme V. Alkylation with the sodium salt of methyl acetoacetate in DMF followed by addition of lithium iodide and sodium cyanide to the alkylation reaction mixture[30]

Scheme V. Synthesis of Dimethyl 3,7-Dimethyl-2,6-decadienedioate[a]

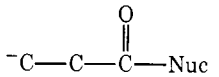


[a] The starting material was a mixture of **40a** and **40b.** [b] This compound is a mixture of *E* and *Z* isomers. [c] The geometrical isomers were separated prior to the next step. [d] CaH_2, PBr_3, ether, 0–5 °C. [e] $CH_3COCH(Na)CO_2CH_3$, DMF, 60 °C and then in situ $LiI \cdot 3H_2O$, NaCN, 130 °C. [f] $(CH_3O)_2P(O)CH(Na)CO_2CH_3$, DMF, 0 °C → room temperature.

effected decarbomethoxylation to allow direct isolation of the ketone **59** after reesterification with diazomethane. Since the sequence started with an *E,Z* mixture, **58** and **59** are a mixture of geometric isomers which were separated into the two isomers at the stage of ketone **59.** Obviously, since the fragmentation is stereospecific, starting with epimerically pure cyclobutanone would lead to geometrically pure olefins **58** and **59.** In any event, the synthesis was completed utilizing an Emmons–Wadsworth–Horner two-carbon-chain extension. The *E,E* isomer **60** was separated from the *Z,E* isomer and found to be identical with a sample prepared in a totally different fashion.[28b]

Conclusions

Annelations of cyclobutanones allow the development of a net synthon **61** in which a carbanion is β to a carbonyl group,



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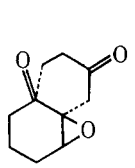
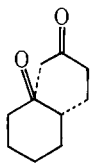
whereas such structural units are normally introduced via a Michael reaction in which this carbon behaves as a carbonium ion. As a consequence, secoalkylation allows creation of an

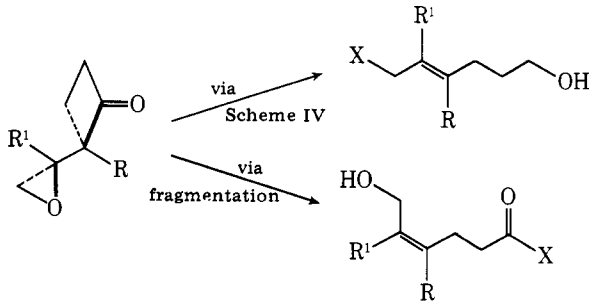


secoalkylation–annelation



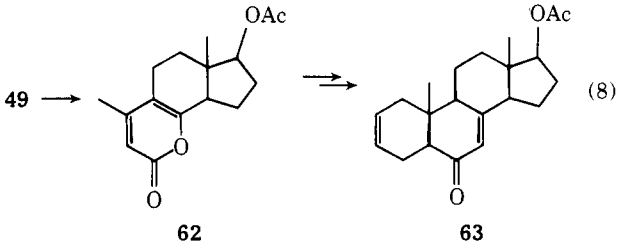
Robinson annelation

annelation that complements the normal Robinson annelation with respect to the orientation of the two components and, thus, the substitution pattern in the final product. Since the fragmentation is stereospecific, to the extent that cyclobutanone geminal annelation is stereocontrolled, this sequence can become a stereocontrolled synthesis of olefins. In fact, from one



isomer of the epoxycyclobutanone, either olefin isomer is stereospecifically available, depending upon the mode of fragmentation.

Utilization of the perhydroindanones in the sequence suggests the possible applications in steroid synthesis. Enol lactone **49** has been converted to α-pyrone **62** which can be envisioned to serve as an intermediate toward **63** (eq 8). The



(8)

62 **63**

substitution pattern in ring B would allow specific access to the insect molting hormones and B-ring dienes which are intermiediates in vitamin D synthesis.

The stereospecific anti elimination observed reveals that even with the tremendous exothermicity of 55 kcal/mol of strain release, Grob-type fragmentations retain high stereoelectronic control. Nevertheless, the possibility that a syn fragmentation has been observed under special conditions cannot be dismissed. The facility of introducing cyclobutanone units into organic substrates when combined with such Grob fragmentations now becomes a useful approach for chain extension.

Experimental Section

General Considerations. Reactions and atmospheric pressure distillations were all performed under a positive pressure of dry nitrogen. In experiments where "dry" solvents or reagents are specified, diethyl ether (ether), tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were distilled from sodium–benzophenone ketyl; dimethyl sulfoxide (Me_2SO), dimethylformamide (DMF), hexamethylphosphoric triamide (HMPA), dichloromethane, and all amines were distilled from calcium hydride; benzene was distilled from sodium; and methanol was distilled from magensium methoxide. Glassware for experiments specifying "dry" conditions was dried by flaming in a stream of dry nitrogen. Room temperature generally means 25 ± 2 °C.

Pentane and hexane are used to refer to Skellysolve A and B, respectively; chloroform refers to Mallinckrodt AR grade, which contains about 0.75% ethanol as a preservative; and "anhydrous ether" is used to designate a freshly opened can of Mallinckrodt AR grade anhydrous ethyl ether.

Preparative thin-layer chromatography (TLC) was performed on 1.0–1.5-mm layers of E. Merck silica gel PF-254 without calcium sulfate binder. These plates were prepared by spreading an aqueous slurry of silica gel onto clean glass plates, air-drying overnight, activating by heating at 110–120 °C for 2 h, and storing in a closed box until use. Bands were visualized by ultraviolet light or by spraying one edge of the plate with saturated (ca. 10%) ethanolic phosphomolybdic acid and heating in a stream of hot air. The desired areas were scraped off the plate, stirred with ether (or, for more polar compounds, methanol or ethyl acetate), suction-filtered, and rotary evaporated. Column chromatography was performed using the following absorbents: silica gel (W. R. Grace, grade 62, 60–200 mesh), alumina (Fisher alumina adsorption, 80–200 mesh), and Florisil (Fisher, 60–100 mesh).

Infrared spectra were obtained as dilute (2–5%) solutions in 0.1-mm sodium chloride cavity cells using Beckman IR-8 or Perkin-Elmer 267 grating spectrophotometers. Ultraviolet spectra were determined on 0.100-cm quartz cells using a Cary 15 spectrophotometer. Proton NMR spectra were obtained on Varian T-60 (60 MHz), Jeolco MH-100 (100 MHz), Varian XL-100, and Bruker WH 270 (270 MHz) spectrometers. Carbon-13 NMR were obtained on a Jeolco FX-60 (60 MHz) spectrometer. NMR chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (Me_4Si). Coupling constants (J) are given in hertz with splitting patterns designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). ^{13}C NMR multiplicities were determined by off-resonance partial proton decoupling. Mass spectra were obtained on an AEI MS 902 high-resolution mass spectrometer at an ionizing current of 98 mA and, unless otherwise specified, at an ionizing voltage of 70 eV.

Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Melting points were determined in open capillaries using a Thomas-Hoover melting point apparatus and are uncorrected. Gas–liquid chromatography (GLC) was performed on a Varian Associates Aerograph Model 90-P3 instrument using helium as a carrier gas and thermal conductivity detection. The following columns were employed: A (copper, 8 ft × 0.25 in., 1% DC-710 on Chromosorb W Reg. 60/80), B (copper, 8 ft × 0.25 in., 10% Carbowax 20M on Chromosorb W Reg. 60/80), C (copper, 8 ft × 0.25 in., 10% UCON 20 HB Polar on Chromosorb W Reg. 60/80).

Preparation of Epoxy Ketones. A. 3,4-Epoxy-2-butanone (38). Following the method of Yang and Finnegan,[31] variable yields (0–60%) of the desired epoxide could be obtained. In the best run, 36.8 g (525 mmol) of 3-buten-2-one, 45.06 g (500 mmol) of 97% (by iodometric titration[32]) *tert*-butyl hydroperoxide, freshly purified by distillation (bp 39–41 °C at 25 Torr), and 1.05 g (2.5 mmol) of a 40% methanolic solution of benzyltrimethylammonium hydroxide in 500

mL of benzene gave 25.95 g, bp 38–43 °C (18 mm) [lit.[31] bp 46 °C (30 mm)], of epoxy ketone **38.**

In a more reproducible procedure, 50 mL (606 mmol) of 3-buten-2-one was added dropwise, over 15 min, to a cold (−10 °C) solution of 29.65 g (243 mmol) of *tert*-butyl hydroperoxide (75%, MCB practical grade) and 0.49 g (4.4 mmol) of potassium *tert*-butoxide in 250 mL of THF. During the addition the solution became straw-colored. The solution was stirred at −10 to −15 °C for 1 h, diluted with 500 mL of ether, washed with 3 × 250 mL of saturated aqueous sodium chloride, dried over anhydrous potassium carbonate, and rotary evaporated in vacuo to yield 11.96 g of an orange oil. Fractional distillation of this material at reduced pressure through a 10-cm Vigreux column gave, after a short forerun, 7.44 g (35%) of a pale yellow liquid, bp 53–58 °C (32 mm).

B. 1,2-Epoxybicyclo[4.3.0]nonan-3-one (6). A solution of bicyclo[4.3.0]non-1-en-3-one (17.30 g, 127 mmol) and hydrogen peroxide (35 mL, 30% aqueous solution) in 150 mL of methanol was cooled to 15 °C. An aqueous 4 N solution of sodium hydroxide, 75 mmol, was added slowly, keeping the temperature between 15 and 20 °C. After the addition was complete the solution was mixed for 7 h at 25 °C. At that time 300 mL of H_2O was added and the mixture extracted with 2 × 30 mL of ether. The ether was dried over magnesium sulfate and evaporated. The resulting oil was distilled [62 °C (0.1 mmHg)] to yield 11.59 g (60%) of the epoxy ketone: IR (CCl_4) 1712 cm^{-1}; NMR (CCl_4) δ 1.1–2.8 (11 H), 3.01 (s, 1 H); MS *m/e* (%) 152 (19), 136 (10), 97 (100); mol wt calcd ($C_9H_{12}O_2$) 152.0837, found 152.0837.

