the excess solvent was removed under reduced pressure to give 0.41 g of **18** as a light brown oil (>95% pure by GLC). An analysis of the carbonyl region of the ^{13}C NMR spectrum of the crude product revealed it to be a mixture (ca. 1:1) of the C-1 epimers (δ 219.03 and 217.67), together with another minor, unidentified component (<5%) (δ 219.75). Although it was not necessary for the synthesis, an apparent thermodynamic mixture of the C-1 epimers could be obtained by base-catalyzed epimerization. Thus, the crude product obtained above was dissolved in 1 N methanolic sodium methoxide (3 mL) and the solution stirred at room temperature for 5 h. After addition of saturated brine (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with saturated NH_4Cl and dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure, followed by distillation of the residue, gave 0.36 g (87%) of **18**, bp 88–89 °C (0.02 mm), which was judged to be an 8:1 mixture of C-1 epimers by ^{13}C NMR. An analytical sample was obtained by preparative GLC (5% Carbowax 20M, firebrick): IR 1740 cm^{-1}; ^1H NMR δ 5.34 (br s, 1 H), 1.71–2.75 (complex, 11 H), 1.63 (br s, 3 H), 1.10 (d, 3 H, J = 7 Hz), 0.96 (d, 3 H, J = 7 Hz), 0.94 (d, 3 H, J = 7 Hz); ^{13}C NMR, C-2 (major diastereomer, ca. 89%), δ 219.03, C-2 (minor diastereomer, ca. 11%) δ 217.67; mass spectrum *m/e* 220, 178, 150, 121 (base), 110, 97, 96, 82, 68; exact mass (calcd for $C_{15}H_{24}O$) 220.1827, found 220.1828.

Acorone (1) and Isoacorone (2). A solution of diborane in THF (3.4 mmol) was added slowly dropwise with vigorous stirring to a solution of the diastereomeric ketones **18** (0.74 g, 3.4 mmol) in anhydrous THF (30 mL) at 0 °C, and the stirring was continued at room temperature for 2 h. To destroy the excess diborane, water (1 mL) was added, and the mixture was stirred at room temperature for an additional 15 min. A solution of chromic acid [prepared by mixing sodium dichromate (2.10 g, 7.6 mmol), 98% H_2SO_4 (1.75 mL, 3.1 mmol), and H_2O (9.3 mL)] was then added with vigorous stirring over the course of 30 min. After completion of the addition, the reaction mixture was heated at reflux for 2 h and then cooled. Saturated brine (40 mL) was added, the layers were separated, and the aqueous layer was thoroughly extracted with ether (6 × 80 mL). The combined organic layers were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure afforded 0.73 g of a light yellow oil. Analytical GLC and TLC analyses of the crude oil showed it to be a mixture of acorone and isoacorone [ca. 75% by comparison with an authentic sample of neoacorone, which is a mixture of (+)-acorone and (−)-isoacorone], along with several minor unidentified components. Preparative high-pressure liquid chromatography (Waters LC 500) using two Prep PAK columns and ethyl acetate–hexane (1:4) as the eluting solvent and a flow rate of 250 mL/min afforded 0.20 g (27%) of pure (±)-isoacorone (**2**) (6.8 min) and 0.18 g (25%) of pure (±)-acorone (**1**) (10 min). Analytical samples of both (±)-acorone and (±)-isoacorone were obtained by recrystallization from hexane, and these were identical with authentic samples of (+)-acorone and (−)-isoacorone[15] by IR, NMR, MS, GLC, and TLC. (±)-Acorone: mp 101.5–102 °C (lit.[1a] 101.5–103.5 °C); exact mass (calcd for $C_{15}H_{24}O_2$) 236.1776, found 236.1780. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.27; H, 10.33.

(±)-Isoacorone: mp 66–67 °C; exact mass (calcd for $C_{15}H_{24}O_2$) 236.1776, found 236.1777.

Acknowledgment. We wish to thank the Robert A. Welch Foundation for their generous support of this work.

Registry No.—**1**, 61475-94-3; **2**, 61475-97-6; **4**, 4746-97-8; **6**, 64715-23-7; **7**, 64715-24-8; **8**, 64715-25-9; **9**, 64715-26-0; **10**, 64715-27-1; **12**, 7560-64-7; **13**, 64715-28-2; **14**, 61426-19-5; **15**, 61426-14-0; **16**, 64728-47-8; **17a**, 61426-21-9; **17b**, 61426-22-0; **18** (isomer 1), 61475-96-5; **18** (isomer 2), 61426-24-2; **19**, 64715-29-3; **20**, 61475-95-4; diethyl pyrrolidinomethylphosphonate, 51868-96-3; 2,3-dibromopropene, 513-31-5; ethylene glycol, 107-21-1; pyrrolidine, 123-75-1; 2-chloro-3-iodopropene, 39557-31-8.

References and Notes

(1) (a) D. A. McCrae and L. Dolby, *J. Org. Chem.*, **42**, 1607 (1977); (b) J. N. Marx and L. R. Norman, *ibid.*, **40**, 1602 (1975).
(2) (a) J. F. Ruppert, M. A. Avery, and J. D. White, *J. Chem. Soc., Chem. Commun.*, 978 (1976); (b) B. M. Trost, K. Hiroi, and N. Holy, *J. Am. Chem. Soc.*, **97**, 5873 (1975); (c) H. Wolf and M. Kolleck, *Tetrahedron Lett.*, 451 (1975); (d) W. Oppolzer and K. K. Mahalanabis, *ibid.*, 3411 (1975).
(3) While this manuscript was in preparation, a related synthesis of acorone appeared. See ref 1a.
(4) (a) S. F. Martin and R. Gompper, *J. Org. Chem.*, **39**, 2814 (1974); (b) S. F. Martin, *ibid.*, **41**, 3337 (1976); (c) S. F. Martin, T. S. Chou, and C. W. Payne, *ibid.*, **42**, 2520 (1977).
(5) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Am. Chem. Soc.*, **74**, 1401 (1952).
(6) E. J. Corey and D. S. Watt, *J. Am. Chem. Soc.*, **95**, 2303 (1973).
(7) (a) E. F. Lutz and G. M. Bailey, *J. Am. Chem. Soc.*, **86**, 3899 (1964); (b) G. I. Fray and R. Robinson, *ibid.*, **83**, 249 (1961).
(8) For a review of such methods, see *Methoden Org. Chem. (Houben-Weyl)*, **7/2a**, 813 (1973); see also T. Mukaiyama, T. Imamoto, and S. Kobayashi, *Chem. Lett.*, 715 (1973).
(9) S. F. Martin and T. S. Chou, unpublished results.
(10) Cf. G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.*, **39**, 3459 (1974).
(11) For an excellent review of cuprate additions to α,β-unsaturated carbonyl systems, see G. H. Posner, *Org. React.*, **19**, 1 (1972).
(12) (a) J. Vrkoc, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **27**, 2709 (1962); (b) J. Vrkoc, J. Jonas, V. Herout, and F. Sorm, *ibid.*, **29**, 539 (1964); (c) see also ref 1a,b.
(13) Similar results were obtained when the reaction was done at −70 °C.
(14) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961).
(15) We wish to thank Professor John N. Marx for a generous gift of neoacorone and Professor Niels H. Andersen for generous samples of authentic (+)-acorone, (−)-isoacorone, and neoacorone.
(16) R. L. Letsinger and J. G. Traynham, *J. Am. Chem. Soc.*, **70**, 2818 (1948).

New Synthetic Methods. Stereocontrolled Bicycloannulation: an Approach to Gibberellins

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An approach for the stereocontrolled annulation of a bicyclo[3.2.1]nonan-5-one onto a cycloalkanone is delineated. Reaction of 2-(2′-trityloxyethyl)cyclopentanone with diphenylsulfonium cyclopropylide provides the spiro-fused cyclobutanone. Regiocontrolled ring expansion converts the cyclobutanone into a cyclopentanone. This approach serves to create spiro[*n*.4] systems in a stereochemically defined fashion. Sulfinylation, reduction of the β-keto sulfoxide to the β-keto sulfide, and conversion of the trityloxy group to a mesylate allows base-catalyzed cyclization to the desired bicyclo[3.2.1]nonan-5-one. Utilizing the bridgehead sulfur as a control element and Wagner–Meerwein shifts, either stereochemical series of fusion of the bicyclic system is available. Methylenation completed the gibberellin model.

Among the structural types of important natural products that are very common are the bicyclo[3.2.1]octanes fused to another ring. Two examples, gibberellic acid (**1**) and aphidicolin (**2**), illustrate two much sought after important targets that possess this feature. In considering the synthesis of gibberellic acids, the vast majority of methods focus on creating ring D onto a preformed ring C system.[1-4] We report a new approach to the stereocontrolled production of the BCD

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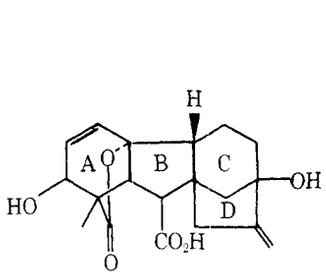

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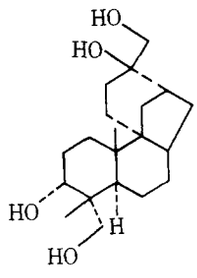
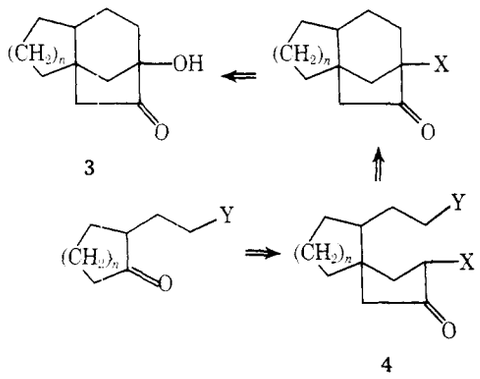


2

fragment which closes ring C to complete the carbon framework. This approach offers one the ability to form either stereochemistry at the BC ring juncture and to manipulate the substitution pattern. Thus, the strategy should be generally applicable and potentially can be extended to the annulation of bicyclo[n.2.1]alkane onto any ketone. Furthermore, this approach illustrates the applicability of the stereocontrolled spiroannulation of cyclobutanones and the versatility of the latter in creating larger cycloalkanones.

In developing an approach to **3**, the problem can factor down to an intramolecular alkylation of a spiro[n.4] system **4**. Thus, a stereocontrolled synthesis of **4** becomes a stereocontrolled synthesis of **3**. The latter simplifies to a spiroalkylation of a five-membered ring onto a cycloalkanone. The importance of spiro[4.5]decanes, for which this methodology will also be applicable, enhances the importance of this approach.



