for *cis*-5-methylproline and *trans*-5-methylproline were 45.5 and 49.7 min, respectively. A slightly different buffer sequence was used previously to separate these isomers.[11] The *cis*-5-ethylproline and *trans*-5-ethylproline isomers had retention times of 55.7 and 63.2 min, respectively. It was determined that these hydrolysis conditions led to a small amount of the trans material. This isomerization was found to be time-dependent by analysis of the hydrolysate of pure *cis*-5-methylprolinamide (6 N HCl, 110 °C) in sealed tubes at various time periods.

(*S*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidinepropionyl Chloride (2).[9] PCl_5 (13.9 g, 66.6 mmol) was added to a solution of oxazolidinone[10] 1 (19.5 g, 66.6 mmol) in 60 mL of benzene (dried over molecular sieves) at 0 °C, and the mixture was stirred at 0 °C for 1 h during which time the reaction mixture became homogeneous. The solvent was removed under vacuum, and the $POCl_3$ byproduct was codistilled with 2 × 25 mL dry toluene to give the solid acid chloride.

General Procedure for 3. Method A. To a cooled solution of acid chloride 2 (6.2 g, 20 mmol) in 30 mL of dry benzene was added excess diazoalkane (30 mmol) in ether (caution). The reaction mixture was stirred at 0 °C for 0.5 h and the excess diazoalkane and solvents were removed at the water aspirator to give a yellow syrup. The syrup was dissolved in 150 mL of $CHCl_3$, shaken with 48% HI in portions (8 mL, 8 mL, 9 mL), washed with water, 2% $Na_2S_2O_3$, water, and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a brown solid. Chromatography of the solid on a silica gel column with EtOAc/hexane (2:3) gave the pure compound.

Method B. To a solution of 67 mmol of the acid chloride 2 in 30 mL of HMPA (toxic) was added the tetraalkyltin (67.32 mmol) and $PhCH_2Pd(PH_3)_2Cl$ (40 mg, 0.033 mmol).[12] The reaction mixture was heated at 65 °C for 4 h, diluted with water, and extracted with EtOAc. The EtOAc layer was washed with H_2O, 5% $NaHCO_3$, H_2O, 5% $NaHSO_4$, H_2O, and brine and was dried over Na_2SO_4. The EtOAc was filtered and concentrated to give an oil. Filtration of the oil through a silica gel column with EtOAc/hexane (2:3) gave the pure product.

General Procedure for 4. To a solution of 3 (35 mmol) in 500 mL of distilled THF was added at 0 °C concentrated NH_4OH (160 mL). The reaction mixture was stirred at 0 °C for 5 h, then at 25 °C overnight. Evaporation of the solvent followed by recrystallization from hot EtOAc gave the desired product.

General Procedure for 7. A total of 1.8 mmol of 4 was dissolved in a mixture of 25 mL of MeOH and 2.5 mL of glacial acetic acid. The catalyst (100 mg) was added and the reduction under H_2 at atmospheric pressure was followed by TLC. Upon completion of the reaction, the mixture was filtered through Celite, concentrated to dryness, and flash chromatographed (CH_2Cl_2/MeOH; 3:1). Recrystallization from CH_2Cl_2 gave the desired product.

Assay for Enantiomeric Purity. The enantiomeric (2*S*,5*S*)- and (2*R*,5*R*)-5-methylprolinamides were characterized by HPLC analysis after derivatization by the GITC procedure.[14] A solution of ~5 mg of the amino acid amide was dissolved in 2.5 mL of 0.4% Et_3N. To this aqueous solution was added 2.5 mL of a solution of 0.5% 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate in CH_3CN. After ~20 min at room temperature, the resulting diastereomeric thiourea adducts were analyzed by reversed-phase HPLC on a 5-μm C-18 column (4.5 × 250 mm; Altex) using isocratic elution (30% CH_3CN, eluent 0.03 M in NH_4OAc, pH 4.5) and absorption at 250 nm.

Acknowledgment. The support and encouragement of Dr. John G. Moffatt is gratefully acknowledged.

Perhydroazulenes. 6. 4-Keto Derivatives with Bridgehead Methyl Substituents[1]

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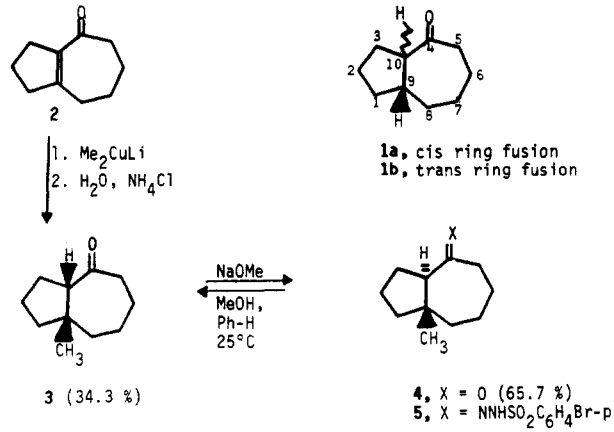
Received November 7, 1985

The two 9-methyl stereoisomers 3 and 4 and the two 10-methyl stereoisomers 8 and 9 of 4-ketoperhydroazulene have been prepared and fully characterized by means of spectra, analyses, and crystal structures. Several routes, including the selective methylation of the enone 2 to form the unsaturated ketone 12, were used (Schemes II and III) to form the 10-methyl compounds 8 and 9. Methylation of the lithium enolate (7) of 4-ketoperhydroazulene yielded a mixture of monoalkylated products containing 97% of the cis isomer 8 and 3% of the trans isomer 9. Probable conformations for the enolates and alkylated products obtained in this study are discussed.

To continue our study[2-4] of the synthesis and conformation of 4-ketoperhydroazulene derivatives 1 (Scheme I), we have examined the stereochemistry and conformation of the products formed when a methyl group is introduced at either of the two bridgehead positions C9 or C10. The 9-methyl ketones 3 and 4 were obtained by the previously described[5] addition of lithium dimethylcuprate to the enone 2.[2] The stereoisomeric products were separated by HPLC and the equilibrium composition (34.2% 3 and 65.7% 48 reported[5a] ca. 1:2) was measured in a C_6H_6–MeOH mixture (1:1 v/v) at 25.0 °C in the presence

Scheme I



(1) A portion of this research was supported by Public Health Service Grant R01-GM-30735 from the National Institute of General Medical Science. The execution of this research was also aided by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and an NMR spectrometer.

(2) House, H. O.; Lee, J. H. C.; VanDerveer, D.; Wissinger, J. E. *J. Org. Chem.* **1983**, *48*, 5285.

(3) House, H. O.; Gaa, P. C.; Lee, J. H. C.; VanDerveer, D. *J. Org. Chem.* **1983**, *48*, 1670.

(4) House, H. O.; Gaa, P. C.; VanDerveer, D. *J. Org. Chem.* **1983**, *48*, 1661.

(5) (a) Marshall, J. A.; Huffman, W. F.; Ruth, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 4691. (b) Balf, R. J.; Rao, B.; Weiler, L. *Can. J. Chem.* **1971**, *49*, 3135.

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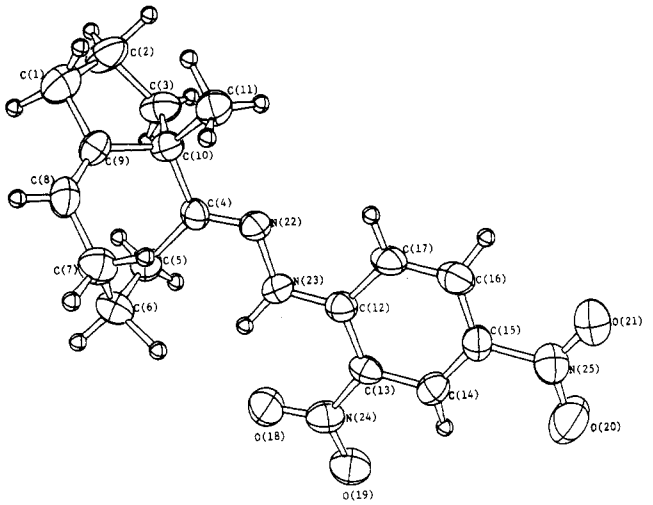


Figure 1. Perspective view of the molecular structure of the (2,4-dinitrophenyl)hydrazone of 10-methyl-4-keto-$\Delta^{8(9)}$-octahydroazulene. (The H atom thermal parameters have been reduced for clarity.)

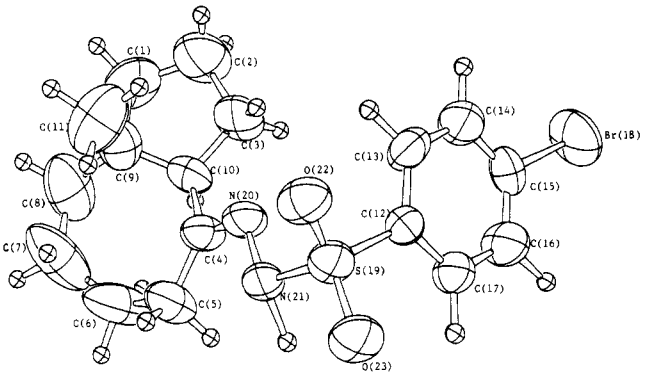


Figure 2. Perspective view of the molecular structure of the ((*p*-bromophenyl)sulfonyl)hydrazone of *trans*-9-methyl-4-ketoperhydroazulene. (The H atom thermal parameters have been reduced for clarity.)

