1948 *J. Org. Chem.* **1986**, *51*, 1948–1954

Studies of the Ketone Obtained from the Ozonolysis of Vitamin D. Molecular Mechanics Calculations for It and Related Hydrindanones[1a]

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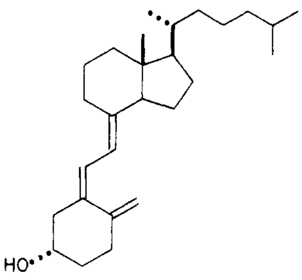
Received December 20, 1984

Vitamin D$_3$ was allowed to react with ozone, followed by LiAlH$_4$, to give the known alcohol **4**. The latter was oxidized to the known ketone **3t**, containing some cis isomer **3c**, by several methods. The percent of **3c** was determined. The ketones **3t** and **3c** were allowed to react with lithiated 1,3-bis(trimethylsilyl)propyne to give enynes. The trans enynes **6** were tentatively assigned as consisting mostly of the *Z* isomer. Molecular mechanics (MM2) calculations were carried out for trans and cis isomers of various 1-, 2-, 3-, and 4-hydrindanones and the results were compared with experimental equilibrium constants and earlier calculations. The amount of cis isomer was underestimated by the MM2 calculations. A limited investigation of multiple conformers, including boats, did not resolve the discrepancy.

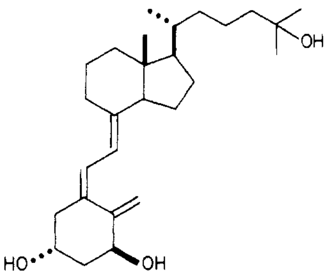
Introduction

Interest in vitamin D3 (**1**) has increased markedly since the discovery that it is dihydroxylated in vivo to the active form **2**.[2] We were interested in the possibility that the ketone **3t**, derived from the ozonolysis of **1**, might serve as a source of analogues derived from reactions with propargylsilanes, previously studied by one of us,[3] or from reactions with silylated propargyl Wittig reagents. In addition we envisioned the possibility that **3t** and related ketones could serve as resolving agents for certain chiral allenes. Finally, we encountered the cis-fused isomer **3c** in the course of our studies and decided to investigate the usefulness of molecular mechanics (MM2) calculations in the study of cis–trans equilibria in **3** and other hydrindanones.



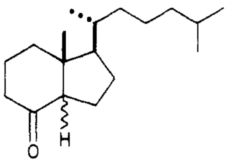
1

Vitamin D$_3$

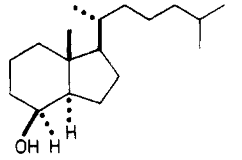


2

1,25-Dihydroxy D$_3$
(Active form)



3t trans
3c cis



4

Table I. Percent Trans Ketone 3t from Oxidation of Trans-Fused Alcohol 4

method	trans/cis, GC ratio
CrO$_3$/pyridine, 15 °C, 3 h	99/1
CrO$_3$/Py/CH$_2$Cl$_2$, 0 °C, 15 min	94/6
PCC/CH$_2$Cl$_2$, 25 °C, 1.5 h	85/15
SO$_3$/pyridine/Me$_2$SO, 25 °C, 4 days	98/2

Description and Results

In the first phase of our work we repeated the original ozonolysis of vitamin D3 (**1**) first carried out by Inhoffen and co-workers.[4] In this procedure the ozonide is subjected to a workup with lithium aluminum hydride to give the alcohol **4** which is oxidized to the ketone **3t**. The direct ozonolysis of **2** to **3t** in propanal solvent (Storey's method)[5] has been used by Okamura and co-workers.[6] Early in our work we repeated the isomerization of the trans-fused ketone **3t** to the cis-fused isomer **3c**. Analyses by capillary gas chromatography indicated that the pure trans ketone tended to form some cis isomer under a variety of conditions—perhaps even in storage at −70 °C. It appeared advantageous for us to isolate the alcohol **4** as the storable intermediate. Also, in our hands the ketone from a Story ozonolysis was difficult to separate from other materials by chromatography.

Since no method for monitoring the trans to cis isomerization, **3t** to **3c**, was available to the early workers, we compared a number of oxidation procedures in regard to this possible isomerization. The results are reported in Table I.

The original method (CrO$_3$–pyridine)[4] is seen to be among the best for avoiding the formation of the undesired cis isomer. A method recommended[7a] for its ability to preserve a chiral center next to a carbonyl group (the Parikh modification of the Moffatt oxidation with dimethyl sulfoxide–SO$_3$)[7b] also was successful. However it was found to be difficult to wash out Me$_2$SO to give ketone suitable for use without chromatography. Other oxidation methods are seen (Table I) to give a substantial amount

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(1) (a) Partial support of this work by the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, USPHS (Grant 1 R01 AM31110-01A1) is gratefully acknowledged. (b) On sabbatical leave at the University of South Carolina, 1983–1984 academic year. (c) Dr. Wayne Guida, Chemistry Department, Eckerd College, St. Petersburg, FL 33733.

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Table II. Isomer Ratios for Enynes 6

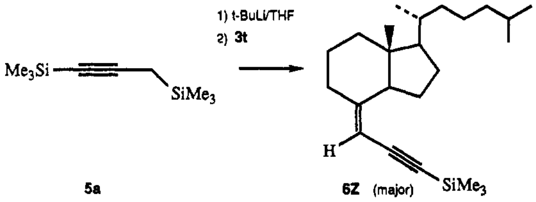
conditions	ratio, Z/E^a
t-BuLi/THF, −78 to 25 °C	5.0/1
t-BuLi/THF, $MgBr_2/Et_2O$, −78 to 25 °C	2.5/1
t-BuLi/THF, $Ti(O\text{-}Pr)_4$/THF, −78 °C	3.7/1

[a] Based on uncalibrated flame detector area response.

of trans to cis isomerization.