C. Preparation of 7,7a-Dihydro-7aβ-methyl-4,7bβ-oxa-1β-tetrahydropyranyloxy-5(6*H*)-indanone (7). 10. 7,7a-Dihydro-7aβ-methyl-1β-tetrahydropyranyloxy-5(6*H*)-indanone (**9**)[14] (17.5 g, 70.0 mmol) in 125 mL of anhydrous ether was added over a 20-min period to a suspension of lithium aluminum hydride (2.64 g, 69.5 mmol) in 125 mL of ether. The reaction mixture was heated at reflux for 25 h, then cooled, and quenched by the successive addition of 2.7 mL of water, 2.7 mL of 4 N sodium hydroxide solution, and 8.1 mL of water. The resulting mixture was filtered and the white crystals were washed with an additional 30 mL of ether. The combined washings and filtrate were dried and concentrated in vacuo to yield 17.5 g (99%) of a colorless oil which showed one spot at R_f 0.7 on analytical TLC (10:1 chloroform–methanol): IR (CCl_4) 3636, 3472, 1117, 1064 cm^{-1}; NMR (CCl_4) δ 5.32 (s, 1 H), 4.63 (s, 1 H), 3.2–4.3 (m, 4 H), 2.7–3.2 [br s, 1 H (disappears upon addition of D_2O)], 1.3–2.7 (m, 4 H), 1.03 (br s, 3 H); MS *m/e* (%) 234 (10), 168 (2), 167 (2), 166 (6), 152 (1), 151 (11), 150 (80), 135 (2), 133 (3), 132 (14), 108 (6), 106 (9), 86 (7), 85 (100), 84 (5); mol wt calcd for ($C_{15}H_{22}O_2$, $M^+ - H_2O$) 234.16169, found 234.16202.

11 (Method A). *m*-Chloroperbenzoic acid (16.0 g, 80 mmol, of active O) was added portionwise to a solution of 7,7a-dihydro-5β-hydroxy-7aβ-methyl-1β-tetrahydropyranyloxy- 6*H*-indan (**10**) (17.5 g, 69.0 mmol) in 200 mL of ether at 0 °C. When addition was complete, the cooling bath was removed and the reaction mixture was stirred at room temperature with TLC (10:1 chloroform–methanol) monitoring. After 4 h, the reaction was diluted with 300 mL of ether and washed with 10% aqueous solutions of sodium sulfite and sodium bicarbonate. The organic phase was dried and concentrated in vacuo to yield a waxy solid which was crystallized from ether–hexane to give 16.7 g (90%) of a white powder: mp 80–86 °C; IR (CCl_4) 3590, 3460, 2913, 2875, 2835 cm^{-1}; NMR (CCl_4) δ 4.66 (s, 1 H), 3.2–4.0 (m, 4 H), 3.07 (s, 1 H), 2.16 (s, 1 H), 1.1–2.1 (m, 14 H), 0.99 (s, 3 H); MS *m/e* (%) [184 (6), 183 (25), 167 (25), 166 (63), 150 (10), 149 (16), 141 (8), 140 (68), 138 (11), 137 (9), 136 (10), 123 (16), 122 (17), 109 (15), 107 (35), 105 (10), 97 (20), 95 (16), 93 (23), 91 (16)] × 10, 86 (5), 85 (100), 84 (5). Anal. ($C_{15}H_{24}O_4$) C, H.

11 (Method B). Allylic alcohol **10** (253 mg, 1.00 mmol) and molybdenum hexacarbonyl (~10 mg) were dissolved in 3 mL of benzene and heated to reflux. *tert*-Butyl hydroperoxide (115 mg of 94% solution, 1.20 mmol) was added dropwise over a period of 20 min. After an additional 30 min at reflux, TLC analysis (10:1 chloroform–methanol) showed complete disappearance of the starting material: spot at R_f 0.7 and a new spot at R_f 0.6. The reaction mixture was cooled, diluted with ether, and washed with 10% aqueous sodium sulfite solution. The organic phase was dried and concentrated in vacuo to yield 250 mg (93%) of a colorless oil which crystallized from ether–pentane to give an amorphous white powder, mp 80–86 °C. See above for spectral data.

7. Chromium trioxide (57.8 g, 578 mmol) was added in one portion to a solution of pyridine (93.6 g, 1.15 mol) in 1.2 L of methylene chloride at 0 °C. the resulting solution was stirred for 20 min; then a solution of epoxide alcohol **11** (15.5 g, 57.8 mmol) in 100 mL of methylene chloride was added by syringe over a 5-min period. The resulting reaction mixture was stirred at room temperature for an additional 20 min and then poured into 1.3 L of ether, and the solid residue was washed with an additional 200 mL of ether. The combined organic phases were washed successively with 10 × 500 mL of saturated aqueous sodium bicarbonate solution, 500 mL of water, and 2 × 500 mL of cold 1% aqueous hydrochloric acid solution. The organic phase was dried and concentrated in vacuo to yield a yellow-brown oil. This material was dissolved in ether and filtered through a 2-in. plug of silica gel to yield 14.2 g (93%) of an almost colorless oil which was homogeneous by analytical TLC (ether, R_f 0.75): IR (CCl_4) 1712 cm^{-1}; NMR (CCl_4) δ 4.59 (s, 1 H), 3.2–4.1 (m, 3 H), 2.90 (s, 1 H), 2.2–2.9 (m, 1 H), 1.2–2.3 (m, 14 H), 1.15 (s, 3 H); MS *m/e* (%) 15 eV [266 (6)] × 30, 183 (6), 182 (16), 167 (2), 166 (12), 154 (5), 153 (21), 140 (3), 139 (3), 138 (4), 137 (5), 136 (10), 86 (6), 85 (100), 84 (13); mol wt calcd ($C_{15}H_{22}O_4$) 266.1518, found 266.1518.

D. Preparation of 7,7a-Dihydro-7aβ-methyl-4,7bβ-oxa-1,5(6*H*)-indandione (12). Epoxy ketone **7** (120 mg, 0.452 mmol) was dissolved in 1 mL of acetic acid and 0.5 mL of water and the resulting solution was heated at 40 °C for 20 min, then cooled, diluted with chloroform, and washed with an equal volume of 10% aqueous sodium carbonate solution. The organic phase was dried and concentrated in vacuo to yield a pale yellow oil which was chromatographed (ether) on a 10 × 20 cm TLC plate to yield 52 mg (63%) of the desired alcohol at R_f 0.5: IR (CCl_4) 3630 (sh), 3470 (br), 1715 cm^{-1}. This material was added to a suspension of the chromium trioxide–pyridine complex, formed by the addition of chromium trioxide (286 mg, 2.86 mmol) to a methylene chloride solution of pyridine (451 mg, 5.72 mmol), and the resulting reaction mixture was stirred at room temperature for 20 min. Powdered sodium bisulfate (754 mg, 6.29 mmol) was added and the resulting mixture was stirred for 15 min and then filtered through a 5-cm silica gel column (excess dichloromethane required) to yield the desired diketone as white crystals. Recrystallization from ether–hexane gave 44 mg (85%) of white crystals: mp 141–142 °C; IR ($CHCl_3$) 1745, 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.23 (s, 1 H), 2.25–2.9 (m, 4 H), 1.6–2.25 (m, 4 H), 1.32 (s, 3 H); MS *m/e* (%) 182 (14), 181 (6), 180 (50), 164 (30), 152 (12), 151 (90), 141 (10), 139 (12), 138 (96), 126 (44), 125 (24), 124 (28), 123 (48), 122 (50), 121 (12), 110 (40), 109 (42), 107 (16), 97 (32), 95 (100), 94 (12), 93 (22), 91 (18), 85 (18), 83 (24), 82 (27), 81 (84), 80 (20), 79 (62), 77 (24), 69 (18), 68 (40), 67 (94), 66 (14), 65 (18), 55 (88); mol wt calcd ($C_{10}H_{12}O_3$) 180.0786, found 180.0785.

E. Preparation of 7,7a-Dihydro-7aβ-methyl-4,7bβ-oxa-1β-tetrahydropyranyloxy-5(6*H*)-indanone (8). 14. Allylic alcohol **10** (10.0 g, 39.7 mmol) and imidazole (8.16 g, 120 mmol) were dissolved in 50 mL of DMF, and the resulting solution was cooled to 0 °C in an ice bath. Chlorotrimethylsilane (6.47 g, 59.5 mmol) was added slowly by syringe over a 5-min period and after an additional 30 min, the ice bath was removed and the reaction was allowed to proceed at room temperature for an additional 16 h, then diluted with ether, and washed three times with a total of 2 vol of water. The organic phase was dried and concentrated in vacuo to yield a pale yellow oil which was dissolved in 100 mL of anhydrous ether. The resulting solution was cooled to 0 °C and *m*-chloroperbenzoic acid (12.1 g of 85% mixture, 59.5 mmol of active oxygen) was added portionwise with stirring. When dissolution was complete, the reaction mixture was sealed under nitrogen and stored in the refrigerator at −5 to 0 °C for 50 h, then diluted with ether, and washed successively with 10% aqueous sodium sulfite solution and 10% aqueous sodium carbonate solution. The organic phase was dried and concentrated in vacuo to yield a colorless oil, which showed two epoxide protons in the NMR at δ 2.84 and 2.73 (relative to the trimethylsilyl ether) in a ratio of ~2:1. This material was dissolved in 20 mL of ethanol and sufficient water was added until the mixture became slightly turbid. This solution was heated at 50 °C for 15 min; then solvents were removed in vacuo. The residue was dissolved in ether and dried over magnesium sulfate. The ether was removed in vacuo and the remaining colorless oil was chromatographed on a 200-g dry-packed silica gel column (9:1 ether–hexane) to yield two isomeric epoxy alcohols which appeared at R_f 0.61 and 0.39, respectively, on analytical TLC (ether). The more polar product, 2.76 g (26%), was identical with the product (**11**) of molybdenum hexacarbonyl catalyzed epoxidation of 7,7a-dihydro-5β-hydroxy-7aβ-methyl-1β-tetrahydropyranyloxy-6*H*-indan. The

less polar product **14**, 6.48 g (61% overall), was a colorless oil with spectral properties as follows: IR (CCl_4) 3613, 3450, 2939, 2860 cm^{-1}; NMR (CCl_4) δ 4.58 (s, 1 H), 3.2-4.2 (m, 5 H), 3.08 (s, 1 H), 2.05-2.5 (m, 2 H), 0.9-2.0 (m, 12 H), 1.08 (s, 3 H); MS *m/e* (%) 12 eV 185 (2), 184 (6), 183 (13), 168 (4), 167 (12), 166 (53), 150 (10), 140 (33), 86 (11), 85 (100), 84 (21). Anal. ($C_{15}H_{24}O_2$) C, H.

8. The chromium trioxide-pyridine complex was prepared by the addition of chromium trioxide (12.3 g, 123 mmol) to a solution of pyridine (19.5 g, 246 mmol) in 250 mL of dichloromethane. After stirring at room temperature for 15 min, epoxy alcohol **14** (3.30 g, 12.3 mmol) in 20 mL of dichloromethane was added by syringe. After an additional 20 min at room temperature, the reaction was diluted with ether and washed several times with saturated aqueous sodium bicarbonate solution, two portions of cold 1% aqueous hydrochloric acid solution, and one additional portion of bicarbonate. The organic phase was dried and concentrated in vacuo to yield a yellow oil which was chromatographed on a 150-g dry-packed silica gel column (3:2 ether-hexane) to yield 3.00 g (92%) of the desired keto epoxide as an almost colorless oil: IR (CCl_4) 2940, 1713 cm^{-1}; NMR (CCl_4) δ 4.58 (s, 1 H), 4.0 (dd, J = 16, 8 Hz), 3.6-3.9 (m, 1 H), 3.25-3.55 (m, 1 H), 3.23 (s, 1 H), 2.05-2.6 (m, 4 H), 1.20-2.05 (m, 10 H), 1.02 (s, 3 H). Anal. ($C_{15}H_{22}O_4$), C, H.