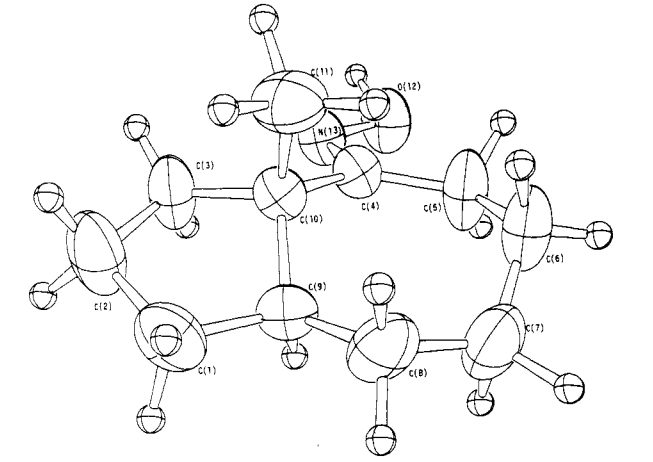


Figure 3. Perspective view of the molecular structure of the oxime of *trans*-10-methyl-4-ketoperhydroazulene. (The H atom thermal parameters have been reduced for clarity.)

of NaOMe as a basic catalyst. Previous workers[5] had assigned the stereochemistry to these two isomers on the basis that the more abundant trans isomer **4** was expected to be more stable[6] and to have a higher field NMR methyl signal (δ 0.74) than the cis isomer **3** (δ 1.18). We have now removed any ambiguity from these assignments by converting the trans ketone **4** to its sulfonylhydrazone derivative **5** and determining the structure by X-ray crystallography (see Figure 2).

The relative stabilities of the various conformers of ketones **3** and **4** were explored by using Allinger's MM2

(6) The equilibrium composition of the parent ketone **1** at 25 °C in a C_6H_6–MeOH mixture (1:1 v/v) was found[4] to be 12.9% cis isomer **1a** and 87.1% trans isomer **1b**.

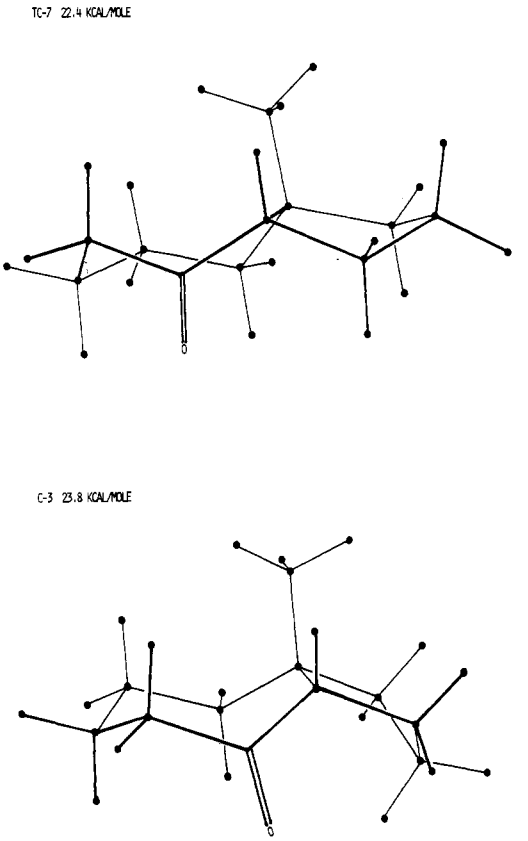


Figure 4. Low-energy conformers of *cis*-9-methyl-4-ketoperhydroazulene.

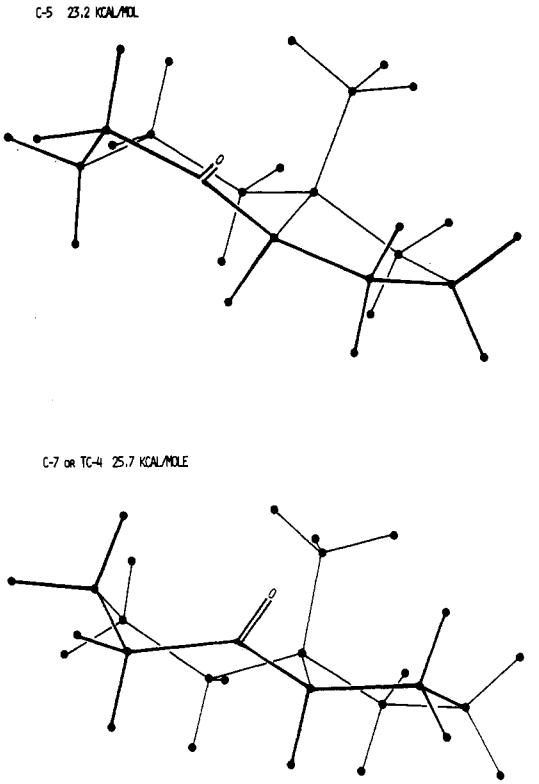
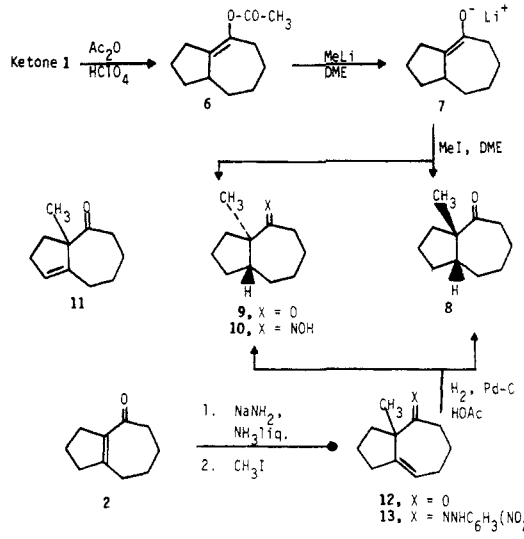
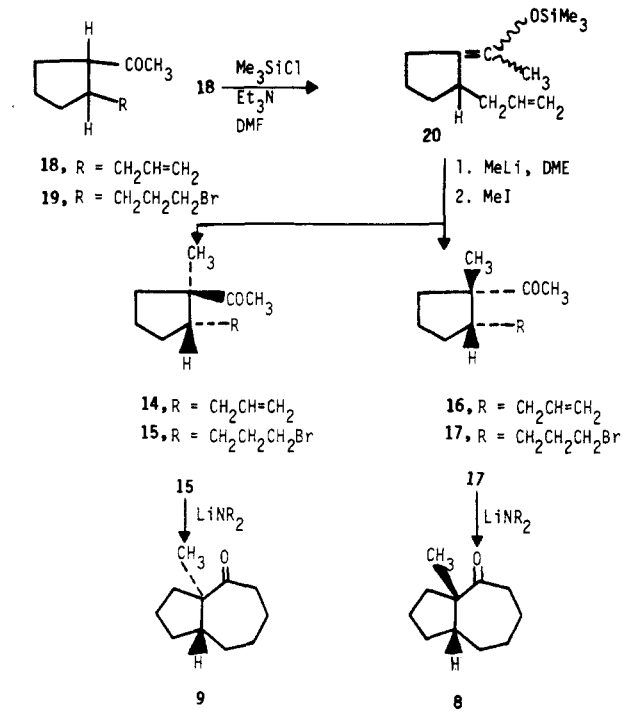


Figure 5. Low-energy conformers of *trans*-9-methyl-4-ketoperhydroazulene.

Scheme II



Scheme III



molecular mechanics program[7] to minimize the energies of the conformers being studied. The conformations to be considered were selected by the systematic method of DeClercq[8,9] in an effort to find all probable conformations for the ketones **3** and **4**. Figure 4 presents drawings of the lowest energy conformers found for the cis ketone **3** and Figure 5 contains the corresponding drawings of the trans ketone **4**. These calculations predict that the cis and trans ketones **3** and **4** will be similar in stability[10] and that the C(5) conformer is the most stable conformation of the trans ketone **4**. The ketone moiety present in the crystalline trans ketone derivative **5** (Figure 2) reveals that this moiety possesses the predicted C(5) conformation.

Methylation of the Ketone 1. We wished to examine the proportion of *cis*- (**8**) and *trans*- (**9**) 10-methyl ketones (see Scheme II) that would be formed in the kinetically controlled reaction of the lithium enolate **7** (from enol acetate **6**) with methyl iodide. To facilitate this study, we needed authentic samples of the *cis*- and *trans*-10-methyl ketones **8** and **9**. Repetition of the previously described[4] conversions of the unsaturated ketone 18 (Scheme III) to the silyl enol ether **20** followed by formation and methylation of the corresponding lithium enolate formed a mixture of the cis (**16**, ca. 80%) and trans (**14**, ca. 20%) methylated ketones. The isomers were separated by preparative HPLC and the cis isomer **16** was converted to the to the *cis*-10-methyl ketone **8** by previously described procedures.[4] This *cis*-10-methyl ketone **8** had been fully characterized previously, including the determination of the crystal structure of the corresponding oxime.

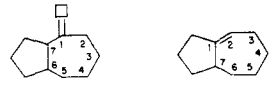
When the same reaction sequence was followed to convert the trans ketone **14** successively to the bromo ketone **15** and the trans bicyclic ketone **9**, we obtained the ketone **9** as a liquid product whose spectra did not correspond with the spectra of the product tentatively identified as the trans ketone **9** in the earlier study. Consequently, we explored other synthetic routes to the ketone **9** including the methylation of the enolate(s) derived from the unsaturated ketone **2** to form the unsaturated ketone **12**. (The absence of the structurally isomeric alkylation product **11** is discussed later.) This product **12**, whose structure was verified by determining the crystal structure of the corresponding dinitrophenylhydrazone **13** (see Figure 1), was hydrogenated under a variety of conditions (see Experimental Section) to form a mixture of the ketones **8** and **9**. Under the most favorable conditions we explored (Pd-on-C catalyst in HOAc), the product mixture contained 28% of the trans ketone **9** that was identical in all respects with the product obtained in the present study from ketone **14**. To remove any uncertainty, the trans ketone **9** was converted to its oxime **10** whose crystal structure was determined (see Figure 3).

