Applications of [2,3]-Sigmatropic Rearrangements to Natural Products Synthesis. The Total Synthesis of (\pm) -Bakkenolide-A (Fukinanolide)

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Abstract: A stereoselective total synthesis of the β -methylene- γ -lactone sesquiterpene, bakkenolide-A, is reported. The use of [2,3]-sigmatropic rearrangements within the context of constructing asymmetric quaternary centers has been explored. It has been found that steric factors appear to play a significant role in defining the levels of stereoselectivity observed in this class of molecular rearrangements.

As a general reaction type, [2,3]-sigmatropic rearrangements constitute an exceptionally versatile class of bond reorganization processes which have many obvious applications in organic synthesis. Over the last decade such rearrangements have been widely studied, and the generality of the basic process illustrated in eq 1 has been established by numerous in-

vestigations.⁴ Some of the permutations that have been reported for this atom pair allylic exchange process include the following cases in the rearrangement $1 \rightarrow 2$ for the atom pair X, Y: C-C,⁵ N-C,⁶ O-C,⁷ S-C,^{4,8} P-C,⁹ Cl⁺-C,¹⁰ N-O,¹¹ N-N,¹² P-O,¹³ S-O,¹⁴ S-N,^{15a} S-P,^{15b} S-S,¹⁶ and Se-O.¹⁷

From the standpoint of synthetic utility, these rearrangements possess several valuable features which include: (a) the regiospecific allylic transposition of heteroatom functions;¹¹⁻¹⁷ (b) the generation of specific olefin geometries;^{8g,18} and (c) the transfer of chirality.^{7c,8k,11b,19} During the last several years numerous applications of these bond reorganization processes have been reported in the context of natural products syntheses.²⁰ The present study demonstrates a new application of [2,3]-sigmatropic rearrangements within the context of a total synthesis of (±)-bakkenolide-A (3),²¹⁻²³ a representative member of the recently discovered class of bakkane sesquiterpenes having the basic carbocyclic structure 4.²⁴⁻²⁶



Results and Discussion

The Bakkanes. Based upon structural similarity, it has been proposed that the eremophilane sequiterpene fukinone (5) could be a biogenetic precursor of bakkenolide-A (3) (Scheme I), the important step involving skeletal reorganization being the Favorskii-type rearrangement of fukinone epoxide (6).^{23c} Naya and co-workers have demonstrated the viability of this process via the conversion of epoxide 6 with ethanolic hydroxide to hydroxy acid 7 in 20% yield.^{23e} Hydroxy acid 7 has been subsequently transformed to bakkenolide-A (3), thus interrelating the absolute configuration and stereocenters at C(4), C(5), and C(10) in both 3 and $5.^{27}$ Earlier degradation studies had also demonstrated this same point via the interrelation of both 3 and 5 with the ketone $8,^{23c}$ an intermediate which has been prepared during the course of the present synthetic study (vide infra).²¹

In addition to the eremophilane \rightarrow bakkane transformation cited above (Scheme I), Marshall has reported the unantici-





pated skeletal rearrangement of 9 to 10 upon attempted oxidation of 9 to fukinone (5) with chlorobenztriazole (Scheme II).²⁸ This interesting ring contraction, which has been rationalized to proceed via chloronium intermediate 11, provides further precedent for related transformations in the biosynthesis of the bakkane sesquiterpenes.

The general approach to the synthesis of bakkenolide-A (3) which was undertaken is illustrated in Scheme III. The central issue in this projected synthesis involved the design of a lactone spiroannelation sequence amenable to the conversion of the hydrindanone 8 to the desired target structure. As a result of





the disposition of functionality proximal to the C(7) quaternary center in bakkenolide-A (3), it was projected that the [2,3]sigmatropic rearrangement $12 \rightleftharpoons 13$ was ideally suited for the establishment of the desired stereochemistry and functionality for eventual elaboration to the desired target structure.²⁹



At the onset of this study, no precedent existed for the stereochemistry of [2,3]-sigmatropic rearrangements such as that illustrated by the transformation of $13 \rightarrow 12$. However, it was anticipated such rearrangements should proceed with *some* level of stereoselectivity across the convex face of cis-fused hydrindane ring system 13 ($13 \rightarrow 12\beta$ vs. $13 \rightarrow 12\alpha$). Accordingly, model studies were initiated to ascertain the general levels of asymmetric induction that could be anticipated in these and related [2,3]-sigmatropic processes.³⁰

Stereoselective Generation of Quaternary Centers via [2,3]-Sigmatropic Rearrangements. A reasonable model system which would provide valuable data on the steric course of such concerted rearrangements is shown below. A priori it was not obvious that there would be a clear-cut energetic preference for transition states leading to either 15 or 16. In addition, one



might expect that the migrating terminus, Y, could play a pronounced, if not dominant, role in defining the level of stereoselectivity in a given [2,3]-sigmatropic process. For those rearrangements where the migrating terminus, Y, is carbon, numerous applications in the area of terpene synthesis could readily be perceived.³¹

Scheme IV summarizes the three systems which were chosen for study. The generation and subsequent addition of dichlorocarbene³² at room temperature to allylic sulfide **17** afforded a presumed diastereoisomeric mixture of chlorosulfides **19a**



and **20a** via ylide **18a**.^{8f,33} Chromatography on silica gel resulted in clean hydrolysis and isolation of the crystalline thioester **21** in 54% yield. Initial preparative experiments failed to reveal the presence of the alternate stereoisomer **22**.

In order to unambiguously determine the degree of stereoselectivity of the rearrangement of ylide **18a**, an independent synthesis of the suspected minor isomer **22** or a transformation product of **22** was undertaken (Scheme V).³⁴ Based on the premise that carbenoids would add selectivity across the equatorial face of the cyclohexylidine enol ether **23** the indicated transformations would be anticipated to lead to the stereoselective formation of vinyl aldehydes **26** and **27**, where the latter diastereoisomer should be the major component. Treatment of enol ether **23** with ethyl diazoacetate in the presence of cuprous chloride-triethyl phosphite catalyst at 25 °C afforded a diastereoisomeric mixture of the four possible cyclopropanes **24**. Lithium aluminum hydride reduction followed by acid-catalyzed rearrangement with 10% aqueous hydrochloric acid gave a mixture of aldehydes **26** and **27** in a Scheme IV



Scheme V



ratio of 8:92. Since this diastereoisomer ratio was defined during the carbene addition step $(23 \rightarrow 24)$, these results confirmed our predictions on the stereochemical course of this reaction.

In order to ascertain the level of stereoselectivity in the rearrangement of ylide 18a, the uncrystallized chromatography fractions containing 21 and presumably traces of 22 were subjected to lithium aluminum hydride reduction followed by Collins oxidation³⁵ to the aldehyde mixture, 26 and 27. Gas chromatographic analysis revealed a 97:3 ratio of 26/27. Consequently, it appears that the ylide rearrangement of 18a and subsequent hydrolysis of 19a and 20a affords a 97:3 ratio of 21/22. Pure samples of both 26 and 27 were obtained and stereochemical assignments were determined by ¹H NMR. The formyl proton resonance (CDCl₃) of the equatorial isomer 26 (δ 9.26) as compared to the axial isomer 27 (δ 9.30) exhibited the expected upfield chemical shift.³⁰

By analogy we have also found that the allylic sulfonium ylide 18b, generated from allylic sulfide 17 and ethyl diazoacetate via the copper carbenoid, undergoes stereoselective rearrangement to a 91:9 mixture of esters 19b and 20b, respectively, in 59% yield. These results parallel our earlier observations on the stereochemical course of the rearrangement of allylic sulfoxide 18c.³⁷ In this study it was found that 18c also underwent preferential rearrangement across the equatorial face of the cyclohexylidine ring, affording 19c and 20c in a 92:8 ratio.³⁸

During the course of this study Mander reported the related rearrangement of ylide 28 shown below, which also demon-

 Table I. [2,3]-Sigmatropic Rearrangements in Cyclohexylidine

 Ring System 14

[2,3]-Sigmatropic process	<i>T</i> , °C	Equatorial-axial ratios 15/16	Ref
18a → 19a + 20a	25	97:3	30
$18b \rightarrow 19b + 20b$	25	91:9	30
$18c \rightarrow 19c + 20c$	25	92:8	37
$28 \rightarrow 29 + 30$	-10	90:10	39



strated a similar stereochemical preference for equatorial entry during bond reorganization (cf. Table I).