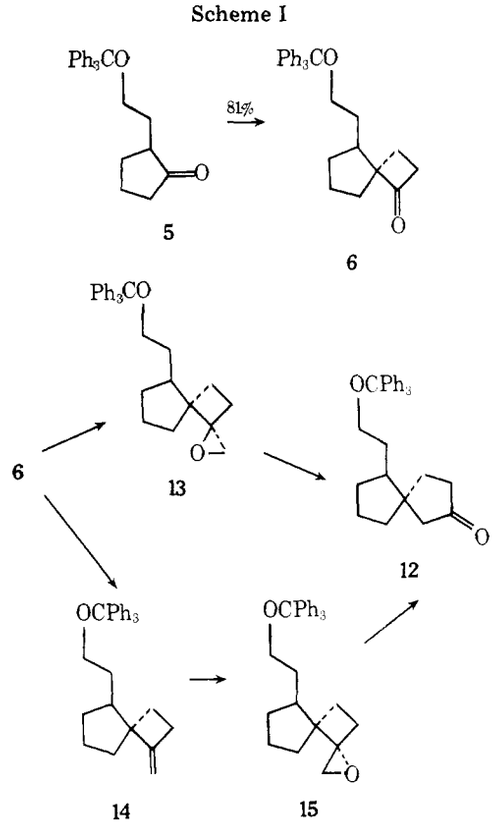
3 4

Results

Treatment of 2-(2′-trityloxyethyl)cyclopentanone (**5**) with cyclopropyldiphenylsulfonium fluoborate and potassium hydroxide in Me_2SO, followed by lithium fluoborate in refluxing benzene, gave a single crystalline cyclobutanone, **6**, in 81% yield (see Scheme I). The stereohomogeneity is confirmed by the appearance of only eleven aliphatic carbons in the ^{13}C NMR spectrum and by a clean ^1H NMR spectrum as well as by chromatographic analysis. As far as can be discerned, a single compound results from this spiroannulation. Assignment of stereochemistry follows by analogy to previous examples[5,6] and from the ^{13}C NMR spectrum.[7] Utilizing the type-II stereoreversed rearrangement,[7] a mixture of **6** and its epimer **7** was available. C(3) appears at 3 ppm higher field in **7** (δ 19) compared to **6** (δ 22) as expected for a γ effect. For comparison, the shifts for this carbon in **8** and **9** are δ 22.8 and 20.0, respectively.[7]

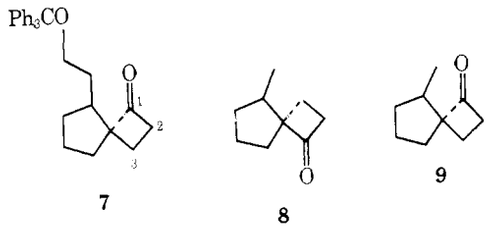
With the stereochemistry of the system fixed, attention turns to the ring expansion.[8,9] In pinacol-type ring expansions (via diol, amino alcohol, bromohydrin, etc.), conformational effects can overcome the normal electronic preference for a more substituted carbon to migrate preferentially. Ring expansion via the bromohydrin **10** can lead to either **11** or **12**. Treatment of cyclobutanone **6** with dimethylsulfonium methylide[5b] to give **13**, followed by lithium bromide in benzene

Scheme I



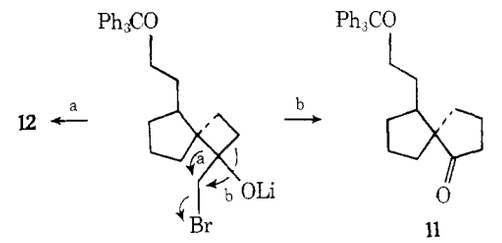
5 6 13 12 14 15

containing 1 equiv of HMPA,[10] produced **12** in 65% yield. Alternatively, conversion of **6** to **15** via MCPBA epoxidation



7 8 9

of the Wittig olefination product **14**, followed by rearrangement, gave **12** in 78% overall yield. The latter procedure, al-



10 11

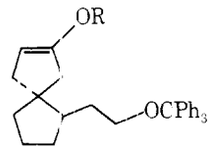
though one step longer, proceeded in higher yield and gave purer product which could be directly crystallized even when crude cyclobutanone was employed. In this sequence, the use of potassium hydride rather than n-butyllithium to generate the Wittig reagent was crucial in avoiding decomposition of starting cyclobutanone, which was apparently catalyzed by the presence of lithium salts.

The stereochemistry of **13** and **15** is based solely upon mechanistic considerations, i.e., least hindered attack of the ylide on **6** and the peracid on **14**, respectively. The former shows the epoxide methylene as an AB pattern with δ_A 2.64, δ_B 2.43, and J = 6 Hz, whereas the latter shows this pattern at δ_A 2.70, δ_B 2.50, and J_{AB} = 5 Hz. The intermediacy of the bromohydrin corresponding to **10** is secured by the isolation of a small amount of this compound when the reaction is taken

to partial completion. The compound showed the methylene group bearing bromine as an AB pattern with δ_A 3.62, δ_B 3.50, and J_{AB} = 15 Hz. Subjection of this compound to lithium carbonate in refluxing benzene containing HMPA led smoothly to the same cyclopentanone, **12.**

The ring-enlarged cyclopentanone, mp 122 °C, is stereo- and regiochemically homogeneous. The ^{13}C NMR shows only 12 signals for sp^3 carbons. The fact that the spiro carbon shifts from δ 73.2 in **6** to δ 49.8 in **12** indicates that a carbonyl group is no longer adjacent. The NMR spectrum upon addition of 14 mol % of Eu(dpm)$_3$ separates out two methylene groups, one of which is an AB pattern at δ 4.2 and 4.5 with J_{AB} = 17 Hz. This fact indicates that the carbonyl group is flanked by two methylene groups, one of which is adjacent to a quaternary carbon as in **12.** The subsequent chemistry of **12** further confirms this assignment. Thus, by the procedure of spiroannulation and ring expansion, a spiro[4.4]nonyl system was available in 62% overall yield from a cyclopentanone.

Surprisingly, the main problem that was encountered was the regiodifferentiation of the unsymmetrical ketone. Enolate formation under kinetic control gave approximately a 3:2 mixture of the two enolates **16** and **17** (R = Li) as determined by quenching with either trimethylchlorosilane or acetic anhydride.[11] Thermodynamic generation of the enol acetates led to an approximately 1:3 ratio of **16** and **17** (R = Ac). Formylation of **12** equally led to unsatisfactory mixtures of hydroxymethylene derivatives.[12]



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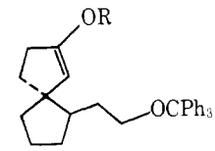
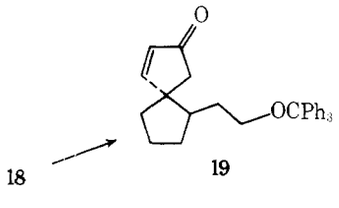


17

The problem was resolved delightfully by use of a more bulky derivatizing agent, methyl *p*-tolylsulfinate,[13,14] which gave a sulfoxide **18** in 91% yield (see Scheme II). Because of the complexity of the stereo- and regioisomerism, as well as the coincidence of chemical shifts, direct determination of the regiochemistry was not possible. However, thermal elimination of *p*-toluenesulfenic acid[15] did give an 89% yield of enone **19,** indicating that at least 89% of the sulfinylated compound was the desired regioisomer **18.** Further characterization was achieved by a Pummerer reaction with iodine in methanol[16] or sodium acetate and acetic anhydride[17] to give **20** (R = *p*-C_7H_7). Interestingly, sulfenylation of the anion of **18** with methylthio methanesulfonate at 0°C led directly to **20** (R = CH_3). Sulfoxide elimination apparently occurred at 0 °C since the intermediate could not be detected.



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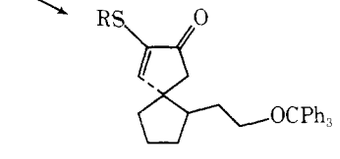


20

Treatment of the sulfoxide **18** with anhydrous stannous chloride in acetic anhydride and acetonitrile[18] reduced the sulfoxide to the sulfide and replaced the trityl group by acetate to give **21** (R = Ac) in 61% yield. For completion of the tricyclic skeleton, the acetoxy group was converted into a mesylate (**21,** R = Ms)[19] and the latter treated with DBN[20] in DMF–THF to give **22** in 55% overall yield as a crystalline solid, mp 64–65 °C. The structure of **22** is supported by elemental analysis and spectral data. In particular, the regiochemistry of the alkylation is demonstrated by the absence of any proton on the carbon bearing sulfur. The similarity of the ^{13}C NMR data to the corresponding portions of gibberellic acid derivatives **23a** and **23b**[21] further supports the assignments (see Table I). Further characterization was provided by the synthesis of the ketal **25** and the hemithioketal **26,** which showed similar ^{13}C NMR spectra. It is interesting to note that the hemithioketal is a single isomer which is tentatively assigned with sulfur exo. This assignment is based upon the substantial shift for C(8) in the ^{13}C NMR spectrum and the anticipation that the reaction involves at some point trapping of an oxygen stabilized

Scheme II

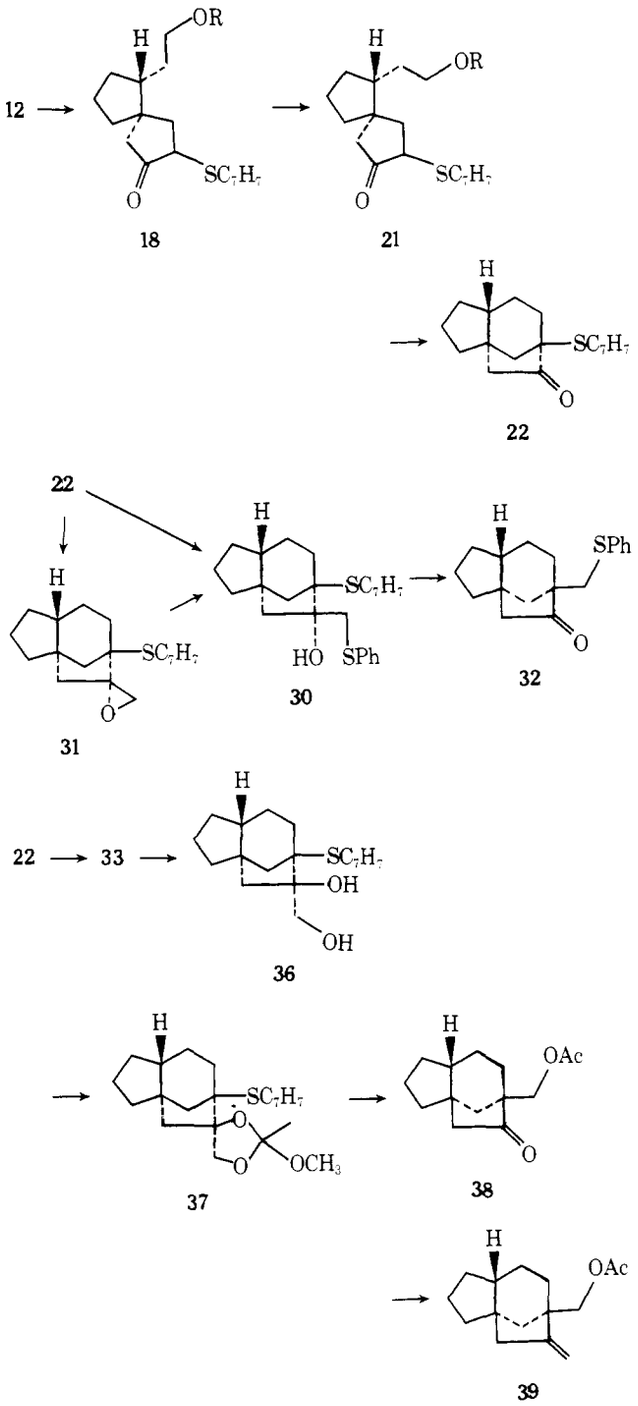
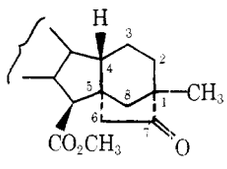
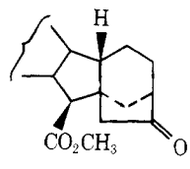


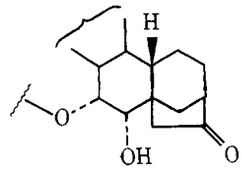
Table I. ^{13}C NMR Data



23a, b



24a, b



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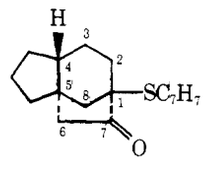

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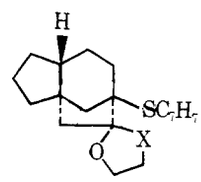
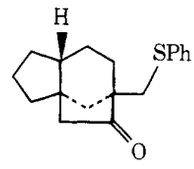


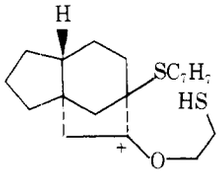
25, 26



32

C atom	23a	23b	24a	24b	I	22	25, X = O	26, X = S	32
1						62.7	62.2	63.8	53.6
2	36.0	35.9	24.9	24.9	26.2	36.6	36.2	37.5	21.7
3	19.9	21.9	16.7	16.9	17.7	21.7	22.0	22.0	22.2
4	54.0 (or 51.0)	50.7 (or 55.2)	54.1	53.4	56.5	46.3	46.3	46.3	50.1
5	51.6	51.3	49.7	51.3	42.8	46.5	46.8	50.5	45.0
6	50.7 (or 47.8)	50.3 (or 47.8)	50.4	50.2	49.8	47.3	49.5	49.5	45.9
7	219.0	218.4	220.1	219.3	221.3	215.3	116.9	96.0	214.3
8	47.8 (or 50.7)	47.8 (or 50.3)	34.5	34.6	31.7	46.1	48.7	53.3	39.3
9						35.2	35.2	35.7	35.2
10						26.0	26.6	27.1	29.1
11						28.5	28.6	28.4	33.6

cation **27** by sulfur, which should occur from the exo face. Finally, reduction of **22** to its corresponding alcohol, mp 39–41 °C, showed the methine proton next to the hydroxyl group as



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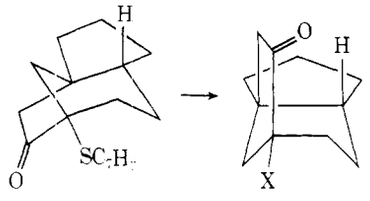
a dd (J = 10, 6 Hz) at δ 4.15, indicative of only an adjacent methylene group.