With samples of both methylated ketones **8** and **9** in hand, we were able to demonstrate that the alkylation of the lithium enolate **7** (Scheme II) in DME formed mainly the cis product **8** (97% of the monoalkylated product) accompanied by only 3% of the trans isomer **9**. MM2 molecular mechanics calculations for various conformers of the alkylated products **8** and **9**, reported in an earlier publication,[4] indicated that the cis and trans products are of approximately equal stability.[11] The creditability of

(7) For reviews, see: (a) Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1–82. (b) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982. We are grateful to Professor Allinger and his associates for providing us with copies of his MM1, MMP1, MM2, and MMP2 programs that can be run on our local CDC Cyber 835 computer. The version of the MMP2 program available to us lacks the necessary parameters for calculations on conjugated systems that incorporate heteroatoms.

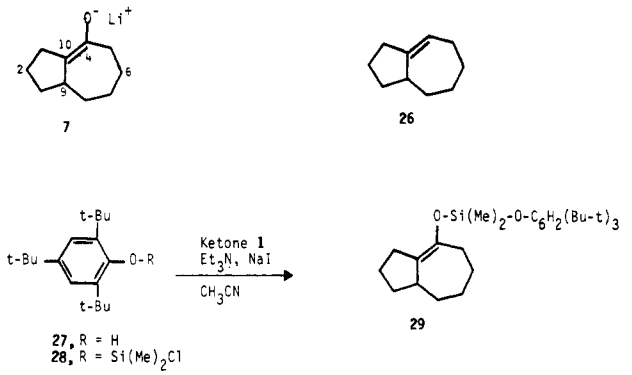
(8) (a) DeClercq, P. J. *J. Org. Chem.* **1981**, *46*, 667. (b) DeClercq, P. J. *Tetrahedron* **1981**, *37*, 4277. (c) DeClercq, P. J. *Tetrahedron* **1984**, *40*, 3717, 3729. We are grateful to Dr. DeClercq for providing us with complete listings for his current programs.

(9) The nomenclature being used to designate conformations of the seven-membered ring is that suggested by DeClercq[8] based upon the earlier cycloheptane designations introduced by Hendrickson [Hendrickson, J. B. *Tetrahedron* **1963**, *19*, 1387]. In this scheme, the chair (C), twist-chair (TC), boat (B), and twist-boat (TB) are designated by the capital letters indicated and the number in parentheses indicates the atom sectioned by the symmetry element. The numbering schemes used to designate conformations for 4-keto derivatives and $\Delta^{4(10)}$-unsaturated derivatives in this paper are shown in the following formulas.



(10) The Boltzman relationship was used to calculate the predicted populations of the 4 lowest energy conformers (Figures 4 and 5) and 4 additional low energy conformers (shown as Figures 11 and 12 in the supplementary material that accompanies this paper) present at 25 °C. The estimated equilibrium composition was 81% cis ketone **3** and 19% trans ketone **4** instead of the actual values, 34% cis (**3**) and 66% trans (**4**).

Scheme IV



these calculations is supported by the facts that both the previously reported[4] crystal structure for the oxime of cis ketone 8 [TC(7) conformer] and the crystal structure reported in this paper for the trans ketone oxime **10** [C(5) conformer or the closely related TC(1) conformer, see Figure 8] correspond to the conformations of ketones **8** and **9** that were previously calculated to be most favorable. As in other cases, we conclude that the very dominant formation of cis alkylated product **8** in the reaction studied here is attributable not to relative product stabilities but to a very selective attack by the alkylating agent in a transition state that has enolate-like geometry.

To examine the question of the probable conformations of the carbocyclic rings in the lithium enolate **7**, we again used DeClercq's procedure to select all reasonable conformers and the MM2 molecular mechanics program to find the relatively low-energy conformers for the olefin **26** (see Scheme IV), a model for the carbocyclic framework of the enolate **7**.[12] The low-energy conformers found for this olefin **26**, presented in Figures 9 and 10, suggest that all of the low-energy conformers of enolate **7** are of comparable energy and would be present in the reaction mixture. An earlier publication[3] noted the possibility of controlling the conformation of the seven-membered ring in such compounds by use of bulky substituent at the C-6 position of the enolate;[7] this idea is explored in an accompanying paper.[13] Presumably, the conformation of the five-membered ring could also be controlled by the use of a bulky substituent at C-2 with the proper stereochemistry. Thus far, we have prepared only one of the two sets of stereoisomeric 2-*tert*-butyl-4-ketoperhydroazulenes (*tert*-butyl group syn to H at C-9);[14] the effect of introducing an epimeric *tert*-butyl group anti to the H atom at C-9 is not known.

We attempted to obtain more direct evidence concerning the favored conformation of the enolate **7** by examining

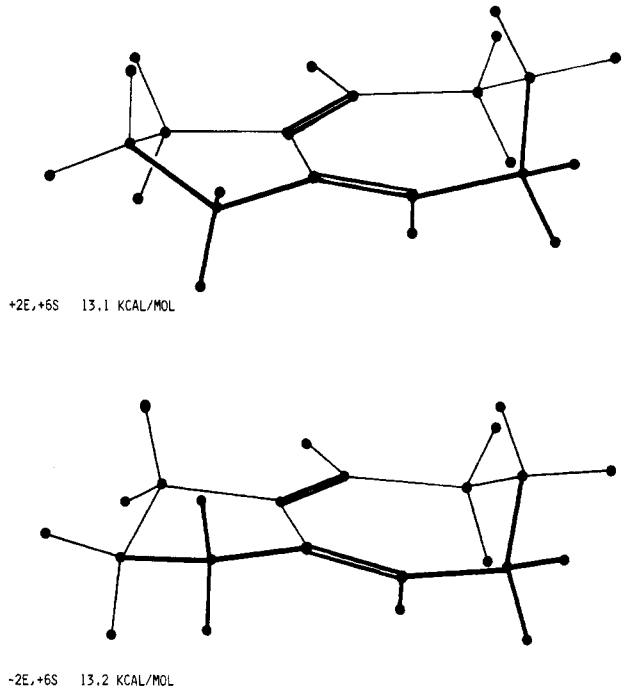


Figure 6. Low-energy conformations of $\Delta^{4(10)}$-, $\Delta^{8(9)}$-hexahydroazulene.

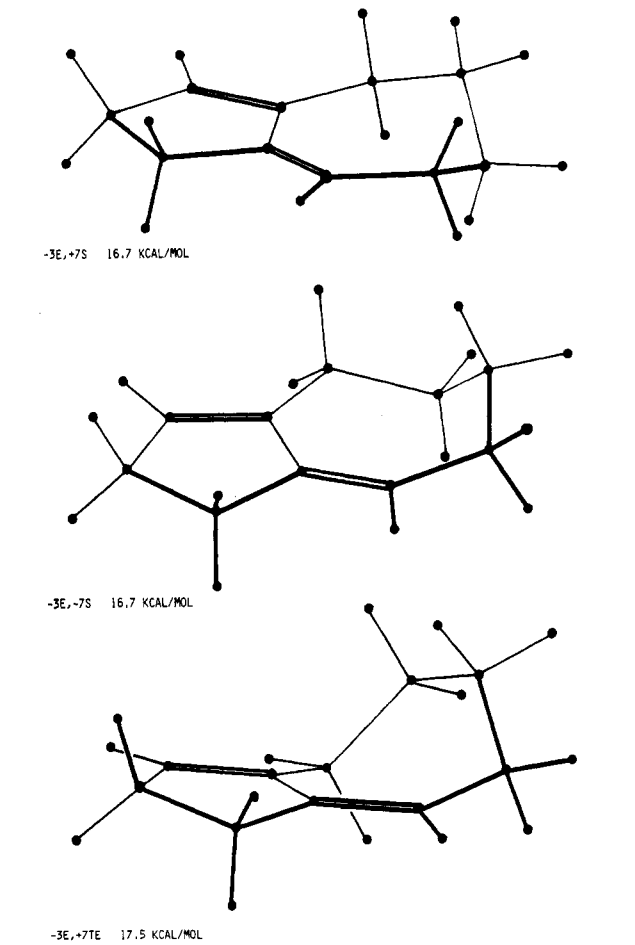


Figure 7. Low-energy conformations of $\Delta^{3(10)}$-, $\Delta^{8(9)}$-hexahydroazulene.

the crystal structure of an enol derivative. Although we succeeded in preparing the crystalline silyl enol ether **29**, our efforts to obtain an unambiguous crystal structure were unsuccessful. Apparently, there was sufficient thermal motion in the crystal of this substance that even data

(11) When the Boltzman relationship was used to calculate the populations present at 25 °C for the eight conformers reported previously,[4] the estimated equilibrium composition was 58% of the cis ketone **8** and 42% of the trans isomer **9**.