Several important conclusions can be made from the above data. With regard to the potential applications of these [2,3]-sigmatropic processes in stereoselective synthesis, these rearrangements are remarkably sensitive to steric factors. A direct comparison of these sigmatropic processes with the related Claisen rearrangement of 31^{40} reveals that comparable



steric factors appear to exert a greater influence in dictating product stereochemistry in the [2,3] as compared to related sigmatropic [3,3] process. The other conclusion from this comparative study is that comparable levels of stereoselectivity are maintained for different [2,3]-sigmatropic rearrangements (cf. Table I) where the migrating terminus has been either carbon or oxygen.

Within the context of projecting the steric course of the proposed sigmatropic rearrangement outlined in Scheme III, as applied to the total synthesis of bakkenolide-A (3), the cases cited in Table I thus serve as ample precedent.

Bakkenolide-A Synthesis. the general approach to the total synthesis of (\pm) -bakkenolide-A (3), as outlined in Scheme III, required the construction of hydrindanone 8 followed by stereospecific elaboration of the spirolactone ring.



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 Table II. Effect of Counterion and Solvent on the Alkylation of 34

Base	Solvent	36a/37a
NaH	C ₆ H ₆	70:30
KH	C ₆ H ₆	83:17
KH	THF	83:17
KO-t-Bu	t-BuOH	83:17

Scheme VI



Based upon intermediates prepared by Piers (cf. Scheme VI) in his synthesis of aristolone,⁴¹ ketone **36a** appeared to be a



readily amenable precursor for the construction of the requisite hydrindanone 8. Alkylation of the butylthiomethylene ketone 34 with 2-methylallyl chloride with a variety of bases and solvents was examined to determine optimal conditions for maximum stereoselectivity. The diastereoisomeric alkylation products 35 were then transformed with aqueous base to the epimeric mixture of ketones 36a and 37a according to the published procedure.⁴¹ At this stage a correlation between diastereoisomer ratio (36a/37a) and alkylation conditions (34 \rightarrow 35) was made (Table II). In contrast to recent observations that both metal cation⁴² and solvent⁴³ effects can be instrumental in changing the stereochemistry of enolate alkylation, the enolate derived from 34 is remarkably insensitive to such changes. The stereochemistry of the desired alkylated cyclohexanone 36a had been previously assigned by Piers⁴¹ and was consistent with the characteristic benzene-induced ¹H-solvent-induced chemical shift $\Delta (=\delta CHCl_3 - \delta C_6H_6)$ of 6 Hz for an axial methyl group α to a carbonyl function in a sixmembered ring.44

Oxidation of the mixture of ketones 36a and 37a with osmium tetroxide-metaperiodate in *tert*-butyl alcohol afforded a 93% yield of the diones 36b and 37b, which were separated by chromatography on silica gel. Successive aldol ring closure of dione 36b to hydrindenone 38 and subsequent catalytic



hydrogenation to the desired cis-fused hydrindanone 8 proceeded in good yield. The stereochemical course of the hydrogenation step is based upon numerous analogies,⁴⁵ and GLC analysis of the reaction mixture indicated that the desired reduction was indeed stereospecific. Comparison of 8 with an authentic sample obtained via the degradation of fukinone established their identity. A sample of hydrindanone 8, which was obtained during degradation studies on fukinone (5), was found to be identical (NMR, IR, MS, and GLC) with the sample prepared via the above synthetic sequence.^{23c,46}

The final stages of the synthesis demand the stereoselective conversion of the carbonyl carbon in hydrindanone 8 to a quaternary center flanked by olefinic and carbon in hydrindanone 8 to a quaternary center flanked by olefinic and carbonyl functions as illustrated in Scheme III in the conversion of 8 into 12. Overall this transformation, which is illustrated in general terms by eq 2 below, is usually difficult to accomplish in high efficiency.⁴⁷

$$R = 0 \qquad --- \qquad R = C = 0 \qquad (2)$$

In addition to the stereoselective solutions to this synthetic operation that have been outlined in Schemes IV and V, it is worth noting that we have also devised a potentially valuable two-step procedure for accomplishing the bis-functionalization of carbonyl centers, which could be applicable to the present synthetic project. Addition of the organozinc reagent **39** to cyclohexanone proceeded regiospecifically in 92% yield, re-



sulting in the α -adduct **40.**⁴⁸ Treatment of **40** with formic acid (100 °C, 3 h) afforded the vinyl-migrated aldehyde **41** in 59% isolated yield. Although this mechanistically intriguing semipinacolic rearrangement might be anticipated to proceed with *inversion* at the hydroxyl-bearing carbon in **40**, this point has not been pursued in the above rearrangement.

The successful route which was employed for the stereospecific elaboration of the C(7) quaternary center is summarized in Scheme VII. Treatment of bicyclic ketone 8 with isopropenyllithium⁴⁹ afforded a 60% yield of epimeric alcohols (9:1) of which 42 was the presumed major isomer. Conversion of 42 to the rearranged allylic bromide 43, as well as its geometrical isomer, was readily accomplished with phosphorus tribromide (0 °C, ether). Without purification, the unstable allylic bromide was converted to the carbazate 45 upon treatment with the sodium salt of the *p*-toluenesulfonyl-*s*methylcarbazate (44) following the procedure reported by Schollkopf.⁵⁰ Overall, the conversion of allylic alcohol 42 to the carbazate 45 was routinely accomplished in ca. 75% yield.

The germane model studies for the base-induced rearrangement of 45 to 46a have precedent in the work of Baldwin Scheme VII







and Walker.²⁹ These investigators have shown that allylic carbazates, upon treatment with sodium hydride, undergo [2,3]-sigmatropic rearrangement to dithioesters. Since Schollkopf has demonstrated that dialkyl carbazates afforded bisthioalkyl carbenes under such conditions,⁵⁰ it was presumed that base-induced rearrangement of **45** might proceed via carbenoid **13** (X = S, Y = SCH₃) as illustrated in Scheme III. However, from a mechanistic standpoint, a carbene intermediate is not obligatory in this and related rearrangements (cf. **47** \rightarrow **49**).



Based upon our model studies (vide supra), it was anticipated that [2,3]-sigmatropic rearrangement of the carbenoid or conjugate base derived from **45** should proceed in a stereoselective fashion across the convex face of the cis-fused bicyclic ring system (cf. Scheme III). Upon treatment of carbazate **45** with sodium hydride in refluxing tetrahydrofuran a 62% yield of the dithioester **46a** was obtained. A careful examination of the reaction mixture failed to reveal the presence of any C(7) isomers of **46a**. It thus appears that the [2,3] rearrangement of **45** was highly stereoselective in nature. This observation is fully consistent with the stereochemical course which we have observed in related [2,3]-sigmatropic processes (cf. Table I).

At this point the C(7) stereochemical assignment in 46a was based upon analogy. Unequivocal proof of the structure of 46a was obtained by the completion of the synthesis of bakkenolide-A (3). This was accomplished by hydrolysis of dithioester 46a to the monothioester 46b with aqueous mercuric chloride-mercuric oxide. Conversion of 46b to bakkenolide-A (3) was accomplished by oxidation with selenious acid in 39% yield.





Experimental Section

Melting points were taken on a Kofler hot stage or with a Büchi SMP-20 melting point apparatus and are uncorrected.