F. Preparation of 7,7a-Dihydro-7aβ-methyl-4,7bα-oxa-1,5(6*H*)-indandione (16). Hydrogen peroxide (2.0 mL of 30% aqueous solution, 24 mmol) was added by syringe to a solution of dione **15**[14] (1.00 g, 6.00 mmol) in 15 mL of methanol. The resulting solution was cooled to 0 °C and sodium hydroxide (750 μL of 4 N aqueous solution, 3.00 mmol) was added by syringe over a 10-min period. The resulting reaction mixture was stirred at room temperature for 5 h, then poured into 5 mL of water, and extracted with 2 × 75 mL of chloroform. The organic phase was dried and concentrated in vacuo to yield a colorless oil which slowly crystallized. Recrystallization from ethyl acetate gave 1.03-g (94%) yield of white crystals: mp 74-76 °C (lit.[33] mp 77-79 °C); IR ($CHCl_3$) 1745, 1712 cm^{-1}; NMR ($CDCl_3$) δ 3.60 (s, 1 H), 1.4-2.9 (m, 8 H), 1.16 (s, 3 H); MS *m/e* (%) 181 (2), 180 (15), 165 (2), 164 (13), 152 (7), 151 (57), 139 (9), 138 (100), 137 (9), 126 (11), 125 (12), 124 (12), 123 (31), 122 (14), 121 (6), 110 (41), 109 (27), 107 (8), 97 (25), 96 (17), 95 (66), 94 (6), 93 (20), 92 (6), 91 (11), 82 (12), 81 (46), 80 (14), 79 (45), 77 (15), 69 (9), 68 (16), 67 (46), 66 (11), 65 (12), 56 (8), 55 (41), 54 (8), 53 (33), 52 (9), 51 (14); mol wt calcd ($C_{10}H_{12}O_3$) 180.0786, found 180.0786.

Cyclobutanone Syntheses. A. Preparation of 5,5-Dimethyl-7,8-epoxyspiro[3.5]nonan-1-one (22). 17. A solution of cyclopropyldiphenylsulfonium fluoroborate (8.60 g, 27.4 mmol) and 2,3-epoxy-5,5-dimethylcyclohexanone (3.83 g, 27.5 mmol) in 50 mL of dimethyl sulfoxide was treated with powdered potassium hydroxide (3.30 g, 50 mmol). After stirring at room temperature for 4 h the reaction was extracted with 2 × 100 mL of hexane. The hexane was washed with 50 mL of a saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated in vacuo to yield an oil. The oil was vacuum distilled at 74 (1 mmHg) or 35 °C (0.20 mmHg) to yield 4.77 g (96%): IR (CCl_4) 3086, 3012, 2967, 2924, 2882, 1081, 1005 cm^{-1}; NMR (CCl_4) δ 0.90 (s, 4 H), 1.00 (s, 3 H), 1.05 (s, 3 H), 1.22 (m, 1 H), 1.48-1.83 (m, 3 H), 2.76 (br d, J = 4 Hz, 1 H), 3.00-3.22 (dt, J = 4, 3 Hz, 1 H); MS *m/e* (%) 180 (3), 165 (5), 152 (10), 138 (15), 137 (25), 131 (30), 124 (68), 123 (68), 121 (22), 109 (72), 95 (100), 93 (44), 81 (59), 79 (46), 69 (54), 67 (73), 41 (100); mol wt calcd ($C_{11}H_{16}O_2$) 180.1150, found 180.1150.

22. Into 40 mL of carbon tetrachloride was dissolved cyclopropylidene-3,3-dimethylcylohex-5-ene diepoxide (**17**) (1.00 g), This solution was shaken with 40 mL of aqueous 1 M HBF_4 for 5 min. The CCl_4 layer was separated, dried, and evaporated to yield 0.99 g (99%) of an oil. The oil showed no trace of starting material by NMR. This oil was flash distilled with a pot temperature of 50 °C (0.2 mm): IR (CCl_4) 1783 cm^{-1}; NMR (CCl_4) δ 0.91 (s, 6 H), 1.2-2.6 (m, 7 H), 2.86-3.25 (m, 3H); MS *m/e* (%) 180 (2), 165 (5), 138 (14), 125 (80), 124 (72), 123 (65), 119 (55), 117 (56), 109 (67), 95 (94), 93 (45), 83 (61), 81 (53), 79 (45), 69 (54), 67 (73), 41 (100); mol wt calcd ($C_{11}H_{16}O_2$) 180.11502, found 180.11431.

B. Preparation of 4,5-Epoxy-5,7,7-trimethylspiro[3.5]nonan-1-one (23). 18. Following the above procedure 4.62 g (30 mmol) of epoxyisophorone **5**, 9.42 g (30 mmol) of cyclopropylsulfonium salt, and 3.36 g (60 mmol) of powdered potassium hydroxide in 75 mL of Me_2SO gave after 4 h 5.13 g (88%) of oxaspiropentane **18**: bp 31 °C (0.01 mm); mp 34-35 °C; IR (CCl_4) 3096, 1003, 947, 912, 903 cm^{-1}; NMR (CCl_4) δ 0.89 (ps, 4 H), 0.98 (s, 3 H), 1.02 (s, 3 H), 1.30 (s, 3 H), 1.2-1.8 (m, 4 H), 2.60 (s, 1 H); MS *m/e* (%) 194 (5), 179 (3), 166 (7), 138 (49), 109 (25), 95 (31), 83 (66), 82 (72), 43 (100); mol wt calcd ($C_{12}H_{18}O_2$) 194.1307, found 194.1325.

23. A solution of cyclopropylidene-3,3,5-trimethylcyclohex-5-ene diepoxide (5.10 g, 26.3 mmol) in 100 mL of pentane was shaken with 100 mL of 1 M aqueous fluoroboric acid. After 15 min the pentane was separated, washed with water (100 mL), and dried over anhydrous sodium sulfate. Removal of the pentane in vacuo resulted in 5.10 g (100%) of an oil. The oil was cooled at −20 °C overnight to induce crystallization: mp 35.5-36.0 °C; IR (CCl_4) 2976, 1779, 1111, 1075, 1059, 941, 914, 872 cm^{-1}; NMR (CCl_4) δ 0.91 (s, 6 H), 1.28 (s, 3 H), 1.29 and 1.40 (AB, J = 15 Hz, 2 H), 1.44 and 1.58 (AB, J = 15 Hz, 2 H), 1.5-2.5 (m, 2 H), 2.84 (s, 1 H), 3.03 (m, 2 H); MS *m/e* (%) 194 (4), 179 (5), 166 (12), 138 (56), 137 (46), 110 (27), 109 (35), 95 (38), 81 (32), 43 (100); mol wt calcd ($C_{12}H_{18}O_2$) 194.1307, found 194.1322.

C. Preparation of 4,5-Epoxybicyclo[4.3.0^{5,9}]spiro[3.8]dodecan-1-one (24 and 25). 19. As above, 1.52 g (10.0 mmol) of **6**, 3.77 g (12.0 mmol) of sulfonium salt, and 1.12 g (20 mmol) of powdered potassium hydroxide in 30 mL of Me_2SO gave after 6 h 2.47 g of crude product which was 52.3% oxaspiropentane and 47.7% diphenyl sulfide by NMR spectroscopy—corresponding to an 85% yield: IR (CCl_4) 3086, 1149, 1005, 948, 915, 887, 875, 846, 825 cm^{-1}; NMR (CCl_4) δ 0.83-1.00 (m, 4 H), 1.05-2.25 (m, 11 H), 2.68 (s, 1 H); NMR (CD_3CN) δ 0.8-1.0 (m, 4 H), 1.1-2.1 (m, 11 H), 2.80 (s, 1 H) [at 100-Hz sweep width 2.80 (86.5%), 2.87 (13.5%) reflects ratio of isomers].

24 and 25. To 910 mg of 67% 5-cyclopropylideneperhydro-4,9-indene diepoxide in diphenyl sulfide dissolved in 50 mL of acetonitrile was added 0.5 g of oxalic acid. The oxalic acid dissolved and the solution was stirred for 2 h at 25 °C. The mixture was poured into a two-phase system of 100 mL of saturated aqueous sodium bicarbonate and 150 mL of ether. The ether layer was removed and another 150 mL of ether added. The combined ether layers were dried over anhydrous sodium sulfate and evaporated to yield an oil. Preparative TLC with a deactivated (water mist and then dry for 1 h at room temperature) silica gel PF-254 plate resulted in 561 mg (92%) of cyclobutanones **24** and **25**: IR (CCl_4) 1779, 1065, 1054, 937, 912, 901 cm^{-1}; NMR (CCl_4) δ 1.0-2.5 (m, 13 H), 3.02 (s, 1 H), 3.09 (m, AA' of AA'BB', 2 H); MS *m/e* (%) 192 (5), 174 (7), 164 (5), 119 (94), 117 (100); mol wt calcd ($C_{12}H_{16}O_2$) 192.1150, found 192.1207.

D. Preparation of 7,7a-Dihydro-7aβ-methyl-4,7bβ-oxa-5-(4'-methyl-2'-oxospirocyclobutyl)-1β-tetrahydropyranoyloxy-6*H*-indan (26). As above, 13.5 g (50.7 mmol) of epoxyindanone **7**, 21.6 g (65.6 mmol) of 2-methylcyclopropyldiphenylsulfonium fluoroborate, and 5.60 g (100 mmol) of powdered potassium hydroxide in 500 mL of degassed Me_2SO gave after 4 h 25.51 g of crude product which deposited white crystals, mp 108-110 °C, of oxaspiropentane still contaminated with diphenyl sulfide upon refrigeration: IR (CCl_4) 1075, 1015 cm^{-1}; NMR (CCl_4, external Me_4Si) δ 4.83 and 4.63 (2 s, ratio 1:9, 1 H), 3.2-4.2 (m, 3 H), 2.62 and 2.54 (2 s, ratio 2.2:1, 1 H), 0.70-2.3 (m, 16 H), 1.12 (s, 3 H), 0.95 (s, 3 H), 0.53 (m, 1 H).