(12) Since reliable parameters for vinyl alcohol derivatives in MM2 calculations are not currently available, we used the olefin **26** as a model for the carbocyclic rings in the enolate **7**. Although it is probable that the lithium enolate **7** exists in solution as a dimeric or tetrameric cluster of Li and O atoms, the favored conformation of the carbocyclic rings bonded to this cluster is probably not substantially altered by the exact structure of the Li–O cluster. For a review of the structure of lithium enolates, see: Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737–2769. More recently, a series of crystal structures for lithium enolates of ketones have been reported. For examples, see: Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. Seebach, D.; Amstutz, R.; Dunitz, J. D. *Ibid.* **1981**, *64*, 2622. Laube, T.; Dunitz, J. D.; Seebach, D. *Ibid.* **1985**, *60*, 1373. Willard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 3345.

(13) House, H. O.; Nomura, G. S.; VanDerveer, D. *J. Org. Chem.*, following paper in this issue.

(14) House, H. O.; Yau, C. C.; VanDerveer, D. *J. Org. Chem.* **1979**, *44*, 3031.

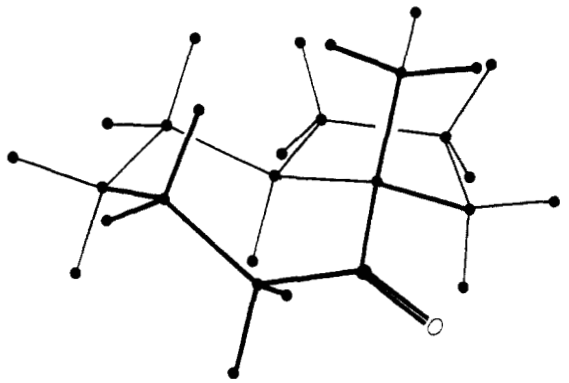


Figure 8. Perspective view of the *trans*-10-methyl-4-ketoperhydroazulene C(5) conformer present in a crystalline derivative.

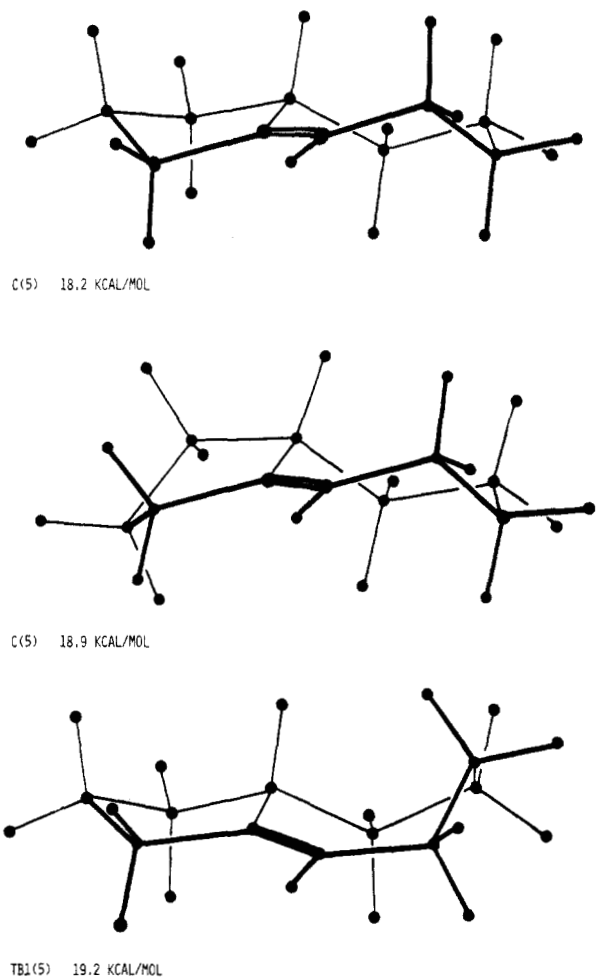


Figure 9. Low-energy conformations of $\Delta^{4(10)}$-octahydroazulene.

collected at about −80 °C failed to provide a structure in which the conformation of the perhydroazulene ring was well defined (see supplementary material).

Methylation of the Enone 2. The formation of the methylated ketone **12** containing, at most, a few percent of the structural isomer **11** is worthy of comment. The method ($NaNH_2$ in liquid NH_3) used to convert the starting enone **2** to its enolate anion(s) would be expected to allow substantial equilibration of the enolates during their formation.[15] Consequently, one would expect the enolate mixture formed to contain a mixture of the more

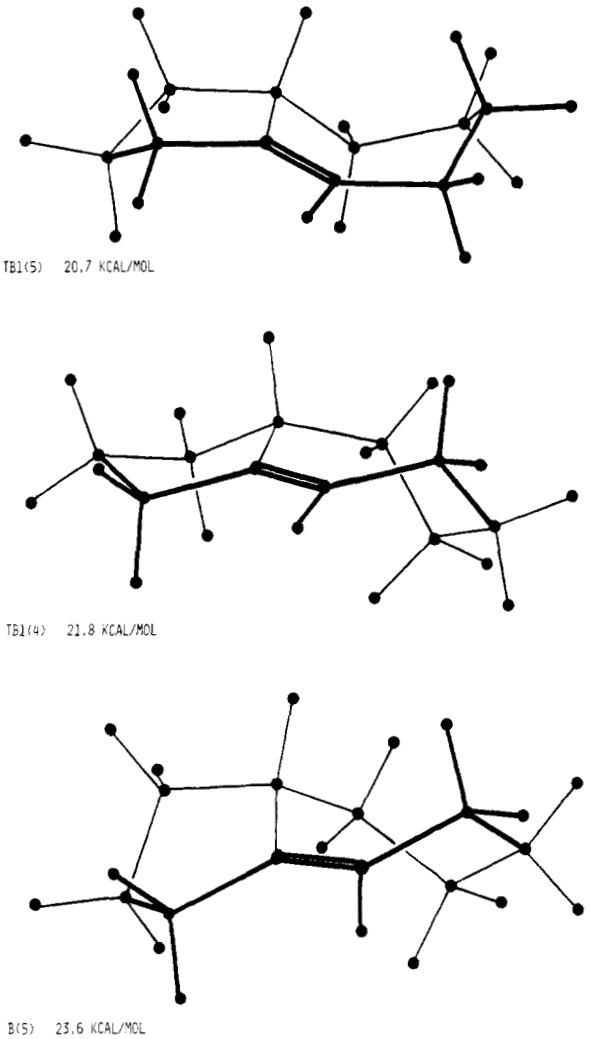
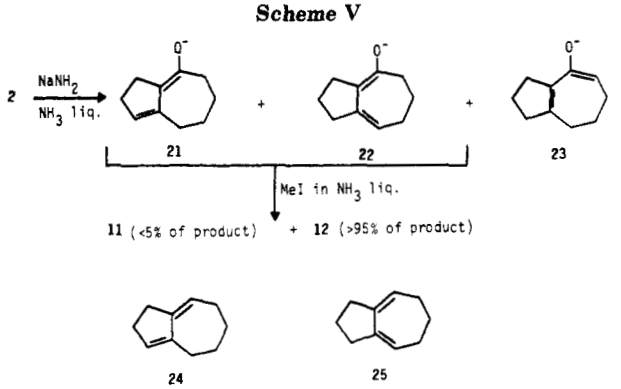


Figure 10. Low-energy conformations of $\Delta^{4(10)}$-octahydroazulene.

Scheme V



stable enolates **21** and **22** with little if any of the less stable cross-conjugated enolate **23** (see Scheme V). To estimate the expected composition of an equilibrium mixture of the enolates **21** and **22**, we used MMP2 molecular mechanics calculations with the related dienes **24** and **25** (the dienes were used as models because reliable parameters for heteroatoms in the MMP2 program are not presently available to us).[12] The results, summarized in drawings of the low-energy conformers in Figures 6 and 7, clearly indicate that the homoannular diene **25** is more stable and suggest that the enolate **22** should be favored at equilibrium. These observations concerning enolate stability are clearly compatible with the predominant formation of a single methylated product **12**. We also used MM2 molecular mechanics calculations to estimate the stabilities of the

(15) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341.
(16) For these diene conformers, the more recent nomenclature system introduced by DeClercq[8c] is used because the older nomenclature[9] is not applicable to these compounds.

various conformers of the two methylated products **11** and **12**.[17] These calculations indicated clearly that if product stability were an important factor, the major product formed from methylation of the enone **2** should be the unsaturated ketone **11** and not the observed product **12**. The results obtained are consistent with our general view that enolate stability and enolate reactivity, but not alkylated product stability, determine the major product formed in the alkylation of an enolate anion. Finally, it should be noted that the conformation of the ketone moiety present in the crystalline derivative **13** corresponds to one of the several low-energy conformers of comparable stability that are predicted for ketone **12**.

Experimental Section[18]

Preparation of the Unsaturated Ketone 2. A published[2] procedure converted 66.0 g (0.50 mol) of tetralin to 60.95 g (89.6%) of octalin distillation fractions containing ca. 77% of the $\Delta^{9(10)}$-isomer and ca. 23% of the $\Delta^{1(9)}$-isomer, bp 57.0–61.8 °C (5 mm); n^{25}_D 1.4935–1.4977. A known[2] ozonolysis–aldol condensation procedure converted 4.16 g of an octalin fraction (containing 94.6% or 28.9 mmol of $\Delta^{9(10)}$-isomer) to 3.381 g (77.9%) of the distilled enone **2** as a pale yellow liquid, n^{25}_D 1.5160, containing (GLC, silicone XE-60 on Chromosorb P) ca. 95% of the enone **2** (16.5 min) accompanied by three minor impurities eluted at 8.9 (3%), 10.1 (1%), and 12.0 min (1%). Chromatography (silica gel, EtOAc–hexane eluent) and subsequent distillation separated the pure (GLC) enone **2**, bp 76–78 °C (0.3 mm); n^{25}_D 1.5247 [lit.[2] bp 62–63 °C (0.25 mm); n^{25}_D 1.5261] (identified by comparison of IR and NMR spectra).