GLC analyses were run on a Varian Aerograph Model 1400 gas chromatograph equipped with a flame ionization detector using the columns indicated in the individual experimental sections. Preparative GLC was carried out using a Varian Aerograph Model 90-P gas chromatograph. Infrared spectra were recorded using a Perkin-Elmer Model 700 or 421 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian Associates Model T-60, A-60, or A-60D spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants, and interpretation.

A "dry" solvent refers to solvents distilled from lithium aluminum hydride or calcium hydride. The term "standard workup conditions", which is used in the following experimental section refers to the following product isolation procedure: dilution of the reaction with ether, successive extraction with water and brine; treatment of the organic extract with anhydrous sodium sulfate; and solvent removal under vacuum.

4-tert-Butyl-w-(phenylsulfinylmethyl)methylenecyclohexane (18c). A dry, nitrogen-purged, 2-L, three-neck round-bottom flask fitted with addition funnel, magnetic stirrer, nitrogen system, thermometer, and reflux condenser was charged with 1 L of anhydrous ether and 90 mL (0.26 mol) of 2.8 M vinyllithium in THF. The flask was cooled to 0 °C and 38.5 g (0.25 mol) of 4-tert-butylcyclohexanone in 100 mL of anhydrous ether was added over a 30-min period. The flask was allowed to reach room temperature and to stir for 1 h. The resulting colorless reaction mixture was cooled (-40 to -45 °C) and 36.5 g (0.25 mol) of phenylsulfenyl chloride⁵¹ in 100 mL of ether was added over 30 min. Upon addition, the phenylsulfenyl chloride was immediately consumed as evidenced by the color change. The yellow-white mixture was allowed to come to room temperature and to stir for an additional 2 h. After workup under standard conditions there was obtained 67 g (89%) of 18c as a white crystalline solid: mp 108-109 °C, NMR (CCl₄) δ 7.65 (5, arom), 4.15 (t, 1, J = 8 Hz, ==CH-), 3.50 $(d, 2, J = 8 Hz, -CH_{2}), 0.91 (s, q, tert-butyl); IR (CCl_4) 1660$ (C-C), 1040 (S=O) cm⁻¹; mass spectrum (70 eV) m/e (relative intensity) 290 (100).

Anal. (C₁₈H₂₆SO): C, 74.34; H, 90.0.

4-tert-Butyl-\omega-(phenylthiomethyl)methylenecyclohexane (17). To a 2-L round-bottom flask equipped with addition funnel, calcium chloride drying tube, magnetic stirrer, and charged with 6.45 g (0.170 mol) of lithium aluminum hydride in 25 mL of dry ether was added a solution of 25.0 g (0.085 mol) of sulfoxide **18c** in 800 mL of ether over a 10-min period. After stirring for 1 h the reaction was quenched by the addition of 50 mL of ethyl acetate. The gelatinous solution upon the sequential addition of 6.45 mL of water, 6.45 mL of a 15% aqueous sodium hydroxide solution, and 10.5 mL of water, formed a white granular precipitate which was removed by filtration. The ether solution was washed successively with water, dilute sodium hydroxide solution, and brine, and dried on anhydrous granular sodium sulfate. Concentration in vacuo afforded 21.4 g of a colorless oil which, after distillation at reduced pressure, yielded 18.8 g (81%) of the pure (>98% by GLC) sulfide 17: bp 128-130 °C (0.10 mm); NMR (CCl₄) δ 7.13 (m, 5, arom), 5.10 (t, 1, J = 8 Hz, =CH), 3.36 (d, 2, J = 8 Hz, -CH₂-), 1.0-2.6 (m, 9), 7.02 [s, 9, (CH₃)₃-]; IR (film) 1665 (w, C=C), 1587 (m, arom) cm⁻¹.

Anal. (C₁₈H₂₆S): C, 78.95; H, 9.65.

trans-4-tert-Butyl-1-phenylthiocarboxylate 1-Vinylcyclohexane (21). A 10-mL round-bottom flask charged with 1.5 g (5.5 mmol) of allylic sulfide 17, 1.0 mL of a 50% aqueous sodium hydroxide solution and a catalytic amount of Triton B was stirred vigorously until the contents of the flask were emulsified. To the rapidly stirring mixture maintained at 40 °C was added 0.67 mL (8.3 mmol, 50% excess) of ethanol-free chloroform. The reaction mixture, which turned yellow-brown after 20 min, was allowed to stir 6 h, acidified with 20% aqueous hydrochloric acid, and treated with 100 mL of ether. The ether was washed with dilute aqueous sodium hdyroxide, water, and brine solution, and dried over anhydrous sodium sulfate. Concentration in vacuo afforded a yellow oil which was placed in 20 g of silica gel in 20 mL of hexane. The black silica was extracted repeatedly with dichloromethane, the combined dichloromethane washings reduced in vacuo, and the resulting crude yellow oil purified by dry column chromatography on silica gel. Elution with carbon tetrachloride yielded a yellow solid $(R_f 0.4)$ which after recyrstallization from methanol yielded 890 mg (53%) of the thioester 21: mp 92-93 °C; NMR (CCl₄) δ 0.85 [s, 9, (CH₃)₃C], 5.0-6.0 (m, 3, vinyl abc), 7.34 (s, 5, arom); IR (CCl₄) 1700 (s, >C=O), 930 and 980 (vinyl), 1640 (w, C=C), 1480 (m, arom) cm⁻¹; mass spectrum (70 eV) m/e (rel intensity) 302 (1).

Anal. (C19H26OS): C, 75.58; H, 8.65.

Determination of the 21/22 Isomer Ratio. The uncrystallized chromatography fractions containing 21 and presumably traces of 22 were subjected to lithium aluminum hydride reduction in ether. The resulting epimeric alcohols A and B were present in a 97:3 ratio as evidenced by GLC (10% SE-30, Chromosorb W). These two carbinols were identical by coinjection with the carbinols independently synthesized by the route outlined in Scheme V. The NMR ((CCl₄) δ 4.82-5.83 (m, 3, vinyl abc), 3.11 (s, 2, -CH₂O-), 2.17-1.0 (m, 9), 0.82 [s, 9, (CH₃)₃C]) of the major isomer A was identical with the NMR of the minor isomer A produced by reduction of 27. Oxidation of the mixture of alcohols A and B to the aldehyde mixture 26 and 27



was carried out with Collins reagent in 70% yield. GLC analysis (6 ft, 10% FFAP, 120 °C) indicated the presence of 26 and 27 in a 97:3 ratio. Coinjection of 26 and 27 independently synthesized (Scheme V) confirmed their identity. A sample of 26 was purified by preparative GLC (10% FFAP): NMR (C_6D_6) δ 9.28 (s, 1, -CHO), 5.8-4.8 (m, 3, vinyl abc), 2.2-0.90 (m, 9, ring -CH-), 0.78 [s, 9, (CH₃)₃C]; IR (film) 1710 (s, CHO), 1640 (w, C=C) cm⁻¹.

Methoxymethylene-4-tert-butylcyclohexane (23).52 A dry nitrogen purged, three-neck, round-bottom flask fitted with addition funnel, magnetic stirring bar, and nitrogen system was charged with 250 mL of anhydrous ether and 6.6 g (60 mmol) of sublimed potassium tertbutoxide. The red-orange ylide was generated immediately upon the addition of 20 g (60 mmol) of methoxymethyltriphenylphosphonium chloride. The solution was allowed to stir for 1 h, whereupon 6 g (39 mmol) of 4-tert-butylcyclohexanone in 100 mL of anhydrous ether was added over 3 h. The dark brown solution was stirred an additional 6 h and decomposed by the addition of 80 mL of water. The organic layer was enriched with 80 mL of benzene, washed three times with water, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was partitioned between petroleum ether and 1:3 aqueous methanol, the methanol layer extracted twice with petroleum ether, and the combined petroleum ether fractions dried over anhydrous sodium sulfate. Removal of the solvent in vacuo afforded a yellow oil which was shown to be 99% pure by GLC. Distillation gave 5.51 g (94%) of 23 as a colorless oil: bp 56-58 °C (0.2 mm); NMR (CCl₄) δ 0.85 [s, 9, (CH₃)₃C], 3.40 (s, 3, -OCH₃), 5.58 (s, 1, -CH-); IR (film) 1690 cm⁻¹

Anal. (C₁₂H₂₂O): C, 79.26; H, 11.96.