The above mixture (25 g) was rearranged utilizing 4.5 g (50 mmol) of oxalic acid in 300 mL of acetonitrile as described above. Dry column chromatography of the crude product on 300 g of silica gel eluting with 5% ether in hexane gave 13.75 g (79%) of cyclobutanone **26** as an almost colorless oil: IR (CCl_4) 1776 cm^{-1}; NMR (CCl_4) (mixture of isomers) δ 4.87 and 4.67 [1 H, 2 s, ratio 1:6, 3.1-4.1 (4 H, m)], 2.2-3.1 (3 H, m), 0.7-2.2 (14 H, m), 1.2 (3 H, d, J = 7 Hz), 0.92 (3 H, br s); MS *m/e* (%) 15 eV [321 (5), 320 (17)] × 30, 293 (5), 292 (17), 278 (17), 236 (8), 235 (5), 219 (9), 218 (30), 208 (11), 207 (5), 203 (7), 200 (10), 194 (15), 193 (10), 192 (10), 191 (7), 190 (20), 180 (6), 179 (5), 178 (14), 177 (11), 176 (21), 175 (7), 174 (30), 173 (5), 172 (15), 166(17), 165 (10), 164 (5), 163 (5), 162 (5), 161 (9), 160 (7), 159 (18), 158 (14), 152 (15), 151 (5), 150 (5), 149 (5), 148 (5), 147 (5), 146 (13), 145 (26), 144 (5), 140 (5), 133 (5), 132 (19), 131 (46), 127 (6), 123 (16) 112 (6), 110 (11), 86 (11), 85 (100), 84 (38); mol wt calcd ($C_{19}H_{28}O_4$) 320.1987, found 320.1960.

E. Preparation of 7,7a-Dihydro-7aβ-methyl-4,7bα-oxa-5-(4'-methyl-2'-oxospirocyclobutyl)-1β-tetrahydropyranyloxy-6*H*-indan (27 and 28). As above, 4.48 g (16.8 mmol) of epoxyindanone **8**, 6.60 g (20.1 mmol) of 2-methylcyclopropyldiphenylsulfonium fluoroborate, and 1.88 g (33.6 mmol) of powdered potassium hydroxide in 150 mL of degassed Me_2SO gave after 1.75 h 6.9 g of crude product. Rearrangement of this oxaspiropentane with 0.5 g of oxalic acid in 100 mL of acetonitrile for 45 min and purification, after the usual workup, by

dry column chromatography consisting of 200 g of silica gel eluting 3:2 hexane–ether gave two isomeric cyclobutanones which had TLC R_f 0.47 and 0.23 and weighed 3.65 and 0.65 g, respectively, for a total overall yield of 80%. Compound R_f 0.47: IR (CCl_4) 2913, 2850, 1776 cm^{-1}; NMR (CCl_4, mixture of diastereomers) δ 4.63 (s, 1 H), 3.6–4.1 (m, 2 H), 3.0–3.6 (m, 3 H), 2.0–3.0 (m, 3 H), 0.8–2.0 (m, 16 H), 1.04 (s, 3 H). Compound R_f 0.23: IR (CCl_4) 2916, 2860, 1782 cm^{-1}; NMR (CCl_4, mixture of diastereomers) δ 4.60 (s, 1 H), 3.6–42 (m, 2 H), 2.8–3.6 (m, 3 H), 2.0–2.6 (m, 3 H), 0.7–2.0 (m, 19 H); MS *m/e* (%) (mixture of cyclobutanones) 320 (4), 292 (3), 289 (4), 288 (13), 264 (2), 263 (4), 262 (15), 237 (3), 236 (15), 220 (10), 219 (17), 218 (55), 209 (5), 203 (11), 202 (6), 201 (8), 200 (20), 195 (5), 194 (23), 193 (21), 192 (24), 191 (15), 190 (26), 180 (11), 179 (13), 178 (21), 177 (28), 176 (32), 175 (15), 174 (36), 172 (12), 166 (26), 165 (14), 164 (15), 163 (19), 162 (15), 161 (29), 160 (19), 159 (21), 158 (15), 152 (29), 151 (22), 150 (15), 149 (17), 148 (21), 147 (26), 146 (31), 145 (32), 140 (13), 138 (10), 137 (11), 136 (10), 135 (19), 134 (15), 133 (31), 132 (38), 131 (43), 130 (11), 127 (11), 123 (15), 122 (14), 121 (20), 120 (11), 119 (20), 117 (13), 110 (30), 109 (13), 107 (15), 106 (12), 105 (20), 97 (15), 95 (11), 93 (21), 90 (16) × 10, 86 (7), 85 (100), 84 (8). Anal. ($C_{19}H_{28}O_4$) C, H.

F. Preparation of 2-Methyl-2-oxiranylcyclobutanones (40a,b). 39a,b. A solution of 1.15 M dimsylsodium in Me_2SO (65 mL, 74.9 mmol) was added by syringe over 5 min to a well-stirred, cold (−40 °C) suspension of cyclopropyldiphenylsulfonium fluoborate (23.54 g, 74.9 mmol) in 500 mL of dry DME. During this addition the sulfonium salt dissolved and the solution became yellow orange in color. After 5 min, 6.45 g (74.9 mmol) of epoxy ketone **38** was added and stirring continued at −40 °C for 15 min. The cold bath was removed and the yellow solution allowed to warm to room temperature over 60 min giving a murky brown mixture. Water (500 mL) was added and the mixture extracted with 3 × 500 mL of ether. The ether extract was washed with 250 mL of saturated aqueous sodium bicarbonate, dried over anhydrous potassium carbonate, and rotary evaporated to give 26.13 g of yellow liquid, which by NMR contained 6.73 g (71.2% yield) of the desired oxaspiropentanes. Distillation from a small amount of potassium carbonate through a Vigreux column gave 2.96 g (44% recovery) of **39a,b** as a colorless liquid [bp 49–50 °C (2.5 Torr)]: IR (CCl_4) 3075, 3000, 2950, 908, 852 cm^{-1}; NMR (CCl_4) δ 0.7–1.1 (m, 4 H), 1.29 (s, 3 H), 2.5–2.9 (m, 3 H); NMR (CD_3CN) δ 0.8–1.1 (m, 4 H), 1.25 and 1.37 (ratio ca. 3:4, 2 s, 3 H total), 2.6–3.2 (m, 3 H).

40a,b. Anhydrous lithium fluoborate (92.7 mg, 0.99 mmol) was added to a solution of the oxaspiropentanes (3.5619 g, 28.2 mmol) in 25 mL of benzene. This mixture was stirred at 25 °C for 400 min, diluted with 100 mL of pentane, and washed with 25 mL of saturated aqueous sodium bicarbonate. The organic solution was dried over anhydrous sodium carbonate and rotary evaporated to give 3.062 g (83%) of colorless liquid. This product and the products from several smaller scale reactions were combined (3.717 g) and distilled (short path), giving 3.185 g of colorless liquid [bp 25 °C (0.1–0.15 Torr)] which was identified as a 3:2 mixture (by NMR in CCl_4, using peak height ratio of the methyl singlets at δ 1.23 and 1.27) of the two diastereomers of 2-methyl-2-(2-oxiranyl)cyclobutanone: IR (CCl_4) 3075, 3000, 2980, 2940, 2890, 1785, 920, 840 cm^{-1}; NMR (CCl_4) δ 1.23 and 1.27 (2 s, 3 H), 1.35–3.08 (m, 7 H); MS *m/e*, (%) 98 (29), 84 (12), 83 (37), 70 (12), 69 (71), 68 (17), 67 (49), 56 (59), 55 (82), 54 (21), 53 (57), 51 (13), 43 (43), 42 (21), 41 (100), 40 (52), 39 (100), 38 (10). Anal. ($C_7H_{10}O_2$) C, H.

Epoxycyclobutanones **40a,b** (ratio 3:2) were separated by preparative GLC (column B, 140 °C, 60 mL of He/min). The major isomer **40a** [(2*R**)-2-methyl-2-[(2*R**)-2-oxiranyl]cyclobutanone] had a retention time of 7.5 min, while minor isomer **40b** [(2*R**)-2-methyl-2-[(2*S**)-2-oxiranyl[cyclobutanone] had a retention time of 10.5 min. The separated diastereomers were shown to be pure (>99%) by NMR, ^{13}C NMR, and GLC. **40a:** IR (CCl_4) 3060, 2965, 2925, 2865, 1787, 925, 840 cm^{-1}. **40b:** IR (CCl_4) 3050, 2960, 2925, 2870, 1782, 923, 843 cm^{-1}. For NMR data see Table II.

Fragmentations with Alcoholic Alkoxide. A. Of 22. Cyclobutanone **22** (0.75 g, 4.17 mmol) was dissolved in 35 mL of methanol and 6 mL of a 1.4 M methanolic solution of sodium methoxide added. After stirring at room temperature for 30 min, the solution was poured into a separatory funnel with 50 mL of carbon tetrachloride and 50 mL of water, neutralized with dilute hydrochloric acid, and extracted with ether. The ether layer was dried and evaporated to yield 0.849 g (96%) of product **31** which was one spot on TLC: IR (CCl_4) 3448, 1739, 1667, 1020, 847 cm^{-1}; NMR (CCl_4) δ 0.86 (s, 3 H), 0.99 (s, 3 H), 1.08–1.67 (m, 2 H), 1.63 (m, 2 H), 2.17–2.50 (m, 4 H), 3.30 (s, 1 H), 3.63 (s, 3 H), 4.14 (br m, 1 H), 5.40 (br s, 1 H); MS *m/e* (%) 212 (not observed), 194 (2), 163 (1), 147 (3), 135 (1), 117 (100); mol wt (mass of M − H_2O ion) calcd ($C_{12}H_{18}O_2$) 194.1307, found 194.1330.

B. Of 24 and 25. To a mixture of 65% 4,5-epoxybicyclo[4.3.0^{5,9}]-spiro[3.8]dodecan-1-one and diphenyl sulfide (153 mg) in 25 mL of methanol was added 5 mmol (0.28 g) of sodium methoxide dissolved in 5 mL of methanol. After stirring for 0.5 h at 25 °C the reaction mixture was poured into 200 mL of a 1:1 ether–water mixture. The ether layer was evaporated to yield an oil which was purified by preparative LC (hexane) to give 108 mg (93%) of ester **35:** IR (CCl_4) 3475, 1739, 1667, 1163, 1042, 962 cm^{-1}; NMR (CCl_4) δ 1.2–2.1 (m, 11 H), 2.32 (m, 4 H), 3.64 (s, 3 H), 5.40 (s, 1 H); MS *m/e* (%) 224 (20), 206 (100), 195 (28), 182 (20), 174 (12), 146 (40), 132 (66), 119 (59), 117 (47); mol wt calcd ($C_{13}H_{20}O_3$) 224.1412, found 224.1403.