Preparation of the Methylated Ketone 12. Since efforts to methylate the enone **2** by forming the enolate with *t*-BuOK in *t*-BuOH[19] formed complex mixtures, the enolate was generated with $NaNH_2$ in liquid NH_3.[20] To a refluxing (−33 °C) solution of $NaNH_2$, prepared from 1.11 g (48.3 mmol) of Na, 41 mg (0.29 mmol) of $FeCl_3$, and 125 mL of liquid NH_3, was added, dropwise during 12 min, 6.73 g (44.9 mmol) of the enone **2**. After the resulting cold, greenish brown solution had been stirred for 1 h, 4.0 mL (9.12 g or 64 mmol) of MeI (purified by distillation from P_2O_5) was added dropwise during 5 min. The resulting yellow solution was stirred for 15 min and diluted with 50 mL of anhydrous ether, and the liquid NH_3 was allowed to evaporate. The mixture was partitioned between ether and saturated aqueous NH_4Cl and the combined ethereal solutions were washed with aqueous NH_4Cl and then dried and concentrated. Distillation of the residual liquid (short-path still) separated 6.59 g of crude product as a pale yellow liquid, bp 55–65 °C (0.45 mm), containing (HPLC on 10-μm silica gel with an EtOAc–hexane eluent, 1:19 v/v) the product ketone **12** (ca 67%, 45.7 min), the starting enone **2** (ca 11%, 102.7 min), and a number of minor unidentified peaks. Separation by preparative HPLC and distillation gave 4.311 g (59%) of the ketone **12** as a colorless liquid, bp 52–54 °C (0.1 mm), n^{25}_D 1.5030; GC analysis (silicone SE-30 on Chromosorb P): ketone **12** (ca 97%, 19.3 min), a minor impurity (ca. 3%, 17.3 min) isomeric (GC–MS) with the product **12** and believed to be the isomeric enone **11**. The spectral properties of the major product **12** follow: IR (CCl_4) 1701 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.3–2.8 (15 H, m, aliphatic CH including a Me singlet at 1.308), 5.59–5.64 (1 H, m, vinyl CH); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling), 214.7 (s), 147.9 (s), 119.7 (d), 58.5 (s), 39.6 (t), 38.0 (t), 33.0 (t), 26.5 (t), 25.4 (t), 22.8 (t), 21.6 (q); mass spectrum, *m/e* (relative intensity) 164 (39, M^+), 121 (21), 108 (86), 93 (100), 91 (22), 81 (26), 79 (31), 77 (21), 41 (23), 39 (25).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.57; H, 9.84.

Reaction of 45-mg (0.27 mmol) of the enone **12** with a solution of 59 mg (0.30 mmol) of 2,4-dinitrophenylhydrazine in 3 mL of a 1:1 mixture (v/v) of EtOH and aqueous 85% H_3PO_4 yielded an orange solid product which was collected and washed with EtOH. The crude product, mp 158–161 °C, was chromatographed (silica gel, CH_2Cl_2–hexane eluent, 3:1 v/v) to separate 63.4 mg (68%) of the derivative **13**, mp 162–163.5 °C, R_f 0.38 (TLC, silica gel, CH_2Cl_2–hexane eluent) from a minor unidentified impurity, R_f 0.27. Recrystallization (EtOH–CH_2Cl_2) separated the derivative **13** as orange plates, mp 161.5–163 °C; IR (CCl_4) 3325 (NH), 1620 cm^{-1} (C=N); UV max ($CHCl_3$) 366 nm (ε 20 600); ^1H NMR (300 MHz, $CDCl_3$) δ 1.3–2.7 (15 H, m, aliphatic CH including a Me singlet at 1.37), 5.48 (1 H, t, J = 7 Hz, vinyl CH), 7.94 (1 H, d, J = 10 Hz, aryl CH), 8.28 (1 H, d of d, J = 2.5 and 10 Hz, aryl CH), 9.11 (1 H, d, J = 2.5 Hz, aryl CH), 11.27 (1 H, br, NH); mass spectrum, *m/e* (relative intensity) 344 (28, M^+), 162 (44), 149 (90), 148 (100), 133 (41), 105 (35), 91 (50), 79 (35), 41 (31).

Anal. Calcd for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.36; H, 5.87; N, 16.19.

Preparation of the Saturated Ketone 1. Known procedures[22] converted cyclopentanone successively to 1-ethynyl-1-hydroxycyclopentane [62% yield, bp 72–75 °C (25 mm), n^{25}_D 1.4694] and to 1-acetylcyclopentene [45% yield, bp 85–92 °C (50 mm), n^{25}_D 1.4795]. The $TiCl_4$-catalyzed reaction of 1-acetylcyclopentene with allyltrimethylsilane in CH_2Cl_2 at −78 °C followed by hydrolysis before warming[4,22] formed a mixture of the cis and trans olefinic ketones **18** [71% yield, bp 69–71 °C (4 mm), n^{25}_D 1.4600]. The light-catalyzed addition of HBr[22b] to the unsaturated ketone **18** formed the bromo ketone **19** [mixture of stereoisomers, 66.5% yield, bp 77–79 °C (0.05 mm), n^{25}_D 1.4932] that reacted with $LiN(i\text{-}Pr)_2$ in boiling THF[4,22] to form a mixture of the cis (**1a**, minor) and trans (**1b**, major) ketones (63.9% yield, n^{25}_D 1.4875).

Preparation of the Enol Acetate 6. A solution of 3.00 g (19.7 mmol) of the ketone **1** (a mixture of stereoisomers), 15 mL (16.2 g, 160 mmol) of acetic anhydride, and 50 μL of aqueous 70% perchloric acid in 75 mL of anhydrous CCl_4 was stirred under an N_2 atmosphere at 25 °C for 2.5 h and then poured into a mixture of hexane and 150 mL of cold (5 °C), aqueous 10% KOH. The resulting mixture, which warmed briefly to 20 °C, was treated with additional aqueous 40% KOH until the pH of the aqueous phase was about 10. Then the layers were separated, the aqueous phase was extracted with additional hexane, and the combined organic layers were washed with aqueous $NaHCO_3$, dried, and concentrated. The residual liquid was distilled in a short-path still to separate 2.751 g (72%) of the crude enol acetate **6** as a pale yellow liquid, bp 68–71 °C (1.0 mm), n^{25}_D 1.4800, containing (GC, Carbowax 20M on Chromosorb P) a minor, unidentified component (t_R 7.7 min, ca. 3%), the starting ketone **1** (8.9 min, ca. 1%), and the enol acetate **6** (10.1 min, ca. 96%). A collected (GC) sample of the enol acetate **6**, n^{25}_D 1.4842, was used for characterization: IR (CCl_4) 1750 (ester C=O) and 1705 cm^{-1} (C=C); ^1H NMR (60 MHz, CCl_4) δ 1.0–2.8 (m, aliphatic CH including a Me singlet at 2.00); ^{13}C NMR ($CDCl_3$, multiplicity

(17) Drawings of the low-energy conformers for the ketone **12**, obtained from MM2 molecular mechanics calculations, are presented as Figures 13 and 14 and corresponding drawings the ketone **11** are presented as Figures 15–18 in the supplementary material that accompanies this paper. When the Boltzman relationship was used to calculate the populations present at 25 °C for the 17 low-energy conformers found for ketones **11** (Figures 15–18) and **12** (Figures 13–14), the estimated equilibrium composition was 98% of ketone **11** and 2% of ketone **12**.

(18) All melting points are corrected and all boiling points are uncorrected. Unless otherwise noted, $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer Model 299 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with either a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Model T-60A NMR spectrometer or at 300 MHz with a Bruker Model WM-300 NMR spectrometer. The ^{13}C NMR spectra were determined at 25 MHz with a JEOL Model PFT-100 NMR spectrometer or at 75 MHz with a Bruker Model WM-300 NMR spectrometer. The NMR chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with either a Hitachi (Perkin-Elmer) Model RMU-7 or a Varian MAT Model 112S mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

(19) For example, see: Ringold, H. J.; Malhotra, S. K. *Tetrahedron Lett.* **1962**, 669.

(20) Buchi, G.; Wuest, H. *J. Am. Chem. Soc.* **1974**, *96*, 7573.

(21) *International Tables for X-Ray Crystallography*, Vol 1, Kynoch Press: Birmingham, England, 1952.

(22) (a) House, H. O.; Phillips, W. V.; Sayer, T. S. B.; Yau, C. C. *J. Org. Chem.* **1978**, *43*, 700. (b) House, H. O.; Sayer, T. S. B.; Yau, C. C. *Ibid.* **1978**, *43*, 2153.

on off-resonance decoupling) 168.3 (s), 142.5 (s), 134.1 (s), 42.1 (d), 35.9 (t), 33.4 (t,2C atoms), 30.4 (t), 30.0 (t), 25.5 (t), 24.8 (t), 20.7 ppm (q); mass spectrum, *m/e* (relative intensity) 194 (2, M^+), 152 (71), 123 (32), 111 (59), 110 (36), 95 (51), 81 (26), 79 (29), 67 (56), 55 (26), 53 (20), 43 (100), 41 (59), 39 (34).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.08; H, 9.38.