Ethyl 2-Methoxy-4-tert-butylspiro[2.5]octane-1-carboxylate (24).

The procedure of Wenkert³⁴ was followed with several modifications. Ethyl diazoacetate, 5.8 g (51.0 mmol), was added over a 1.5-h period to a stirred solution of 4.80 g (25.4 mmol) of enol ether **23** and 20 mg of triethyl phosphite-copper(I) catalyst⁵³ in 10 mL of hexane. The reaction was diluted with hexane and extracted with water and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo afforded a yellow oil. Short-path distillation afforded 500 mg (10%) of the starting enol ether **23** and 2.10 g (30%) of the cyclopropyl ester **24**: bp 89–90 °C (0.03 mm); NMR (CCl₄) δ 4.07 (q, 2, J = 7 Hz, OCH₂-), 3.35 (m, 1, -OCH); IR (film) 1730 (s, C=O) cm⁻¹. A sample for analysis was obtained by preparative GLC (6 ft, 10% SE-30 column on Chromosorb W at 200 °C).

Anal. (C16H28O3): C, 71.62, H, 10.38.

1-Hydroxymethyl-2-methoxy-4-tert-butyl[2,5]spirooctane (25). A 500-mL round-bottom flask equipped with addition funnel, magnetic stirrer, and charged with 0.5 g (13.5 mmol) of lithium aluminum hydride in 200 mL of ether was cooled to 0 °C and treated with a solution of 1.64 g (6.1 mmol) of the ethyl ester 24 in 20 mL of ether over a 2-h period. The mixture was allowed to stir 1 h at room temperature, whereupon the excess hydride was quenched with 10 mL of ethyl acetate, and the resulting gray gelatinous mass worked up by the addition of 0.5 mL of water, 0.5 mL of 15% aqueous sodium hydroxide solution, and 1.5 mL of water. The ether was filtered from the granular aluminate salt, dried over anhydrous granular sodium sulfate, and the solvent removed in vacuo to yield 1.33 g (96%) of the crude alcohol 25. Distillation afforded 1.06 g (77%) of the pure alcohol (>97% pure by GLC): bp 180-185 °C (0.03 mm); NMR (CCl₄) δ 3.25 (s, 3, - OCH_3), 2.66 (d, 1, J = 3 Hz, >CH-), 3.32 (d, 2, J = 3 Hz, -CH₂O-), 0.80 (s, 9, tert-butyl); IR (film) 3400 (s, OH) cm⁻¹; mass spectrum (70 eV) m/e (M⁺) 226. Preparative GLC on a 10% SE-30 column at 180 °C provided a pure sample for analysis.

Anal. (C14H26O2): C, 74.45; H, 11.65.

Acid-Catalyzed Rearrangement of Alcohol 25. A solution of 3 mL of methanol, 3 mL of 5% aqueous hydrochloric acid, and 294 mg (1.30 mmol) of the carbinol 25 was heated at reflux for 30 min, diluted with 50 mL of water, and the phases separated. The ethereal layer was washed with saturated sodium bicarbonate solution and brine, and dried over anhydrous granular sodium sulfate. Concentration in vacuo yielded a clear oil which was molecularly distilled (45 °C (0.05 mm)) to afford 240 mg (95%) of the pure (>99% by GLC) aldehydes 26 and 27 in a ratio of 8:92, the minor isomer 26 being eluted first on a 6 ft, 10% FFAP column. A sample of the major isomer 27 was purified by preparative GLC (6 ft, 10% SE-30, Chromosorb W, 22%): NMR (CCl₄) δ 9.26 (s, 1, -CHO), 4.85-5.9 (m, 3, vinyl abc system), 0.84 (s, 9, *tert*-butyl), 2.40–0.90 (m, 9, ring -CH₂-); IR (film) 1732, 1637 (w, -CH=CH₂), (s, -CHO) cm⁻¹; mass spectrum (70 eV) *m/e* (M⁺) 194.

Anal. (C13H22O): C, 80.21; H, 11.32.

The minor aldehyde isomer **26** formed in this reaction was identical by GLC coinjection with an authentic sample prepared from thioester **21**.

Ethyl 2-Thiophenoxy-2-(1a-vinyl-4e-tert-butylcyclohexyl)acetate (19b). A 100-mL three-neck round-bottom flask equipped with magnetic stirrer, nitrogen inlet, and addition funnel was charged with 4.26 g (15.5 mmol) of allylic sulfide 17, 302 mg (0.84 mmol) of triethyl phosphite-copper(1) chloride complex,53 and 50 mL of spectroquality n-hexane, purged with nitrogen and treated dropwise with 2.21 g (19.3 mmol) of ethyl diazoacetate in 10 mL of hexane. The reaction mixture turned a dark yellow with slow evolution of gas. After 6 h another 1.1 g (9.6 mmol) of ethyl diazoacetate in 10 mL of hexane was slowly added. Analysis by GLC showed starting sulfide and the two isomeric rearranged esters in a ratio of 91:9. The yellow hexane solution was concentrated in vacuo, and the crude yellow oil purified by column chromatography on 125 g of activity I alumina. Elution with hexane afforded 0.97 g (3.5 mmol, 23%) of starting sulfide 17, while elution with hexane-ether (70:30) afforded, after molecular distillation (60 °C (10.05 mm)), 3.28 g (59%) of the sulfide ester 19 as a yellow oil (99% by GLC): NMR (CCl₄) δ 7.29 (m, 5, arom), 6.06-4.83 (m, 3, vinyl abc), 4.03 (q, 2, J = 7.4 Hz, $-CH_2-$), 3.36 (s, 1, -CHR-), 1.13 $(t, 3, J = 7.4 \text{ Hz}, \text{CH}_{3}), 0.85 \text{ [s, 9, (CH_3)_3C]}; \text{ IR (film) } 1742 \text{ (s,})$ C=O), 1640 (w, C=C), 1582 (m, arom) cm⁻¹; mass spectrum (70 eV) m/e (rel intensity) 360.5.

Anal. $(C_{22}H_{32}O_2S)$: C, 73.40; H, 9.01.

2,3-Dimethyl-2-methylallyl-6-*n***-butylthiomethylenecyclohexanone** (**35**). The title compound was prepared in accordance with the procedure reported by Piers.⁴¹ To 150 mL of dry *tert*-butyl alcohol under

nitrogen was added 3.1 g (0.78 mol) of potassium metal. The solution was heated at reflux for 1 h to complete the formation of potassium tert-butoxide. To this solution at room temperature was added 5.0 g (0.022 mol) of ketone 34. The solution was allowed to stir for 10 min as a deep red color formed, and was then cooled to 0 °C with the aid of an ice bath. At this point 11.5 g (0.127 mol) of methylallyl chloride was added and the solution was heated at reflux for 2 h. During this time the red color changed slowly to pink, with the formation of a white precipitate. The reaction solvent was removed on a rotary evaporator, and the residue was diluted with 100 mL of water and extracted three times with 50-mL portions of ether. The combined ether extracts were dried with magnesium sulfate and the solution was removed on a rotary evaporator leaving an oil which was molecularly distilled (50 °C (0.1 mm)), giving 5.2 g (84%) of the alkylated thiomethylene derivative 35 as a yellow oil [lit.41 bp 106-109 °C (0.25 mm)].

cis- and trans-2,3-Dimethyl-2-methylallylcyclohexanone (36a and 37a). The *n*-butylthiomethylene ketone 35 which was obtained as a mixture of diastereoisomers was hydrolyzed to the mixture of ketones 36a and 37a according to the procedure reported by Piers.⁴¹ In general, the unpurified ketone 35 was carried through this hydrolysis step. A typical procedure employed 55.0 g (0.243 mol) of 34, which was al-kylated as previously described. The crude 35 obtained after workup was placed in a 2-L, three-neck, round-bottom flask equipped with a stirring bar, a nitrogen inlet, and a condenser. The reaction vessel was charged with 350 mL of diethylene glycol and 325 mL of 25% potassium hydroxide, and the mixture was heated at reflux for 20 h.

