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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Received November 9, 1985

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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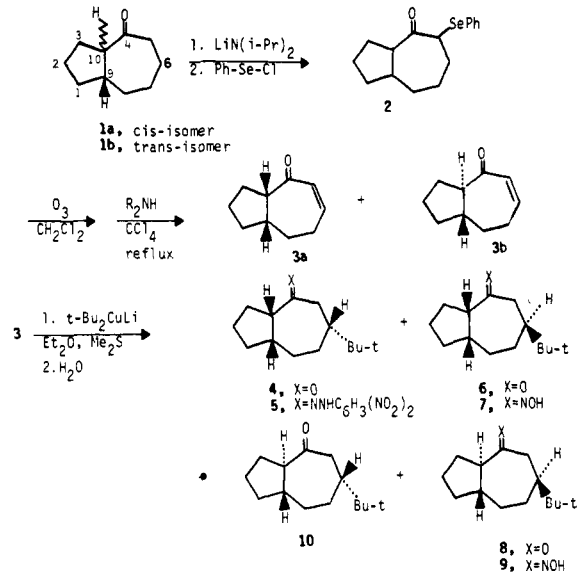
Scheme I



controlled by the introduction of a bulky substituent at position C-6. Thus, introduction of a 6-*tert*-butyl substituent syn to the bridgehead H atom at C-9 in the trans isomer **1b** is expected to favor conformers with TC-1 or TC-2 conformations of the seven-membered ring while introduction of a 6-*tert*-butyl group anti to the C-9 H atom is expected to favor TC-4 or TC-5 conformations of the seven-membered ring.[5,6] We are also led to expect that the preferred conformation of the five-membered ring in these compounds could be controlled by introduction of either a syn or anti *tert*-butyl group or another bulky substituent at position C-2. Although the 4-ketoperhydroazulene isomers with a 2-*tert*-butyl group syn to the bridgehead H atom at C-9 were described several years ago,[9] the corresponding anti isomers have not yet been studied.

A potential application for this sort of conformational

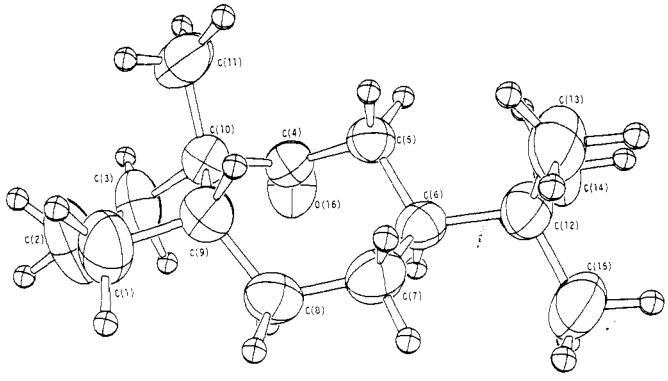


Figure 1. Perspective view of the molecular structure of 6-*syn-tert*-butyl-*cis*-10-methyl-4-ketoperhydroazulene.

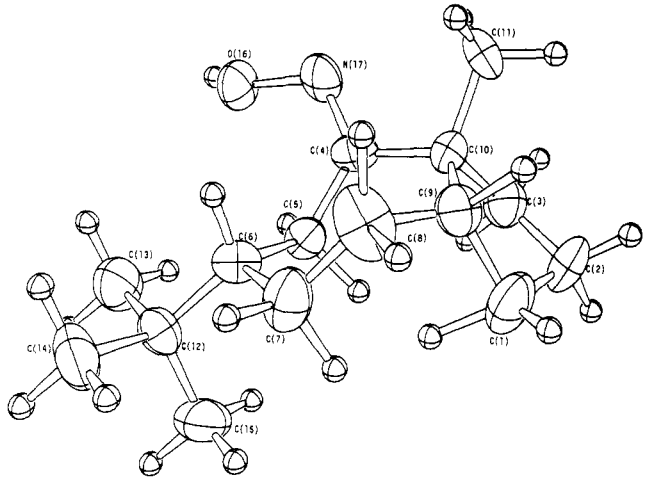


Figure 2. Perspective view of the molecular structure of 6-*anti-tert*-butyl-*cis*-10-methyl-4-ketoperhydroazulene oxime.

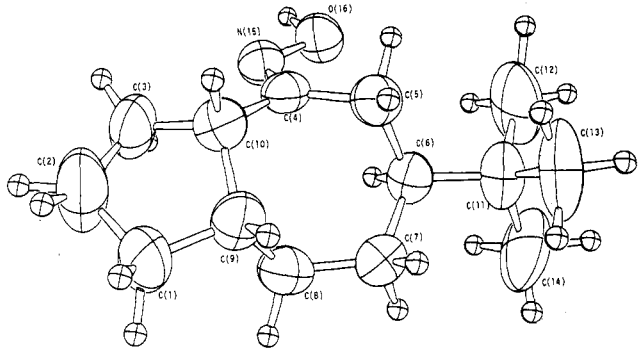


Figure 3. Perspective view of the molecular structure of 6-*syn-tert*-butyl-*cis*-4-ketoperhydroazulene oxime.

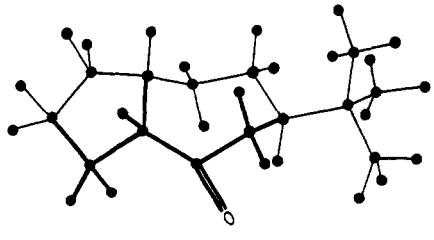


Figure 4. Perspective view of the 6-*syn-tert*-butyl-*cis*-4-ketoperhydroazulene conformer present in the oxime derivative.

(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.

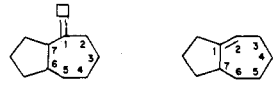
(2) House, H. O.; Gaa, P. C.; VanDerveer, D. *J. Org. Chem.* **1983**, *48*, 1661.

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

(4) House, H. O.; Nomura, G. S.; VanDerveer, D.; Wissinger, J. E. *J. Org. Chem.*, previous paper in this issue.