Preparation of the 10-Methyl Ketones 8 and 9. A. From the Monocyclic Precursor 18. In a modification of a previously described[4] experiment, 11.2 g (73.7 mmol) of the ketone **18** in 11 mL of DMF was added, dropwise during 45 min, to a reluxing solution of 14.9 g (147 mmol) of Et_3N and 15.4 g (143 mmol) of Me_3SiCl in 83 mL of DMF. After the mixture had been refluxed for 15 h, use of the previously described isolation procedure separated the crude product as a brown liquid that contained (GC, Apiezon M on Chromosorb P) ca. 25% of the starting ketone **18** (t_R 5.8 min), ca. 9% of an unidentified component (10.3 min) that may be the structurally isomeric enol ether, and ca. 66% of a mixture of the two stereoisomers of enol ether **20** (13.4 and 16.4 min). Fractional distillation (60-cm Teflon spinning-band column) separated 4.82 g (43% recovery) of the starting ketone **18**, bp 42–44 °C (1.3 mm), 2.21 g of a mixture (GC) of components, bp 48–57 °C (1.3 mm), and 8.896 g (54%) of a mixture of the stereoisomeric enol ethers **20**, bp 57–62 °C (1.3 mm), n^{25}_D 1.4599–1.4600, identified by comparison of IR and NMR spectra).

The enol ether **20** was converted to its enolate and methylated as previously described[4] by employing 30.6 mmol of MeLi (from concentration of 20.0 mL of ethereal 1.53 M MeLi), 10 mg of Ph_3CH (an indicator), 4.798 g (21.4 mmol) of enol ether **20**, and 50 mL of DME followed by 11.4 g (80.3 mmol) of MeI with a reaction time of 5 min. Distillation (short-path still) separated 3.44 g of the crude product as a colorless liquid, bp 50–55 °C (0.3 mm), containing (GC, Silicone XE-60 on Chromosorb P) 78% of the cis ketone **16** (16.9 min) and 16.5% of the trans ketone **14** (19.8 min). In two different experiments, we found the composition of the alkylated product to be about 4:1 cis ketone **16** to trans ketone **14** rather than the 1:1 mixture reported earlier.[4] The material was separated by HPLC (10-μm silica gel, EtOAc–hexane, 1:19 v/v) and the fractions containing each pure component were distilled under reduced pressure (short-path still). The cis isomer **16** amounted to 1.875 g (55.6%) of colorless liquid, bp 48 °C (0.3 mm), n^{25}_D 1.4639 (lit.[4] n^{25}_D 1.4614) with IR and NMR spectra corresponding to those reported previously. The trans isomer **14** was obtained as 346 mg (10.3%) of colorless liquid, bp 51.5 °C (0.3 mm), n^{25}_D 1.4658 (lit.[4] n^{25}_D 1.4617) with IR and NMR spectra corresponding to those reported previously.

The cis ketone **16** (492 mg, 2.97 mmol) was converted to the corresponding bromo ketone **17** (685 mg or 93% of crude product) as previously described[4] and then treated with $(i\text{-Pr})_2NLi$ in THF (with $PhCH{=}NCH_2Ph$ indicator[23]) to form 294 mg of a colorless liquid that contained (GC, Silicone XE-60 on Chromosorb P) ca. 8% of an unknown component (t_R 4.5 min), ca. 11% of the ketone **16** (6.1 min), and ca. 70% of the *cis*-10-methyl ketone **8** (12.5 min). This mixture was separated by HPLC (10-μm silica gel, EtOAc–hexane, 1:19 v/v) and appropriate fractions were distilled short-path still) to separate 135.5 mg (27.5% based on ketone **16**) of the *cis*-10-methyl ketone **8**, n^{25}_D 1.4841 (lit.[4] n^{25}_D 1.4921), identified with previously described samples by comparison of IR, NMR, and mass spectra.

A 346-mg (2.08 mmol) sample of the trans ketone **14** was converted to the corresponding bromo ketone **15** (545 mg or 100% of crude product) by the previously published procedure[4] and identified with the previous sample by comparison of IR and NMR spectra. However, the product formed upon reaction of this bromo ketone **15** with $(i\text{-Pr})_2NLi$ in THF, subsequently shown to be the *trans*-10-methyl ketone **9**, has spectral properties that *are not identical* with the spectral properties of the material *tentatively identified* as the trans ketone **9** in our earlier publication.[4] Since none of the earlier sample remains, we are unable to define the composition of the material reported previously. To a cold (−78 °C), red solution, prepared from 50 mL of THF, $PhCH{=}NCH_2Ph$ indicator,[23] and 5.6 mL of pentane containing 3.09 mmol of $(i\text{-Pr})_2NLi$, was added, dropwise and with stirring during 10 min, 514 mg (2.08 mmol) of the crude trans bromo ketone **15** in 10 mL of THF. The resulting pale orange (excess strong base) solution was warmed during 5 min and then refluxed for 45 min. The reaction mixture was partitioned between ether and aqueous NH_4Cl and the organic layer was dried, concentrated, and distilled (short-path still) to separate 205 mg of a pale yellow liquid containing (GC, Silicone XE-60 on Chromosorb P) ca. 5% of the ketone **14** (t_R 7.2 min), ca. 9% of the cis ketone **8** (12.6 min), ca. 79% of the trans ketone **9** (16.5 min), and several minor unidentified components. This mixture was separated by HPLC (10-μm silica gel, EtOAc–hexane, 1:19 v/v); the retention times were 63.3 min for ketone **16**, 69.4 min for ketone **8**, 76.7 min for ketone **14**, and 82.6 min for the trans ketone **9**. Fractions containing the ketone **9** were distilled (short-path) still to separate 89.1 mg (26% based on ketone **14**) of the pure (GC) ketone **9** as a colorless liquid, n^{25}_D 1.4800: IR (CCl_4) 1691 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.5–2.6 (2 H, m, CHCO), 1.3–2.0 (13 H, m, aliphatic CH), 1.08–1.09 (3 H, d, J = 0.7 Hz, Me group with long range W coupling); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling) 217.5 (s), 57.2 (s), 45.4 (d), 44.1 (t), 37.7 (t), 31.3 (t), 29.9 (t), 29.6 (t), 23.9 (t), 19.7 (t), 18.3 ppm (q); mass spectrum, *m/e* (relative intensity) 166 (18, M^+), 97 (24), 95 (85), 83 (42), 81 (100), 69 (29), 67 (89), 56 (21), 55 (42), 43 (20), 41 (62), 39 (31).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.20; H, 10.98.

B. From the Unsaturated Ketone 12. A solution of 1.10 g (6.70 mmol) of the enone **12** in 350 mL of HOAc was stirred under a hydrogen atmosphere (1 atm) and over the catalyst obtained by prereducing a slurry of 5% Pd-on-C catalyst (Engelhard) in HOAc. After 78 min, when 1.05 equiv of hydrogen had been absorbed, the mixture was filtered (Celite) and then partitioned between water and CH_2Cl_2. The CH_2Cl_2 solution was washed with aqueous $NaHCO_3$ and then dried and concentrated. The crude product from a comparable small-scale hydrogenation of the enone **12** (71 mg) contained (GC, Carbowax 20M on Chromosorb P at 180 °C, apparatus calibrated with known mixtures) 72% of the cis ketone **8** (t_R 13.06 min) and 28% of the trans ketone **9** (16.88 min) along with the internal standard (1-phenyloctane, 10.30 min) but none of the starting enone **12** (14.96 min). The crude product from the larger scale hydrogenation was first chromatographed (silica gel, EtOAc–hexane, 1:19 v/v) and the fractions enriched in one or another of the ketones **8** or **9** were separated by HPLC (10-μm silica gel, EtOAc–hexane, 1:19 v/v); retention times: cis isomer **8**, 46.7 min; trans isomer **9**, 55.0 min. Appropriate fractions were distilled (0.6 mm, short-path still) to separate each pure ketone as a colorless liquid. The yield of the cis ketone **8** was 665 mg (59.9%), n^{25}_D 1.4854 (lit.[4] n^{25}_D 1.4921) (identified by comparison of GC retention times and IR, ^1H NMR, and mass spectra). The yield of the trans isomer **9** was 205 mg (18.4% corresponding to a 24:76 mixture of ketones **9** to **8**), n^{25}_D 1.4868; this product was identified with the sample described in the previous section of this paper by comparison of GC retention times and IR, ^1H NMR, and mass spectra.

Small samples (50–337 mg) of the enone **12** were hydrogenated at 1 atm in various solvents and over various catalysts and the crude reaction products, separated as described above, were mixed with known weights of internal standard (1-phenyloctane) and analyzed (GC). The following is a list of the catalyst, solvent, and corresponding percent of cis isomer **8** in the mixture: 5% Pt-on-C, EtOH, 97%; 5% Pt-on-C, HOAc, 97%; 5% Rh-on-alumina, EtOH, 95%; 5% Pd-on-C, EtOH, 82%; 30% Pd-on-C, EtOH, 85%; 5% Pd-on-C, HOAc, 72%. These results are in agreement with the idea[24] that hydrogenations over Pd catalysts tend to allow more isomerization than hydrogenations over other noble metal catalysts.

Methylation of the Lithium Enolate 7. This reaction used 1,2-dimethoxyethane or DME, distilled from $LiAlH_4$ and MeI that had been refluxed for 5 h over P_2O_5 and through a column packed with sections of Cu wire[25] and then distilled, bp 41 °C, n^{25}_D 1.5272.

(23) Duhamel, L.; Plaquevent, J. C. *J. Org. Chem.* **1979**, *44*, 3404. This indicator gives a deep red color in the presence of RLi reagents or strong bases.

(24) Augustine, R. L.; Yaghmaie, F.; Van Peppen, J. F. *J. Org. Chem.* **1984**, *49*, 1865.

(25) Gand, E. *Ann. Faculte Sci. Marseille* **1941**, *15*, 29; *Chem. Abstr.* **1944**, *38*, 3951.