The flask was fitted for steam distillation and the steam distillate was collected until it was clear (volume about 2 L). The distillate was saturated with sodium chloride and extracted with ether. The combined ether extracts were successively washed with 10% sodium hydroxide, then with brine, and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation leaving a residue which was distilled, yielding 33.5 g (0.186 mol, 76% from **34**) of **36a** and **37a**, bp 98-107 °C (7 mm) [lit.⁴¹ bp 76-80 °C (3.6 mm)]. GLC (6 ft, 2.5% Carbowax 4000, Chromosorb W, 2.5% KOH) analysis revealed the presence of the isomeric ketones **36a** and **37a** in a ratio of 83:17. Preparative HPLC (30 cm, Micro-Poracil) afforded a sample of the major isomeric ketone **36a**: NMR (CDCl₃) δ 4.7, 4.82 (m, 2, =:CH₂), 1.62 (d, 3, J = 1 Hz, -CH₃), 0.97 (s, 3, -CH₃), 0.90 (d, 3, J = 6 Hz, -CH₃); NMR (C₆D₆) δ 0.88 (s, 3, -CH₃); 0.74 (d, 3, J = 6.5 Hz, -CH₃); IR (film), 3080, 3050, 1700, 1640 cm⁻¹.

cis- and trans-2,3-Dimethyl-2-acetonylcyclohexanone (36b and 37b). To a stirred solution of 1.92 g (89.5 mmol) of sodium metaperiodate and 20 mg of osmium tetroxide in 155 mL of water was added 2.68 g (14.9 mmol) of olefinic ketones 36a and 37a (ratio 83:17) in 120 mL of tert-butyl alcohol. After 4 h an additional 190 mL of water was added and the reaction was allowed to proceed to completion (40 h). The reaction mixture was extracted with ether and the product isolated under standard conditions. The isomeric diketones 36b and 37b were separated by column chromatography on 30 g of silica gel upon elution with 0-30% ether-hexane. The initial chromatographic separation gave 1.70 g of 36b, 0.227 g of 37b, and 0.602 g of a mixture of both, giving a total yield of 2.53 g (93%). The sample of 36b was molecularly distilled at 50 °C (0.1 mm): NMR (CDCl₃) δ 2.13 (s, 3, CH_3CO), 1.06 (s, 3, CH_{3^-}), 0.91 (d, 3, J = 7 Hz, CH_{3^-}); NMR $(C_6D_6) \delta 1.86 (s, 3, CH_3CO_-), 0.79 (s, 3, CH_{3^-}), 0.64 (d, 3, J = 7 Hz,$ CH3-); IR (film) 1700 cm-1

Anal. (C₁₁H₁₈O₂): C, 72.71; H, 9.82.

cis-1,2-Dimethylbicyclo[4.3.0]non-6-en-8-one (38). To a 250-mL round-bottom flask was added 10.4 g (93 mmol) of potassium tertbutoxide (MSA Research Corporation). The flask was then charged with a solution consisting of 128 mL of tert-butyl alcohol and 26 mL of ether. To the clear solution was added 2.34 g (12.8 mmol) of dione **36b** in 26 mL of ether. The reaction was allowed to stir for 1 h and then diluted with 500 mL of ether, 50 mL of brine, and enough water to obtain two clear, distinct phases. The two phases were washed and extracted; the combined organic phases were dried with anhydrous sodium sulfate and concentrated in vacuo leaving an oil which was molecularly distilled, yielding 1.37 g of **38** (65%) as a clear colorless oil: NMR (CDCl₃) δ 5.76 (d, 1, J = 1 Hz, ==CH), 2.21 (s, 2, -CH₂CO), 1.10 (s, 3, -CH₃); IR (film) 1703, 1618 cm⁻¹.

Anal. (C₁₁H₁₆O): C, 80.59; H, 9.65.

cis-1,2-Dimethyl-cis-bicyclo[4.3.0]nonan-8-one (8). A 500-mL round-bottom flask was equipped with a stirring bar and charged with

250 mL of ethanol and 0.2 g of 10% palladium on powdered charcoal (Matheson, Coleman, and Bell). To this suspension was added 3.38 g (20.6 mmol) of enone **38**. The reaction was then stirred for 35 h under hydrogen while the disappearance of starting material was monitored with GLC (6 ft Carbowax 4000, Chromosorb, 2% KOH). The catalyst was removed by filtration through Celite, and the solvent was removed on a rotary evaporator, yielding an oil which was molecularly distilled at water aspirator pressure (80 °C (25 mm)), yielding 3.16 g (92%) of **8** as a colorless oil.³² This synthetic compound was compared to a sample supplied to us by Professor Naya, which he obtained as a degradation product from fukinone.^{23c,46} The compounds were identical as compared by GLC, IR, NMR, and mass spectra: NMR (CDCl₃) δ 2.24 (br s, 2, -CH₂CO), 2.17 (d, 2, J = 18 Hz, -CH₂CO), 1.04 (s, 3, -CH₃), 0.81 (d, 2, J = 6 Hz, -CH₃); IR (film) 2960, 2920, 2850, 1737, 1458, 1440, 1400, 1377 cm⁻¹.

Anal. (C11H18O): C, 79.33; H, 10.88.

cis-1,2-Dimethyl-8-hydroxy-8-isopropenyl-cis-bicyclo[4.3.0]nonane(42). To 19.9 mmol of isopropenyllithium⁴⁹ in 500 mL of ether at 0 °C was added 0.514 g (3.09 mmol) of ketone 8. The reaction was allowed to stir for 1 h. Upon quenching the reaction with saturated ammonium chloride solution a white granular precipitate was formed. The supernatant was decanted and the precipitate was extracted with ether. The combined ethereal extracts were washed with brine and dried (Na₂SO₄). The solvent was removed on a rotary evaporator, leaving an oil which was distilled through a short-path distillation apparatus, yielding 0.385 g (60%) of 42 as a colorless oil, bp 105 °C (25 mm). GLC analysis revealed a mixture of isomers in a ratio of 9:1. A sample of this material was chromatographed on Florisil (hexane elution) to yield the crystalline alcohol 42, which was recrystallized and sublimed for analytical purposes, mp 56-57 °C: NMR (CDCl₃) δ 5.1-4.6 (m, 2, =CH₂), 1.82 (s, 3, -CH₃), 0.87 (s, 3, -CH₃), 0.81 $(d, 3, J = 6.5 Hz, -CH_3)$; IR (film) 3430, 3100, 1640, 1460, 1365, 895 cm⁻¹.

Anal. (C14H24O): C, 80.63; H, 11.48.

Formation of the p-Toluenesulfonylhydrazone-S-methylcarbazate 45. A solution of 70 mL of dry ether at 0 °C and 0.570 g (2.74 mmol) of 42 was prepared. To this solution was added 0.13 mL (0.37 g, 1.4 mmol) of phosphorous tribromide. The reaction was allowed to stir for 3 h, at which time ice was added. The reaction mixture was poured into a water, ice, and ether mixture. The aqueous layer was extracted with ether and the combined ether extracts were washed with brine and dried (Na₂SO₄). The solvent was removed on a rotary evaporator at or below room temperature. The unstable bromide 43, obtained as an oil, was immediately added to an acetonitrile solution of the sodium salt of p-toluenesulfonylhydrazine-S-methyldithiocarbazate (44) (prepared with sodium hydride).⁵⁰ The reaction mixture was allowed to stir 4 h, during which time a white precipitate formed. The solvent was removed on a rotary evaporator, leaving a residue which was extracted with ether. The ether was washed with brine and dried (Na₂SO₄). Removal of the solvent on a rotary evaporator afforded 0.953 g of 45 as a brown gum (75% crude yield). It was assumed that 45 was obtained as a mixture of E and Z olefinic isomers: NMR $(CDCl_3) \delta$ 7.9, 7.33 (AB quartet, 4, J = 9 Hz, aromatic protons), 3.6 (m, 2, -CH₂S), 2.4, 2.3 (s, CH₃Ar, CH₃S-); IR (film) 3200, 1170, 730 cm⁻¹.