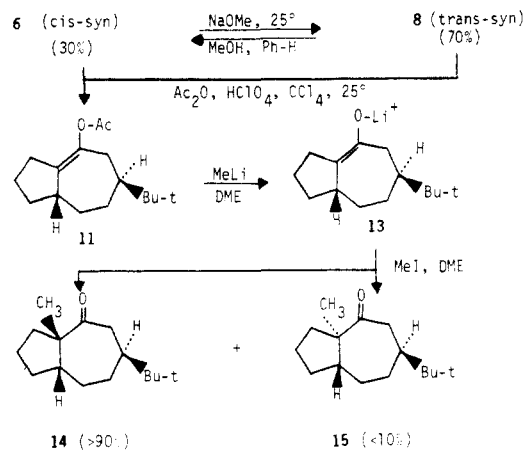
(5) Perspective drawings of the low-energy conformations of the ketones **4**, **6**, **8**, and **10** are presented elsewhere.[3] These conformers were derived from sets of possible conformations selected by the procedure of DeClercq[7] and then modified to minimize their conformational energies by Allinger's MM2 molecular mechanics program.[8]

(6) The nomenclature being used to designate conformations of the seven-membered ring is that suggested by DeClercq[7] 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.

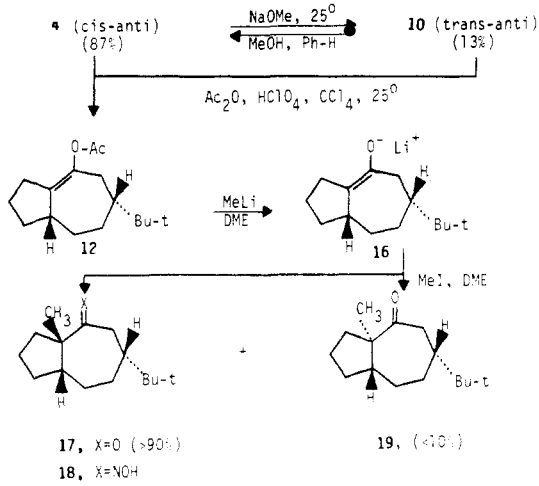


(7) (a) DeClercq, P. J. *J. Org. Chem.* **1981**, *46*, 667. (b) DeClercq, P. J. *Tetrahedron* **1981**, *37*, 4277. (c) DeClercq, P. J. *Ibid.* **1984**, *40*, 3717, 3729. We are grateful to Dr. Clercq for providing us with complete listings for his current programs.

Scheme II



Scheme III



characterized. Upon repeating this synthesis, we have now isolated all four diastereoisomers and also found that the previously reported[3] order of elution of the cis isomers from HPLC and GLC columns was in error. To remove any ambiguity about the identities of these isomers, the cis-anti **4**, eluted first from HPLC, was converted to its 2,4-dinitrophenylhydrazone derivative **5** and its X-ray crystal cell parameters were redetermined. This determination established the identity of this derivative with the material whose crystal structure was determined earlier;[3] the ketone moiety in this derivative **5** has a B-3 conformation that is closely related to the TB-4 conformers predicted[5] to be one of the low-energy conformers of the ketone **4**. The cis-syn ketone **6**, eluted second from HPLC and not isolated in the earlier study, was characterized in this study and also converted to its oxime **7** to obtain a crystal structure (see Figure 3). The ketone moiety in this oxime **7** has a TC-7 conformation (Figure 4) that is predicted[3] to be the low-energy conformer for the ketone **6**. The stereochemistries of the two trans ketones, the trans-syn isomer **8** eluted third from HPLC and the trans-anti isomer **10** eluted last

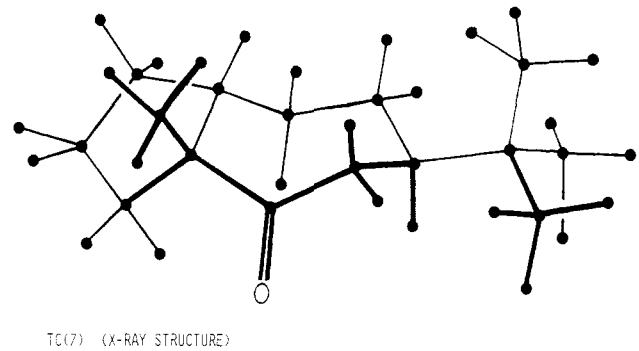


Figure 5. Perspective view of the 6-*syn*-*tert*-butyl-*cis*-10-methyl-4-ketoperhydroazulene conformer present in the crystal.

control would be the possible selection of reaction stereochemistry at various sites in the perhydroazulene ring system by the appropriate introduction of a substituent at C-2 or at C-6. In this paper, we have explored the effect a *tert*-butyl substituent at C-6 exerts on the stereochemistry of alkylation of a $\Delta^{4(10)}$–enolate derived from 4-ketoperhydroazulene (**1**). Methylation of the lithium enolate derived from the parent ketone **1** yields a mixture of 10-methyl derivatives containing 97% of the cis isomer.[4] Thus, this enolate alkylation is much more stereoselective than alkylation of the structurally isomeric enolate of 1-decalone where the cis isomer from an analogous reaction comprises only 83% of the monoalkylated product.[10]

The 6-*tert*-butyl-4-ketoperhydroazulene isomers **4**, **6**, **8**, and **10** were prepared by a previously studied[3] route in which the saturated ketone **1** was converted via the α-phenylselenyl ketone **2** (see Scheme I) to the cis and trans enones **3** followed by reaction with lithium di-*tert*-butylcuprate. In this previous study one of the cis isomers **4** or **6** and both trans isomers **8** and **10** were isolated and from HPLC, were correctly assigned in the earlier paper.