The ketone **3t** and the corresponding ketone in the vitamin D2 series (which has the methylated, unsaturated C17 side chain, $CH_3CHCH{=}CHCH(CH_3)CH(CH_3)_2$) have been converted to the two D vitamins in Lythgoe's group.[8] These workers utilized the Horner modification of the Wittig reaction to attach the diene and ring A. In conjunction with other work, these attachments provided total syntheses of the vitamins. Since the preparation of the Wittig reagent required approximately 25 steps, we began the exploration of other methods for elaborating the ketone into a precursor for vitamin D or its analogues. Other synthetic studies relevant to the present work have appeared.[9]

We now turn to studies of the preparation of the enyne **6**, eq 1. The first method involved the propargylsilane **5a** whose lithiation and reaction with cyclohexanone to give silylated enynes was reported by Yamamoto and coworkers.[10] E. J. Corey's group has studied comparable isopropylsilanes.[11] Several questions presented themselves: Would the basic lithiated **5a** isomerize the ketone **3t** to the undesired cis isomer? Would the intermediate β-hydroxysilane be isolable? (If so base and acid elimination would be expected give, respectively, the Z and E isomers of the enyne **6**.)



(1)

In a number of reactions (eq 1) enynes **6** were obtained with one isomer (E or Z) predominating. The presence of two compounds was inferred from the presence of two peaks for the alkene hydrogens in the 90-MHz ^1H NMR spectrum. That isomerization to a cis-fused ring system had not occurred was implied when a sample of 90% cis-fused ketone was allowed to react with lithiated **5a**. The resulting NMR spectrum indicated that a previously undetected enyne was the main or exclusive product. Strong additional evidence for the trans fusion of enynes **6** was obtained by ozonolysis of **6**, followed by dimethyl sulfide workup, which gives the ketone directly. Capillary column GC analysis of the crude mixture showed a high ratio (86/14) of trans-fused to cis-fused ketones **3**, with the cis isomer ascribable to acid catalyzed isomerization during the dimethyl sulfide workup (referee's suggestion).

A preliminary assignment of E/Z geometry to the enynes was made by analogy with steric effects found in other reactions of the lithiated propargylsilane **5a**.[10] The cyclic transition state of the type previously proposed for the reaction of lithiated **5a** should show severe steric interactions of the trimethylsilyl group is on the right (Figure 1). Accordingly the prodominant isomer which we observed in a number of reactions (Table II) is expected to be the Z isomer, having the opposite double bond geometry to that in vitamin D. This tentative conclusion is not without interest in regard to the use of **6** for the construction of vitamin D analogs. The unnatural isomers around the 5,6 double bond have been of substantial interest in regard to deducing the nature of the binding site for vitamin D.[12] On the other hand, isomers of the 7,8 double have not been studied.

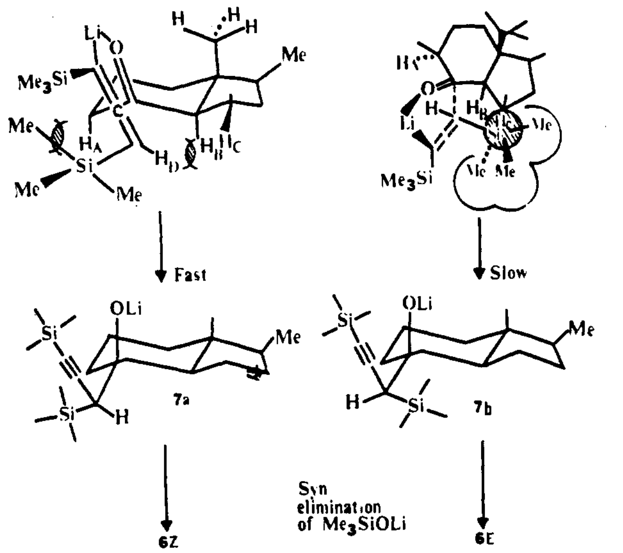


Figure 1. Transition state for the reaction of ketone **3t** with lithiated **5a**.

In order to obtain the enyne isomer having the vitamin D geometry around the 5,6 bond we investigated the reaction of the silylated propargyl Wittig reagent **5b** with the trans ketone **3t**. Previously an allylic Wittig reagent had given the vitamin D geometry upon reaction with **3t** in Lythygoe's synthesis of the vitamin.[8] Although the analogous triphenylphosphonium Wittig reagent was known[13] we elected to prepare the new reagent **5b** (see eq 2) because an allylic triphenylphosphonium reagent had failed to react with ketone **3t** in Lythygoe's study.[8]

Gratifyingly, reaction of the ketone **3t** with the propargyl Wittig reagent **5b** (eq 2) gave one major isomer (containing less than 4 percent of the other isomer, based on ^{13}C NMR). The isomer was identical with the minor isomer from the abovementioned propargylsilane reaction, as shown by ^{13}C NMR. This observation, in conjunction with Lythgoe's results[8] and other evidence of the tendency of Peterson and Wittig olefinations to give, respectively, Z and E isomers[14] constitutes strong evidence our initial assignment of double bond geometry was correct. The Wittig derived enyne is the E isomer, having the vitamin D geometry.