Rearrangement of 45 to Dithioester 46a. A suspension of 65 mg (2.3 mmol) of sodium hydride and 25 ml of dry THF was prepared. To this suspension was added 883 mg (1.89 mmol) of 45. Formation of the sodium salt was followed by the evolution of hydrogen. The brown reaction mixture was filtered,54 diluted to 70 mL, and heated at reflux for 6 h. GLC analysis (6 ft, 10% SE-30, Chromosorb W) showed a 90:10 ratio of 46a to all other volatile substances. The solvent was removed on a rotary evaporator, leaving a heterogeneous residue which was dry-column chromatographed⁵⁵ on 100 g of silica gel (hexane elution). The desired dithioester 46a, 334 mg (62%), that was isolated from the chromatography as a pale yellow oil was homogeneous by TLC and GLC. No other chromatography fraction exhibited NMR characteristics consistent with an isomer of 46a: NMR (CDCl₃) δ 5.22 (s, 1, =CH), 4.95 (s, 1, =CH), 2.55 (s, 3, SCH₃), 1.67 (s, 3, -CH₃), 0.89 (s, 3, -CH₃), 0.78 (d, 3, J = 6 Hz, -CH₃); IR (film) 3110, 1640, 1460, 1115, 890 cm⁻¹; mass spectrum (70 eV) *m/e* (rel intensity) 284 (3), 283 (6), 282 (28), 269 (10), 268 (18), 267 (93), 250 (3.1), 237 (7.5), 236 (21), 235 (100).

Anal. Calcd for C₁₆H₂₆S₂: 282.1476. Found: 282.1477.

Hydrolysis of the Dithioester 46a to Thioester 46b. A suspension of 164 mg (7.6 mmol) of mercuric oxide and 810 mg (30 mmol) of

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mercuric chloride in 12 mL of 70% acetone-water was prepared. To this suspension was added 107 mg (0.379 mmol) of 46a. The reaction mixture was heated at reflux for 3 h, during which time the yellow color of the supernatant faded. The reaction mixture was filtered, the solvent was removed on a rotary evaporator, and the residue was extracted with ether. The ether was washed with brine, dried (Na₂SO₄), and removed on a rotary evaporator leaving a semisolid. Preparative thin layer chromatography of this mixture on silica gel (hexane) afforded 16 mg of 46a and 57 mg (66% based on consumed 46a) of the thioester 46b. GLC analysis failed to reveal a second isomer. An analytical sample was obtained by preparative GLC (179 °C, 68 mL/min; 2.5 ft, 10% SE-30 on 60-80 mesh Chromosorb W DMCS): NMR (CDCl₃) δ 5.15 (s, 1, =CH), 5.00 (s, 1, =CH), 2.22 (s, 3, $-SCH_3$, 2.07 (m), 1.73 (br s, 3, J = 1 Hz, vinyl CH₃), 0.92 (s, 3, $-CH_3$, 0.80 (d, 3, J = 6 Hz, $-CH_3$); IR (film) 3100, 1680, 1640, 1450, 1380, 890 cm^{-1}

Anal. (C16H26OS): C, 72.14; H, 9.86.

(±)-Bakkenolide-A (3). To a solution of 25 mL of benzene and 2 mL of tert-butyl alcohol was added 90 mg (0.704 mmol) of selenious acid, causing the solution to turn a pale yellow color. The thioester 46b was added (44 mg, 0.165 mmol) and the reaction was heated at reflux for 5 h. After cooling, the reaction mixture was treated with 10% sodium thiosulfate and then diluted with 500 mL of ether and 50 mL of brine. The resulting organic phase was separated, dried (Na₂SO₄), and the solvent removed on a rotary evaporator. The oily residue was dry-column chromatographed 55 on 100 g of silica gel (elution with 30% dichloromethane-hexane). The oil thus obtained was found to contain three compounds in a ratio of 75:20:4 by GLC analysis. The mixture was separated by preparative GLC (182 °C, 64 mL/min; 2.5 ft, 10% SE-30 on 60-80 mesh Chromosorb W DMCS), yielding 15 mg (0.064 mmol, 39%) of (\pm) -bakkenolide-A (3), 5 mg of unknown compound A, and 2 mg of unknown compound B. Compound A had a molecular weight of 280 and exhibited two bands in the infrared spectrum at 1770 and 1695 cm⁻¹. Compound B had a molecular weight of 280 and was not further characterized. Synthetic bakkenolide-A was compared by NMR, mass spectra, and GLC with an authentic sample⁵⁶ to confirm its identity.

Anal. (C15H22O2): C, 76.92; H, 9.25

1-(1-Hydroxycyclohexyl)allyl Methyl Ether (40). To a dry, nitrogen-purged, 250-mL, three-neck flask previously charged with a solution of 79 mL (50 mmol) of 0.63 M sec-butyllithium (hexane) in 150 mL of dry THF was added 3.6 g (50 mmol) of methyl allyl ether at -65 °C. After stirring for 30 min, a solution of 6.8 g (50 mmol) of anhydrous zinc chloride in 100 mL of THF was added, maintaining the internal reaction temperature in the range of -50 to -30 °C. To the resulting allylzinc reagent 3948 cyclohexanone was added and the reaction mixture was allowed to warm to -20 °C where it was held for 10 min prior to warming to room temperature. The reaction was quenched with ca. 2 mL of saturated aqueous ammonium chloride solution and the inorganic precipitate removed by filtration. The solvent was removed in vacuo, leaving an oil which was dissolved in ether and washed successively with water and brine and dried over anhydrous sodium sulfate. Solvent removal in vacuo afforded 6.66 g of the adduct 40. Molecular distillation (58 °C (0.02 mm)) afforded 5.93 g (82%) of allyl ether 40 which was pure by GLC (6 ft, 10%Carbowax 20M, 200 °C): NMR (CDCl₃) δ 6.09-5.00 (m, 3 vinyl H), 3.3 (s, 3, OCH₃), 3.2 (s, 1, CH), 2.43 (s, 1, OH), 1.53 (m, 10, -CH₂-); IR (film) 3500, 1640 cm⁻¹

Anal. (C₁₀H₁₈O₂): C, 70.52; H, 10.54.

1-Vinylcyclohexanecarboxaldehyde (41). A solution of 1.04 g (6.05 mmol) of allyl ether 40 in 1.5 g of 98% formic acid was heated at reflux under nitrogen for 55 min. The reaction mixture was added to water, extracted with ether, and the organic layer washed with saturated aqueous K₂CO₃. After drying over anhydrous granular sodium sulfate, the solvent was removed in vacuo to afford 488 mg (59%, 90% pure by GLC) of the aldehyde 41. An analytical sample was prepared by preparative GLC (6 ft, 10% SE-30, Chromosorb-W, 160 °C): NMR (CDCl₃) δ 9.23 (s, 1, -CH=O), 5.62 (q, 1, -CH=), 5.40-4.82 (m, 2, -CH₂), 1.50 (m, 10, -CH₂); IR (film) 1730 (s, C=O), 1642 (w, C = C cm⁻¹.

Anal. (C₉H₁₄O): C, 78.05; H, 10.30.