Because of the earlier confusion about the identities of the cis ketones **4** and **6**, we also repeated the previously reported[3] cis–trans equilibration of each pair of ketones **4** and **10** or **6** and **8** with NaOMe in MeOH–C_6H_6 at 25 °C (see Schemes II and III). Although the values reported[3] earlier for the syn isomers (30% of cis-syn **6** and 70% of trans-syn **8**) were confirmed, the previous values for the anti isomers were in error. The correct values for the equilibrium composition are 87% of the cis-anti isomer **4** and 13% of the trans-anti ketone **10**. Each ketone was converted to the corresponding enol acetate (syn-acetate **11** from **6** or **8** and anti-acetate **12** from **4** or **10**), providing additional support for the stereochemical assignments given.

Each enol acetate **11** or **12** was allowed to react with excess MeLi to form the corresponding lithium enolate **13** or **16** (Schemes II and III). Subsequent reaction of each enolate with excess MeI yielded the alkylated product. The product from the syn enolate **13** was isolated as a crystalline material that was shown to be the cis ketone **14** by determining the crystal structure (Figure 1). The seven-membered ring has a TC-7 conformation in the crystal (Figure 5). The calculated yield (GLC analysis) of this product **14** was 73%. Examination of the minor byproducts by HPLC analysis, GLC analysis, and GC–MS analysis indicated the presence of only minor amounts (5% of the product or less) of byproducts isomeric with the ketone **14** that could be the trans ketone **15**. Accordingly, we conclude that more than 90% of the monoalkylated product formed by methylation of the syn enolate **13** is the cis isomer **14**.

Similarly, methylation of the anti enolate **16** formed a liquid product **17** whose calculated yield was 75% (GLC

(8) 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.

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

(10) (a) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 502. (b) Caine, D.; McCloskey, C. J.; VanDerveer, D. *Ibid.* **1985**, *50*, 175.

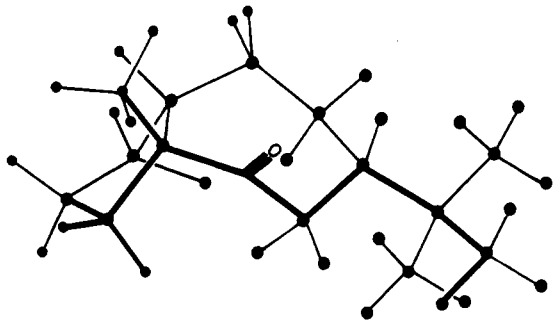
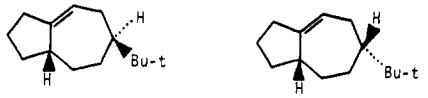


Figure 6. Perspective view of the 6-*anti*-*tert*-butyl-*cis*-10-methyl-4-ketoperhydroazulene conformer present in the crystalline oxime derivative.

Scheme IV



20 21

analysis). The structure and stereochemistry of this product were shown to be the cis-anti isomer **17** by determining the crystal structure of the corresponding oxime **18** (Figure 2). The ketone moiety in this crystalline oxime **18** has the C-3 conformation (Figure 6). Again, examination of the minor byproducts in this reaction by HPLC analysis, GLC analysis, and GC–MS analysis failed to indicate the presence of substantial amounts of a product with the molecular weight of the trans isomer **19**. Consequently, in this case also we conclude that more than 90% of the monoalkylated product formed from the anti enolate **16** is the cis-anti ketone **17**.

To obtain estimates of the probable conformations for the enolates **13** and **16** used in these alkylation reactions, we used the corresponding olefins **20** and **21** (see Scheme IV) as models.[11] The probable conformations for each of these olefins was selected by DeClercq's procedure[7] and then Allinger's MM2 molecular mechanics program[8] was used to minimize the energy of each conformer. The lowest energy conformers found for these two olefins **20** and **21** are presented in Figures 7 and 8. It is apparent from these figures that the favored conformations for the seven-membered ring are altered substantially by changing the stereochemistry of the 6-*tert*-butyl substituent with a syn substituent favoring a chair conformer while an anti substituent favors a boat or twist-boat conformer. However, the proportion of cis isomer (e.g., **14** or **17**) found in the alkylated product is rather similar for the methylation of either stereoisomeric enolate **13** or **16**. For that matter, the amount of cis isomer formed in both cases studied here is comparable to the fraction of cis isomer formed by methylating the analogous enolate with no 6-substituent.[4] We can therefore conclude that the conformational bias introduced into the seven-membered ring by a substituent at C-6 does not offer a useful way to control alkylation stereochemistry at C-10. Whether such stereochemical control can be achieved by controlling the conformation of the five-membered ring with a C-2 substituent will require further experimental investigation.

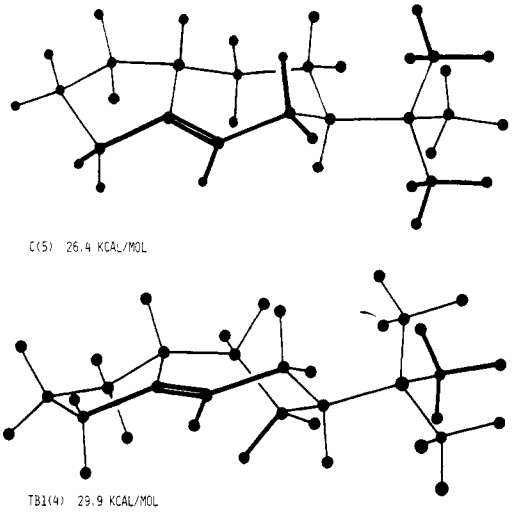


Figure 7. Low-energy conformers of 6-*syn*-*tert*-butyl-$\Delta^{4(10)}$-octahydroazulene.

We also utilized molecular mechanics calculations to explore the conformations of the alkylated products **14**, **15**, **17**, and **19**. We found a sizeable number of conformers with comparable energies for these products; use of the Boltzman relationship with the conformers we found suggested that the cis ketones would be slightly more stable than the trans isomers in both the syn and anti series. It was of interest to note that the lowest energy conformers found for both cis ketones were those with a TC-7 conformer in the seven-membered ring. This TC-7 conformation and the closely related C-3 conformer were found in the crystal structures of the two alkylated products (Figures 5 and 6).