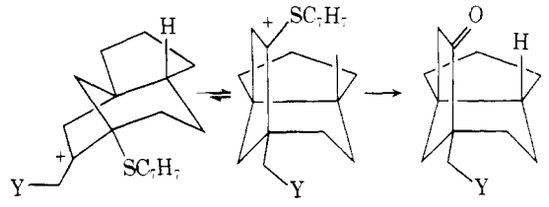
The versatility of the substitution pattern is quite high. For example, desulfurization can, in principle, lead to the parent system—thus constituting a fully stereocontrolled synthesis of substituted bicyclo[3.2.1] systems. Use of Wagner–Meerwein shifts allows modification of the stereochemistry (from that in **28** to, for example, that in **29** as represented by the gibberellins) as well as modification of bridge substitution. The bridgehead sulfur serves as a control element in directing the carbonium ion rearrangements. In fact, the lack of rearrangement in the derivatization reactions mentioned above is noteworthy in this regard. The greater stabilization by oxygen of adjacent positive charge, combined with the necessary conversion of the six-membered ring from a chair to a boat conformation (i.e., **28** → **29**), apparently prevents the



28 **29**

rearrangement. In fact, the facility of the reverse process[22] (i.e., **29** → **28**) in steviols and the facile rearrangement of the CD rings of the gibberellins suggested that a synthon for an oxygen at the bridgehead carbon in **29** (i.e., X ≠ OH) would be most desirable to avoid skeletal rearrangements in a projected synthesis of these plant growth hormones.

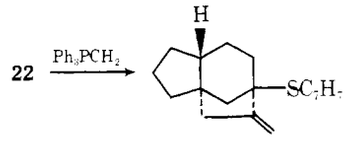
The introduction of a substituted carbon as an unreactive synthon for the hydroxy group in **29**, which by a Baeyer–Villager or carboxy inversion reaction could be converted to the bridgehead hydroxy compound, is outlined in eq 1. Two ap-



(1)

proaches were successful. In the first (see Scheme II), addition of lithiothioanisole[23] to **22** gave **30**. Alternatively, condensation of **22** with dimethyloxosulfonium methylide gave the epoxide **31** which, in turn, was reacted with thiophenol. The hydroxy sulfide appears to be homogeneous, utilizing chromatographic and spectroscopic criteria. The presence of the phenylthio group serves not only as the entry to an oxidized bridgehead substituent but also as a neighboring group to facilitate the generation of the corresponding cation (see eq 1). Exposure of **30** to TosOH in refluxing benzene[24] leads rapidly to inverted ketone **32** in 75% yield in contrast to its behavior with trifluoroacetic acid or stannic chloride. The structure of the ketone is supported by spectroscopic data. IR spectroscopy indicates a five-membered ring ketone (1740 cm^{-1}). NMR shows the loss of the p-tolyl group, a singlet for the methylene group adjacent to sulfur (δ 3.07), and an AB pattern at δ 2.21 and 1.87 (J = 17 Hz) for the methylene group α to the carbonyl group. The ^{13}C NMR spectrum (see Table I) shows sufficient similarities to the corresponding carbons of the gibberellic acid derivatives **24a** and **24b**[25] to confirm their structural correlation. Most noteworthy is the upfield shift experienced at C(2) and C(8) as a function of the ring juncture of the [6,5] system.

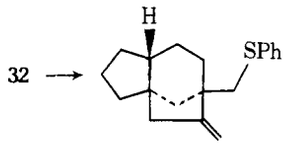
Further support derives from the relative rates of methylenation of **32** compared to **22**. The latter reacts quite nor-



33

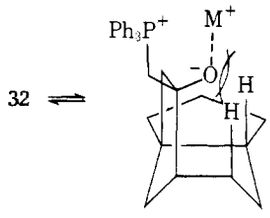
mally to give the methylene derivative **33** at 0 °C; however, under the same conditions **32** is almost inert. For best results,

salt-free phosphorus ylide[26] should be employed, in which case an 81% yield of **34** is obtained after 3 h at reflux in THF. House[27] noted a requirement for the absence of lithium salts



34

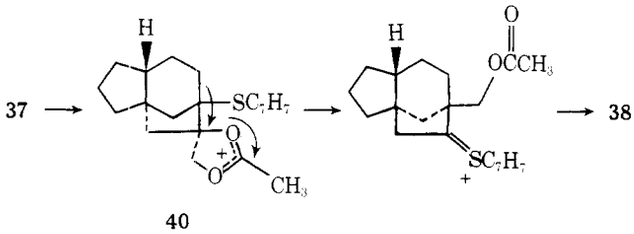
in his synthesis of epiallogibberic acid. One rationalization relates the absence of the lithium salt to the rate of elimination of the intermediate phosphetane or betaine. It can be envisioned that steric crowding in **35** facilitates the reversal reaction in the presence of this salt due to coordination of the



35

salt with the ylide adduct. In the absence of salt, interaction of the oxygen and phosphorus is enhanced and thus facilitates the desired elimination. Such steric crowding is less severe in the ylide adduct of **22,** and thus it behaves normally.

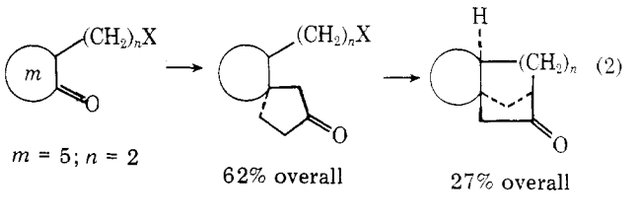
Alternatively, an oxymethyl substituent can be introduced at the bridgehead carbon. Hydroxylation of **33,** available from **22** as outlined above, gives diol **36.** Stereochemistry is assigned on the basis of least hindered attack by the osmium tetraoxide from the exo face. Ortho ester formation with methyl orthoacetate to **37,** followed by dissolving in a 2:1 ratio of carbon tetrachloride–trifluoroacetic acid, gave rearranged ketone **38.** The course of this reaction could be conveniently followed by NMR spectroscopy. Immediately after mixing the absorption for the acetate methyl group shifted from 1.6 to 2.9 and that for the methylene group bearing oxygen from 3.8 to 5.1 (AB, δ 5.08 and 5.15, J = 12 Hz)—indicative of the formation of the acetoxonium ion **40.**[28] Over a period of several hours, a singlet at δ 2.1 and an AB pattern at δ 4.1 (J = 13 Hz) grew in. Quenching the reaction mixture into aqueous hydrochloric acid gave the keto acetate **38** in 57% yield. The IR spectrum showed two carbonyl groups (1743 and 1753 cm^{-1}) and no aryl absorptions. The NMR spectrum confirmed the absence of the p-tolylthio group and the mass spectrum gave a formula of $C_{14}H_{20}O_3$. The similarity of the spectral properties of **38** to those of **32** further supports the structure. Finally, **38** behaved very similarly toward methylenation to give **39** as did **32.** Again similarity of the spectra of **39** to **34** indicates their structural similarity.



40

Conclusions

A straightforward stereocontrolled sequence has been developed for the annulation of a bicyclo[3.2.1] system onto a 2-alkylcycloalkanone by capitalizing upon the spiroannulation of a cyclobutanone (eq 2). In the process, both diastereoisomeric series of the [3.2.1] system were generated without contamination by the alternative isomer. The entire sequence proceeds in high yield and purification need be done at only a few places. In addition, a stereo- and regiocontrolled synthesis of spiro[n.4] ketones is now also available (see eq 2). Since the stereochemistry is established by the cyclobutanone annulation and since either stereoisomer is now available from the same oxaspiropentane,[7] this approach has special merit.



(2)

Furthermore, the products have functionality of sufficient versatility to allow considerable manipulation. For example, bridgehead substitution can vary from hydrogen (by desulfurization of **22** or oxidation and decarboxylation of **32** or **38**) to oxygen (by oxidation and carboxy inversion of **32** or **38**) to carbon (as derived from **32** and **38**). The stereocontrol and chemical flexibility make this sequence of particular use for the preparation of terpenoids such as the kauranes, cedrene, and zizaene, as well as the very complex gibberellins.

Experimental Section

All reactions were run using magnetic stirring under a positive pressure of dry nitrogen at room temperature, unless otherwise indicated. All reaction temperatures were measured externally. All reactions requiring anhydrous conditions were done in glassware flamed under a stream of dry nitrogen. All solvents for anhydrous reactions were distilled as follows: diethyl ether (ether), 1,2-dimethoxyethane (DME), and tetrahydrofuran (THF) from sodium benzophenone ketyl; toluene, benzene, acetonitrile, dimethyl carbonate, dichloromethane, pyridine, dimethyl sulfoxide (Me_2SO), dimethylformamide (DMF), hexane, and hexamethylphosphoric triamide (HMPA) from calcium hydride. Diisopropylamine was distilled from potassium hydroxide. Lithium bromide was pulverized and then dried overnight at 120 °C in a vacuum oven. All other reagents were used as obtained commercially. Drying agents are indicated in the separate experiments and were all anhydrous grade. The term "concentration in vacuo" refers to the removal of the solvents on a Büchi-Brinkman rotoevaporator at water aspirator pressure, followed by the removal of the last traces of solvents with a vacuum pump, except where the product had a boiling point below 100 °C at 0.1 mm.

Purifications are indicated in the text. Kügelrohr distillation refers to the use of the apparatus available from Aldrich Co. connected to a vacuum pump. The term TLC (thin-layer chromatography) is used for microscope slides coated with silica gel PF_{254} (vide infra), by dipping in a slurry of the silica gel in chloroform, and used exclusively for monitoring of a reaction's progress. The term PLC (preparative layer chromatography) refers to purification on 1.5–2.0 mm thick plates of E. Merk and Co. (Darmstadt) silica gel G with PF_{254} spread on glass as an aqueous slurry and activated (after air drying) at 120 °C for 2 h. Typical loadings were up to 80 mg on 20 × 10 cm; 80–200 mg on 20 × 20 cm; and 200–450 mg on 20 × 40 cm plates. Larger amounts were done on appropriate combinations. Eluting solvents are indicated in the text. All plates utilized 17 cm from baseline to maximum elution. Visualization of the bands (spots) on these plates was done with the aid of a UV lamp in conjunction with iodine or spraying with an ethanolic solution of phosphomolybdic acid, followed by heating. The bands were extracted with ether to remove the material.

The term HPLC is used for high (or medium) pressure solid–liquid chromatography and refers to the use of a standard 2.5 (i.d.) × 100 cm column with a precolumn filter of 1.5 (i.d.) × 25 cm dimensions, both of which were packed with the indicated solvent mixture. The system utilized a single stage constant flow pump at approximately 22 mL/min. Sample preparation consisted of filtration of an ether solution through a 1.5-cm cake of W. R. Grace grade 62 silica gel and concentration in vacuo. The sample was dissolved in a minimum

amount of the solvent mixture and injected onto the column. Typically a forerun of 350 mL was taken and discarded, and the outlet was then connected to a Gilson fraction collector to collect 12-mL samples. The solvent systems are such as to give the desired material and R_f on TLC of approximately 0.2. In place of an R_f in these systems, the tube numbers containing the product are given.

Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Boiling points are uncorrected. Infrared spectra were obtained as solutions in the indicated solvent on a Beckman IR-8 or a Perkin-Elmer 267 spectrophotometer and are given in reciprocal centimeters. Proton NMR spectra were determined in the indicated solvent on a Varian A-60A (60 MHz), a Jeolco MH-100 (100 MHz), or a Bruker WH270 (270 MHz); ^{13}C NMR spectra were determined on a Jeolco FX-60 (60 MHz); chemical shifts for both are given in parts per million downfield from tetramethylsilane (Me_4Si). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Coupling constants are given in hertz. Mass spectra were obtained on an AEI MS-902 high-resolution mass spectrometer at an ionizing current of 100 mA and an ionizing voltage of 70 eV, except for compounds containing trityl ethers (39–40 eV) or benzyl ethers (50 eV) (due to ease of fragmentation), and are reported as *m/e* (%). Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Preparation of 2-(2′-Hydroxyethyl)cyclopentanone. In a three-neck 2-L round-bottom flask fitted with a condenser and mechanical stirrer were placed 60 g (0.40 mol) of commercial 2-cyclopentanone carboxylate ester (1:1 methyl–ethyl by NMR), 220 g (1.60 mol, 4.0 equiv) of anhydrous potassium carbonate, and 300 mL of reagent grade acetone. A solution of 68 g (0.48 mol, 1.20 equiv) of 2-bromoethyl acetate in 200 mL of acetone was added over 20 min with vigorous stirring. The mixture was then vigorously refluxed for 21 h, cooled, poured into 1.5 L of a 1:1 mixture of water and saturated aqueous sodium chloride solution, and extracted with 3 × 400 mL of ether. The combined organic layers were dried with sodium sulfate and potassium carbonate and concentrated in vacuo to yield 100 g of a crude yellow oil.

To the crude alkylated mixture was added 1 L of 10% (v/v) aqueous sulfuric acid and this mixture heated at 65 °C until 30 min beyond the cessation of carbon dioxide evolution (4 h). After cooling, the reaction mixture was neutralized carefully with solid sodium carbonate and extracted with 3 × 400 mL of chloroform. The combined organic layers were dried over sodium sulfate and potassium carbonate and concentrated at aspirator pressure with an ice-cold bath to yield 54 g of crude oil. Distillation through a short-path column yielded 36.3 g (0.28 mol, 71%) of the desired alcohol: bp 89–95 °C (16–18 mm) [lit.[29] 126–130 °C (14 mm)];[30] NMR ($CDCl_3$) 1.2–2.5 (9 H, m), 2.5 (variable, 1 H, br s), 3.75 (2 H, t, J = 7 Hz); IR ($CHCl_3$) 3600, 3450, 2990, 2970, 2870, 1735, 1040; MS 128 (5), 111 (5), 110 (20), 109 (15), 100 (10), 99 (100), 98 (8), 97 (17), 95 (10), 85 (25), 84 (40), 83 (80), 82 (15), 81 (25), 67 (40). Anal. Calcd for $C_7H_{12}O_2$: mol wt, 128.0837. Found: mol wt, 128.0838.

Preparation of 2-(2′-Trityloxyethyl)cyclopentanone (5). To a solution of 150 mL each of dry benzene and dry pyridine was added 32 g (0.098 mol, 1.05 equiv) of commercial trityl bromide, and the mixture was stirred until complete dissolution was effected (on some occasions the mixture was warmed slightly to assist dissolution). To this was added the crude alcohol in 50 mL of benzene. This mixture was stirred for 5 days until TLC indicated that no further alcohol was present and that only the desired trityl ether (R_f 0.55) and triphenylcarbinol (R_f 0.6) were present. A small (approximately 0.5 mL) aliquot was removed and partitioned between ether and aqueous 3 N hydrochloric acid. The ether was dried and concentrated at a water aspirator to yield a sample whose NMR showed none of the alcohol (m at δ 3.5–3.8) and only trityl ether (br t, δ 3.0–3.3, in CCl_4). The remainder of the mixture was worked up in a like manner to yield 41 g of crude material. Kügelrohr distillation (90 °C, 0.1 mm) removed the last traces of solvent and 2.5 g of an oligomer derived from 2-(2′-hydroxyethyl)cyclopentanone to yield 34 g (approximately 0.091 mol, approximately 98%) of crude trityl ether as a deep yellow glass. This material was suitable for further transformations with the only discernible impurity being a small amount of triphenylcarbinol, which could be removed only with considerable difficulty by PLC. A 100-mg sample was purified by PLC to yield 95 mg of **5** as a glass. Repeated attempts to crystallize this sample finally yielded crystals from carbon tetrachloride–methanol: mp 77–79 °C; NMR (CCl_4) 1.2–2.3 (9 H, m), 3.10 (2 H, t, J = 7 Hz), 7.0–7.5 (15 H, m); IR (CCl_4) 3090, 3060, 3030, 2970, 2880, 1740, 1490, 1450, 1150, 1090, 1040, 700; MS 370 (~0.001), 260 (15), 259 (13), 245 (5), 244 (40), 243 (100), 184 (5), 183 (35), 182 (9), 167 (5), 166 (5), 165 (20), 155 (9), 154 (12), 128 (6), 127 (85), 112 (5), 111 (55), 109 (7), 105 (40), 84 (4), 83 (11), 77 (10), 55 (9). Anal. Calcd for $C_{26}H_{26}O_2$: C, 84.32; H, 7.02; mol wt, 370.1933. Found: C, 84.24; H, 6.97; mol wt, 370.1944.

Preparation of (4*S,5*R**)-5-(2′-Trityloxyethyl)spiro[3.4]-octan-1-one (6).** To a stirred solution of 370 mg (1.0 mmol) of glassy 2-(2′-trityloxyethyl)cyclopentanone and 360 mg (1.15 mmol, 1.15 equiv) of cyclopropyldiphenylsulfonium fluoborate in 2 mL of Me_2SO (commercial) was added 65 mg (1.16 mmol, 1.16 equiv) of freshly powdered potassium hydroxide in three equal portions at 1-h intervals. The reaction was stirred for 18 h, at which time an additional 65 mg (0.2 mmol, 0.2 equiv) of the sulfonium salt and 15 mg (0.26 mmol, 0.26 equiv) of powdered potassium hydroxide were added all at once, and stirring was continued for 2 h. The reaction mixture was poured into a 1:1 mixture of water and saturated aqueous sodium bicarbonate solution and extracted three times with ether. The combined organic layers were washed twice with water, dried over sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 550 mg of crude oxaspiropentane and diphenyl sulfide: NMR (CCl_4, crude) 0.5–1.0 (m), 1.1–2.1 (m), 2.96 (br t, J = 7 Hz), 7.0–7.5 (m); IR (CCl_4, crude) 3060, 3000, 2960, 2870, 1080, 1070, 1025, 1000.

The crude material was dissolved in 5 mL of dry benzene and 10 mg of anhydrous lithium fluoborate was added. The mixture was refluxed for 1 h, cooled, diluted with ether, washed with water, dried over magnesium sulfate, and concentrated in vacuo to yield 0.6 g of crude oil. Kügelrohr distillation [80 °C (0.1 mm)] evaporated 151 mg (0.81 mmol, 81%) of diphenyl sulfide. Trituration of the crude glass from the pot of the distillation yielded 65 mg (0.158 mmol) of crystalline product, mp 90–95 °C. Purification of the mother liquor by PLC in 2:1 hexane–ether yielded an additional 265 mg (0.646 mmol) of cyclobutanone, mp 92–96 °C, for a total of 330 mg (0.805 mmol, 80.5%). A sample was recrystallized from a concentrated hexane solution to get a sample for analysis: mp 110.5–111.5 °C.

Essentially the same procedure was used on larger scales; however, the starting material was a glass. A 34-g (0.092 mol) sample of glassy **5** in 200 mL of Me_2SO was treated with 40 g (0.127 mmol, 1.4 equiv) of diphenylcyclopropylsulfonium fluoborate and 5.6 g (0.10 mol, 1.1 equiv) of powdered potassium hydroxide in four portions. Additional sulfonium salt (5.0 g, 0.016 mol, 0.17 equiv) and potassium hydroxide (1.0 g, 0.018 mol, 0.2 equiv) were added after 2 days and again after 5 days. After an additional 2 days (7 days total) the reaction was worked up as usual to yield 13.4 g of highly crystalline cyclobutanone, mp 109–111 °C, and a 25.8-g sample, still containing considerable amounts of entrained solvent. By isolation utilizing a 100-mg aliquot, this latter sample contains 45% cyclobutanone for a total yield of 72%. The crude material thus obtained is normally directly employed: NMR (CCl_4) (100 MHz) 1.1–2.2 (11 H, m), 2.66 (2 H, td, J = 8, 4 Hz), 2.90–3.15 (2 H, m), 7.0–7.5 (15 H, m); NMR ($CDCl_3$) (270 MHz) 1.0–2.06 (m), 2.73 (ddd, J = 7, 10, 18 Hz), 2.82 (ddd, J = 18, 9.6, 6.5 Hz), 3.02 (ddd, J = 9.0, 7.0, 6.5 Hz), 3.13 (ddd, J = 9.0, 7.0, 5.5, plus aromatics as an undefined multiplet); ^{13}C NMR ($CDCl_3$) 214.41 (s), 143.45 (s), 127.83 (d), 126.86 (d), 126.07 (d), 85.96 (s), 73.23 (s), 62.27 (t), 45.22 (d), 42.38 (t), 35.28 (t), 31.25 (t), 30.90 (t), 22.95 (t), 22.72 (t); IR (CCl_4) 3090, 3060, 3020, 2950, 2870, 1770, 1490, 1445, 1210, 1070, 700; MS 410 (below 0.01%), 259 (1), 244 (23), 244 (100), 242 (4), 241 (4), 228 (3), 215 (2), 183 (4), 167 (8), 166 (4), 165 (20), 151 (7), 99 (3), 95 (8). Anal. Calcd for $C_{29}H_{30}O_2$: C, 84.87; H, 7.31; mol wt, 410.2246. Found: C, 84.82; H, 7.28; mol wt, 410.2233.

Preparation of (5*S,6*R**)-6-(2′-Trityloxyethyl)spiro[4.4]-nonan-2-one (12).** To a slurry of 2.0 g (50 mmol, 2.05 equiv) of potassium hydride (prepared by slurrying the commercial slurry with hexane and pipetting off the liquid, repeating twice, and then removing the residual hexane with a vacuum pump) in 35 mL of THF was added 18.5 g (52 mmol, 2.13 equiv) of methyltriphenylphosphonium bromide in four portions over 15 min. After stirring for 2 h the solution was maintained at 50 °C for 20 min and cooled to 0 °C. To the yellow slurry was added 10.0 g (24.4 mmol) of crystalline **6** in 25 mL of THF over a period of 5–10 min. Vigorous stirring was maintained for 4.5 h, during which time the reaction came to room temperature and showed only one spot at R_f 0.9 (1:1 hexane–ether) corresponding to 1-methylene-5-(2′-trityloxyethyl)spiro[3.4]nonane (**14**) with none of the starting material (R_f 0.6) present. The mixture was poured into 3 vol of water and extracted twice with ether. The ether fractions were combined, washed twice with water, dried over magnesium sulfate, and concentrated in vacuo to yield a semisolid which was tritrated with hexane and filtered through a 3-in. column of Florisil to remove the precipitated triphenylphosphine oxide. The column was washed with 1.5 L of hexane (until no further product came off) and the combined fractions were concentrated in vacuo to yield 9.7 g of crude **14** as a clear, colorless glass. Some samples kept for over 6 months showed crystals in the glass but brief attempts to

recrystallize the sample failed. The purity of this material was such that it could be used for further transformations without additional purification (one spot by TLC, R_f 0.8, 9:1 hexane–ether): NMR (CCl_4) 0.9–2.0 (11 H, m), 2.4 (2 H, br t, J = 8 Hz), 3.0–3.25 (2 H, m), 4.52 (1 H, t, J = 2 Hz), 4.61 (1 H, t, J = 1 Hz), 7.0–7.5 (15 H, m); IR (CCl_4) 3100, 3070, 2950, 2870, 1660, 1070, 875, 705, 695; MS 408 (0.001), 260 (16), 245 (7), 244 (50), 243 (100), 183 (20), 167 (20), 166 (14), 165 (42), 149 (12), 105 (38), 91 (12), 77 (15). Anal. Calcd for $C_{30}H_{32}O$: mol wt, 408.2453. Found: mol wt, 408.2438. To a 0 °C solution of the crude methylenecyclobutane **14** in 35 mL of dichloromethane was added a slurry of 6.75 g (37.5 mmol, 1.54 equiv) of 85% *m*-chloroperbenzoic acid in 40 mL of dichloromethane over 10 min. The resulting solution was stirred for 8 h, during which time it came to room temperature and precipitated a considerable amount of white solid. The reaction showed to be complete by TLC (R_f 0.6) and was diluted with 200 mL of ether, washed with saturated aqueous sodium carbonate solution, dried over sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 10.0 g of 1-epoxymethylene-5-(2′-trityloxyethyl)-spiro[3.4]octane (**15**) as a clear colorless glass. This material again showed itself to be a single spot by TLC and quite clean by NMR and thus was used immediately without further purification: NMR (CCl_4) 0.7–2.4 (13 H, m), 2.50 (1 H, d, J = 5 Hz), 2.70 (1 H, d, J = 5 Hz), 2.9–3.3 (2 H, m), 7.0–7.5 (15 H, m); IR (CCl_4) 3110, 3100, 3070, 2960, 2940, 2870, 1070, 705, 695.