C. Of 26. As for fragmentation of **24** and **25,** 1.35 g (4.22 mmol) of epoxycyclobutanone **26** in 5 mL of methanol for 4 h produced 1.43 g (94%) of hydroxy ester **34a** after preparative LC (4:1 ether–hexane): IR (CCl_4) 3636, 3570, 1738 cm^{-1}; NMR (CCl_4) δ 5.30 (s, 1 H), 4.56 (br s, 1 H), 3.2–4.0 (m, 3 H), 3.55 (s, 3 H), 1.2–2.7 (m, 18 H), 0.8–1.2 (m, 6 H); MS *m/e* (%) 15 eV [335 (2), 334 (5)] × 10, [268 (10), 251 (10), 250 (20), 238 (5), 237 (5), 233 (12), 232 (20), 230 (9), 219 (12), 218 (7), 211 (24)] × 3, 210 (47), [209 (7), 200 (7), 195 (11), 177 (15), 174 (20), 172 (9), 159 (10), 158 (9), 149 (13), 145 (15), 135 (10), 132 (11), 131 (24), 109 (28), 102 (15), 86 (21)] × 3, 85 (100), 84 (10), 55 (5); mol wt calcd ($C_{20}H_{30}O_4$) (M^+ − H_2O) 334.2143, found 334.2144.

It was further characterized as its trimethylsilyl ether **34b.** *O,N*-bis(trimethylsilyl)acetamide (10.8 g, 53.4 mmol) was added by syringe over a 2-min period to a solution of 9.40 g (26.7 mmol) of **34a** in 250 mL of DMF. The resulting reaction mixture was stirred at room temperature for 22 h, then diluted with 750 mL of ether, and washed with 3 × 250 mL of water. The organic phase was dried and concentrated in vacuo to yield a yellow oil which was chromatographed on a 300-g silica gel dry column (4:1 ether–hexane) to yield 10.2 g (90%) of a very pale yellow oil: IR (CCl_4) 2950, 2882, 1735, 1656 cm^{-1}; NMR (CCl_4, silyl ether = 0.00) δ 5.25 (br s, 1 H), 4.46 (br s, 1 H), 3.1–3.9 (m, 3 H), 3.54 (s, 3 H), 2.0–2.7 (m, 3 H), 1.2–2.0 (m, 14 H) 0.99 (d, J = 7 Hz, 3 H), 0.76 (2 s, 3 H), 0.00 (s, 9 H); MS *m/e* (%) 15 eV [424 (12)] × 10, 368 (2), 367 (7), 366 (24), 350 (2), 349 (7), 325 (1), 324 (5), 323 (4), 322 (7), 296 (5), 293 (5), 283 (7), 282 (28), 281 (22), 280 (60), 250 (5), 249 (12), 239 (6), 232 (5), 230 (5), 221 (9), 207 (5), 182 (5), 181 (7), 166 (6), 153 (5), 86 (7), 85 (100), 84 (7), 75 (8); mol wt calcd ($C_{23}H_{40}O_5Si$) 424.2645, found 424.2642.

D. Of 27 and 28. Sodium ethoxide (10.0 mmol) was prepared by the portionwise addition of sodium metal (230 mg, 10.0 mmol) to 20 mL of absolute ethanol at 0 °C. When dissolution was complete, a solution of 7,7a-dihydro-7aβ-methyl-4,7α-oxa-5-(4′-methyl-2′-oxaspirocyclobutyl)-1β-tetrahydropyranyloxy-6*H*-indan (**57**) (640 mg, 2.00 mmol) in 5 mL of absolute ethanol was added by syringe. The resulting reaction mixture was stirred for 3 h, then diluted with ether, and washed with several portions of ice water. The organic phase was dried and concentrated in vacuo to yield 670 mg of an almost colorless oil which showed one spot at R_f 0.7 on analytical TLC (4:1 ether–hexane). This material was dissolved in ~5 mL of DMF to which was added *O,N*-bis(trimethylsilyl)acetamide (1.49 g, 7.32 mmol). The resulting solution was heated at ~70 °C for 32 h, then cooled, diluted with ether, and washed with several portions of water. The organic phase was dried and concentrated in vacuo to yield a mixture of yellow oil and white crystals. This material was chromatographed on three 20 × 40 cm TLC plates to yield 710 mg (81% overall) of a pale yellow oil at R_f 0.6: IR (CCl_4) 2938, 1737 cm^{-1}; NMR (CCl_4, silyl ether = 0.00) δ 5.50 and 4.06 (2 br s, ratio ~1:3, total 1 H), 4.5 (br s, 1 H), 3.93 (m, 2 H), 3.2–3.9 (m, 3 H), 1.2–2.8 (m, 17 H), 0.6–1.2 (m, 9 H), 0.00 (s, 9 H).

E. Of 40a,b with Sodium Methoxide. As for fragmentation of **24** and **25,** 1.0182 g (8.077 mmol) of a 1:1 mixture of epoxycyclobutanones in 25 mL of methanol gave 746 mg (58%) of a 1:1 mixture of **46a** and **46b.** The aqueous solutions from the initial quench and extractions were combined, acidified (litmus paper) with 1 N HCl, and extracted with 4 × 100 mL of ether. The ether extract was washed with 200 mL of saturated aqueous ammonium chloride, dried over anhydrous magnesium sulfate, and rotary evaporated to give 310.55 mg (27%) of pale yellow oil which was identified by IR as the corre-

sponding unsaturated hydroxy acid: IR (CCl_4) 3500 (br), 3000, 2950, 2880, 1700 cm^{-1}. Esterification of this material with excess ethereal diazomethane gave a product identical with the mixture of hydroxy esters. The yield of the fragmentation is thus 85%. Some hydrolysis of the esters was caused by the initial aqueous quench which could be avoided by quenching into aqueous ammonium chloride solution (vide infra).

Similarly, fragmentation of the two diastereomeric epoxycyclobutanones was performed as follows. Epoxycyclobutanone **40a** (43.85 mg, 0.348 mmol) was stirred for 6 min at room temperature in 3 mL (0.57 mmol) of 0.19 M methanolic sodium methoxide (prepared from MCB sodium methoxide in dry methanol). The reaction mixture was poured into 10 mL of saturated aqueous ammonium chloride and this solution was extracted with 6 × 10 mL of ether. The combined ethereal extract was washed successively with 20-mL portions of saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The ether solution was dried over anhydrous potassium carbonate and rotary evaporated to yield 49.5 mg (90%) of a pale yellow oil. By this procedure **40a** gave *only* (by GLC on column B at 195 °C, 60 mL of He/min, retention time 13.0 min) the *Z* olefin **46a** plus unchanged starting epoxycyclobutanone **40a** (retention time 2.6 min) in a 3:1 ratio, respectively. Similarly, epoxycyclobutanone **40b** (35.25 mg, 0.28 mmol) gave *only* (by GLC, retention time 15.0 min) the *E* olefin **46b** [by ^1H NMR $Eu(dpm)_3$ shift] plus unreacted **40b** (retention time 3.1 min) in a 1:1 ratio (40.85 mg, 92%). Resubmission of these partially reacted materials to the same reaction conditions for 30 min permitted the isolation as above of the *Z* and *E* olefins, **46a,** (21.6 mg, 39%) and **46b** (30.55 mg, 69%), respectively. GLC examination (as above) of the crude products confirmed that only one olefin (>99%) was formed from each diastereomer. **46a:** IR (CCl_4) 3650, 3600 (br), 2994, 2967, 2950, 1739 cm^{-1}; NMR (CCl_4) δ 1.71 (br s, 3 H), 2.21 (br s, 1 H), 2.37 (br s, 4 H), 3.62 (s, 3 H), 3.98 (d, J = 7 Hz, 2 H), 5.45 (br t, J = 7 Hz, 1 H) [addition of 5 mol % $Eu(dpm)_3$ shifted the δ 1.71 methyl singlet to δ 1.87]; MS *m/e* (%) 126 (10), 111 (29), 99 (10), 98 (49), 91 (13), 84 (10), 83 (21), 82 (11), 81 (12), 79 (13), 77 (10), 71 (18), 69 (38), 67 (68), 65 (11), 56 (54), 55 (49), 54 (14), 53 (29), 52 (10), 51 (20), 50 (13), 44 (32), 43 (57), 42 (14), 41 (100), 40 (16), 39 (66). Anal. ($C_8H_{14}O_3$) C, H. **46b:** IR (CCl_4) 3650, 3600 (br), 2985, 2960, 2924, 1739 cm^{-1}; NMR (CCl_4) δ 1.67 (br s, 3 H), 2.18 (br s, 1 H), 2.3–2.4 (m, 4 H), 3.61 (s, 3 H), 4.01 (d, J' = 7 Hz, 2 H), 5.34 (t, J = 7 Hz, 1 H) [addition of 5 mol % $Eu(dpm)_3$ shifted the δ 1.67 methyl singlet to δ 2.11]; MS *m/e* (%) 141 (7), 140 (21), 111 (16), 98 (48), 97 (26), 96 (12), 91 (24), 85 (13), 84 (26), 83 (32), 82 (14), 91 (90), 80 (18), 79 (32), 78 (10), 77 (23), 74 (28), 71 (35), 69 (23), 68 (13), 67 (40), 66 (12), 65 (18), 64 (9), 63 (10), 59 (19), 57 (24), 56 (27), 55 (53), 54 (13), 53 (40), 52 (15), 51 (24), 50 (15), 44 (85), 43 (56), 42 (14), 41 (100), 40 (15), 39 (70). Anal. ($C_8H_{14}O_3$) C, H.

F. Of 40a,b with Magensium Methoxide. Epoxycyclobutanone **40a** (49.5 mg, 0.392 mmol) was dissolved in 3 mL of dry methanol, 3 mL of 0.4 M methanolic magnesium methoxide was added, and the solution was stirred at room temperature for 30 min. After workup as above, the crude yellow oil, which was a 3:1 mixture of *Z* and *E* olefins as determined by the ratio of δ 1.72–1.80, gave 40.3 mg (65%) of this olefinic mixture after preparative LC (ether).

Similarly, epoxycyclobutanone **40b** (54.6 mg, 0.433 mmol) was treated as above to give 51.2 mg (75%) of oil, which by NMR contained a 1:3 mixture of the *Z* and *E* olefins **46a** and **46b,** respectively.

Fragmentation of the two diastereomeric epoxycyclobutanones was carried out using magnesium methoxide in THF as follows. One milliliter of 2 M methanolic magensium methoxide (2 mmol) was placed in a small round-botton flask and distilled to dryness, leaving a white powdery residue. A solution of epoxycyclobutanone **40a** (67.5 mg, 0.535 mmol) in 5 mL of dry THF was added and the resulting suspension stirred at room temperature, monitoring the progress of the reaction by GLC. After 6 days only a small amount (<5%) of starting epoxycyclobutanone remained. The light yellow suspension was diluted with 25 mL of ether and washed successively with 5-mL portions of saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The ether solution was dried over anhydrous sodium sulfate and rotary evaporated, giving 49.5 mg (58.5%) of orange oil. IR and MNR analysis indicated that this was a 3:4 (by peak height of methyl singlets at δ 1.72 and 1.80) mixture of *Z* and *E* olefins **46a** and **46b,** respectively, with a trace of starting material remaining.