The general technique[26] for converting an enol acetate to a lithium enolate was followed with 2.5 mL of an ether solution containing 4.1 mmol of MeLi, 10 mg of Ph_3H (indicator), 45 mL of DME, and 259 mg (1.26 mmol) of the enol acetate **6** in 0.5 mL of DME. After the resulting orange (excess MeLi) solution had been stirred for 3 min, 1.5 mL (24 mmol) of MeI was added and the resulting mixture was stirred vigorously for 45 s and then quenched with 15 mL of aqueous 1 M HCl. The resulting solution was partitioned between water and ether and the ethereal extract was dried and concentrated. The residual liquid (after filtration through a short column of silica gel with an EtOAc–hexane eluent) was mixed with 105.9 mg of 1-phenyloctane (an internal standard) for GC analysis (Carbowax 20M on Chromosorb P, apparatus calibrated with known mixtures of authentic samples). The crude product contained 1-phenyloctane (t_R 22.5 min), the cis methylated ketone **8** (26.7 min, 66% yield), the unmethylated ketone **1** (29.2 min, 14% yield), the trans methylated ketone **9** (34.3 min, 1.8% yield), and two minor unidentified components (16.2 min and 18.9 min). Thus, our mixture of methylated ketones was composed of 97% cis isomer **8** and 3% trans isomer **9**.

A second experiment was performed by employing 475 mg (2.45 mmol) of the enol acetate **6**, 7.35 mmol of MeLi, 45 mL of DME, and 24 mmol of MeI. The crude product was distilled (short-path still) and the distillate, 347 mg of colorless liquid, was purified by HPLC (10-μm silica gel, EtOAc–hexane, 3:97 v/v) to separate the cis ketone **8** (t_R 88 min) from the starting ketones **1** (cis 110 min, trans 130 min). The resulting material was distilled in a short-path still under reduced pressure to separate 75.5 mg (19%) of the pure cis ketone **8**, n^{25}_D 1.4922 (lit.[4] n^{25}_D 1.4921); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling) 215.5 (s), 59.1 (s), 47.6 (d), 40.4 (t), 35.0 (t), 33.7 (t), 32.9 (t), 29.3 (t), 27.4 (t), 26.0 (q), 22.6 ppm (t), identified with the previously described sample[4] by comparison of IR, ^1H NMR, ^{13}C NMR, and mass spectra.

Preparation of the Oxime 10 Derived from the *trans*-10-Methyl Ketone 9. A solution of 14.1 mg (0.085 mmol) of the trans ketone **9** and 36.0 mg (0.52 mmol) of $HONH_3Cl$ in 0.25 mL of water and 0.5 mL of EtOH was refluxed for 45 min and then cooled to separate 8.3 mg (54%) of the oxime. Recrystallization (water–EtOH) afforded the oxime **10** as colorless square needles, mp 146–147 °C: IR (CCl_4) 3605 (unassociated OH), 3260 cm^{-1} (associated OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.8 (1 H, br s, OH), 2.98–3.08 (1 H, m, CHC=N), 2.30–2.42 (1 H, m, CHC=N), 1.0–2.0 (16 H, m, aliphatic CH including a Me doublet at 1.075, J = 0.7 Hz); mass spectrum, m/e (relative intensity) 181 (16, M^+), 164 (100), 149 (19), 107 (19), 81 (15), 79 (18), 73 (17), 55 (16), 41 (25).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.81; H, 10.59; N, 7.67.

Preparation of the Silyl Enol Ether 29. Following a known procedure,[27] a mixture of 26.2 g (0.10 mol) of the phenol **27**, 13.4 mL (0.11 mol) of dichlorodimethylsilane, 100 mL of acetonitrile, and 17 mL (12 g, 0.122 mol) of Et_3N was converted to 15.0 g (42%) of the crude chlorosilane **28** as colorless crystals from heptane, mp 70–75 °C (lit.[27] mp 79–81 °C), that contained (IR and NMR analysis) small amounts of the starting phenol **27**. To an anhydrous solution of 97 mg (0.647 mmol) of NaI, 203 mg (0.573 mmol) of the silyl chloride **28**, and 53 mg (0.349 mmol) of the ketone **1** (mixture of isomers) in 2.0 mL of acetonitrile was added 91 mg (0.75 mmol) of triethylamine. The mixture, from which a colorless solid separated immediately, was refluxed for 2 h, allowed to stand for 12 h at room temperature, and then partitioned between pentane and water. The pentane layer was dried and concentrated and the crude product was chromatographed (silica gel, hexane eluent) to separate 68.2 mg (45%) of the crude enol ether **29**, mp 97–98 °C. Sublimation raised the melting point of the enol ether **29** to 100–101 °C; recystallization from EtOH afforded the enol ether **29** as prisms that seemed suitable for crystallographic analysis. The spectral properties follow: IR (CCl_4) 1680 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (2 H, s, aryl CH), 1.1–2.4 (42 H, m, aliphatic CH including a peak attributable to 2 *t*-Bu groups at 1.42 and a peak attributable to a *t*-Bu group at 1.27), 0.33 (3 H, s, Me), 0.31 (3 H, s, Me); ^{13}C NMR [$CDCl_3$, multiplicity determined by a D(istortionless) E(nhancement) by P(olarization) T(ransfer)] 150.0 (s), 144.5 (s), 142.3 (s), 139.6 (s), 126.8 (s), 122.6 (d), 41.7 (d), 36.6 (t), 36.0 (t), 35.4 (s), 34.4 (s), 34.3 (t), 31.6 (2C,q), 31.4 (2C,q), 31.1 (t), 30.3 (t), 25.7 (t), 25.2 ppm (t); mass spectrum, m/e (relative intensity) 470 (8, M^+), 414 (40), 413 (100), 357 (14), 133 (15), 75 (53), 73 (20), 57 (85), 41 (15).

Anal. Calcd for $C_{30}H_{50}O_2Si$: C, 76.53; H, 10.71. Found: C, 76.65; H, 10.75.

Preparation of the 9-Methyl-4-ketoperhydroazulenes 3 and 4. To a colorless solution, from 1.42 g (6.90 mmol) of Me_2SCuBr, 10 mL of ether, 10 mL of Me_2S, and 9.5 mL of an ether solution containing 12.7 mmol of MeLi, kept at 15–20 °C, was added a solution of 752 mg (5.00 mmol) of the enone **2** in 3.0 mL of ether. The resulting mixture, from which yellow MeCu separated, was stirred at 25 °C for 45 min and then partitioned between ether and aqueous NH_4Cl and NH_3 (pH 8). The organic layer was dried and concentrated to leave 846 mg of crude product as a yellow liquid that contained (NMR analysis) a mixture of the cis and trans ketones **3** and **4**. Distillation (short-path still) separated 701 mg (85%) of the mixture of ketones as a colorless liquid, 78–80 °C (1.6 mm), n^{25}_D 1.4904, that contained (GC, silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) 41% of cis ketone **3** (t_R 13.7 min) and 59% of trans ketone **4** (17.4 min) and two very minor unidentified impurities (3.6 and 4.1 min) but no unchanged enone **2** (23.3 min). Under these same GC conditions, the retention time of *n*-hexadecane, our internal standard, was 7.8 min. The isomeric ketones were separated by preparative HPLC (10-μm silica gel, EtOAc–hexane, 5:95, v/v); the retention times of the ketones were 73.9 min for the cis ketone **3** and 87.9 min for the trans ketone **4**. Each of the collected ketones was distilled (short-path still) to obtain a sample for characterization.

The properties of the pure cis ketone **3** follow: bp 52 °C (0.15 mm) [lit.[5b] bath 80 °C (0.2 mm)]; n^{25}_D 1.4885; IR (CCl_4) 1705 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.77 (1 H, t, J = 6.9 Hz, CHCO), 2.37–2.43 (2 H, m), 2.16–2.22 (1 H, m), 1.91–1.97 (1 H, m), 1.55–1.77 (7 H, m), 1.23–1.43 (3 H, m), 1.18 (3 H, s, Me, lit.[5] 1.18); ^{13}C NMR (75 MHz, $CDCl_3$, multiplicity on off-resonance decoupling) 213.3 (s), 60.0 (d), 43.9 (s), 42.8 (t), 42.6 (t), 38.2 (t), 27.5 (q), 26.2 (t), 23.7 (t), 23.5 (t), 23.0 ppm (t); mass spectrum, m/e (relative intensity) 166 (21, M^+), 151 (29), 125 (100), 109 (30), 96 (20), 95 (36), 82 (27), 81 (55), 67 (49), 55 (32), 41 (29), 39 (20).

The properties of the pure trans ketone **4** follow: bp 49.5–50 °C (0.10 mm) [lit.[5b] bath 82 °C (0.2 mm)]; n^{25}_D 1.4911; IR (CCl_4) 1697 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (1 H, dd, J = 9.7 and 7.6 Hz, CHCO), 2.5–2.6 (1 H, m), 2.2–2.3 (2 H, m), 1.4–2.0 (11 H, m), 0.74 (3 H, s, Me, lit.[5] 0.72); ^{13}C NMR (75 MHz, $CDCl_3$, multiplicity on off-resonance decoupling) 213.0 (s), 59.5 (d), 44.5 (t), 44.4 (s), 44.1 (t), 43.7 (t), 25.2 (t), 24.4 (t), 23.9 (t), 20.8 (t), 19.9 ppm (q); mass spectrum, m/e (relative intensity) 166 (8, M^+), 151 (9), 110 (9), 109 (100), 95 (10), 81 (19), 67 (23), 55 (17), 41 (19), 39 (9).