To a solution of the crude epoxide in 50 mL of benzene and 4.5 mL (4.5 g, 25.0 mmol, 1.0 equiv) of dry HMPA was added 2.2 g (25.3 mmol, 1.0 equiv) of anhydrous powdered lithium bromide (dried overnight at 120 °C under 0.5-mm vacuum), at which time the solution became a bright deep yellow. This mixture was immersed in 100 °C oil bath and refluxed for 3 h, at which time TLC showed only a spot at R_f 0.45. The mixture was cooled, diluted with ether, washed three times with water, dried over magnesium sulfate, and concentrated in vacuo to yield a yellow-brown oil, from which was obtained 7.55 g of crystalline **12**, mp 122 °C (hexane). Further purification of the mother liquor by PLC yielded an additional 300 mg of the spiro ketone (R_f 0.5 in 1:1 ether–hexane) (7.85 g total, 18.5 mmol, 76%) and 450 mg (0.89 mmol, 3.6%) of a second material (R_f 0.6), mp 154–157 °C (hexane). From its NMR and IR spectra (see below) this second material was assigned 1-bromomethylene-5-(2′-trityloxyethyl)spiro[3.4]octan-1-ol. Utilizing the 25.8-g sample of the previous crude cyclobutanone (45% pure), **14** was prepared employing 3.90 equiv of triphenylphosphonium methylide and **15** by employing 2.81 equiv of MCPBA to give after rearrangment a 73% yield of **12**: NMR (CCl_4) 1.0–2.25 (15 H, m), 2.9–3.3 (2 H, m), 7.0–7.5 (15 H, m). The addition of 7.3 mg of $Eu(dpm)_3$ (14 mol %) showed a multiplet (2 H) at 5.74–6.0 and an AB pattern [4.2 (1 H, d, J = 18 Hz), 4.5 (1 H, d, J = 17 Hz)] as the only signals significantly shifted downfield. The rest of the spectrum (methylene region) was spread over 1.3–3.5: ^{13}C NMR ($CDCl_3$) 217.7, 143.5, 127.8, 126.9, 126.0, 86.0, 62.5, 49.8, 45.2, 44.0, 38.1, 37.0, 33.4, 31.1, 30.4, 21.3; IR (CCl_4) 3100, 3070, 3050, 2970, 2870, 1745, 1070, 705, 695; MS (70 eV) 425 (0.35), 424 (1), 348 (1), 347 (5), 260 (1.5), 259 (7), 245 (3), 244 (20), 243 (100), 242 (3), 241 (3), 239 (2), 228 (2), 215 (2), 183 (10), 167 (5), 166 (6), 165 (22), 105 (15), 91 (13), 81 (5), 79 (7). Anal. Calcd for $C_{30}H_{32}O_2$: C, 84.85; H, 7.60; mol wt, 424.2402. Found: C, 85.10; H, 7.60; mol wt, 424.2400.

1-Bromomethylene-5-(2′-trityloxyethyl)spiro[3.4]octan-1-ol: NMR ($CDCl_3$) 1.1–2.1 (13 H, m), 2.28 (1 H, br s), 3.12 (2 H, t, J = 6 Hz), 3.50 and 3.62 (2 H, AB, J_{AB} = 15 Hz), 7.0–7.6 (15 H, m); IR (CCl_4) 3550, 3400, 3080, 3050, 3010, 2950, 2870, 1590, 1480, 1445, 1220, 1060, 700; MS 424 (1), 348 (3), 388 (2), 264 (2), 263 (2), 261 (3), 260 (6), 259 (5), 245 (10), 244 (50), 243 (100), 242 (6), 241 (5), 171 (12), 167 (19), 166 (15), 165 (50), 77 (15). No M^+ was observed.

A 350-mg (0.69 mmol) sample of the bromohydrin was mixed with 3 mL of dry benzene, 50 mg (0.67 mmol, 1 equiv) of anhydrous lithium carbonate, and 120 μL (120 mg, 0.67 mmol, 1 equiv) of HMPA, and the solution was refluxed for 12 h. After cooling and workup as above, the crude 320 mg was purified by PLC in 1:1 ether–hexane to yield 200 mg (0.47 mmol) of the desired spiro ketone in addition to 28 mg (0.055 mmol) of recovered bromohydrin for a 68% conversion and 73% yield.

Preparation of 12 via Dimethylsulfonium Methylide. A suspension of 55 mg (1.1 mmol, 2.24 equiv) of a 50% dispersion of sodium hydride in mineral oil in 1 mL of Me_2SO was heated at 70 °C for 1 h and cooled, 1 mL of THF was added, and the solution was further cooled to 0 °C. To this was added 250 mg (1.25 mmol, 2.56 equiv) of trimethylsulfonium iodide in 1.2 mL of Me_2SO, followed 2–3 min later by 200 mg (0.49 mmol) of **6** in 0.5 mL of THF. After 30 min the bath was removed and the reaction allowed to warm to room temperature over 1.5 h. The reaction mixture was then diluted with water and extracted with ether; the organic layer was dried over sodium sulfate and potassium carbonate and concentrated in vacuo to yield 250 mg of a slightly smelly pale yellow glass. This material showed a spot in TLC at the same R_f (0.55 in 3:2 hexane–ether) as the starting cyclobutanone in addition to mineral oil; however, the absence of a carbonyl absorption in the IR showed the compound to be the epoxide. The NMR (CCl_4) was identical with that reported above, with the exception that the AB patterns were at 2.43 (J = 6 Hz) and 2.64 (J = 6 Hz).

This material was treated as above with 50 mg (0.57 mmol, 1.17 equiv) of lithium bromide and 100 μL (100 mg, 0.56 mmol, 1.16 equiv) of HMPA in 3 mL of benzene and refluxed for 12 h. Workup as above and PLC in 1:1 ether–hexane yielded 135 mg (0.32 mmol, 65%, R_f 0.5) of the same spiro ketone as was obtained by the alternate route through the Wittig ylide as described above.

Preparation of (3ξ*,5*S,6*R**)-3-(*p*-Tolylsulfinyl)-6-(2′-trityloxyethyl)spiro[4.4]nonan-2-one (18).** To a refluxing suspension of 3.30 g (19.6 mmol, 1.1 equiv) of methyl *p*-tolylsulfinate[31] and 1.71 g (35.7 mmol, 2.1 equiv) of a 50% dispersion of sodium hydride in mineral oil in 35 mL of DME was added 7.17 g (16.9 mmol) of **12**. The mixture was maintained at a gentle reflux until the cessation of hydrogen evolution (approximately 45 min) and then cooled, and the excess hydride was destroyed with absolute ethanol. The mixture was then poured into saturated aqueous ammonium chloride and extracted twice with ether; the organic fractions were combined and dried with sodium sulfate. Concentration in vacuo yielded 11.5 g which was purified by HPLC (ether–hexane, 4:6) to yield from tubes 42–72 8.69 g (91.4%) of an off-white foam, typically melting in the range 86–96 °C. No attempt to further purify the mixture of diastereoisomers was made.

Care must be taken with the reflux to see that it does not become too vigorous due to a sudden increase in the rate of evolution of hydrogen after 15–30 min, after which the rate falls off sharply. In addition, this material must be kept cold and/or used immediately to prevent substantial decomposition: NMR (CCl_4) 0.9–2.6 (13 H, m), 2.4 (3 H, s), 2.9–3.3 (3 H, m), 7.0–7.5 (19 H, m); IR (CCl_4) 3080, 3060, 2960, 2895, 1745, 1570, 1490, 1450, 1170, 1090, 1070, 710.

Preparation of (5*R,6*R**)-6-(2′-Trityloxyethyl)spiro[4.4]-non-3-en-2-one (19).** A solution of 30 mg (0.053 mmol) of sulfoxide **18** in 1 mL of carbon tetrachloride was heated at 60 °C for 7 h. After cooling, the reaction mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate solution. The organic fraction was dried over potassium carbonate and the solvent removed at reduced pressure to yield 33 mg of oil. Purification by PLC yielded 20 mg (89%, R_f 0.5 in 50% ether–hexane) of the desired product: mp 141.5–142.5 °C (methanol–carbon tetrachloride); NMR (CCl_4) 1.0–2.0 (10 H, m), 2.12 (1 H, d, J = 17 Hz), 3.04 (2 H, t, J = 6 Hz), 5.90 (1 H, d, J = 6 Hz), 7.0–7.45 (16 H, m); IR (CCl_4) 3060, 3010, 2940, 2880, 1710, 1580, 1495, 1460, 1080, MS 422 (2), 346 (14), 260 (7), 259 (30), 245 (7), 244 (35), 243 (100), 228 (5), 183 (20), 165 (32), 105 (21), 91 (2), 77 (3). Anal. Calcd for $C_{30}H_{30}O_2$: mol wt, 422.2246. Found: mol wt, 422.2248.

Preparation of (5*R,6*R**)-6-(2′-Trityloxyethyl)-3-methylthiospiro[4.4]non-3-en-2-one (20, R = CH_3).** To a 0 °C slurry of 54 mg (1.1 mmol, 1.65 equiv) of a 50% dispersion of sodium hydride in mineral oil in 2 mL of DME was added 386 mg (0.67 mmol) of **18** in 2 mL of DME. After 30 min ~130 mg (130 μL, 1.0 mmol, 1.5 equiv) of methylthio methanesulfonate[32] in 150 μL of HMPA was added and stirring continued for 6 h, during which time the reaction came to room temperature. The reaction mixture was diluted with ether, extracted with saturated aqueous sodium bicarbonate solution, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 400 mg of crude oil. Purification by PLC in 1:1 hexane–ether yielded 148 mg of the methylthio enone (R_f 0.4, 46%) as a glass: NMR (CCl_4) 1.0–2.50 (14 H, m with a singlet at 3.25), 3.04 (2 H, t, J = 7 Hz), 6.50 (1 H, s), 7.0–7.6 (15 H, m); IR (CCl_4) 3110, 3080, 3060, 2940, 2880, 1715, 1490, 1450, 1080, 710; MS 468 (0.1), 264 (2), 259 (4), 244 (45), 243 (100), 228 (10), 226 (13), 183 (16), 167 (17), 165 (50), 153 (13), 139 (13), 105 (22), 91 (13), 77 (10). Anal. Calcd for $C_{31}H_{32}O_2S$: mol wt, 468.2123. Found: mol wt, 468.2104.

Preparation of (3ξ,5*S,6*R**)-6-(2′-Acetoxyethyl)-3-(*p*-tolylthio)spiro[4.4]nonan-2-one (21, R = Ac).** To a solution of 8.69 g (15.5 mmol) of **18** in 32 mL of acetic anhydride and 125 mL of dry acetonitrile at 0 °C was added 3.46 g (18.4 mmol, 1.2 equiv) of freshly prepared anhydrous stannous chloride. The reaction mixture was stirred for 24 h, during which time it warmed to room temperature. It was then poured into saturated aqueous sodium bicarbonate solution and extracted with ether. The ethereal layer was dried over sodium sulfate and concentrated under reduced pressure. The crude material was triturated three times with 50 mL of hexane; the supernatants were combined and concentrated in vacuo to yield 5.6 g

of crude semisolid. Purification by HPLC yielded 3.24 g (9.4 mmol, 61%) of the desired acetoxy ketone as a pale yellow oil: NMR ($CDCl_3$) 0.9–2.5 (19 H, m with singlets at 2.08 and 2.36), 3.45–3.75 (1 H, m), 4.0–4.25 (2 H, m), 7.16 (2 H, d, J = 8 Hz), 7.45 (2 H, d, J = 8 Hz); IR (CCl_4) 3020, 2960, 2870, 1740, 1480, 1360, 1240, 1030, 905; MS 348 (3), 347 (10), 346 (43), 303 (1), 222 (6), 164 (3), 163 (10), 162 (9), 151 (6), 150 (30), 149 (10), 140 (10), 139 (4), 136 (10), 135 (6), 134 (25), 133 (12), 109 (6), 107 (20), 95 (40), 91 (100), 77 (40), 43 (90). Anal. Calcd for $C_{20}H_{26}O_3S$: mol wt, 346.1603. Found: mol wt, 346.1606.