Reaction of epoxycyclobutanone **40b** (39.5 mg, 0.313 mmol) as described above gave 32.9 mg (66.5%) of yellow oil, which by IR and NMR was identified as a 2:3 mixture of the *Z* and *E* olefins **46a** and **46b,** respectively, along with a trace of the starting epoxycyclobutanone.

Organolithium Addition and Fragmentation. A. Of 24 and 25. A solution of 410 mg of epoxycyclobutanones **24** and **25** in 25 mL of ether was cooled to −78 °C. Methyllithium (2 mL of a 1.6 M solution, 3.2 mmol) was added and after 1 min quenched with water (10 mL). The reaction mixture was then extracted with ether, dried, and evaporated to yield an oil, 436 mg (98%). The oil was purified by TLC on silica gel PF-254 by elution with 25% ethyl acetate in hexane to give a solution of 4,5-epoxy-1-methylbicyclo[4.2.0^{5,9}]spiro[3.8]dodecan-1-ol: IR (CCl_4) 3484, 926, 909, 898, 870, 830 cm^{-1}; NMR (CCl_4) δ 1.0–2.6 (m, 16 H), 1.35 (s, 3 H), 3.02, 3.43, 3.70 (s, total 1 H); MS *m/e* (%) 208 (11), 190 (26), 180 (24), 150 (41), 147 (44), 137 (30), 132 (44), 119 (37), 117 (37), 108 (30), 81 (91), 43 (100); mol wt calcd ($C_{13}H_{20}O_2$) 208.1463, found 208.1478.

A solution of the cyclobutanol (50 mg) in 10 mL of methanol was treated with 1 mmol of sodium methoxide. After 30 min at 25 °C the solution was extracted with a 1:1 mixture of ether and water. The ether layer was separated, dried over anhydrous magnesium sulfate, and evaporated in vacuo to yield 37 mg (74%) of **57** as an oil which could be further purified by preparative LC (hexane). By preparing the cyclobutanol and immediately subjecting it to ring cleavage an 83% yield of **37** was obtained: IR (CCl_4) 3448, 1718, 1667, 1044, 962 cm^{-1}; NMR (CCl_4) δ 1.1–2.05 (m, 11 H), 2.10 (s, 3 H), 2.1–2.6 (m, 4 H), 5.38 (br s, 1 H); MS *m/e* (%) 208 (10), 190 (44), 147 (55), 132 (51), 119 (23), 117 (71); mol wt calcd ($C_{13}H_{20}O_2$) 208.1463, found 208.1467.

B. Of 23. 50a. A solution of 0.650 g (3.35 mmol) of epoxycyclobutanone in 20 mL of dry ether was cooled to −78 °C. Methyllithium (5.6 mL of a 1.2 M solution in ether, 6.70 mmol) was added rapidly and the solution stirred for 1 min. Then 15 mL of water was introduced and the solution stirred for 1 min. Another 15 mL of water was introduced and the mixture warmed until the ice just melted. The ether was separated and the aqueous layer extracted with 50 mL of ether. The combined ether layers were dried over anhydrous sodium sulfate and the ether was removed in vacuo. The resulting oil was purified on a silica gel PF-254 thin-layer plate eluted with 25% ether in hexane to afford 40 mg (6%) of starting ketone and 654 mg (93%) of cyclobutanol as a mixture of two isomeric alcohols, 42% alcohol and epoxide syn, 58% anti, assigned from the chemical shift of the epoxide singlets (syn 3.42, anti 2.91): IR (CCl_4) 3636, 3480, 1377, 1364 cm^{-1}; NMR (CCl_4) δ 0.8–1.0 (m, 6 H), 1.0–2.2 (m, 8 H), 1.2–1.4 (m, 6 H), 2.91 (s, 0.58 H), 3.05 (br s, 1 H, -OH), 3.42 (s, 0.42 H); MS *m/e* (%) 210 (0.42), 192 (13), 177 (6), 149 (14), 119 (52); mol wt calcd ($C_{13}H_{20}O$) 192.1514, found 192.1515. **50b.** An ethereal solution (25 mL) of 4,5-epoxy-5,7,7-trimethylspiro[3.5]nonan-1-one (1.76 g, 9.06 mmol) was cooled to −78 °C. Methyllithium (20.8 mL of a 1.2 M solution in ether, 25 mmol) was added and the resultant solution mixed for 5 min. Then acetyl chloride (2.47 mL, 2.73 g, 35 mmol) was added and the mixture warmed to 0 °C. The reaction mixture was clear at −78 °C; however, upon warming to 0 °C a white solid appeared. This mixture was stirred for 45 min at 0 °C. A solution of sodium acetate (5 g) in 20 mL of water was added and the ether layer separated quickly. The solid disappeared upon treatment with water. The aqueous layer was extracted with 50 ml of ether and the ether layers were combined. This solution was dried over anhydrous sodium sulfate and evaporated in vacuo to yield an oil which was purified by preparative LC (20 ether in pentane) to give 1.86 g (83%) of **50b** as an oil: IR (CCl_4) 1733, 1370, 1235, 1018, 899, 870 cm^{-1}; NMR (CCl_4) δ 0.87 (s, 3 H), 0.98 (s, 3 H), 1.25 (s, 3 H), 1.60 (s, 3 H), 1.2–2.4 (m, 8 H), 1.93 (s, 3 H), 2.91, 3.07 (2 s, ratio ~1:3, total 1 H); MS *m/e* (%) 252 (0.8), 237 (0.8), 244 (8), 210 (6), 195 (17), 193 (14), 192 (26), 182 (10), 177 (48), 149 (62), 139 (74), 137 (56), 135 (70), 134 (76), 119 (100), 111 (31), 109 (65), 93 (47); mol wt calcd ($C_{15}H_{24}O_3$) 252.1723, found 252.1725. **52.** To a solution of 1-acetoxy-4,5-epoxy-1,5,7,7-tetramethylspiro[3.5]nonane (100 mg, 0.40 mmol) in 25 mL of methanol was added 1 mL of 0.5 M sodium methoxide in methanol solution (0.5 mmol). This was stirred for 2 h at 25 °C. The reaction mixture was extracted with 3 × 50 mL of ether after addition of 100 mL of water. The ether was dried over anhydrous sodium sulfate and evaporated in vacuo to yield an oil which was purified by preparative LC [20% ether in pentane to give 74 mg (89%) of hydroxy ketone **52**]: IR (CCl_4) 3472, 1718, 1667 cm^{-1}; NMR (CCl_4) δ 0.92 (s, 3 H), 0.99 (s, 3 H), 1.28 (s, 3 H), 1.6 (m, 2 H), 2.08 (s, 3 H),

1.8–2.6 (m, 7 H), 5.27 (br s, 1 H); MS *m/e* (%) 195 (5), 192 (24), 177 (12), 149 (29), 134 (21), 119 (100); mol wt (mass of M − H_2O ion) calcd ($C_{13}H_{20}O$) 192.1514, found 192.1526.

Cyclohexenone Annelation. A. Preparation of Ketoacetate 53. A solution of 1-acetoxy-4,5-epoxy-1,5,7,7-tetramethylspiro[3.5]nonane (0.88 g, 3.50 mmol) and anhydrous lithium perchlorate (37 mg, 10 mol %) in benzene (50 mL) was refluxed for 8 h. The initally light amber solution turned a deep purple as the reaction progressed. The benzene was washed with water which discharged the purple color. Upon drying with anhydrous magnesium sulfate, the magnesium sulfate turned to a brilliant purple. Evaporation of the benzene in vacuo resulted in an oil which was purified by preparative LC (10% ether in pentane) to give 0.63 g (72%) of 1-acetoxy-4-oxo-1,5,7,7-tetramethylspiro[3.5]nonane: IR (CCl_4) 1742, 1706, 1376, 1368, 1233, 1161, 1131, 1018 cm^{-1}; NMR (CCl_4) δ 0.92 (s, 3 H), 0.95 (d, J = 6.5 Hz, 3 H), 1.20 (s, 3 H), 1.30 (s, 3 H), 1.99 (s, 3 H), 1.1–2.7 (m, 9 H); MS *m/e* (%) 242 (0.1), 237 (0.4), 210 (6), 192 (9), 177 (7), 167 (5), 149 (17), 139 (26), 135 (15), 134 (15), 42 (100); mol wt calcd ($C_{15}H_{24}O_3$) 252.1725, found 252.1697.

B. Preparation of 6,6,8-Trimethyl-$\Delta^{1,9}$-octal-3-one (55). A solution of 0.45 g (1.8 mmol) of ketoacetate **53** in 50 mL of a 50% ethanol-benzene mixture was treated with 5 mL of a 0.5 M sodium ethoxide in ethanol solution. This mixture was refluxed for 4 h. Then 100 mL of water was added and the mixture extracted with 3 × 100 mL of ether. The ether layer was shaken for 10 min with 0.1 N aqueous hydrochloric acid and subsequently washed with water. After drying over anhydrous sodium sulfate and evaporation in vacuo, an oil (0.27 g) resulted which was then crystallized from 1 mL of pentane to give octalone **55** (0.24 g, 71%, mp 65–66 °C): IR (CCl_4) 3058, 1676, 1615, 1387, 1368 cm^{-1}; NMR (CCl_4) δ 0.98 (s, 3 H), 1.08 (d, J = 6.5 Hz, 3 H), 1.11 (s, 3 H), 1.2–2.5 (m, 10 H), 5.68 (br s, 1 H); UV (EtOH) 228 nm (ϵ 7895); MS *m/e* (%) 192 (100), 177 (46), 164 (22), 152 (20), 149 (16), 137 (41), 136 (72), 121 (35), 119 (48), 108 (61), 93 (46), 91 (34), 79 (43), 41 (64); mol wt calcd ($C_{13}H_{20}O$) 192.1514, found 192.1514.

C. Preparation of (4*R,5*R**)- and (4*R**,5*S**)-5,6-Epoxy-4-hydroxy-4-methylhexanoic 1,4-Lactone (42a,b).** Anhydrous sodium bicarbonate (175.2 mg, 2.08 mmol) was added to a solution of epoxycyclobutanone **40a** (167.45 mg, 1.32 mmol) in 6 mL of dichloromethane, followed by the addition of 347.4 mg (1.72 mmol) of 85% *m*-chloroperbenzoic acid. After refluxing for 2.25 h the reaction mixture was cooled to room temperature and diluted with 30 mL of dichloromethane. The organic solution was washed successively with 6-mL portions of 1 N aqueous sodium hydroxide, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried over anhydrous potassium carbonate, and rotary evaporated to yield 156 mg (83%) of (4*R**,5*R**)-5,6-epoxy-4-hydroxy-4-methylhexanoic 1,4-lactone **42a** as a colorless oil. This material was homogeneous (R_f 0.4) on silica gel TLC (ether): IR (CCl_4) 3065, 2976, 1795, 1233, 1136, 946, 894 cm^{-1}: NMR (CCl_4) δ 1.40 (s, 3 H), 1.8–2.7 (m, 6 H), 2.88 (dd, J = 3.5, 2.5 Hz, 1 H); MS *m/e* (%) 99 (100), 71 (10), 56 (12), 43 (64), 39 (10); mol wt calcd ($C_7H_{10}O_3$) 142.0630, found 142.0633.