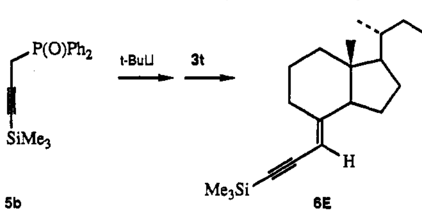


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Table III. Equilibrium Constants for Trans- and Cis-Fused Hydrindanones and Comparison of $RT \ln K$ with MM2 Energy Differences

structure	% cis-fused	E/cis-eq	E/cis-ax	E/trans	ΔE, MM2[a]	$-RT \ln K$, T → °C[b]
8	76[c]	17.28	18.03	16.50	0.78	−0.77
9	92[c]	19.31	19.30	19.57	−0.27	−1.13
10	6[c]	19.49	20.70	16.97	2.52	1.84
11	31[c]	22.37	21.66	20.85	0.81	0.54
12	100[c]	18.36	18.33	19.26	0.93	
13	81[d]	25.09	26.19	25.35	−0.26	−0.97
14[e]		18.48	18.14	20.65	−2.46	
15[e]		17.03	16.59	18.86	−2.27	
16[e]		18.22	16.84	19.60	−2.76	

[a] Negative numbers indicate that a cis isomer is calculated to be more stable. [b] Negative numbers indicate that the cis isomer was found to be more stable experimentally. The temperature for calculation of $RT \ln K$ was taken to be 65 °C, the approximate temperature of most of the base equilibrations. [c] Reference 14. [d] This work. The 81% value is for compound 3. The calculations are for 13. [e] For comparison with values in ref 13; cf. Table V.

That our Z enyne has retained the trans ring fusion is indicated by the ^{13}C chemical shift of the angular methyl group, 12.00. The cis-fused compounds of our study showed shifts near 19.0 for this group. Substantial differences in the peaks attributable to the ring methylene hydrogens of the E and Z isomers may be noted in the Experimental Section. Further studies may be of interest in defining the shielding and deshielding regions in these enynes, since their geometry is known, owing to the rigidity of the trans-fused ring system.

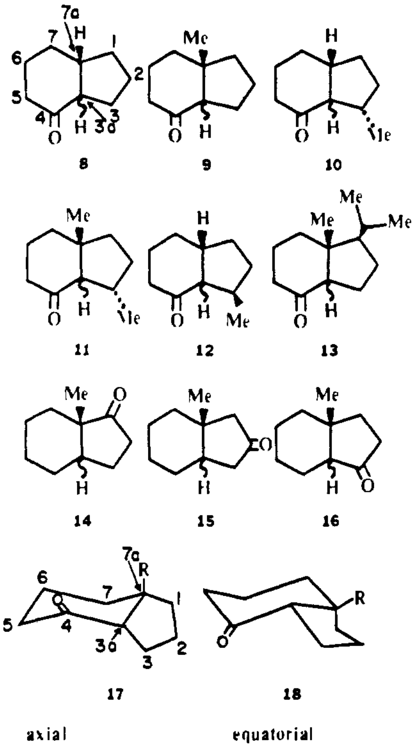
While we were preparing the cis-fused ketone we took the opportunity to redetermine the cis/trans equilibrium constant. We obtained $K = 4.02$ and $K = 3.89$ for methoxide-catalyzed isomerization in methanol, starting from trans and cis isomers, respectively. Okamura has found a value 4.3:1 for the cis/trans ratio obtained by equilibration in benzene using CF_3CO_2H. Since hydrindanones were a major focus of early molecular mechanics calculations,[15] we decided to do some calculations with emphasis on 4-hydrindanones, not considered in the earlier study.[15] Recently a number of equilibrium constants in this series have been discussed from a qualitative standpoint.[16]

We used Allinger's MM2 program,[17] which has been developed since the original hydrindanone calculations[15] were done. The program was adapted for computation at USC by Dr. Wayne Guida.[1c] The calculations were based on dihedral angles estimated from molecular models or from earlier MM2 calculations, and upon other data, which were input to an IBM pc program which calculated the initial coordinates.

The MM2 program produced a file listing both the input and the optimized output coordinates. Both sets were transferred via a modem to an IBM PC disk. In the early work they were then input to a program which depicted the molecule on a screen and allowed it to be rotated for optimum viewing and printing. The z coordinates were used to control the size of the depicted atoms (cf. Figure 4). In later searches for multiple conformers, it was more expedient to examine the output dihedral angles directly (see below). The previously calculated energy difference (1.78 kcal) between the chair conformers of methylcyclohexane[17] was reproduced exactly using our methods.

In the first calculations we found the energies for those conformers previously considered for various 4-hydrindanones[16] (identified in Chart I) and for the ketone 13, a model[15] for 3. The calculated energies for the conformers of lowest energy were compared (Table III) with the experimental equilibrium constants. This phase of the study showed the calculations to underestimate the percent of cis-fused isomers present at equilibrium in most cases, even when both cis chairs were considered to contribute to the equilibrium.

Chart I



It became desirable to determine whether additional cis conformers contribute to the overall percent of cis-fused isomer present at equilibrium. Accordingly an extensive investigation of possible combinations of five-membered and six-membered ring conformers was made for the parent *cis*-hydrindan-4-one using the approach of De Clercq,[18] with manual matching, as also used by House et al.[19] The inclusion of multiple conformers was found to affect the calculated equilibrium constant substantially (cf. Table IV). However, a reevaluation in data in House's paper[19] in conjunction with our own results revealed a substantial discrepancy between calculated and observed equilibrium constants (cf. discussion section). Finally, a brief comparison of the older and MM2 methods was made in the hydrindanone series, Table VI, in order to assess whether the earlier discussion remained largely intact.