Preparation of (3aS^*,8aR^*)-6-(*p*-Tolylthio)-1,2,3,3a,4,-5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-one (22). To a 0 °C solution of 3.04 g (8.8 mmol) of (3ξ,5S^*,6R^*)-6-(2′-acetoxyethyl)-3-(*p*-tolylthio)spiro[4.4]nonan-2-one in 20 mL of methanol was added 11 mL (11 mmol, 1.25 equiv) of 1 M aqueous potassium hydroxide solution. An additional 90 mL of methanol was added to clarify the solution. After 2 h TLC showed no starting material (R_f 0.6 in 1:1 ether–hexane) and only a new spot at R_f 0.1. The solution was concentrated in vacuo to approximately 50 mL, diluted with brine, and extracted twice with ethyl acetate. The combined organic fractions were dried with sodium sulfate and concentrated at the water aspirator to yield 2.9 g of the crude alcohol (~100%). This material invariably also indicated some decomposition by its odor and, thus, was used immediately due to the apparent instability: NMR ($CDCl_3$) 1.0–2.6 (18 H, m with a s at 2.36), 3.4–3.8 (3 H, m), 7.12 (2 H, d, J = 8 Hz), 7.40 (2 H, d, J = 8 Hz); IR ($CHCl_3$) 3600, 3450, 3000, 2960, 2870, 1740, 1490, 1240, 1050, 910.

The 2.9 g of alcohol was dissolved in 25 mL of dichloromethane and cooled to −30 °C. To this was added 1.6 mL (1.15 g, 11.5 mmol, 1.30 equiv) of triethylamine and then 0.725 mL (1.05 g, 9.25 mmol, 1.05 equiv) of methanesulfonyl chloride dropwise over 5 min. The solution was stirred for 1 h at −30 °C, during which time it developed a substantial amount of a white precipitate. The mixture was diluted with water and extracted with ethyl acetate. The organic fraction was washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, and concentrated in vacuo to yield 3.6 g (~100%) of very clean (NMR), almost colorless oil as a mixture of isomers. Early attempts at purification by PLC gave a low recovery of material. Thus, it was used immediately without further purification: NMR ($CDCl_3$) 1.0–2.5 (16 H, m with a singlet at 2.32), 2.98 (3 H, s), 3.5–3.8 (1 H, overlapping dd in unequal amounts), 4.1–4.4 (2 H, m), 7.08 (2 H, d, J = 8 Hz), 7.36 (2 H, d, J = 8 Hz); IR (CCl_4) 3020, 2950, 2860, 1740, 1490, 1370, 1350, 1080.

The crude mesylate above was dissolved in 125 mL of THF, cooled to 0 °C, and treated with 2.3 g (18.7 mmol, 2.1 equiv) of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), followed by 20 mL of dimethylformamide. The cooling bath was removed, the mixture was stirred for 48 h, at which time TLC showed that only a trace of the starting mesylate (R_f 0.2 in 2:1 ether–hexane) remained, and the reaction was diluted with water and extracted three times with ether. The combined organic fractions were washed with aqueous 3 N hydrochloric acid, water, and saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and concentrated in vacuo to yield a yellow oil. Purification by HPLC with 3:1 hexane–ether yielded 1.38 g (4.8 mmol, 55% from **21**, R = Ac) from tubes 31–70 of the desired tricyclic ketone, mp 55–57 °C (hexane). While upon further recrystallization the melting point rose to 64–65 °C, the material of the lower melting point was normally quite satisfactory for further work: NMR (CCl_4) 1.0–2.50 (18 H, m with an s at 2.36), 7.08 (2 H, d, J = 8 Hz), 7.36 (2 H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$) 215.28, 138.82, 136.72, 129.43, 127.22, 62.70, 47.29, 46.51, 46.29, 46.07, 36.62, 35.19, 28.50, 25.96, 21.71, 21.16; IR (CCl_4) 3020, 2970, 2860, 1745, 1490, 1450, 14300, 1050; MS 288 (5), 287 (15), 286 (82), 230 (15), 194 (5), 183 (8), 166 (6), 165 (4), 164 (10), 163 (20), 162 (6), 161 (6), 160 (5), 149 (18), 138 (8), 136 (6), 135 (12), 134 (100), 133 (57), 132 (7), 125 (8), 124 (50), 123 (20), 122 (6), 121 (6), 120 (6), 119 (28), 108 (6), 107 (20), 106 (15), 105 (36), 95 (17), 94 (6), 93 (45), 92 (26), 91 (100), 79 (75), 77 (55), 67 (55), 55 (35). Anal. Calcd for $C_{18}H_{22}OS$: C, 75.52; H, 7.69; S, 11.18; mol wt, 286.1391. Found: C, 75.56; H, 7.77; S, 11.18; mol wt, 286.1392.

Preparation of the Ethylene Glycol Ketal of (3aS^*,8aR^*)-6-(*p*-Tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-one (25). To a solution of 60 mg (0.21 mmol) of ketone in 2 mL of benzene was added 0.25 mL of ethylene glycol (dried over 4Å molecular sieves) and 10 mg of *p*-toluenesulfonic acid. The solution was refluxed with azeotropic removal of water for 5 h, cooled, diluted with ether, washed with water, dried over sodium sulfate, and concentrated in vacuo to yield 80 mg of yellow oil. Purification by PLC yielded 45 mg (0.135 mmol, 65%, R_f 0.7 in 2:1 hexane–ether) of the desired ketal and 5 mg (0.017 mmol, 8%) of the starting ketone, giving a corrected yield of 70%: NMR (CCl_4) 0.9–2.4 (18 H, m with a singlet at 2.32), 3.7–4.2 (4 H, m), 7.0 (2 H, d, J = 8 Hz), 7.32 (2 H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$) 138.26, 127.08, 129.16, 129.01, 116.93, 65.66, 64.72, 62.18, 49.51, 48.73, 46.87, 46.33, 36.15, 35.17, 28.57, 26.56, 21.97, 21.18; IR (CCl_4) 3060, 3020, 2950, 2870, 1730 (br), 1490, 1450, 1290, 1180, 1170, 1045, 980, 950, 890; MS (40 eV) 332 (6), 331 (22), 330 (100), 286 (2), 244 (5), 243 (19), 223 (8), 208 (12), 207 (80), 179 (15), 155 (10), 91 (15). Anal. Calcd for $C_{20}H_{26}O_2S$: mol wt, 330.1753. Found: mol wt, 330.1661.

Preparation of the 2-Mercaptoethanol Ketal of (3aS^*,8aR^*)-6-(*p*-Tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-one (26). To a solution of 65 mg (0.23 mmol) of the ketone in 0.5 mL of ether was added 150 μL (2.1 mmol, 9.5 eq) of distilled 2-mercaptoethanol and 3 drops of freshly distilled colorless boron trifluoride etherate. The mixture was stirred for 2 h, diluted with ether, washed with water and saturated aqueous sodium bicarbonate, and dried with sodium sulfate and potassium carbonate. Concentration in vacuo yielded 85 mg of crude, unpleasant smelling material from which was obtained by PLC in 2:1 hexane–ether 53 mg (0.154 mmol, R_f 0.7, 66%) of the ketal as a colorless odorless oil and 10 mg (0.035 mmol, 15%) of the starting ketone (R_f 0.6). Thus the corrected yield is 80%. From the sharpness of the signals in the NMR and a single set of signals in the ^{13}C NMR, this material is apparently a single isomer, although assignment of which one cannot be made: NMR (CCl_4) 0.9–2.5 (18 H, m with a singlet at 2.34), 2.75–3.2 (2 H, m), 3.80 (1 H, dt, J = 5, 8 Hz), 4.36 (1 H, ddd, J = 3, 5, 9 Hz), 7.00 (2 H, d, J = 8 Hz), 7.32 (2 H, d, J = 8 Hz); ^{13}C NMR 138.21, 137.33, 129.02, 102, 70.06, 63.85, 53.29, 50.45, 49.43, 46.25, 37.60, 35.74, 33.29, 28.36, 27.13, 22.00, 21.17; IR (CCl_4) 3020, 2940, 2860, 1490, 1450, 1260, 1155, 1080, 945, 880; MS (40 eV) 349 (3), 348 (7), 347 (25), 346 (100), 318 (10), 287 (4), 286 (15), 195 (25), 151 (30), 135 (50), 124 (50), 91 (100). Anal. Calcd for $C_{20}H_{26}OS_2$: mol wt, 346.1425. Found: mol wt, 346.1424.

Preparation of (3aS^*,8aR^*)-5-Methylene-6-(*p*-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulene (33). To a slurry of 36 mg (0.90 mmol, 3.21 equiv) of potassium hydride in 1.2 mL of THF was added 390 mg (1.09 mmol, 3.89 equiv) of methyltriphenylphosphonium bromide. The bright yellow mixture was stirred for 2 h at room temperature and then for 20 min at 50 °C and cooled to 0 °C, and 80 mg (0.28 mmol) of the ketone in 0.2 mL of THF was added. The mixture was stirred for 5 h, during which time it came to room temperature. After 30 min at 50 °C, the mixture was diluted with ether and washed with water. The organic layer was dried over magnesium sulfate and concentrated in vacuo to yield 120 mg of crude olefin and phosphine oxide. Purification by PLC yielded 70 mg (0.255 mmol, 91%, R_f 0.6 in 1:9 ether–hexane) as a colorless oil: NMR (CCl_4) 0.9–2.2 (14 H, m), 2.2–2.55 (4 H, m), 4.90 (1 H, br s), 5.22 (1 H, br s), 7.0 (2 H, d, J = 8 Hz), 7.32 (2 H, d, J = 8 Hz); IR (CCl_4) 3060, 3020, 2940, 2860, 1490, 1450, 1290, 1190, 1165, 1045, 890, 710; MS 286 (4), 285 (12), 184 (60), 269 (4), 255 (4), 228 (3), 227 (13), 215 (3), 214 (12), 162 (7), 161 (35), 160 (11), 145 (9), 133 (17), 124 (21), 123 (18), 105 (50), 93 (28), 92 (20), 91 (100). Anal. Calcd for $C_{19}H_{24}S$: mol wt, 284.1599. Found: mol wt, 284.1594.

Preparation of (3aS^*,5S^*,8aR^*)-5-Epoxymethylene-6-(*p*-tolylthio)-1,2,3,3a,4,5,6,7,8,8a,-decahydro-3a,6-methanoazulene (31). A slurry of 58 mg (1.21 mmol, 6.3 equiv) of a 50% sodium hydride dispersion in 0.7 mL of Me_2SO was heated at 70 °C for 40 min, cooled to room temperature, diluted with 0.7 mL of THF, and cooled to 0–5 °C when a solution of 280 mg (1.4 mmol, 7.4 equiv) of trimethylsulfonium iodide in 0.7 mL of Me_2SO was added. Two minutes later a solution of 55 mg (0.19 mmol) of the ketone in 0.25 mL of THF was added and the reaction allowed to warm to room temperature over 2 h. The mixture was then quenched by dilution with water and extraction with ether. The organic layers were dried over sodium sulfate and potassium carbonate and concentrated in vacuo to yield 75 mg of an oil, which was purified by PLC to yield 42 mg (0.14 mmol, 63%) of an epoxide as a colorless oil, R_f 0.7 (2:1 hexane–ether). The crude NMR is very clean and the material can be used without purification, especially since in some preparations new peaks appeared around δ 4.0 after purification: NMR (CCl_4) 1.0–2.4 (18 H, m), 2.62 (1 H, d, J = 6 Hz), 3.30 (1 H, d, J = 6 Hz), 7.04 (2 H, d, J = 8 Hz), 7.28 (2 H, d, J = 8 Hz); IR (CCl_4) 3020, 2960, 2860, 1490, 1450, 1360, 1030; MS 302 (2), 301 (6), 300 (25), 286 (3), 285 (2), 284 (7), 273 (3), 272 (17), 244 (4), 243 (8), 219 (8), 196 (3), 195 (6), 187 (7), 186 (5), 149 (17), 148 (17), 148 (17), 133 (15), 131 (10), 124 (22), 123 (18), 122 (3), 121 (11), 120 (12), 119 (32), 105 (35), 93 (25), 92 (35), 91 (100), 81 (25), 79 (53), 77 (50). Anal. Calcd for $C_{19}H_{24}OS$: mol wt, 300.1548. Found: mol wt, 300.1528.