Experimental Section[12]

Preparation of the Unsaturated Ketone 3. Following general procedures,[3] a cold (−78 °C), deep red solution of 17.5 mmol of $(i\text{-Pr})_2\text{NLi}$ and 20 mg of $\text{PhCH=NCH}_2\text{Ph}$ (an indicator)[14] in 30 mL of hexane[13a] and 100 mL of THF was treated, dropwise and the stirring during 30 min, with 1.99 g (13.2 mmol) of the ketone **1** (a mixture of cis and trans isomers). After 20 min, 3.36 g (17.5 mmol) of PhSeCl in 15 mL of THF was added, the cooling bath was removed, and the mixture was allowed to warm to 25 °C. The reaction mixture was partitioned between a pentane–ether mixture (1:1 v/v) and aqueous 0.5 M HCl and the organic layer was washed successively with aqueous NaHCO_3 and aqueous NaCl and then dried and concentrated. The residual brown liquid (5.1 g) was chromatographed (silica gel, hexane and EtOAc–hexane eluents) to separate first PhSeSePh and then 2.688 g (67%) of the crude keto phenyl selenide **2** as a pale green liquid (mixture

(11) Since reliable parameters for vinyl alcohol derivatives in MM2 calculations are not currently available, we used the olefins **20** and **21** as models for the carbocyclic rings in the enolates **13** and **16**. Although it is probable that these lithium enolates exist in solution as a dimeric or tetrameric clusters of Li and O atoms, the favored conformation of the carbocyclic rings bonded to these clusters is probably not substantially altered by the exact structure of the Li–O cluster.

(12) 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.

(13) (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.

(14) 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.

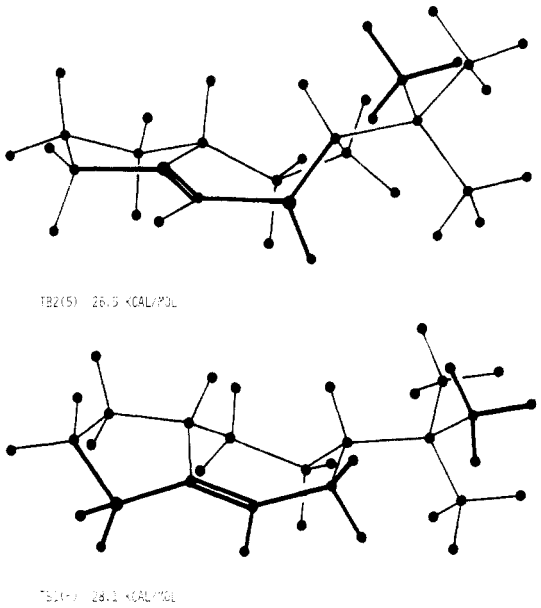


Figure 8. Low-energy conformers of 6-*anti*-*tert*-butyl-$\Delta^{4(10)}$-octahydroazulene.

of stereoisomers), n^{25}_D 1.5808 (lit.[3] n^{25}_D 1.4725–1.4738) (identified by comparison of IR and NMR spectra). An additional 625 mg of this keto selenide **2** (total yield 82%) was separated when mixed fractions were rechromatographed.

Ozone (2–3% O_3 from a Welsbach, Model T-408, ozonator) was passed through a cold (−78 °C) solution of 3.113 g (10.1 mmol) of the selenide **2** in 100 mL of anhydrous CH_2Cl_2 for 10 min and then N_2 was passed through the cold, blue solution for 15 min to sweep out the excess O_2 and O_3. After 2.5 mL (18 mmol) of $HN(Pr\text{-}i)_2$ has been added to this cold solution, the solution was siphoned into a refluxing solution of 2.5 mL of $HN(Pr\text{-}i)_2$ in 100 mL of CCl_4 to decompose the selenoxide.[15] The resulting solution was refluxed for 15 min and cooled and then washed successively with aqueous 1 M HCl, with aqueous $NaHCO_3$, and with aqueous NaCl. The resulting solution was dried, concentrated, and distilled (short path still) to separate 1.863 g of pale yellow liquid, bp 63–66 °C (0.4 mm), n^{25}_D 1.5000 [lit. for mixture of epimers **3**,[3] bp 44–46 °C (0.2 mm), n^{25}_D 1.5213–1.5220], that contained (GLC, Carbowax 20M on Carbowax) about 12% of the saturated ketones **1a** and **1b** (t_R 14.0 and 15.0 min), about 35% of material believed to be the cis enone **3a** (20.0 min), and about 53% of material believed to be the trans enone **3b** (24.0 min). The crude product was subjected to HPLC (10-μm silica gel, EtOAc–hexane, 1:19 v/v). The approximate composition of the mixture and the retention times for the various components were as follows: cis ketone **1a** (4%), 44 min; cis enone **3a** (33%), 45 min; trans ketone **1b** (7%), 49 min; trans enone **3b** (54%), 55 min; an unidentified component (2%), 67 min. Appropriate HPLC fractions were combined and distilled to separate fractions enriched in each of the enone epimers **3**. Samples of each pure enone epimer for spectra were collected from GC (Carbowax 20M on Chromosorb P).

The enriched cis enone **3a**, bp 64–66 °C (0.6 mm), amounted to 437 mg (29%) of colorless liquid. A collected (GLC) sample, n^{25}_D 1.5095, exhibited the following spectra: IR (CCl_4) 1683 cm^{-1} (conjugated C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 6.4–6.6 (1 H, m, vinyl CH), 5.9–6.1 (1 H, m, vinyl CH), 3.0–3.3 (1 H, m, bridgehead CHCO of cis isomer), 1.1–2.5 (11 H, m, aliphatic CH); mass spectrum, *m/e* (relative intensity) 150 (18, M^+), 109 (24), 82 (20), 81 (46), 80 (25), 79 (25), 68 (100), 67 (26), 53 (21), 42 (27), 40 (36).

Anal. Calcd for $C_{10}H_{14}O$: M_r 150.1045. Found: M_r 150.1039.