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References and Notes

- Camille and Henry Dreyfus Teacher-Scholar Recipient (1971-1970)
- (2) Present address: Laboratories of Chemistry, California Institute of Technolgy.
- (3) Abstracted from the thesis of Charles L. Sims.
- (4) J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, Chem. Commun., 576 (1970).
- J. E. Baldwin and F. J. Urban, Chem. Commun., 165 (1970)
- (6) (a) S. W. Kantor and C. R. Hauser, J. Am. Chem. Soc., 73, 4122 (1951);
 (b) R. W. Jemison and W. D. Ollis, Chem. Commun., 294 (1969); (c) C. Huynh, S. Julia, R. Lorne, and D. Michelot, Bull. Soc. Chim. Fr., 4057 (1972); (d) G. V. Kaiser, C. W. Ashbrook, and J. E. Baldwin, J. Am. Chem. Soc., 93, 2342 (1971), and references cited therein
- (a) V. Rautenstrauch, *Chem. Commun.*, 4 (1970); (b) J. E. Baldwin, J. De-Bernardis, and J. E. Patrick, *Tetrahedron Lett.*, 353 (1970); (c) J. E. Baldwin and J. E. Patrick, J. Am. Chem. Soc., **93**, 3556 (1971). (a) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *J. Am. Chem. Soc.*, **90**, 4758
- (1968); (b) B. M. Trost and R. LaRochelle, Tetrahedron Lett., 3327 (1968); (c) R. B. Bates and D. Feld, Ibid., 417 (1968); (d) G. M. Blackburn, W. D. Ollis, J. D. Plackett, C. Smith, and I. O. Sutherland, Chem. Commun., 186 (1968); (e) J. E. Baldwin and R. E. Hackler, J. Am. Chem. Soc., 91, 3645 (1969); (f) W. Ando, T. Yagihara, S. Kondo, K. Nakayama, H. Yamato, S. Nakaido, and T. Migata, J. Org. Chem., **36**, 1732 (1971); (g) V. Rautenstrauch, *Helv. Chim. Acta.*, **54**, 739 (1971); (h) E. Hunt and B. Lythgoe, J. Chem. Soc., Chem. Commun., 757 (1972); (i) S. Julia, C. Huynh, and D. Michelot, *Tet*rahedron Lett., 3587 (1972); (j) P. A. Grieco, D. Boxler, and K. Hiroi, J. Org. Chem., 38, 2572 (1973); (k) B. M. Trost and W. G. Biddlecom, *ibid.*, 38, 3438 (1973); (l) D. Michelot, G. Linstrumelle, and S. Julia, J. Chem. Soc., Chem. Commun., 10 (1974); (m) W. Kreiser and H. Wurziger, Tetrahedron Lett., 1669 (1975); (h) E. Vedejs and J. P. Hagen, J. Am. Chem. Soc., 97, 6878 (1975).
- (9) J. E. Baldwin and C. H. Armstrong, *Chem. Commun.*, 631 (1970).
 (10) (a) D. D. Phillips, *J. Am. Chem. Soc.*, **76**, 5385 (1954); (b) W. Ando, S. Kondo, and T. Migata, *ibid.*, **91**, 6516 (1969).
- (11) (a) R. F. Kleinschmidt and A. C. Cope, J. Am. Chem. Soc., 66, 1929 (1944); (b) M. Moriwaki, S. Sawada, and Y. Inouye, Chem. Commun., 419 (1970); (c) K. Takabe, T. Katagiri, and J. Tanaka, Tetrahedron Lett., 3005 (1975).
- (12) (a) D. G. Morris, Chem. Commun., 1345 (1969); (b) J. E. Baldwin, J. E. Brown, and R. W. Cordell, ibid., 31 (1970); (c) J. E. Baldwin, J. E. Brown, and G. Höfle, J. Am. Chem. Soc., 93, 788 (1971).
- (13) (a) For a general review see: V. Mark, *Mech. Mol. Migr.*, 2, 319 (1969); (b)
 R. D. Baechler, W. B. Farnham, and K. Mislow, *J. Am. Chem. Soc.*, 91, 5686 (1969); (c) M. Huche and P. Cresson, *Tetrahedron Lett.*, 4291 (1973).
- (14) (a) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Misłow, J. Chem. Soc., 90, 4869 (1968); R. Tang and K. Mislow, *ibid.*, 92, 2100 (1970); (b) D. A. Evans, G. C. Andrews, and C. L. Sims, *ibid.*, 93, 4956 (1971).
- (15) (a) R. S. Atkinson and S. B. Awad, J. Chem. Soc., Chem. Commun., 651 (1975); (b) W. B. Farnham, A. W. Herriott, and K. Mislow, J. Am. Chem. Soc., 91, 6878 (1969).
- (16) (a) C. G. Moore and B. R. Trego, Tetrahedron, 18, 205 (1962); (b) G. Höfle and J. E. Baldwin, J. Am. Chem. Soc., 93, 6307 (1971)
- (17) K. B. Sharpless and R. F. Lauer, J. Am. Chem. Soc., 94, 7154 (1972).
 (18) (a) D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *Tetrahedron*
- ett., 1385 (1973); (b) ibid., 1389 (1973).
- (19) J. G. Miller, W. Kurz, K. G. Untch, and G. Stork, J. Am. Chem. Soc., 96, 6774 (1974)
- (20) For a general overview of the applications of allylic sulfoxides via [2,3] rearrangement to natural products synthesis see: D. A. Evans and G. C. Andrews, Acc. Chem. Res., 7, 147 (1974).
- (21) For a preliminary account of this work see: D. A. Evans and C. L. Sims, Tetrahedron Lett., 4691 (1973).
- (22) K. Naya, I. Takagi, M. Hayashi, S. Nakamura, and M. Kobayashi, 11th Symposium on the Chemistry of Natural Products, Symposium Papers, 88 (1967); Y. Kitahara, *ibid.,* 96 (1967).
- (23) (a) K. Naya, I. Takagi, M. Hayashi, S. Nakamura, M. Kobayaski, and S. Katsumura, *Chem. Ind.* (*London*), 318 (1968); (b) K. Shirahata, N. Abe, T. Kato, and Y. Kitahara, *Bull. Chem. Soc. Jpn.*, 41, 1732 (1968); (c) N. Abe and R. Onoda, *Tetrahedron Lett.*, 369 (1968); (d) K. Shirahata, T. Kato, and . Kitahara, Tetrahedron, 25, 3179 (1969); (e) K. Naya, M. Hayashi, I. Takagi, S. Nakamura, and M. Kobayashi, Bull. Chem. Soc. Jpn., 45, 3673 (1972); (f) K. Shirahata, T. Kato, Y. Kitahara, and N. Abe, Tetrahedron, 25, 4671 (1969)
- (24) The names bakkane as well as fukinane have been independently assigned to the carbon skeleton 4. Consequently, the name fukinanolide as well as bakkenolide-A have been ascribed to 3.
- (25) The numbering system for the bakkane ring system is based on that of the presumed biogenetic precursor possessing the eremophilane skeleton.
- (26) For additonal bakkane sequiterpene derivatives that have been isolated see: (a) K. Naya, M. Kawai, M. Massami, and T. Kasai, Chem. Lett., (1972); (b) N. Abe, R. Onoda, K. Shirahata, T. Kato, M. C. Woods, Y. Kita-hara, K. Ro, and T. Kurihara, *Tetrahedron Lett.*, 1993 (1968); (c) C. Katayama, A. Furusaki, I. Nitta, M. Hayashi, and K. Naya, Bull. Chem. Soc. Jpn., 43, 1976 (1970).
- (27) K. Hayashi, H. Nakamura, and H. Mitsuhashi, Chem. Pharm. Bull., 21, 2806 (1973)
- (28) J. A. Marshall and G. M. Cohen, J. Org. Chem., 36, 877 (1971). These workers did not deduce the C(7) stereochemistry in 10.
- (29) An analogy for the process 13 → 12 had been reported: J. E. Baldwin and J. A. Walker, *J. Chem. Soc., Chem. Commun.*, 354 (1972).
 (30) For a preliminary account of this study see: G. C. Andrews and D. A. Evans,
- Tetrahedron Lett., 5121 (1972).
- (31) (a) R. E. Ireland and L. N. Mander, J. Org. Chem., 32, 689 (1967); (b) E. P. Serebryakov, A. V. Simolin, V. F. Kucherov, and B. V. Rosynov, Tetrahedron Lett., 5215 (1970); (c) G. Mehta, U. R. Noyak, and S. Dev, *ibid.*, 1119 (1973);

(d) K. Shirahata, N. Abe, T. Kato, and Y. Kitahara, Bull. Chem. Soc. Jpn., 41, 1732 (1968).