Preparation of (3aS^*,5S^*,8aR^*)-5-Phenylthiomethyl-6-(*p*-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-ol (30). Via the Epoxymethylene. To a slurry of 26 mg (0.5 mmol, 5.2 equiv) of a 50% sodium hydride dispersion in 0.5 mL of THF was

added 0.10 mL (107 mg, 0.98 mmol, 10 equiv) of thiophenol. After 20 min, 29 mg (0.096 mmol) of **31** in 0.2 mL of THF was added to the white slurry and the mixture stirred overnight, during which time it warmed to room temperature. The mixture was diluted with ether, washed with aqueous 1 M potassium hydroxide solution, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 40 mg of the crude alcohol. Purification by PLC yielded 30 mg (0.073 mmol, 76%) of the alcohol as a colorless glass: R_f 0.6 in 3:1 hexane–ether; NMR (CCl_4) 0.9–2.6 (18 H, m with a singlet at 2.32), 3.20 (1 H, d, J = 13 Hz), 3.67 (1 H, d, J = 13 Hz), 6.9–7.6 (10 H, m); IR (CCl_4) 3600, 3500, 3050, 3020, 2940, 2860, 1580, 1480, 1475, 1450, 1435, 1120, 1020, 690; MS 412 (1), 411 (2), 410 (7), 313 (3), 312 (13), 299 (6), 288 (4), 287 (16), 286 (21), 285 (18), 283 (12), 244 (2), 243 (8), 242 (27), 226 (5), 213 (4), 191 (7), 177 (12), 149 (23), 147 (7), 145 (10), 135 (20), 133 (12), 131 (12), 124 (48), 123 (36), 121 (20), 120 (15), 110 (12), 109 (12), 108 (5), 107 (18), 106 (10), 105 (30), 91 (100). Anal. Calcd for $C_{25}H_{30}OS_2$: mol wt, 410.1738. Found: mol wt, 410.1730.

Via Lithiothioanisole. To a 0 °C solution of 211 mg (200 μL, 1.70 mmol, 2.34 equiv) of thioanisole and 220 mg (1.96 mmol, 2.70 equiv) of 1,4-diazabicyclo[2.2.2]nonane in 2 mL of THF was added 1 mL (1.4 mmol, 1.9 equiv) of 1.4 N n-butyllithium solution in hexane, and the mixture was stirred for 1.5 h. To this was added over 5 min 208 mg (0.727 mmol) of **22** in 0.5 mL of THF. The reaction mixture was allowed to warm to room temperature over 3 h, diluted with ether, washed with water, dried with potassium carbonate, and concentrated in vacuo to yield 280 mg of crude alcohol. Purification by PLC in 4:1 hexane–ether yielded 208 mg (0.51 mmol, 71%) of the phenylthiomethyl alcohol (R_f 0.4) and 35 mg (0.12 mmol, 17%) of the starting ketone (R_f 0.3). Thus the yield is 85%, allowing for recovered starting material.

Preparation of (3a*R,8a*R**)-6-Phenylthiomethyl-1,2,3,3a,4,5,6,7,8,8a-decahaydro-3a,6-methanoazulen-5-one (32).** To a solution of 40 mg (0.1 mmol) of alcohol **30** in 0.5 mL of benzene was added 40 mg (0.22 mmol, 2.2 equiv) of p-toluenesulfonic acid monohydrate and the solution heated to 75 °C. After 15 min, TLC showed some starting material (R_f 0.06 in 3:1 hexane–ether) in addition to product (R_f 0.5). After an additional 15 min the solution was diluted with ether, washed with 1 M aqueous potassium hydroxide solution, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 32 mg of the crude keto phenyl sulfide. Purification by PLC yielded 21 mg (0.76 mmol, 76%) of the desired product: NMR (CCl_4) 0.8–2.4 with AB at δ 2.21 and 1.87 (J = 17 Hz, 15 H, m), 3.07 (2 H, br s), 6.95–7.40 (5 H, m); ^{13}C NMR ($CDCl_3$) 214.31, 137.24, 129.13, 125.8, 53.55, 50.13, 45.87, 45.05, 40.02, 39.25, 35.16, 33.62, 29.15, 22.25, 21.70; IR (CCl_4) 3080, 2960, 2940, 2840, 1740, 1580, 1540, 1480, 1080, 1020; MS 288 (7), 287 (23), 286 (95), 258 (8), 243 (9), 195 (5), 186 (6), 178 (10), 177 (70), 149 (29), 136 (13), 135 (100), 134 (21), 133 (25), 122 (22), 121 (22), 110 (26), 109 (18), 107 (26), 105 (34), 93 (34), 91 (42), 81 (26), 79 (37), 77 (33). Anal. Calcd for $C_{18}H_{22}OS$: mol wt, 286.1391. Found: mol wt, 286.1395.

Preparation of a "Salt Free" Solution of Triphenylphosphonium Methylide. To a slurry of 45 mg (1.1 mmol) of potassium hydride in 1 mL of THF was added 450 mg (1.25 mmol, 1.13 equiv) of methyltriphenylphosphonium bromide, and the mixture was stirred for 2 h at 25 °C and 30 min at 50 °C. The bright yellow slurry was cooled and added to 0.5 mL of benzene in a centrifuge tube capped with a septum. The slurry was centrifuged to give a bright yellow solution which was used without further handling.

Preparation of (3a*R,8a*R**)-5-Methylene-6-phenylthiomethyl-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulene (34).** To 0.5 mL of the salt free phosphonium methylide solution above (~0.3 mmol, 8.3 equiv) was added 10 mg (0.036 mmol) of ketone **32** in 0.25 mL of THF, and the solution was heated to 80 °C for 3 h, at which time TLC showed only the desired methylene compound (R_f 0.9, 3:1 hexane–ether). The solution was diluted with ether and washed with water, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo. A carbon tetrachloride solution of the crude olefin was filtered through Florisil and concentrated in vacuo to yield 15 mg of crude olefin. Purification by PLC yielded 8 mg (0.029 mmol, 81%) of the desired methylene compound: NMR (CCl_4) 1.0–2.7 (15 H, m), 3.10 (2 H, br s), 4.85 (1 H, br s), 4.95 (1 H, br s), 7.0–7.45 (5 H, m); IR (CCl_4) 3000, 2960, 2920, 2870, 1475, 1435, 1360, 1030; MS 285 (3), 284 (15), 190 (25), 177 (12), 175 (10), 165 (8), 162 (10), 161 (100), 133 (19), 124 (12), 105 (16), 91 (39), 81 (14), 79 (19), 77 (23). Anal. Calcd for $C_{19}H_{24}S$: mol wt, 284.1609. Found: 284.1609.

Preparation of (3a*S,5*R**,8a*R**)-5-Hydroxymethyl-6-(*p*-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-ol (36).** To a solution of 160 mg (0.56 mmol) of **33** in 2 mL of pyridine was added 180 mg (0.71 mmol, 1.26 equiv) of osmium tetraoxide. The solution became black within 3 min. After 3 h, 3 g (30 mmol, 42 equiv) of solid sodium bisulfite was added and the mixture stirred for 3 h, after which time it was partitioned between ethyl acetate and water. The ethyl acetate was dried with sodium sulfate and concentrated in vacuo to yield 200 mg of a colorless diol as an oil. Purification by PLC in 4:1 dichloromethane–ether yielded 4 mg (0.014 mmol, 2.5%, R_f 0.9) of the starting olefin and 164 mg (0.54 mmol, 97%) of the desired diol as a clear colorless oil: NMR (CCl_4) 0.8–2.0 (14 H, m), 2.3–2.45 (4 H, m with singlet at 2.36), 3.0 (1 H, br s), 3.38 (2 H, br s), 7.08 (2 H, d, J = 8 Hz), 7.36 (2 H, d, J = 8 Hz); IR (CCl_4) 3480, 3450, 3020, 2950, 2870, 1490, 1450, 1340, 1290, 1210, 1060; MS 320 (5), 319 (10), 318 (30), 288 (3), 287 (4), 286 (4), 284 (24), 279 (6), 243 (19), 195 (6), 177 (12), 167 (10), 149 (24), 132 (23), 124 (35), 121 (100), 95 (21), 92 (40), 91 (50). Anal. Calcd for $C_{19}H_{26}O_2S$: mol wt, 318.1653. Found: mol wt, 318.1665.

Preparation of (3a*R,8a*R**)-6-Acetoxymethyl-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-one (38).** To a solution of 114 mg (0.36 mmol) of **36** and 0.25 mL of trimethyl orthoacetate in 1 mL of benzene was added 2 mg of p-toluenesulfonic acid monohydrate and the mixture stirred overnight. The mixture was diluted with ether, washed with saturated aqueous sodium bicarbonate solution, dried with sodium sulfate and potassium carbonate, and concentrated in vacuo to yield 125 mg of the crude orthoacetate **37** as a colorless oil: NMR (CCl_4, crude) 0.8–2.1 (m with a sharp singlet at 1.60), 2.3–2.6 (m with a singlet at 2.36); IR (CCl_4, crude) 2960, 2860, 1740 (weak), 1490, 1450, 1380, 1250, 1150, 1040, 860.

This sample was dissolved in 200 μL of carbon tetrachloride, placed in a 5-mm NMR tube, and cooled to −40 °C to freeze the sample. To this was added 100 μL of trifluoroacetic acid at −40 °C and the mixture shaken until homogeneous while warming to 25 °C. The progress of the reaction was monitored by periodic NMR investigation to observe the immediate disappearance of the δ1.67 methyl signal to be replaced by one at δ 2.9. The reaction was followed by the gradual disappearance of the δ 2.9 signal and its replacement by a typical acetate methyl signal at ~2.0. After 12 h the δ 2.9 signal was ~5% of its initial intensity, and the reaction mixture was poured into 5 mL of 3 N aqueous hydrochloric acid and stirred for 30 min. The aqueous mixture was extracted with ether. The organic fraction was dried with potassium carbonate and concentrated in vacuo to yield 65 mg of crude pale yellow oil. Purification by PLC with 2:1 hexane–ether yielded 50 mg (R_f 0.35) of a mixture of the desired rearranged keto acetate and the monoacetate of the starting diol in a ratio (NMR) of 2:1. Kügelrohr distillation [120 °C (0.07 mm)] separated the keto acetate from the nonvolatile hydroxy acetate, 40 mg (0.17 mmol, 48% conversion, 57% yield), and 20 mg of the hydroxy acetate (0.044 mmol, 17%).

Keto acetate 38: NMR (CCl_4) 1.3–2.4 (18 H, m with a singlet at 1.98), 3.98 (2 H, br s); IR (CCl_4) 2960, 2870, 1753, 1743, 1450, 1380, 1360, 1240, 1035; MS 236 (2), 218 (10), 193 (3), 177 (12), 176 (92), 175 (10), 174 (40), 156 (35), 135 (23), 134 (95), 133 (46), 132 (50), 119 (29), 105 (20), 43 (100). Anal. Calcd for $C_{14}H_{20}O_3$: mol wt, 236.1412. Found: mol wt, 236.1416.