The enriched trans enone **3b**, bp 69–71 °C (0.45 mm), amounted to 638 mg (42%) of colorless liquid. A collected (GLC) sample, n^{25}_D 1.5131, exhibited the following spectra: IR (CCl_4) 1672 cm^{-1} (conjugated C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 6.4–6.6 (1 H, m, vinyl CH), 5.9–6.1 (1 H, m, vinyl CH), 1.1–2.7 (12 H, m, aliphatic CH); mass spectrum, *m/e* (relative intensity) 150 (15, M^+), 93 (18), 81 (49), 80 (27), 79 (28), 68 (100), 67 (27), 53 (19), 42 (27), 40 (34).

Anal. Calcd for $C_{10}H_{14}O$: M_r, 150.1045. Found: M_r, 150.1051.

The tentative stereochemical assignments for these enones **3** are based on the observation for various 4-ketoperhydroazulenes with H atoms at bridgehead carbons C9 and C10[2,3,9,13b] that the cis isomer exhibits a ^1H NMR multiplet in the region δ 3.0–3.3 (presumably from the CHCO grouping at C10) while the trans epimer lacks NMR absorption in this region. These assignments are supported by reaction of each enriched enone **3a** or **3b** with $(t\text{-Bu})_2CuLi$ to form a mixture of either the *cis*-6-*tert*-butyl-4-ketoperhydroazulenes **6** and **4** described in this paper (from **3a**, NMR and HPLC analysis) or the known[3] *trans*-6-*tert*-butyl-4-ketoperhydroazulenes **8** and **10** (from **3b**, NMR and HPLC analysis). The same stereochemical assignments for enones **3** have recently been described by Bohlmann and Paul;[16] the basis for their stereochemical assignments was not stated.

Preparation of the 6-*tert*-Butyl-4-ketoperhydroazulenes 4, 6, 8, and 10. A cold (−78 °C) partial solution of 5.46 g (26.6 mmol) of Me_2S–CuBr in 200 mL of ether–Me_2S (1:1 v/v) was treated, dropwise and with stirring, with 53.8 mmol of *t*-BuLi in 32 mL of pentane. After 30 min, 3.07 g of a mixture containing (GC) 2.24 g (14.9 mmol) of enones **3** (along with the saturated ketone **1** and other minor impurities) was added, dropwise and with stirring during 9 min. The resulting cold, red solution was stirred for 1 h and then slowly warmed to 0 °C. As the cold solution warmed, a black precipitate began to separate at about −40 °C and a copper mirror was deposited on the wall of the reaction flask at about −30 °C. The reaction mixture was partitioned between ether and saturated aqueous NH_4Cl and the combined ether layers were dried and concentrated to leave 3.65 g of liquid containing (GC, Carbowax 20M on Chromosorb P) about 67% of the ketones **4**, **6**, **8**, and **10** (partially resolved into two peaks with t_R 36.2 and 38.5 min, yield about 78%) and about 19% of the unsubstituted ketones **1** (13.2 and 14.2 min) along with several minor unidentified byproducts.

A 150-mg aliquot of the product mixture was distilled (short-path still, 0.5 mm, GC pattern of distillate unchanged) to give a sample with four ^1H NMR (300 MHz in $CDCl_3$) singlets attributable to the *tert*-butyl groups of ketones **4**, **6**, **8**, and **10** (relative peak areas): δ 0.872 (1.0, **4**), 0.866 (2.4, **6**), 0.860 (1.2, **8** or **10**), 0.853 (1.3, **8** or **10**). HPLC analysis (10-μm silica gel, EtOAc–hexane, 3:97 v/v) exhibited a number of minor unidentified peaks and four peaks of approximately equal area at the following retention times (min): 41.4 for **4**; 45.2 for **6**; 46.2 for **8**; 47.2 for **10**. The HPLC elution order previously reported[3] for trans ketones **8** and **10** and the earlier stereochemical assignments have been confirmed in this paper. However, the one cis isomer isolated previously[3] has now been shown to have the cis-anti stereochemistry **4** (not stereochemistry **6** previously assigned) and the cis-syn isomer **6** has been isolated for the first time in the present study. In a comparable experiment, a 365-mg of the cis-enone **3a** was treated with $(t\text{-Bu})_2CuLi$ to give 462 mg (91%) of product containing (NMR and HPLC analysis) the cis-anti ketone **4** (ca. 25%) and the cis-syn isomer **6** (ca. 75%); GC curve: two partially resolved peaks at 37.2 min (ca. 75%, **6**) and 39.4 min (ca. 25%, **4**). Similarly, the reaction of 612 mg of the trans-enone **3b** with $(t\text{-Bu})_2CuLi$ yielded 619 mg (73%) of product containing (NMR and HPLC analyses) an approximately equal mixture of the trans-syn ketone **8** and the trans-anti isomer **10**.

Enriched samples of each of the four ketones **4**, **6**, **8**, and **10** were obtained by a series of HPLC separations. The ^1H NMR spectrum (300 MHz, $CDCl_3$) of each ketone exhibited a characteristic set of multiplets within the region δ 2.1–3.3 (3 H α to C=O). These characteristic patterns were used both to analyze ketone mixtures and to confirm the identities of three products **4**, **8**, and **10** with samples described previously.[3] The trans-syn isomer **8** was obtained as a semisolid material that was contaminated (HPLC) with ca. 28% of the cis isomer **6** and ca. 15% of the trans-anti compound **10**. The trans-anti ketone **10** was obtained as a liquid that contained (HPLC) ca. 10% of the trans-syn isomer **8**. The rapidly eluted cis-anti ketone **4** was obtained as

(15) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(16) Bohlmann, F.; Paul, A. H. K. *Tetrahedron Lett.* **1984**, *25*, 1697.

a colorless solid, mp 45–47 °C (lit.[3] mp 34–36 °C) that was identified with the previously described sample (erroneously assigned the cis-syn stereochemistry 6) by comparison of IR, NMR (300 MHz), and mass spectra. A sublimed (37–40 °C, 0.1 mm) sample of the ketone 4 was colorless prisms, mp 49–51 °C.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61; M_r 208.1827. Found: C, 80.67; H, 11.67; M_r 208.1852.