Preparation of the ((*p*-Bromophenyl)sulfonyl)hydrazone 5. A solution of 0.53 g (3.2 mmol) of the ketones **3** (minor) and **4** (major), 0.76 g (3.0 mmol) of ((*p*-bromophenyl)sulfonyl)-hydrazide, and 0.15 mL of HOAc in 10 mL of EtOH was stirred at 25 °C for 2 h and then concentrated to dryness. Recrystallization (EtOH–water) followed by chromatography (silica gel, CH_2Cl_2–hexane eluent) separated (TLC analysis) the crude trans derivative **5**. Recrystallization (EtOH–water) afforded the pure derivative **5** as colorless needles, mp 155–156 °C; IR ($CHCl_3$) 3290 (NH), 1600 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (2 H, d, J = 8.7 Hz, aryl CH), 7.84 (2 H, d, J = 8.7 Hz, aryl CH), 1.0–2.7 (16 H, m, aliphatic CH), 0.52 (3 H, s, Me); mass spectrum, m/e (relative intensity) 400 and 398 (5 each, M^+ ions), 311 (18), 180 (99), 179 (100), 162 (51), 157 (37), 155 (38), 149 (48), 135 (50), 122 (22), 121 (42), 108 (22), 107 (26), 95 (25), 93 (56), 91 (25), 81 (47), 79 (48), 77 (27), 76 (21), 67 (47), 55 (44), 41 (63).

Anal. Calcd for $C_{17}H_{23}BrN_2O_2S$: C, 51.13; H, 5.81; Br, 20.01; N, 7.02; S, 8.03. Found: C, 51.08; H, 5.85; Br, 19.93; N, 6.99; S, 8.07.

Equilibration of the Stereoisomeric Ketones 3 and 4. Mixtures of the isomeric ketones **3** and **4** and the internal standard, *n*-hexadecane, were analyzed by GC employing known mixtures of authentic samples to calibrate the apparatus. The solvent system, C_6H_6–MeOH (1:1 v/v), and temperature correspond to conditions used for previous equilibration studies with

(26) Gall, M.; House, H. O. *Org. Synth.* **1972**, *52*, 39.
(27) Rathke, M. W.; Manis, P. A. *J. Org. Chem.* **1981**, *46*, 5348.

this system.[5a] A solution of 14.0 mg (0.084 mmol) of the trans ketone **4** and 5.3 mg of *n*-hexadecane in 1.5 mL of benzene was mixed with 1.5 mL of a MeOH solution containing 0.15 mmol of NaOMe. The resulting solution was kept at 25.0 °C and 0.8-mL aliquots were removed at 12-h intervals and quenched in an aqueous phosphate buffer (pH 6.9). The organic layer from each aliquot was separated, dried, and analyzed (GC). The mixture of ketones (constant after 24 h) contained 34.3% of the cis isomer **3** and 65.7% of the trans isomer **4**; the calculated recovery of material was 98%. A comparable experiment was performed with 13.7 mg (0.083 mmol) of the cis ketone **3**, 5.4 mg of *n*-hexadecane, 1.5 mL of benzene, 1.5 mL of MeOH, and 0.15 mmol of NaOMe. The composition of the mixture (95% recovery, constant after 24 h) was 34.3% of the cis isomer **3** and 65.7% of the trans isomer **4**.

Crystal Structure of the (2,4-Dinitrophenyl)hydrazone 13. A crystal of the hydrazone **13** was mounted and data were collected by procedures described in the supplementary material. The crystal belonged to the triclinic system and the data collected were consistent only with space groups $P1$ or $P\bar{1}$ (No. 1 or 2).[21] Assuming the latter space group, a successful refinement was obtained. From a total of 3020 reflections collected in a complete hemisphere of data, 1643 were accepted as statistically above background. In the refinement, described in the supplementary material, 246 parameters were varied for the 1643 observations. The full-matrix least-squares refinement converged at $R = 0.090$ and $R_w = 0.094$. A perspective view of the hydrazone **13** is presented in Figure 1. Lists of the final atomic coordinates and the bond distances and angles are available in the supplementary material as Tables 1 and 2.

Crystal Structure of the ((*p*-Bromophenyl)sulfonyl)hydrazone of *trans*-9-Methyl-4-ketoperhydroazulene (5). A crystal of the sulfonylhydrazone **5** was mounted and data were collected by procedures described in the supplementary material. The crystal belonged to the monoclinic system and the data collected were consistent only with space group $P2_1/c$ (No. 14).[21] From a total of 3250 reflections collected in a complete quadrant of data, 1741 were accepted as statistically above background. In the refinement, described in the supplementary material, 231 parameters were varied for the 1741 observations. The full-matrix least-squares refinement converged at $R = 0.085$ and $R_w = 0.067$. A perspective view of the sulfonylhydrazone **5** is presented in Figure 2. Lists of the final atomic coordinates and the bond distances and angles are available in the supplementary material as Tables 3 and 4.

Crystal Structure of the Oxime 10. A crystal of the oxime **10** was mounted and data were collected by procedures described in the supplementary material. The crystal belonged to the monoclinic system and the data collected were consistent only with space group $P2_1/n$ (a nonstandard setting of space group $P2_1/c$, No. 14).[21] From a total of 1862 reflections collected in a complete quadrant of data, 1128 were accepted as statistically above background. In refinement, described in the supplementary material, 137 parameters were varied for the 1128 observations. The full-matrix least-squares refinement converged at $R = 0.079$ and $R_w = 0.065$. A perspective view of the oxime **10** is presented in Figure 3. Lists of the final atomic coordinates and the bond distances and angles are available in the supplementary material as Tables 5 and 6.

Crystal Structure of the Silyl Enol Ether 29. A crystal of the silyl enol ether **29** was mounted and data were first collected at 25 °C by procedures described in the supplementary material. In an effort to reduce thermal motion in the crystal, data for subsequent refinement were collected at about −80 °C. The crystal belonged to the triclinic system and the data collected were consistent only with space groups $P1$ or $P\bar{1}$ (No. 1 or 2).[21] Assuming the latter space group, a successful refinement was obtained. From a total of 5322 reflections collected in a complete hemisphere of data, 4042 were accepted as statistically above background. In refinement, described in the supplementary material, 345 parameters were varied for the 4042 observations. Because of excessive distortion of the geometry at atoms C-7, C-8, and C-9 in the structure, the calculated position of the H atom (H-48) bound to C-9 was not reasonable. Therefore, this H atom was deleted. After this deletion, the full-matrix least-squares refinement converged at $R = 0.088$ and $R_w = 0.092$. Perspective views of the silyl enol ether **29** and the enol moiety present within it are presented in the supplementary material as Figures 19 and 20. Lists of the final atomic coordinates and the bond distances and angles are available in the supplementary material as Tables 7 and 8.

Registry No. **1a**, 5365-37-7; **1b**, 5365-38-8; **2**, 13031-01-1; **3**, 32166-44-2; **4**, 32166-45-3; **5**, 102261-81-4; **6**, 102261-82-5; **7**, 102261-83-6; **8**, 85318-95-2; **9**, 85318-94-1; **10**, 102261-84-7; **11**, 102261-85-8; **12**, 102261-86-9; **13**, 102261-87-0; **14**, 85318-98-5; **15**, 85335-09-7; **16**, 85318-97-4; **17**, 85318-99-6; *cis*-**18**, 65682-09-9; *trans*-**18**, 65682-10-2; *cis*-**19**, 65682-05-5; *trans*-**19**, 65682-06-6; (*E*)-**20**, 102261-88-1; (*Z*)-20, 102261-90-5; **27**, 732-26-3; **28**, 79746-31-9; **29**, 102261-89-2; 1-ethynyl-1-hydroxycyclopentane, 17356-19-3; 1-acetylcyclopentene, 16112-10-0; allyltrimethylsilane, 762-72-1; dichlorodimethylsilane, 75-78-5; ((*p*-bromophenyl)sulfonyl)hydrazide, 2297-64-5.

Supplementary Material Available: Descriptions of the determination of crystal structures for the (2.4-dinitrophenyl)hydrazone **13**, the ((*p*-bromophenyl)sulfonyl)hydrazone **5**, the oxime **10**, and the silyl enol ether **29**, including tables of atomic coordinates and bond distances and angles for each compound and perspective drawings of low-energy conformers for ketone **3** (Figure 11), ketone **4** (Figure 12), ketone **12** (Figures 13 and 14), ketone **11** (Figures 15–18), and the molecular structure of the silyl enol ether **29** (Figure 19) as well as the conformation of the enol moiety contained in this structure (Figure 20) (28 pages). Ordering information is given on any current masthead page.

Perhydroazulenes. 7. Effect of a *tert*-Butyl Substituent at C-6 upon the Properties of the 4-Keto Derivatives[1]

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The four diastereoisomeric 6-*tert*-butyl-4-ketoperhydroazulenes **4**, **6**, **8**, and **10** have been prepared. The previously unknown cis-syn isomer **6** was characterized with spectra, an analysis, and a crystal structure of its oxime. The two stereoisomeric enol acetates **11** and **12** were prepared and each isomer was used to generate the corresponding lithium enolate **13** or **16**. In each case methylation of one of these enolates formed a monoalkylated product containing more than 90% of the cis-fused isomer **14** or **17**. The alkylated products were characterized by spectra, analyses, and crystal structures. The probable conformations for the enolates and the alkylated products are discussed.

Our previous study[2-4] of the conformations of the 4-ketoperhydroazulenes **1** (see Scheme I) and the corresponding enol derivatives suggested that the conformation of the seven-membered ring in these materials could be

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