- (32) M. Makosza and M. Wawrzyniewicz, Tetrahedron Lett., 4659 (1969); I. Tabushi, Z. Yoshida, and N. Takahashi, J. Am. Chem. Soc., 93, 1820 (1971).
- (33) For analogous rearrangements see: (a) W. E. Parham and S. H. Groen, J. Org. Chem., 30, 728 (1965); (b) *ibid.*, 31, 1694 (1966); (c) W. Kirmse and M. Kapps, Chem. Ber., 101, 994 (1968).
- (34) E. Wenkert, R. A. Mueller, E. J. Reardon, S. S. Sathe, D. J. Scharf, and G. Tosi, *J. Am. Chem. Soc.*, **92**, 7428 (1970).
 (35) R. Ratcliffe and R. Rodehurst, *J. Org. Chem.*, **35**, 4001 (1970).
 (36) G. W. Buchanan and J. B. Stothers, *Chem. Commun.*, 179 (1967); G. W.
- Buchanan and A. R. McCarville, Can. J. Chem., 50, 1965 (1972)
- (37) D. A. Evans and G. C. Andrews, J. Am. Chem. Soc., 94, 3672 (1972). (38) In this study the kinetically generated sulfenate esters were trapped with trimethyl phosphite.
- (39) L. N. Mander and J. V. Turner, J. Org. Chem., 38, 2915 (1973).
- (40) H. O. House, J. Lubinkowski, and J. J. Good, J. Org. Chem., 40, 86 (1975).
- (41) E. Piers, R. W. Britton, and W. deWaal, Can. J. Chem., 47, 831 (1969).
- (42) G. Stork and R. K. Boeckman, Jr., J. Am. Chem. Soc., 95, 2016 (1973).
- (43) Y. Nakadaira, J. Hayashi, H. Sato, and K. Nakanishi, J. Chem. Soc., Chem. Commun., 282 (1972).
- (44) For a general review see: J. Ronayne and D. H. Williams, Annu. Rev. NMR Spectrosc., 2, 83 (1969).
- (45) F. F. Giarrusso and R. E. Ireland, J. Org. Chem., 33, 3560 (1968); R. L. Augustine and A. D. Broom, ibid., 25, 802 (1960); T. L. Jacobs and N. Ta-

kahashi, J. Am. Chem. Soc., 80, 4865 (1958).

- (46) K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Y. Hirose, and N. Shinoda, *Tetrahedron*, 24, 5871 (1968). After completion of this study a route to.8 similar to that described herein was published: S. Sarma and B. Sarkar, Indian J. Chem., 10, 950 (1972).
- (47) Other approaches related to the conversion of carbonvi carbon to quaternary centers have been described; E. J. Corey and J. I. Schulman, J. Am. Chem. Soc., 92, 5522 (1970).
- (48) D. A. Evans, G. C. Andrews, and B. Buckwalter, J. Am. Chem. Soc., 96, 5560 (1974).
- (49) E. A. Braude and C. J. Timmons, J. Chem. Soc., 2000 (1950).
 (50) V. Schollkopf and E. Wiskott, Justus Liebigs Ann. Chem., 694, 44 (1966)
- (1966).
 (51) Prepared according to the analogous procedure reported for *p*-toluene sulfenyl chloride: F. Kurzer and J. R. Powell, "Organic Syntheses", Collect. Vol. 4, Wiley, New York, N.Y., 1963, p 934.
 (52) Cf. G. Wittig, W. Boll, and K. Kruck, *Chem. Ber.*, 95, 2514 (1962).
 (53) W. R. Moser, *J. Am. Chem. Soc.*, 91, 1135, 1141 (1969).

- (54) Filtration of the solution at this point appears to be necessary to the achievement of good yields of rearrangement; private communication from Professor J. E. Baldwin, Department of Chemistry, Massachusetts Institute of Technology
- B. Loev and M. M. Godman, Chem. Ind. (London), 2026 (1967)
- (56) For a published mass spectrum and NMR spectrum of bakkenolide-A, see ref 23f and 23b, respectively. An authentic sample of bakkenolide-A was kindly provided by the late Professor Y. Kitahara, Department of Chemistry, Tohoku University, Sendai, Japan.

Computer Simulation of Phosphorane Structures¹

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Abstract: Parametrization of a molecular mechanics program to include terms specific for five-coordinate phosphorus compounds results in computer simulated structures of phosphoranes which compare favorably with structures obtained by x-ray diffraction. The principal new feature peculiar to five coordination is a term which measures the effect of electron pair repulsion modified by the ligand electronegativity for the two sets of bonds around phosphorus and takes into account the trigonal bipyramid and square pyramid as structural possibilities. The structures treated are HPF₄, $(CH_3)_n PF_{5-n}$ (n = 0, 1, 2, 3), the catechol derivative, $(C_6H_4O_2)_2PCH_3$, the dioxaphospholane $[(CF_3)_2CO]_2P[C(CH_3)_2CH_2C(CH_3)_2]C_6H_4Br$, the ephedrine derivative, (OCHPhCH(CH₃)NCH₃)₂PH, and (PhO)₅P. The good agreement between geometries obtained by computer simulation and x-ray diffraction suggests that application to phosphorus reaction mechanisms should result in a quantitative structuring of reaction intermediates and transition states.

Parametrization of molecular mechanics programs for use with organic compounds has been extensive.³⁻⁹ Their application to conformational problems in general, gives very good results both in the reproduction of structural parameters and in the determination of relative configurational energies.³⁻⁷ The principal terms that form a basis for these programs deal with bond stretching, bond bending, torsional motions, and nonbonded interactions.

$$E_{\text{steric}} = \sum E_{\text{str}} + \sum E_{\text{bend}} + \sum E_{\text{tors}} + \sum E_{\text{nb}} \qquad (1)$$

The stretch and bend terms are modified Hooke's law expressions. Minimization of these terms relative to a "strainless" set by successive alterations in atomic coordinates leads to a configuration of minimum steric energy.^{6,7} This empirical approach can give insight into the relationship between energy, structure, and reactivity for systems that are too complex for most orbital calculations of the requisite sophistication.

When dealing with pentacoordinate phosphorus compounds, existing programs must be altered to differentiate between the two basic five-coordinate geometries, the trigonal bipyramid (TP) and the square pyramid (SP). Structures close to each type have been observed as well as a range of structures in between the two basic types.¹⁰⁻¹² Any program to be useful then must be sufficiently versatile to reflect the factors which favor one geometry over the other in order to reproduce known structures for five-coordinate phosphorus molecules.

We have made an initial effort in constructing an appropriate force field for small phosphorane molecules based on the extensive spectroscopic data that have been accumulated over the past decade.^{10,13} The resulting parametrization was tested by calculating the reproducibility of the geometries of larger phosphoranes whose x-ray structures have been determined. As a basis of our treatment, we have extended the well developed program MMI of Allinger et al.^{6,7} A detailed description follows.

Force Field Modifications

Interactions between atoms bonded to a common atom (1,3 interactions) are not specifically included in eq 1 in Allinger's approach because these interactions are effectively already included in the bond length and bond angle "strainless" parameters.⁵ However, for five-coordinate structures, there is a need to consider the effect of 1,3 interactions because an energy term is needed for ligand-ligand repulsion (1) to account for the stability difference of various geometries possible and (2) to account for structural effects due to the variation of ligand electronegativity.

For example, if no 1,3 interaction is included, the steric