To further confirm the identity and stereochemistry of ketone 4, a 10.2-mg sample was allowed to react with 9.6 mg of 2,4-dinitrophenylhydrazine and 0.01 mL of aqueous 1 M HCl in 2 mL of MeOH to yield 9.6 mg (51%) of the derivative 5 as an orange solid, mp 147–149 °C (lit.[3] mp 147–148 °C). Recrystallization from EtOAc afforded a second crystalline form of the dinitrophenylhydrazone 5 as dark orange needles, mp 157.5–159 °C (lit.[3] mp 154–155 °C). A crystal was mounted on the same X-ray diffractometer used previously, and 15 reflections whose 2π angles varied from 3.31° to 12.86° were used to determine the unit cell parameters: a = 6.908 (2) Å, b = 17.70 (1) Å, c = 17.14 (1) Å, β = 91.10 (5)°, V = 2096 (2) Å^3. These parameters correspond to those previously found,[3] thereby establishing the identity of the two samples.

The cis-syn ketone 6 was obtained as a colorless solid, mp 59–64 °C, that contained (NMR analysis) about 27% of the isomeric trans ketone 8. Repeated HPLC separation gave a sample of the cis-syn ketone 6 containing (NMR analysis) about 14% of the trans-syn ketone 8. The ^{13}C NMR spectrum of the major component in this mixture, cis-syn ketone 6, has the following peaks ($CDCl_3$, multiplicity determined by a off-resonance decoupling) 214.2 (s), 56.5 (d), 48.9 (d), 45.8 (t), 40.6 (d), 35.6 (t), 33.6 (t), 33.2 (t), 30.5 (t), 27.6 (3C,q), 25.9 (s), 25.2 ppm (t). A 55-mg sample was fractionally recrystallized (aqueous EtOH) to separate 20.3 mg of the cis-syn ketone 6 as colorless plates, mp 77–80 °C, that contained (NMR analysis) about 5% of the isomeric trans-syn ketone 8. The spectral properties of this sample of the cis-syn ketone 6 follow: IR (CCl_4) 1705 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 3.01 (1 H, m, 916.2, 907.2, 897.8, 889.7 Hz, CHCO), 2.3–2.5 (3H, m, CH and CHCO), 1.0–2.1 (11 H, m, aliphatic CH), 0.865 (9 H, s, t-Bu); mass spectrum, m/e (relative intensity) 208 (13, M$^+$), 167 (25), 152 (61), 151 (61), 123 (43), 111 (57), 110 (23), 95 (27), 81 (100), 69 (21), 67 (68), 57 75), 55 (41), 41 (73), 39 (20).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61; M_r 208.1827. Found: C, 80.81; H, 11.61; M_r 208.1824.

Because of earlier confusion in assignments for cis ketones 6 and 4,[3] the cis-trans equilibration for both pairs of ketones was repeated. A solution of 15.0 mg (0.072 mmol) of the cis-anti ketone 4 and 0.18 mmol of NaOMe in 2.0 mL of MeOH and 2.0 mL of C_6H_6 was stirred at 24–25 °C for 48 h and then neutralized (pH 6.9) and partitioned between ether and water. The organic products were dried, concentrated, and then analyzed (^1H NMR, 300 MHz in $CDCl_3$) by employing integrals of peaks in the regions δ 2.43 (4) and 2.56 (10). The material contained 87% of the cis isomer 4 and 13% of the trans isomer 10. Repetition of this procedure with 14.6 mg of the trans-ketone 10 gave the same equilibrium mixture (87:13). Comparable equilibrations starting with 14.6 mg of the cis-syn ketone 6 or 14.1 mg of the trans-syn isomer 8 gave mixtures containing 70–71% of the trans ketone 8 (NMR peak at δ 2.81) and 30–29% of the cis ketone 6 (NMR peak at δ 3.01). The earlier values reported for the anti isomers (97.5% of 10) are in error.

Preparation of the Oxime 7 of the Cis-syn Ketone 6. After a solution of 30.7 mg (0.148 mmol) of the crude cis-syn ketone 6 (containing about 27% of the trans-syn ketone 8, NMR) and 54.3 mg (0.79 mmol) of hydroxylamine hydrochloride in 3 mL of aqueous EtOH (2:1 v/v) had been refluxed for 45 min and cooled, the crude oxime crystallized as a mixture of two crystal forms, the cis-syn oxime 7 as colorless rods, and the crude trans-syn oxime 9 as thin needles. The two crystal types were separated mechanically to provide 9.6 mg of the oxime 7, mp 172–173 °C, and 6.6 mg of the crude oxime 9, 150–155 °C dec with prior softening at 140 °C. The spectral properties of the cis-syn oxime 7 follow: IR ($CHCl_3$) 3620, 3300 (free and associated OH) with no absorption corresponding a C=O group in the 6-μm region; ^1H NMR (300 MHz, $CDCl_3$) δ 3.23 (1 H, m, CHC=N), 2.71 (1 H, m, CHC=N), 2.20 (1 H, m, CHC=N), 0.8–2.1 (22 H, m, aliphatic CH including a t-Bu singlet at 0.894); mass spectrum, m/e (relative intensity) 223 (21, M$^+$), 182 (30), 166 (100), 135 (33), 126 (53), 95 (24), 81 (28), 79 (22), 67 (41), 57 (92), 55 (32), 55 (32), 41 (78).

Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27; M_r 223.1936. Found: C, 75.32; H, 11.30; N, 6.24; M_r 223.1981.