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Table IV. Energies and K/K_{trans} for Conformers of 4-Hydrindanone

			dihedral angles					
conformer	energy	K/K_{trans}	3a–7a	7a–1	1–2	2–3	3–3a	type[a]
trans-chair	16.496	1.0	46.7		15.1			hc
cis-eq-1	17.2838	0.249	42.6	−34.6	13.7	12.8	−34.5	hc
cis-eq-2	17.2646	0.249	41.4	−27.8	3.5	22.2	−39.3	env
cis-ax-1	17.828	0.099	−39.4	38.0	−22.3	−2.2	25.9	env
cis-ax-2	18.030	0.070	−36.9	18.2	7.3	−30.0	41.4	?
cis-boat-1	17.694	0.123	7.6	−31.2	42.9	−38.4	19.1	?
cis-boat-2	18.606	0.026	13.2	13.0	−34.2	42.5	−34.4	hc
cis(sum)		0.816						

[a] Approximate half-chair (hc), envelope (env), or intermediate (?) type.

Table V. MM2-Based Equilibrium Constants from Reference 19, Obtained by Summing the Contributions of Conformers, and Comparison with Experimental Values, Also from Reference 19

compd (Figure 3)	*K* from MM2 sum	*K* from expt	$-RT \ln K$, MM2 sum	$-RT \ln K$, expt	difference[a]
26	0.562	6.75	0.339	−1.126	1.46
27	0.102	2.37	0.701	−0.511	1.21
28	0.324	39	0.664	−2.16	2.83

[a] $-RT \ln K$ (experimental) minus $-RT \ln K$ (MM2), both in kcal/mol. The MM2 value of $-RT \ln K$ (fourth column) was obtained by calculating the amount of each conformer of each cis- or trans-fused isomer in equilibrium with the conformer and isomer of lowest MM2 energy and summing the amounts of cis and trans isomers.

Discussion

As has been mentioned, our approach to adding various structural units to the ketone **3t** via the enynes **6** would have been promising for forming either isomer of **6** using the first investigated route starting from propargylsilane (eq 1) if the presumed intermediate, a β-silylated alcohol, had been isolable. In one of our preparations of **6**, samples were isolated and analyzed by gas chromatography as the reaction temperature was raised using a thermostated refrigerated bath. No intermediate was evident. Enyne formed at −20 to 0 °C before the ketone had completely reacted.

Although evidence for the buildup of silylated alcohols (present as the alkoxides) was cited for the enyne preparations in the literature,[10] the direct formation of alkenes from relatively stable silylated carbanion precursors is the usual result in olefinations using the method discovered by D. J. Peterson.[20] A recent result reported by Hudrlik[21] indicated that lithioalkoxides may not even be intermediates in such reactions, although the alternative is unknown. In our own reaction (eq 1) the failure to observe the large steric descrimination suggested by the examination of models of the transition states, (Figure 1), may be suggestive that an irreversable formation of the proposed[10] alkoxide product is not operative.

Our observation that Peterson and Wittig olefinations of ketone **3t** provided predominantly enynes of opposite geometry provides an interesting extension of previous observations[14] involving these types of olefinations. The availability of both isomers **6*Z*** and **6*E*** will allow us to pursue synthetic schemes which may generate natural and unnatural isomers in the vitamin D series.

Our MM2 calculations may be discussed with reference to the data in Tables III, IV, V, and VI. Although the potential energies calculated by molecular mechanics are not identical with the thermodynamic quantities, ΔG and ΔH, in practice the calculated quantities are useful when they serve to estimate the experimental ones. The results of Table III represent the traditional approach to conformational studies in which a trans chair and two cis chairs are considered. Examination of the energies indicates that the calculations underestimate the percent of cis present at equilibrium when these conformers are considered.

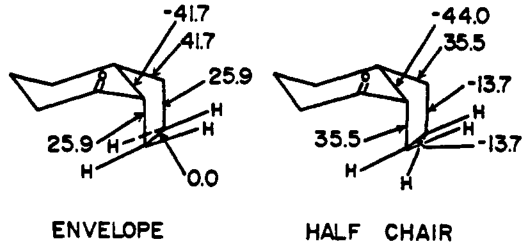

Figure 2. Dihedral angles proposed (ref 22) for cyclopentane in the envelope and half-chair conformers, shown incorporated in a cis–axial 4-hydrindanone conformer.

More recently efforts to take into account all reasonable conformers for each ring of a fused system have been made. In the approach of De Clercq[18] dihedral angles at the ring fusion in five-membered and six-membered rings are noted to be matched. Accordingly only conformers having the same sign and approximate magnitude need be combined.

The dihedral angles for five-membered envelopes and chairs, as given by Henderson[22] are shown by the examples in Figure 2, in which the conformers are shown fused to *cis*-axial-4-hydrindanone (cf. Chart I). An examination of dihedral angles at the ring fusion in earlier calculations showed that only the dihedral angles of largest magnitude in the five-membered ring envelopes or half-chairs were likely to occur at the ring fusion (with the exception of the angles in boats). All conformers which matched in this way were examined for the parent *cis*-4-hydrindanone, along with others having the next largest five-membered dihedral angle at the ring fusion. The substantial number on input conformers led to a smaller number of output conformers, detailed in Table IV. Two five-membered ring conformers appear to be found for each chair of the cis-fused system, and also for the only six-membered ring boat conformer which was found to be present to a significant extent (**24** and **25**, Figure 4).