Similarly, treatment of epoxycyclobutanone **40b** (88.70 mg, 0.703 mmol) in 4 mL of dichloromethane with 97.35 mg (1.157 mmol) of anhydrous sodium bicarbonate and 183.3 mg (0.904 mmol) of *m*-chloroperbenzoic acid as described above yielded 83.15 mg (83%) of (4*R**,5*S**)-5,6-epoxy-4-hydroxy-4-methylhexanoic 1,4-lactone **42b** as a colorless oil. This material was homogeneous (R_f 0.4) on silica gel TLC (ether): IR (CCl_4) 3050, 2980, 2930, 1790, 1208, 1143, 945 cm^{-1}; NMR (CCl_4) δ 1.43 (s, 3 H), 1.6–2.1 (m, 2 H), 2.3–2.8 (m, 4 H), 3.06 (dd, J = 4.0, 3.5 Hz, 1 H); MS *m/e* (%) 99 (100), 84 (12), 83 (19), 71 (11), 56 (13), 43 (86), 41 (12), 39 (14); mol wt calcd ($C_7H_{10}O_3$) 142.0630, found 142.0632.

D. (4*R,5*S**)- and (4*R**,5*R**)-4,5-Dihydroxy-4-methyl-6-phenylthiohexanoic 1,4-Lactone.** A solution of epoxy lactone **42a** (156.0 mg, 1.23 mmol) in 4 mL of dry methanol was added to a solution of thiophenol (185 μL, 1.74 mmol) in 2 mL of methanolic sodium methoxide [prepared from 36 mg (1.56 mg-atoms) of sodium in 2 mL of dry methanol]. After stirring for 10 min at room temperature the reaction mixture was poured into a mixture of 5 mL of water and 25 mL of chloroform. The layers were separated and the organic phase was washed successively with 5-mL portions of 1 N aqueous sodium hydroxide, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The chloroform solution was dried over anhydrous sodium sulfate and rotary evaporated, giving 168.15 mg (54%) of (4*R**,5*S**)-4,5-dihydroxy-4-methyl-6-phenylthiohexanoic 1,4-lactone as a pale yellow oil which crystallized upon standing. This material was homogeneous (R_f 0.5) by silica gel TLC (ether). Recrystallization from carbon tetrachloride yielded powdery white crystals (mp 70.5–71.5 °C): IR (CCl_4) 3480 (br), 3070, 2980, 2940, 2875, 1785, 1086, 689 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.6–2.7 (m, 4 H), 2.80 (X portion of AMX system, J = 13, 10 Hz, 1 H), 3.21 (M portion of AMX system, J = 13, 2.5 Hz, 1 H), 3.36 (br s, disappears on addition of D_2O, 1 H), 3.68 (A portion of AMX system, J = 10, 2.5 Hz, 1 H), 7.1–7.5 (m, 5 H); MS *m/e* (%) 252 (19), 123 (25), 109 (10), 99 (100); mol wt calcd 252.0820, found 252.0835. Anal. ($C_{13}H_{16}O_3S$) C, H, S.

Similarly, addition of epoxy lactone **42b** (83.15 mg, 0.658 mmol) to a solution of thiophenol (130 μL, 1.23 mmol) in methanolic sodium methoxide [from 25 mg (1.08 mg-atoms) of sodium in 2 mL of dry methanol] and continuing as described above yielded 117.15 mg (71%) of (4*R**,5*R**)-4,5-dihydroxy-4-methyl-6-phenylthiohexanoic 1,4-lactone as a colorless oil which was homogeneous (R_f 0.5) on silica gel TLC but could not be persuaded to crystallize: IR (CCl_4) 3460 (br), 3065, 2980, 2940, 2880, 1780, 1075, 689 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.6–2.7 (m, 4 H), 2.92 (X portion of AMX system, J = 13, 10 Hz, 1 H), 3.1 (br s, disappears on addition of D_2O, 1 H), 3.22 (M portion of AMX system, J = 13, 2.5 Hz, 1 H), 3.56 (A portion of AMX system, J = 10, 2.5 Hz, 1 H), 7.1–7.5 (m, 5 H); MS *m/e* (%) 252 (32), 123 (31), 110 (18), 109 (20), 99 (100), 85 (34), 83 (54), 47 (18); mol wt calcd ($C_{13}H_{16}O_3S$) 252.0820, found 252.0837.

E. (4*R,5*S**)- and (4*R**,5*R**)-4-Methyl-6-phenylthio-1,4,5-hexanetriol (43a,b).** Lithium aluminum hydride (120 mg, 3.16 mmol) was added to a solution of the lactone in the a series (168.15 mg, 0.666 mmol) in 12 mL of dry THF at room temperature. After the foaming subsided the mixture was refluxed for 3 h, cooled in an ice bath, and quenched by successive dropwise addition of 120 μL of water, 120 μL of 15% aqueous sodium hydroxide, and 360 μL of water. The resulting mixture was filtered and the solid residue washed with chloroform. The combined organic solutions were rotary evaporated to yield 136.90 mg (80%) of (4*R**,5*S**)-4-methyl-6-phenylthio-1,4,5-hexanetriol **43a** as a colorless oil. This material was homogeneous (R_f 0.2) on silica gel TLC (ethyl acetate): IR ($CHCl_3$) 3400 (br), 3060, 2970, 2930, 2870, 1583, 1050 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.59 (br s, 4 H), 2.90 (X portion of AMX system, J = 14, 10 Hz, 1 H), 3.14 (M portion of AMX system, J = 14, 2 Hz, 1 H), 3.3–3.7 (m, 6 H), 7.1–7.4, (m, 5 H).

Similarly, reduction of the lactone in the b series (117.15 mg, 0.464 mmol) as above in 9 mL of dry THF using 94 mg (2.47 mmol) of lithium aluminum hydride yielded 113.50 mg (90%) of (4*R**,5*R**)-4-methyl-6-phenylthio-1,4,5-hexanetriol **43b** as a pale yellow oil. This material was homogeneous (R_f 0.2) on silica gel TLC (ethyl acetate), but NMR indicated the presence of a small amount of residual THF: IR ($CHCl_3$) 3400 (br), 3060, 2930, 2870, 1583, 1070 cm^{-1}; NMR ($CDCl_3$) 1.16 (s, 3 H), 1.58 (br s, 4 H), 2.84 (X portion of AMX system, J = 14, 10 Hz, 1 H), 3.24 (M portion of AMX system, J = 14, 2 Hz, 1 H), 3.4–3.8 (m, 6 H), 2.1–7.4 (m, 5 H).

F. (*E*)- and (*Z*)-6-Acetoxy-3-methyl-1-phenylthio-2-hexane (44a,b). A solution of triol **43a** (136.90 mg, 0.534 mmol) in 2 mL (15 mmol) of dimethylformamide dimethyl acetal (Columbia Organic Chemicals) was heated at 60 °C for 2 h and then at 80 °C for 30 min. Excess reagent was then evaporated at reduced pressure (0.5 Torr) with slight heating (50 °C) to give a cloudy oil. This material was dissolved in 3 mL of acetic anhydride and heated at 130 °C for 1.5 h, at which time TLC (silica gel, ethyl acetate) showed no remaining starting material (R_f 0.2) and a single new product (R_f 0.8). The brown reaction mixture was poured into 25 mL of chloroform and 25 mL of saturated aqueous sodium bicarbonate. The layers were separated and the chloroform was washed with 25 mL of saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous potassium carbonate and rotary evaporated to yield a brown oil which by NMR appeared to be the desired olefin plus a large amount of acetic anhydride. Preparative TLC (ether) of this material yielded 87.1 mg (62%) of (*E*)-6-acetoxy-3-methyl-1-phenylthio-2-hexene (**44a**) as a colorless oil (R_f 0.6–0.8). An analytical sample was obtained by an additional preparative TLC: IR (CCl_4) 3060, 2950, 2925, 2850, 1740, 1660, 1580, 1235, 690, 650 cm^{-1}; NMR (CCl_4) δ 1.59 (s, 3 H), 1.5–1.8 (m, 2 H), 2.00 (s, 3 H), 2.07 (t, J = 7 Hz, 2 H), 3.51 (d, J = 8 Hz, 2 H), 3.97 (t, J = 6 Hz, 2 H), 5.36 (br t, J = 8 Hz, 1 H), 7.1–7.4 (m, 5 H); MS *m/e* (%) 264 (11), 110 (46), 109 (30), 95 (100), 94 (38), 85 (36), 79 (38), 67 (54), 65 (22), 55 (34), 43 (99); mol wt calcd 264.1184,

found 264.1194. Anal. ($C_{15}H_{20}O_2S$) C, H, S.

Similarly, reaction of triol **43b** (113.50 mg, 0.443 mmol) is 2 mL (15 mmol) of dimethylformamide dimethyl acetal as above, followed by reaction in acetic anhydride (3 mL) and work-up as above, yielded, after preparative TLC (ether), 65.25 mg (56%) of (*Z*)-6-acetoxy-3-methyl-1-phenylthio-2-hexene (**44b**) as a yellow oil (R_f 0.6–0.8). An analytically pure sample was obtained by an additional preparative TLC (chloroform): IR (CCl_4) 3070, 2960, 2930, 1745, 1660, 1580, 1230, 690 cm^{-1}; NMR (CCl_4) 1.3–1.7 (m, 2 H), 1.75 (s, 3 H), 1.99 (s, 3 H). 2.08 (t, J = 8 Hz, 2 H) 3.51 (d, J = 8 Hz, 2 H), 3.99 (t, J = 6.5 Hz, 2 H), 5.38 (br t, J = 8 Hz, 1 H), 7.1–7.4 (m, 5 H); MS *m/e* (%) 264 (9), 121 (22), 119 (68), 117 (71), 95 (28), 47 (20), 43 (100); mol wt calcd 264.1184, found 264.1188. Anal. ($C_{15}H_{20}O_2S$) C, H, S.

G. Formation of 4-Hydroxy-4-methyl-5-hexenoic 1,4-Lactone (57). A solution of 185.3 mg (1.17 mmol) of hydroxy ester **40** in 6 mL of dichloromethane was cooled to −5 °C and 0.25 mL (1.80 mmol) of triethylamine was added. Methanesulfonyl chloride (100 μL, 1.28 mmol) was added in 9-μL portions over 10 min and the solution was stirred at −5 °C for 15 min. This solution was transferred, using 5 mL of dichloromethane to wash out the reaction flask, into a 25-mL separatory funnel containing 10 mL of ice water. The layers were separated and the dichloromethane solution was washed successively with 10 mL of 1 N aqueous hydrochloric acid, 10 mL of saturated aqueous sodium bicarbonate, and 10 mL of saturated aqueous sodium chloride. The organic solution was dried over anhydrous sodium sulfate and rotary evaporated to give 105.5 mg (72%) of γ-lactone **57** homogeneous (retention time 8.6 min) by VPC (column C at 150 °C, 60 mL of He/min): IR (CCl_4) 3100, 2990, 2960, 2900, 1780, 987, 932 cm^{-1}; NMR (CCl_4) δ 1.50 (s, 3 H), 2.0–2.7 (m, 4 H), 5.25 (br d, J = 10 Hz), 5.40 (br d, J = 20 Hz, 1 H), 6.04 (dd, J = 20, 10 Hz, 1 H).