A solution of 21.3 mg (0.096 mmol) of the oxime 7, 29.3 mg (0.425 mmol) of $NaNO_2$, and 0.5 mL of aqueous 1 M HCl in 1 mL of EtOH was stirred at 25 °C for 24 h[17] and then treated with 38 mg (0.63 mmol) of urea. After the resulting solution had been neutralized (NaOH) and extracted with CH_2Cl_2, the organic extract was dried, concentrated, and chromatographed (silica gel, EtOAc–hexane, 1:19 v/v) to separate 7.9 mg (37%) of the starting oxime 7 and 9.2 mg (46%) of the cis-syn ketone 6. The ketone 6 was tentatively identified by its R_f value, 0.37, on TLC analysis (silica gel, EtOAc–hexane, 1:19 v/v); after recrystallization from aqueous EtOH, the product separated as colorless plates, mp 76–79 °C. The identity of the product was confirmed with the ^1H NMR spectrum (300 MHz, $CDCl_3$); integration in the region δ 2.1–3.2 established that the ketone product contained ca. 90% of the cis-syn ketone 6 and ca. 10% of the trans-syn ketone 8.

Preparation of the Syn- and Anti-enol Acetates 11 and 12.[18] A solution of 552 mg (2.65 mmol) of the ketones 8 (ca. 50%) and 10 (ca. 50%), 2.0 mL (21.2 mmol) of Ac_2O, and 0.015 mL of aqueous 70% perchloric acid in 15 mL of CCl_4 was stirred at 25 °C for 4 h and then partitioned between hexane and cold (2 °C), aqueous KOH. After the hexane layer had been washed with aqueous $NaHCO_3$ and dried, the solution was concentrated and the residual liquid was distilled (short-path still) to separate 553 mg (83%) of yellow liquid, bp 113–115 °C (0.8 mm), that contained (GLC, Carbowax 20M on Chromosorb P) two minor unidentified components (t_R 11.4 and 13.4 min, ca. 2.5%), the syn-enol acetate 11 (29.0 min, ca. 50%), and the anti-enol acetate 12 (33.1 min, ca. 47%). On HPLC (10-μm silica gel, EtOAc–hexane, 1:49 v/v) the retention times were 43.4 min for the syn isomer 11 and 46.0 min for the anti isomer 12. The mixture was separated by preparative HPLC and each enol acetate fraction was distilled (0.5 mm, short-path still).

The syn-enol acetate 11 was obtained was 156 mg (23.6%) of colorless liquid: n^{25}_D 1.4682; IR (CCl_4) 1745 cm^{-1} (ester C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 0.8–2.6 (26 H, m, aliphatic CH including an acetyl singlet at 2.09 and a t-Bu singlet at 0.83); ^{13}C NMR ($CDCl_3$, multiplicity determined by off-resonance decoupling) 169.2 (s), 142.7 (s), 134.7 (s), 46.6 (d), 42.6 (d), 35.9 (t), 35.7 (t), 34.4 (t), 33.4 (s), 32.4 (t), 30.4 (t), 27.5 (3C,q), 25.0 (t), 20.8 ppm (q); mass spectrum, m/e (relative intensity) 250 (9, M$^+$), 209 (16), 208 (100), 167 (26), 151 (39), 123 (15), 43 (26), 41 (17).

Anal. Calcd for $C_{16}H_{26}O_2$: M_r 250.1933. Found: M_r 250.1887 (mass spectrum).

The anti-enol acetate 12 was obtained as 80.6 mg (12.2%) of colorless liquid; n^{25}_D 1.4838; IR (CCl_4) 1745 cm^{-1} (ester C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 0.8–2.6 (26 H, m, aliphatic CH including an acetyl singlet at 2.09 and a t-Bu singlet at 0.84); ^{13}C NMR ($CDCl_3$, multiplicity determined by off-resonance decoupling) 169.1 (s), 142.0 (s), 133.7 (s), 44.9 (d), 40.0 (d), 35.7 (t), 33.3 (t), 31.8 (t), 30.6 (t), 29.4 (t), 27.4 (s), 27.2 (3C,q), 23.9 (t), 20.8 ppm (q); mass spectrum, m/e (relative intensity) 250 (9, M$^+$), 209 (15), 208 (100), 167 (32), 151 (36), 123 (15), 43 (29), 41 (15).

Anal. Calcd for $C_{16}H_{26}O_2$: M_r 250.1933. Found: M_r 250.1988.

A sample of each of the enriched ketone isomers 4, 6, 8, and 10 was treated with 1.7 mL (18 mmol) of Ac_2O and 0.005 mL of aqueous 70% perchloric acid in 25 mL of CCl_4 for 12 h and then subjected to the previously described isolation and separation procedures. The yields of enol acetates and amounts of starting ketones were 75 mg (62%) of anti acetate 12 from 100 mg of ketone 4; 64 mg (53 %) of syn acetate 11 from 100 mg of ketone 6; 177 mg (74%) of syn acetate 11 from 200 mg of ketone 8; 249 mg (69%) of anti acetate 12 from 300 mg of ketone 10.

Methylation of the Enolate from the Syn-enol Acetate 11. After an enolate solution, prepared from 2.22 mmol of MeLi in

(17) The reaction of oximes with nitrous acid to form carbonyl compounds was used in the carbohydrate series by Wolfrom, M. L.; Georges, L. W.; Soltzberg, L. *J. Am. Chem. Soc.* **1934**, *56*, 1794. The reaction has been used with an acid-sensitive ketone: House, H. O.; DeTar, M. B.; VanDerveer, D. *J. Org. Chem.* **1979**, *44*, 3793. The reaction has been reviewed [Freeman, J. P. *Chem. Rev.* **1973**, *73*, 283.] and the mechanism has been studied; Kliegman, J. M.; Barnes, R. K. *J. Org. Chem.* **1972**, *37*, 4223.

(18) Gall, M.; House, H. O. *Org. Synth.* **1972**, *52*, 39.