Two conformers which we have listed have identical energies. It is possible that they represent points at which the calculation stopped, owing to the flatness of the barrier to conformational interconversion on the five-membered ring. Nevertheless, we count them as separate conformers in order to find the maximum percentage of cis isomer predicted by the MM2 method. The resulting calculated

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Table VI. Comparison of MM2 and Earlier Calculations for Hydrindanones

	E, eq–ax[a] (A or E)[b]		*E* trans – *E* stable	*E* trans–*E* cis-axial[d]	
structure, Chart I	1972, ref 15	MM2, this work	1972, ref 15	1972, ref 15	MM2, this work
14	-0.2 (E)	0.34 (A)	2.5	2.5	2.51
15	0.2 (A)	0.44 (A)	2.1	1.9	2.27
16	1.1 (A)	1.38 (A)	2.6	1.5	2.26
13					0.26[e]

[a] Energy difference between the cis chairs with the 7a-methyl designated as equatorial or axial (cf. Chart I). [b] Conformation of the 7a-methyl in the cis chair of lower energy (cf. Chart I). [c] Energy of the trans form minus that of the more stable cis chair. [d] Energy of the trans form minus that of the cis chair having an axial 7a-methyl (cf. Chart I). [e] Not calculated in ref 15. Included for contrast with other isomers.

equilibrium constant (0.816) is still smaller than the observed one (4.4) but is substantially better than a calculated value based on only one or two cis conformers.

Calculations confirmed that only one conformer of *trans*-4-hydrindanone, having a five-membered ring half-chair, needed to be considered. Our results indicate that the consideration of multiple conformers may be of major importance in the calculation of the energetics of hydrindanones and other multicyclic systems. The less comprehensive consideration of traditional major conformers (our Table III and earlier papers[15]) may be insufficient. If so, the routine use of molecular mechanics as an adjunct to syntheses becomes much more difficult. Qualitative discussions based on examination of models also lose usefulness.

As noted above, even the consideration of multiple conformers did not lead to the prediction that *cis*-4-hydrindanone is more stable that the trans isomer, as reported. We reviewed the somewhat confusing literature to see if the cis and trans assignments for 4-hydrindanone might need to be reversed. Originally Hückel and Goth[23] appear to have attached the "cis" label to 4-indanols derived from hydrogenation of indenol without discussion of the assignment. Hydrogenation of acetylaminoindene, followed by deamination led to the same compounds.[24] Careful oxidation was thought to give mostly *cis*-4-hydrindanone, whose benzoyloxime was prepared.[24,25]

Later Foote and Woodward[26] used the Hückel assignment in identifying the products of solvolysis of bicyclo[3.3.1]nonan-9-yl tosylate. Dauben and Jiu[27] used the assignment in reinterpreting the Hückel amine deaminations. Finally, H. C. Brown and E. Negeshi used the assignment in identifying *tran*-4-hydrindanone as the product of a hydroboration and carbonylation.[28] The Hückel assignment may be based on the assumption that hydrogenation produces a cis-fused ring. However, subsequent studies provide evidence that hydrogenation might lead to trans-fused rings, although these studies do not involve the hydrogenation of indenes.[29] Whatever the basis for the early assignment, the results of the more recent above-cited studies would be difficult to interpret if the original cis assignment were not correct. The recent work appears to us to constitute a reasonably secure independent assignment, although not intended for that purpose.

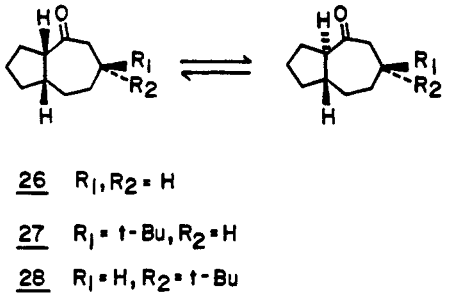

Figure 3. Fused ring ketone equilibrations reported in ref 19, for use in conjunction with Table V (this paper) and the Discussion (this paper).

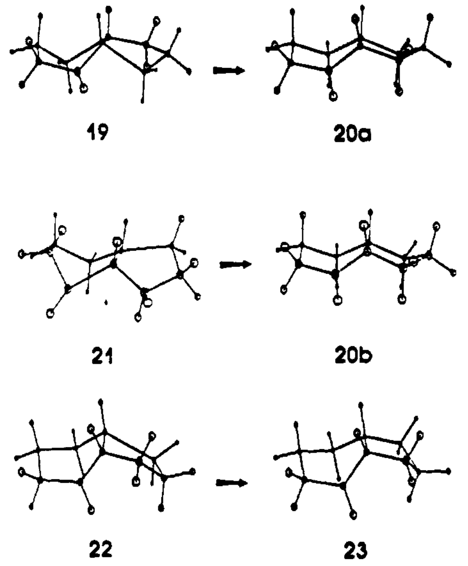

Figure 4. Boat forms for 4-hydrinanone.

Recently House et al.[19] have reported a study in which both ketone equilibrations and MM2 calculations for fused ring ketones **26**, **27**, and **28**, shown in Figure 3, were carried out.[24] The De Clercq procedure was used to try to consider all reasonable conformers. Although the authors discussed only the relation of calculated and observed conformations, we have calculated the MM2-based cis–trans equilibrium constants from their data and compared them to the experimental values which were reported.[19] The results (Table V) show remarkably large discrepancies, which will be of interest to synthetic chemists planning to use molecular mechanics calculations in conjunction with synthetic studies, and to theoreticians. Hopefully our results and those of Table IV will stimulate a reexamination of the application of molecular mechanics to ketone energetics. Several persons have pointed out that solvent effects may affect the experimental equilibrium constants. Both theoretical and experimental work appear to be needed.