(3a*S,5*R**,8a*R**)-5-(Acetoxymethyl)-6-(*p*-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-ol:** NMR (CCl_4) 1.3–2.5 (21 H, m with singlets at 2.06 and 2.36), 3.1 (1 H, br s), 3.90 (1 H, d, J = 12 Hz), 4.20 (1 H, d, J = 12 Hz), 7.1 (2 H, d, J = 8 Hz), 7.4 (2 H, d, J = 8 Hz); IR (CCl_4) 3480, 3060, 3020, 2950, 2860, 1742, 1490, 1450, 1380, 1360, 1225, 1040, MS 362 (5), 361 (17), 360 (74), 300 (3), 287 (7), 246 (6), 244 (17), 143 (100), 195 (2), 186 (5), 178 (12), 177 (85), 166 (4), 165 (35), 159 (24), 149 (25), 138 (38), 133 (19), 124 (82), 123 (27), 120 (15), 109 (5), 107 (13), 105 (17), 97 (7), 95 (24), 93 (23), 92 (15), 91 (89), 77 (24), 43 (80).

Preparation of (3a*R,8a*R**)-6-Acetoxymethyl-5-methylene-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulene (39).** To 0.5 mL (~0.3 mmol, 10 equiv) of the salt free phosphonium methylide solution was added 7 mg (0.03 mmol) of ketone **38** in 0.25 mL of THF. The solution was heated at 80 °C for 3 h until no further starting ketone (R_f 0.4 in 3:1 hexane–ether) was present and only acetoxy methylene (R_f 0.7) and hydroxy methylene (R_f 0.35, from reaction to cleave the acetate) were evident. The solution was cooled, diluted with ether, washed with water, dried with sodium sulfate, and concentrated with a water aspirator. The crude material was filtered through a small amount of Florisil with 50 mL of carbon tetrachloride. The filtrate was concentrated to yield 20 mg of crude olefin. Due to the partial hydrolysis of the acetate, the crude olefin mixture was treated with 0.25 mL each of acetic anhydride and pyridine for 8 h, diluted with ether, and washed with aqueous 3 N hydrochloric acid, followed by saturated aqueous sodium bicarbonate solution. The organic layer was dried with sodium sulfate and concentrated with

a water aspirator to yield 18 mg of the crude acetoxy olefin. Purification in 10:1 hexane–ether by PLC gave 4 mg of the desired olefin (R_f 0.4) (~50%): NMR (CCl_4) 0.9–2.6 (18 H, m with a singlet at 2.00), 4.0 (2 H, br s), 4.80 (1 H, br s), 4.90 (1 H, br s); IR (CCl_4) 2930, 2860, 1740, 1450, 1370, 1360, 1230, 1030; MS 235 (3), 234 (10), 192 (10), 175 (12), 174 (80), 161 (20), 159 (28), 146 (36), 145 (36), 133 (30), 132 (78), 131 (42), 119 (39), 118 (30), 117 (24), 107 (15), 106 (24), 105 (40), 43 (100). Anal. Calcd for $C_{15}H_{22}O_2$: mol wt, 234.1620. Found: mol wt, 234.1618.

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Registry No.—**5,** 64715-45-3; **6,** 64715-46-4; **12,** 64715-47-5; **13,** 64715-48-6; **14,** 64715-49-7; **15,** 64753-45-3; **18** (isomer I), 64715-50-0; **18** (isomer II), 64753-46-4; **19,** 64715-51-1; **20** (R = CH_3), 64715-52-2; **21** (R = Ac), 64715-53-3; **21** (R = H), 64715-54-4; **21** (R = Ms, isomer I), 64715-55-5; **21** (R = Ms, isomer II), 647-47-5; **22,** 64715-56-6; **25,** 64715-34-0; **26,** 64715-35-1; **30,** 64715-36-2; **31,** 64715-37-3; **32,** 64715-38-4; **33,** 64715-39-5; **34,** 64715-40-8; **36,** 64715-41-9; **37,** 64740-23-4; **38,** 64715-42-0; **39,** 64715-43-1; 2-(2′-hydroxyethyl)cyclopentanone, 24804-46-4; 2-cyclopentanone methyl carboxylate, 10472-24-9; 2-cyclopentanone ethyl carboxylate, 611-10-9; 2-bromoethyl acetate, 927-68-4; trityl bromide, 596-43-0; cyclopropyldiphenylsulfonium tetrafluoroborate, 33462-81-6; methyltriphenylphosphonium bromide, 1779-49-3; 1-bromomethylene-5-(2′-trityloxyethyl)spiro[3.4]octan-1-ol, 64740-19-8; trimethylsulfonium iodide, 2181-42-2; methyl *p*-tolylsulfinate, 672-78-6; acetic anhydride, 108-24-7; methanesulfonyl chloride, 124-63-0; ethylene glycol, 107-21-1; 2-mercaptoethanol, 60-24-2; thiophenol, 108-98-5; thioanisole, 100-68-5; trimethyl orthoacetate, 1445-45-0; (3a*S**,5*R**,8a*R**)-5-(acetoxymethyl)-6-(*p*-tolylthio)-1,2,3,3a,4,5,6,7,8,8a-decahydro-3a,6-methanoazulen-5-ol, 64715-44-2.

References and Notes

(1) For a review, see J. MacMillan and R. J. Pryce, *Phytochemistry*, **3,** 283 (1973).
(2) K. Mori, M. Shiozaki, N. Itaya, M. Matsui, and Y. Sumiki, *Tetrahedron*, **25,** 1293 (1969); W. Nagata, T. Wakabayashi, M. Narisada, Y. Hayase, and S. Kumata, *J. Am. Chem. Soc.*, **93,** 5740 (1971); H. J. E. Loewenthal and S. Schatzmiller, *J. Chem. Soc., Perkin Trans. 1,* 2149 (1975), and earlier references.
(3) For some recent efforts, see U. R. Ghatak, B. Sanyal, and S. Ghosh, *J. Am. Chem. Soc.*, **98,** 3721 (1976); H. J. E. Loewenthal and S. Schatzmiller, *J. Chem. Soc., Perkin Trans 1,* 944 (1976); H. O. House, R. C. Strickland, and E. J. Zaiko, *J. Org. Chem.*, **41,** 2401 (1976); L. J. Dolby and C. N. Skold, *J. Am. Chem. Soc.*, **96,** 3276 (1974).
(4) Cf. E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, **41,** 260 (1976); F. E. Ziegler and J. A. Kloek, *Tetrahedron*, **33,** 373 (1977); G. Jammaer, H. Martens, and G. Hoornaert, *ibid.*, **31,** 2293 (1975), M. Shimagaki and A. Tahara, *Tetrahedron Lett.*, 1715 (1975); D. J. Beames, T. R. Kose, and L. N. Manders, *Aust. J. Chem.*, **27,** 1269 (1974); H. O. House, D. G. Melillo, and F. J. Sauter, *J. Org. Chem.*, **38,** 741 (1973); D. J. Beames, J. A. Halleday, and L. N. Manders, *Aust. J. Chem.*, **25,** 127 (1972); K. Mori, Y. Nakahava, and M Matsui, *Tetrahedron*, **27,** 4907 (1971); L. J. Dolby, S. E. Esfandari, C. A. Elliger, and K. S. Marshall, *J. Org. Chem.*, **36,** 1277 (1971); F. E. Ziegler and M. E. Condon, *ibid.*, **36,** 3707 (1971); R. A. Finnegan and P. L. Bachman, *ibid.*, **36,** 3196 (1971); M. Kitadani, K. Ito, and A. Yoshikoshi, *Bull. Chem. Soc. Jpn.*, **44,** 3431 (1971); F. E. Ziegler and J. A. Kloek, *Tetrahedron Lett.*, 2201 (1971); R. A. Bell, R. E. Ireland, and L. N. Mander, *J. Org. Chem.*, **31,** 2536 (1966); R. B. Turner, K. H. Ganshirt, P. E. Shaw, and J. D. Tauber, *J. Am. Chem. Soc.*, **88,** 1776 (1966); G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *ibid.*, **87,** 1148 (1965); L. J. Dolby and R. H. Iwamoto, *J. Org. Chem.*, **30,** 2420 (1965).
(5) (a) For reviews see B. M. Trost, *Acc. Chem. Res.*, **7,** 85 (1974); *Pure Appl. Chem.*, **43,** 563 (1975; (b) B. M. Trost and L. S. Melvin, Jr., "Sulfur Ylides: Emerging Synthetic Intermediates", Academic Press, New York, N.Y., 1975.
(6) B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95,** 5298, 5311, 5321 (1973).
(7) B. M. Trost and P. H. Scudder, *J. Am. Chem. Soc.*, **99,** 7601 (1977).
(8) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions", Academic Press, New York, N.Y., 1968.
(9) For ring expansions of cyclobutanones to cyclopentanones, see (a) H. J. Liu and T. Ogino, *Tetrahedron Lett.*, 4937 (1973); (b) J. d'Angelo, *Bull. Soc. Chim. Fr.*, 333 (1975); (c) E. Nakamura and I, Kuwajima, *J. Am. Chem. Soc.*, **99,** 961 (1977). Subsequent to the completion of our work on this initial ring expansion, a report of a similar approach for ring expansion of cyclobutanones has appeared. See M. L. Leriverend, P. Leriverend, and H. Normant, *C. R. Hebd. Seances Acad. Sci.*, **280,** 791 (1975).
(10) B. Rickborn and R. M. Berkin, *J. Am. Chem. Soc.*, **93,** 1693 (1971).
(11) H. O. House and B. M. Trost, *J. Org. Chem.*, **30,** 2502 (1965).
(12) In the spiro[4.5]decanone system, formylation achieved the desired regioselectivity: J. A. Marshall and P. C. Johnson, *J. Org. Chem.*, **35,** 192 (1970).
(13) J. W. Wilt, R. G. Stein, and W. J. Wagner, *J. Org. Chem.*, **32,** 2097 (1967).
(14) R. M. Coates and H. D. Pigott, *Synthesis*, 319 (1975); H. J. Monteiro and J. P. De Souza, *Tetrahedron Lett.*, 921 (1975).
(15) B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95,** 6840 (1973); B. M. Trost, T. N. Salzmann, and K. Hiroi, *ibid.*, **98,** 4887 (1976).
(16) T. L. Moore, *J. Org. Chem.*, **32,** 2786 (1967).
(17) S. Iriuchijima, K. Maniwa, and G. Tsuchihasi, *J. Am. Chem. Soc.*, **96,** 4280 (1974).
(18) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. a. Webber, I. G. Wright, and E. M. Van Heyningen, *J. Org. Chem.*, **35,** 2430 (1970).
(19) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35,** 3195 (1970).
(20) H. Oediger, F. Moller, and K. Eiter, *Synthesis*, 591 (1972).
(21) R. Radeglia, G. Adam, and P. D. Hung, *Tetrahedron Lett.*, 605 (1976).
(22) E. Mosettig, V. Beglinger, F. Dolder, H. Lichti, P. Quitt, and J. A. Waters, *J. Am. Chem. Soc.*, **85,** 2305 (1963); C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge, and L. H. Briggs, *ibid.*, **83,** 3720 (1961).
(23) E. J. Corey and D. Seebach, *J. Org. Chem.*, **31,** 4097 (1966).
(24) P. Brownbridge and S. Warren, *Chem. Commun.*, 820 (1975).
(25) R. Evans, J. R. Hanson, and M. Siverns, *J. Chem. Soc., Perkin Trans. 1,* 1514 (1975); see also J. R. Hanson, G. Savona, and M. Siverns, *ibid.*, 2001 (1974).
(26) For a discussion of salt-free phosphorus ylides, see J. Rencroft and P. G. Sammes, *Q. Rev. Chem. Soc.*, **1,** 135 (1971); H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 701–709.
(27) H. O. House and D. G. Melillo, *J. Org. Chem.*, **38,** 1398 (1973).
(28) B. G. Ramsey and R. W. Taft, *J. Am. Chem. Soc.*, **88,** 3058 (1966).
(29) H. Booth, F. E. King, K. G. Mason, J. Parriek, and R. L. St. D. Whitehead, *J. Chem. Soc.*, 1050 (1959).
(30) This alcohol showed a great tendency to oligomerize upon purification or storage. It can be most conveniently utilized crude (i.e., without distillation). The oligomer could be hydrolyzed in 3 N aqueous hydrochloric acid at 100 °C for 2 h.
(31) A. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **67,** 894 (1948).
(32) M. A. Qasseem, N. A. J. Rogers, and A. A. Othman, *Tetrahedron*, **24,** 4535 (1968).