H. Methyl (*Z*)- and (*E*)-6-Bromo-4-methyl-4-hexenoate (58). A stirred suspension of calcium hydride (65.8 mg, 1.563 mmol) in 2.0 mL of anhydrous ether was cooled to 0 °C and 105.0 mg (0.664 mmol) of hydroxy ester **40** was added, resulting in rapid evolution of hydrogen. Then 26.0 μL (0.274 mmol) of phosphorus tribromide was added slowly (5 min) and the solution subsequently stirred for 15 h at 0–5 °C. Celite (ca. 1 g) was added and the mixture gravity filtered. The solution was dried over anhydrous potassium carbonate and rotary evaporated to give 99.55 mg (68%) of bromide as a yellow oil which was used for subsequent reactions without further purification: IR (CCl_4) 2965, 1742, 1665 cm^{-1}; NMR (CCl_4) δ 1.77 and 1.80 (2 s, ratio 1:1, 3 H total), 2.40 and 2.44 (2 s, ratio 1:1, 4 H total), 3.67 (s, 3 H), 3.96 and 4.00 (2 d, J = 8 Hz, ratio 1:1, 2 H total), 5.61 (br t, J = 8 Hz, 1 H); MS *m/e* (%) 140 (32), 125 (12), 109 (11), 98 (32), 82 (10), 81 (100), 80 (16), 79 (30), 67 (15), 59 (17), 55 (17), 53 (27), 51 (10), 44 (27), 43 (14), 41 (40), 39 (21).

I. Methyl (*Z*)- and (*E*)-4-Methyl-8-oxo-4-nonenoate (59). Sodium hydride (33.25 mg of 57% dispersion, 0.79 mmol) was suspended in 3 mL of dry DMF at room temperature and 67.5 μL (0.63 mmol) of methyl acetoacetate was added, resulting in rapid evolution of hydrogen. After 40 min a solution of allylic bromide **58** (115 mg, 0.2 mmol) in 1 mL of dry DMF was added and this solution stirred at 60 °C for 5 h. Sodium cyanide (64.55 mg, 1.32 mmol) and lithium iodide trihydrate (986.75 mg, 5.25 mmol) were added and the mixture was stirred at 130–135 °C for 24 h. The brownish orange reaction mixture was poured into 25 mL of saturated aqueous sodium bicarbonate, resulting in formation of a white precipitate. This aqueous mixture was washed with 2 × 25 mL of ether, acidified (to litmus paper) by careful dropwise addition of concentrated hydrochloric acid, and extracted with 4 × 25 mL of ether. The ethereal extract was washed with 2 × 25 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and rotary evaporated to give 108.15 mg of a yellow oil which still contained much DMF. This material was dissolved in 10 mL of ether and washed with 2 × 10 mL of saturated aqueous ammonium chloride. The aqueous washings were combined and extracted with 2 × 10 mL of ether. The combined ether solutions were dried over anhydrous magnesium sulfate and rotary evaporated to yield 77.80 mg (81%) of crude keto acid as a viscous yellow oil: IR (CCl_4) 3400–2500 (br), 1715 cm^{-1}; NMR (CCl_4) δ 1.69 and 1.73 (2 s, 1:1 ratio, 3 H total), 2.13 (s, 3 H, 2.2–2.7 (m, 8 H), 5.26 (br t, J = 8 Hz, 1 H), 10.87 (br s, 1 H).

A solution of this crude keto acid (77.8 mg, 0.42 mmol) in 25 mL of ether was treated with ethereal diazomethane until the yellow color persisted. Rotary evaporation yielded 60.5 mg (72%, 58% overall from bromide **58**) of keto ester **59** as a yellow oil: IR (CCl_2) 2970, 2875, 1738 cm^{-1}; NMR (CCl_4) δ 1.63 and 1.67 (2, s, 1:1 ratio, 3 H total), 2.05 (s, 3 H), 2.2–2.5 (m, 8 H), 3.67 and 3.69 (2 s, 1:1 ratio, 3 H total), 5.08 (br t, J = 6 Hz, 1 H).

Preparative VPC (column C at 180 °C 120 mL of He/min) of the keto esters (1:1 ratio) yielded methyl (*Z*)-4-methyl-8-oxo-4-nonenoate (retention time 11.5 min) and methyl (*E*)-4-methyl-8-oxo-4-nonenoate (retention time 12.5 min). The separated isomers were homogeneous by VPC. *Z* isomer: IR (CCl_4) 2972, 2955, 2935, 2920, 1742, 1723, 1250, 1160, cm^{-1}; NMR (CCl_4) δ 1.67 (br s, 3 H), 2.06 (s, 3 H), 2.1–2.5 (m, 8 H), 3.62 (s, 3 H), 5.08 (br t, J = 6 Hz, 1 H); MS *m/e* (%) 198 (4, molecular ion), 180 (12), 167 (10), 166 (12), 141 (6), 140 (7), 123 (17), 109 (12), 98 (15), 95 (13), 81 (46), 74 (13), 69 (13), 67 (13), 55 (19), 53 (11), 43 (100), 41 (16); mol wt calcd 198.1255, found 198.1257. Anal. ($C_{11}H_{18}O_3$) C, H. *E* isomer: IR (CCl_4) 2955, 2920, 2860, 1742, 1722, 1255, 1155 cm^{-1}; NMR (CCl_4) δ 1.63 (br s, 3 H), 2.04 (s, 3 H), 2.1–2.5 (m, 8 H), 3.58 (s, 3 H), 5.07 (br t, J = 6 Hz, 1 H); MS *m/e* (%) 198 (7, molecular ion), 180 (23), 167 (21), 166 (23), 141 (12), 140 (14), 125 (13), 124 (17), 123 (34), 111 (14), 109 (33), 108 (12), 107 (13), 99 (19), 98 (24), 95 (22), 83 (12), 82 (19), 81 (89), 80 (13), 79 (13), 74 (25), 71 (10), 70 (9), 69 (16), 68 (10), 67 (24), 59 (14), 58 (12), 55 (26), 53 (17), 43 (100), 41 (37); mol wt calcd 198.1255, found 198.1254. Anal. ($C_{11}H_{18}O_3$) C, H.

J. Dimethyl (2*Z*,6*E*)- and (2*E*,6*E*)-3,7-Dimethyl-2,6-decadienedioate (60). Methyl dimethylphosphonoacetate (100 μL, 129.7 mg. 0.71 mmol) was added to a cold (0 °C) suspension of sodium hydride (24.5 mg of 57% dispersion, 0.58 mmol) in 0.30 mL of dry DMF. This mixture was stirred at 0 °C for 5 min and then keto ester **59** (19.9 mg, 0.10 mmol) was added. The ice bath was removed and the yellow solution stirred at room temperature for 18 h. The reaction mixture was cooled to 0 °C and quenched by rapid addition of 1 mL of water. The resulting aqueous solution was extracted with 4 × 1 mL of ether. The combined ethereal extracts were washed with 1 mL of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and rotary evaporated to give a yellow oil. Preparative TLC ($CHCl_3$–ether, 9:1 v/v) yielded 18.45 mg (73%) of *Z,E* and *E,E* olefins. VPC examination (column A at 200 °C, 120 mL of He/min) showed two components: (2*Z*,6*E*)-3,7-dimethyl-2,6-decadienedioate (retention time 11.5 min, 30% of mixture) and (2*E*,6*E*)-3,7-dimethyl-2,6-decadienedioate (retention time 14.0 min, 70% of mixture). Preparative VPC allowed isolation of the pure isomers and comparison of the spectral properties to those of authentic samples.

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A Base-Induced Coupling–Condensation of Aryl *o*-Methylarenesulfonates and *o*-Methylarenesulfonanilides[1]

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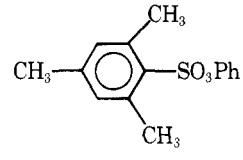
Abstract: The product, resulting from treatment of aryl *o*-methylarenesulfonates or *o*-methylarensulfonanilides with *n*-butyllithium in THF at −72 °C, has a bibenzyl backbone substituted in the 2 position with a sulfinic acid moiety and in the 2′ position with an unchanged aryl sulfonate or sulfonanilide unit. Possible mechanisms for this novel coupling–condensation are discussed.

Base-induced rearrangements of *o*-methylaryl aryl sulfones have been studied extensively in this laboratory over the last several years.[2] In attempting to extend the scope of these rearrangements to related compounds, a novel coupling–condensation reaction of aryl *o*-methylarenesulfonates and *o*-methylarenesulfonanilides has been encountered.

Results and Discussion

When phenyl mesitylenesulfonate (**1**) is treated with *n*-butyllithium at −72 °C for 4 h, a 63% yield of the bibenzyl condensation product **2** is isolated. The structural assignment for **2** is based on spectral and analytical data for the corresponding magnesium salt and for the 2-hydroxy-3,5-dichlorobenzyl sulfone derivative. This coupling–condensation has been extended to four additional aryl *o*-methylarenesulfonates as summarized in Table I.

When phenyl mesitylenesulfonate is treated with *n*-butyllithium at 0 °C or above, the reaction takes a different course and the major products are *n*-butyl mesityl sulfone and 1,1-bis(mesitylsulfonyl)butane (**7**). Displacement of phenoxide by the organometallic accounts for *n*-butyl mesityl sulfone, while the geminal disulfone presumably arises from a subsequent reaction of metalated *n*-butyl mesityl sulfone with phenyl



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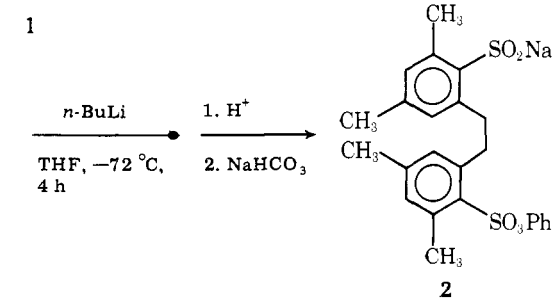

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mesitylenesulfonate. Even at −72 °C displacement of phenoxide by butyl is a competing reaction, thereby limiting the overall yield of the bibenzyl condensation product.

o-Methylarenesulfonanilides also undergo this coupling condensation reaction (Table II). In addition to the requirement that there be an *N*-aryl substituent, it is also required that

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