Comparisons of old[19] and new (MM2)[17] calculations are given in Table VI. One involves the energy differences

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between the methyl axial and methyl equatorial conformers of the cis isomers of the same hydrindanones. The maximum difference between the two methods is 0.54 kcal. The second comparison is of the energy of the cis conformers relative to the trans for 7a-methyl 1-, 2-, and 3-hydrindanones. The maximum difference is 0.76 kcal, although the difference is less if the cis conformer of lower energy is compared for each method (Table VI). Although one might hope that the differences represent inaccuracies in the less sophisticated older method, the comparison of MM2 and experimental results, as cited in this paper, suggests that caution in interpreting the results of either method is advisable.

Conclusion

Our synthetic studies have shown that the ketone **3t** may be elaborated without isomerization of the ring fusion using the lithiated derivative of propargylsilane **5a** or the Wittig reagent **5b**. Enynes having both the 'natural' and 'unnatural' double bond geometry of vitamin D have been made available for further synthetic studies (in progress). The molecular mechanics calculations have provided one of the early examples where multiple conformers have been considered in conjunction with experimental results. The results, with those of a previous study, indicate that the factors influencing cis–trans equilibrations are not well accounted for by the calculations made to date.

Experimental Section

General. Distillations were performed using a short-path distillation unit. The recorded boiling points are uncorrected. Proton nuclear magnetic resonance spectra were recorded with chloroform (δ 7.28) as an internal standard. Carbon magnetic resonance spectra were obtained with deuteriochloroform as an internal standard. High-performance liquid chromatography was carried out on a 5-μmC18 reversed phase radial-PAK column. Gas chromatography analyses were performed on a SE-30 cross-linked capillary column (12.5 m × 0.2 mm). Tetrahydrofuran was dried prior to use by distillation from a sodium/benzophenone mixture. Diethyl ether was dried by distillation from lithium aluminum hydride.

De-*A*,*B*-8-cholestanone (3t, Grundmann's Ketone). Ozone was passed through a solution of vitamin D_3 (5.0 g, 13 mmol) in hexane (125 mL) for 45 min at −25 °C. The reaction mixture was transferred via a cannula tube to an ice-cold solution of $LiAlH_4$ (4.9 g, 102 mmol) dissolved in ether (200 mL). The transfer was completed with additional ether (95 mL) as a rinse. After the reduction, ethyl acetate (50 mL) and ice-cold 10% aqueous sulfuric acid (150 mL) were used to destroy the unreacted $LiAlH_4$ and complete the hydrolysis. Ether extraction, water wash, and drying over $MgSO_4$ afforded a crude yellow product. Flash chromatography over silica gel (230–400 mesh) using 5% ethyl acetate-cyclohexane gave 2.3 g (67%) of the alcohol **4**,[4] a viscous oil: ^{13}C NMR ($CDCl_3$), eighteen peaks, including 69.38 (C–O), 56.76, 52.55 (ring CH), 13.41 (7a angular methyl), no impurity peaks evident (5% detectable).

Oxidation of **4** was carried out using four published methods.[4,7,30,31] (a) To a premixed solution of chromic anhydride (0.40 g, 3.9 mmol) in pyridine (2 mL) at 5 °C, was added **4** (0.15 g, 0.56 mmol) dissolved in pyridine (2 mL). The mixture was kept at ice-bath temperature for 3 h and then at room temperature overnight. Dilution of the reaction mixture with water, ether extraction, and 6 N HCl and $NaHCO_3$ washing afforded 0.14 g (97%) **3t** and **3c** as a viscous oil in a 99:1 ratio. (b) To a premixed solution of chromic anhydride (2.30 g, 23 mmol) in pyridine (12 mL) and methylene chloride (25 mL) at 5 °C, was added a solution of **4** (1.00 g, 3.76 mmol) in methylene chloride (5 mL). The resulting solution was stirred for 15 min at 5 °C. The solution was decanted from the residue and the residue extracted with ether. The organic layers were combined, washed with 5% aqueous NaOH, 5% aq. HCl, 5% aqueous $NaHCO_3$ and salt solution before drying over $MgSO_4$. Evaporation of the solvent afforded **3t** and **3c** in a 94:6 ratio. (c) To a stirred mixture of PCC (0.37 g, 1.7 mmol) in methylene chloride (15 mL) at 25 °C was added a solution of **4** (0.30 g, 1.1 mmol) in methylene chloride (10 mL). The mixture was stirred for 1.5 h at room temperature. The solution was diluted with ether, and the solvent was decanted from the dark residue. The residue was extracted with ether and the organic layers were combined. The orange solvent was concentrated in vacuo and passed rapidly through a short silica gel column to remove the residual colored impurities. The resulting colorless solution was evaporated to dryness to afford **3t** and **3c** in a 85:15 ratio. (d) To a stirred solution of **4** (0.266 g, 1.0 mmol), Et_3N (0.70 g, 7.0 mmol) in Me_2SO (2 mL) was added dropwise, under argon and at room temperature, a solution of pyridine/sulfur trioxide complex (0.50 g, 3.0 mmol) in Me_2SO (3 mL). The resulting yellow solution was stirred for 96 h at 25 °C, acidified with dilute HCl, diluted with water, and extracted with ether. The ethereal extracts were washed with water and dried. Evaporation of the solvent afforded **3t** and **3c** in a 98:2 ratio. A sample of predominantly trans ketone, previously reported in ref 4 and 6, showed ^{13}C NMR, eighteen peaks, 211.88 (C=O), 61.93, 55.72 (ring CH), 12.43 (angular methyl).

Preparation of 1,3-Bis(trimethylsilyl)propyne (5a)[10] and Reaction with Ketone 3t To Give *Z*-Silylated Enyne 3*Z*. To a stirred solution of 1-trimethylsilylpropyne (5.60 g, 0.050 mol) in dry ether (150 mL) at −5 °C and under an argon atmosphere was added *tert*-butyllithium (3.20 g, 0.055 mol, 28 mL of a 2.0M pentane solution) over a period of 10 min. The resulting light yellow solution was maintained at −5 °C for 1 h and the temperature then lowered to −15 °C. Chlorotrimethylsilane (6.00 g, 0.050 mol, 7.00 mL) was added dropwise via syringe over a period of 5 min. The reaction mixture was stirred for 2 h at −5 °C and for 1 h at room temperature. The reaction mixture was then poured into aqueous 10% NH_4Cl solution (100 mL) and extracted into ether. The combined ethereal extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent and vacuum distillation of the crude product afforded **5** as a colorless liquid: bp 87–89 °C (35 mm);[10] 7.0 g (76%); ^{1}H NMR ($CDCl_3$) 1.56 (s, 1, CH_2), 0.16 (s, 9, Me_3Si), 0.14 (s, 9, Me_3Si); ^{13}C NMR ($CDCl_3$) 105.32 (s, =CC), 82.91 (s, C=CC), 8.64 (s, CH_2), 0.24 (s, Me_3SiC=), −2.29 (s, Me_3SiCH_2).

Modifications of the procedures developed by Yamamoto and co-workers[10,32] were used for the additions of lithiated, magnesiated, and titaniated 1,3-bis(trimethylsilyl)propyne to **3t**. (a) Addition of lithiated 1,3-bis(trimethylsilyl)propyne to **3t**: To a stirred solution of 1,3-bis(trimethylsilyl)propyne (**5a**, 35 mg, 0.19 mmol) dissolved in THF (2 mL) at −78 °C was added dropwise under an argon atmosphere *tert*-butyllithium (12.5 mg, 0.19 mmol, 0.10 mL of a 2.0 M pentane solution). The resulting solution was stirred for 1 h at −78 °C. At this time, a solution of **3t** (50 mg, 0.19 mmol) in THF (1 mL) was added in one portion. The solution was stirred at −78 °C for 5 min and the cooling bath removed. The solution was allowed to come to room temperature over a period of 1 h. Water (5 mL) was added and the mixture extracted with ether. The ethereal extracts were combined, washed with aqueous salt solution, and dried ($MgSO_4$). Capillary GC showed the *Z*/*E* isomer ratio to be 4.5:1. In addition, varying amounts (0 to 27%) of the *tert*-butyllithium adduct to **3t** was found along with some unreacted **3t**. Separation of the enynes **6*Z*** and **6*E*** was accomplished by HPLC using a 5-μm C18 reversed phase column and ethanol carrier. ^{1}H NMR ($CDCl_3$): 5.44 (s, 1, CH=, *Z*-isomer), 5.13 (s, 1, CH=, *E*-isomer), 0.71 (s, 3, 18-CH_3), 0.23 (s, 9, Me_3Si, *E*-isomer), 0.20 (s, 9, Me_3Si, *Z*-isomer). ^{13}C INEPT NMR ($CDCl_3$): *Z* isomer 155.9, 104.6, 102.6, 94.8 (alkene and alkyne), 56.8, 55.6 (ring CH), 40.3, 37.6, 24.2, 24.0, 23.8 (tentative ring methylene), −0.18 (Me_3Si). Other ^{13}C δ values were C, 47.1; CH 28.0, 36.1; CH_2 39.5, 36.2, 23.87, CH_3, 22.8, 22.6, 19.0, 12.4.

Anal. Calcd. for $C_{24}H_{42}Si$: C, 80.37; H, 11.80. Found: C, 80.53; H, 11.77. (b) Addition of magnesiated 1,3-bis(trimethylsilyl)propyne to **3t**: The same procedure described in a was used except

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that after stirring the *tert*-butyllithium/propyne mixture for 1 h, a solution of magnesium bromide (37 mg, 0.20 mmol) in dry ether (2 mL) was added and stirred for 15 min at −78 °C before the addition of the ketone **3t**. Capillary GC analysis showed the *Z*/*E* isomer ratio to be 2.5:1. (c) Addition of titaniated 1,3-bis(trimethylsilyl)propyne to **3t**: The procedure described in a was used with the addition of titanium isopropoxide (54 mg, 0.19 mmol, 55 μL) following the 1 h stirring period for *tert*-butyllithium/propyne. The resulting solution was stirred for 10 min at −78 °C and the ketone **3t** was added. Stirring at −78 °C was continued for 2 h before quenching with water. Capillary GC showed a *Z*/*E* isomer ratio of 3.7:1.

Addition of Lithiated 1,3-Bis(trimethylsilyl)propyne to 3c. The procedure a, used to prepare the trans enynes *6Z* and *6E*, was employed for the synthesis of the cis enynes. The material isolated by reverse-phase chromatography showed ^{1}H NMR ($CDCl_3$) 5.33 (s, 1, CH=), 5.31 (s, 1, CH=), 0.97 (s, 3, 18-CH_3), 0.17 (s, 9, Me_3Si). ^{13}C NMR ($CDCl_3$) showed peaks at 56.3, 51.5 (Ring CH), 19.9, 20.6 (one of these is the angular CH_3). Further characterization was not carried out, since these results were sufficient for our purpose–to rule out the presence of this isomer in our desired trans-fused enynes.

Preparation of Impure [3-(Trimethylsilyl)propynyl]diphenylphosphine Oxide 5b and Reaction with Ketone 3t To Give *E*-Silylated Enyne 3*E*. 1-Bromo-3-(trimethylsilyl)propyne was prepared from the alcohol (Petrarch Chemical Co.) by the reported[33] procedure. The bromide (2.60 g, 13.65 mmol) was allowed to react with lithiated triphenylphosphine (from 3.55 g, 19.1 mmol of triphenylphosphine and 7.0 mL of 2.5 M butyllithium in hexane). The general method is described in ref 8. Oxidation with H_2O_2 and isolation by chloroform extraction gave an oil (3.29 g) which was then dissolved in ether and filtered through a medium porosity glass frit to remove an unidentified crystalline solid (mp >250 °C). The ether was evaporated and the proton spectrum of the crude oil showed four peaks in the hydrocarbon region which comprised 20% of the proton area. The oil (3.30 g) was dried by distilling toluene from it 3 times, using reduced pressure. Attempts to purify the product by chromatography on silica (30% hexanes in ether) were unsuccessful. The estimated yield based the weight of oil and on relative proton areas is 35%. Spectral data were obtained from an earlier small scale preparation for which no yield data are available. ^{1}H NMR: 0.00 (Me_3Si), 3.25 (d, $J = 17$, CH_2P), 7.48–7.97 (phenyl). IR (CCl_4): 2198 cm^{-1} (silylated alkyne).

Reaction of the dried phosphine oxide **5b** (0.256 g, 0.9 mmol) from an earlier preparation, with butyllithium (0.53 mL, 2.5 M) was carried out in 4.5 mL dry tetrahydrofuran at −30 to −40 °C for 30 min. At −58 °C, with dry-ice cooling, ketone **3t** (0.295 g, 1.12 mmol), was added in 6 mL of tetrahydrofuran. Evaporation, extraction with ether–aqueous sodium bicarbonate, drying, and chromatography on silica with hexanes, and then evaporation until no hexanes were present as evidenced by ^{1}H NMR, gave enyne **6*E***, (0.108 g, 26%), plus other fractions containing unreacted ketone **3t** and isomerized ketone **3c** (together, 28 percent of the initial amount of ketone).

The enyne exhibited ^{1}H and ^{13}C NMR peaks previously seen in the minor isomer from Peterson olefination of **3t**: ^{1}H NMR (400 MHz) 0.54 (angular Me), 0.85 (dd, diasteriotopic *i*-Pr methyls), 0.95 (d, side chain, Me), 1.85 (m, H of *i*-Pr group), 1.99 (dt, methylene adjacent to double bond), 2.98 (dd, ring fusion), 5.10 (vinyl); ^{13}C NMR ($CDCl_3$) δ 157.4, 103.3, 100.6, 96.2, (alkene or alkyne), 56.5, 55.9 (ring CH), 40.2, 31.5, 27.6, 23.4 (tentative ring methylenes), 0.2 (Me_3Si). Other ^{13}C peaks occurred at δ 46.3, 39.5, 36.1, 36.0, 28.0, 23.8, 22.8, 22.5, 21.9, 18.8, and 12.0 (angular CH_3). Also present were five impurity peaks having heights approximately 10% of that of the larger enyne peak. Although analytical purity was not achieved, the material serves our need to assign the *E*–*Z* stereochemistry of the enynes in our study. IR of *E*-enyne: 3030 cm^{-1}, 2128 (SiC≡C), 1625 (double bond), 1246 (SiMe).

Isomerization of 3t to 3c. (a) A solution of sodium methoxide/methanol (0.5 mL of a 1 M solution) and **3t** (18 mg, 0.07 mmol) was stirred at room temperature for 17 h. Acidification, extraction, washing, and drying afforded a mixture of **3c** and **3t** in a 82:18 ratio, ^{13}C NMR for ketone prepared also in ref 4 and 6:213.3 (C=O), 18.96 (angular methyl?). NMR values are for cis ketone in the mixture. (b) An ethereal solution (75 mL) of **3t** (0.40 g, 0.15 mmol) saturated with dry HCl was stirred at room temperature for 120 h. The solution was washed with water and dried over $MgSO_4$. Removal of the solvent afforded a mixture of **3c** and **3t** having the uncalibrated area ratio, 82:18, based on capillary gas chromatography. Eventually our capillary GC column lost the ability to analyze ketones without isomerization. Another equilibration was carried out at 22 ± 1 °C, with analyses done on a 5-μm silica analytical liquid chromatography column with cyclohexane–ethyl acetate carrier. Calibration of peaks heights from refractive index detection was done by using standards isolated from the same column. In this case the *K* values were 3.89 and 4.02, starting from cis and trans isomers. Equilibration was shown not to be accompanied by disappearance of ketone.

Ozonolysis of Enyne (6*Z* and 6*E*) Mixture. Ozone was passed through a solution of **6*Z*** and **6*E*** (30 mg, 0.084 mmol) in methanol (6 mL) and methylene chloride (5 mL) at −30 °C until there was no further uptake (approximately 2 min). The solution was flushed with nitrogen for 5 min at −30 °C before dimethylsulfide (1 mL) was added. Stirring was continued at −30 °C for 1 h, at 0 °C for 1 h, and at room temperature for 20 h. The solvents were removed in vacuo and the capillary GC determined. **3t** and **3c** were found in an 86:14 ratio.

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