1.6 mL of ether, 5 mg of Ph_3CH, 86.4 mg (0.346 mmol) of the enol acetate **11**, and 53 mL of DME, had been stirred for 15 min, 1.5 mL (24.1 mmol) of freshly purified[19] MeI was added rapidly. The resulting pale green solution was stirred for 45 s and then quenched with 15 mL of aqueous 1 M HCl and partitioned between ether and water. After the organic phase had been dried and concentrated, the residual brown liquid was distilled (reduced pressure, short-path still) to afford a mixture of a colorless solid and a brown liquid. Recrystallization from hexane and from ethanol separated 21 mg (27%) of the ketone **14** as colorless, flat prisms, mp 61–63 °C: IR (CCl_4) 1702 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 0.8–2.6 (26 H, m, aliphatic CH including a 3 H methyl singlet at 1.17 and a 9 H *t*-Bu singlet at 0.87); mass spectrum, *m/e* (relative intensity) 222 (20, M^+), 167 (26), 165 (31), 147 (33), 137 (29), 109 (21), 96 (22), 95 (94), 83 (21), 81 (100), 69 (24), 67 (56), 57 (65), 55 (49), 43 (30), 41 (81), 39 (21).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79; M_r 222.1984. Found: C, 80.88; H, 11.80; M_r 222.2008.

After a comparable experiment with 96.8 mg (0.387 mmol) of the enol acetate **11**, 1.6 mL of ether containing 2.22 mmol of MeLi, and 3.0 mL (48 mmol) of MeI in 50 mL of DME, the crude liquid organic product was mixed with 67.4 mg of 1-phenyloctane (an internal standard) and analyzed (GC, Carbowax 20M on Chromosorb P, apparatus calibrated with known mixtures of authentic samples). The organic product contained 1-phenyloctane (t_R 7.7 min), the cis ketone **14** (23.2 min, calcd yield (73%), and a minor component (ca. 5% of the mixture) at 24.9 min. Analysis of the mixture of GC–MS indicated the presence of ketone **14** and several minor nonisomeric components (apparent molecular ions at *m/e* 182 and 244). The GC–MS analysis of the entire reaction mixture revealed only one minor component (less than 5% of mixture) with an apparent molecular ion at *m/e* 222, the molecular weight of the ketones **14** and **15**; this minor component may be the trans-syn isomer **15**. A portion of this product mixture was separated (HPLC, silica gel, EtOAc–hexane, 1:49 v/v) to afford 40.7 mg of the cis-syn ketone **14** (t_R 48.8 min), mp 59–62 °C (identified with the previous sample by comparison of ^1H NMR spectra, 300 MHz, $CDCl_3$). The remaining material from this separation contained HPLC peaks at 51.2 min and two broad partially resolved peaks at 58.3 min with ^1H NMR (300 MHz, $CDCl_3$) singlets at 1.153 and 0.867 ppm that may be attributable to the trans-syn isomer **15**. GC–MS analysis of this fraction enriched in minor components indicated the presence of the syn-cis ketone **14** (major) and two minor, unidentified peaks with *m/e* values of 222 corresponding to isomers of the major product **14**; one minor component may be the trans ketone **15**. In addition, there were two other minor, unidentified peaks with *m/e* values of 182 and 220.

Methylation of the Enolate from the Anti-enol Acetate 12. The enolate solution, prepared from 4.99 mmol of MeLi in 3.6 mL of ether, 5 mg of Ph_3CH, 72.0 mg (0.288 mmol) of the enol acetate **12**, and 53 mL of DME, was treated with 1.5 mL (24.1 mmol) of freshly purified[19] MeI. The resulting pale green solution was stirred or 45 s and then quenched with 15 mL of aqueous 1 M HCl and partitioned between ether and water. After the organic phase had been dried and concentrated, the residual brown liquid was chromatographed (silica gel, EtOAc–hexane, 1:19 v/v). The later fractions (TLC R_f values 0.13 to 0.51, silica gel, EtOAc–hexane, 1:19 v/v) were combined and subjected to preparative HPLC (10-μm silica gel, EtOAc–hexane, 1:49 v/v) to separate 25.7 mg (40.2%) of the cis-anti ketone **17** as a colorless liquid, t_R 63 min. The spectral properties of the ketone **17** follow: IR (CCl_4) 1695 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.3–2.5 (14 H, m, aliphatic CH), 1.16 (3 H, s, Me), 0.88 (9 H, s, *t*-Bu); mass spectrum, *m/e* (relative intensity) 222 (14, M^+), 181 (20), 167 (24), 165 (21), 147 (27), 137 (23), 96 (22), 95 (76), 81 (100), 69 (20), 67 (55), 57 (64), 55 (49), 43 (31), 41 (69).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79; M_r 222.1984. Found: C, 80.96; H, 11.75; M_r 222.1998.

In a second, comparable experiment with 2.22 mmol of MeLi in 1.6 mL of ether, 101.8 mg (0.407 mmol) of the enol acetate **12**, 3.0 mL (48 mmol) of MeI, and 50 mL of DME, the crude neutral liquid product was mixed with 52.3 mg of phenyloctane (internal standard). Analysis (GLC, Carbowax 20M on Chromosorb P, apparatus calibrated with known mixtures of authentic samples) indicated the presence of phenyloctane (t_R 7.6 min), the cis ketone **17** (22.9 min, 75% yield), and a minor unidentified impurity (ca. 7% of the product mixture) at 26.4 min. GC–MS analysis of the entire crude product mixture on a capillary GLC system also showed only two peaks corresponding to the ketone **17** and the minor impurity that was not isomeric with ketone **17**. The highest mass peaks in the spectrum of this minor impurity were at *m/e* (relative intensity) 245 (15), 244 (87), and 243 (19). A portion of the mixture was subjected to preparative HPLC (silica gel, EtOAc–hexane, 1:49 v/v) to separate the cis-anti ketone **17** (t_R 46.4 min) as a liquid that was identified with the previously described sample by comparison of ^1H NMR (300 MHz, $CDCl_3$) spectra. The remaining mixture from this separation contained an HPLC peak at 50.1 min and two broad partially resolved peaks at 57.2 min. The ^1H NMR (300 MHz, $CDCl_3$) spectrum of this mixture of minor components included a singlet at 1.160 and as well as a series of *t*-Bu singlets at 0.876, 0.873, 0.854, and 0.843 ppm. GC–MS analysis of this fraction enriched in minor components indicated the presence of four peaks, two of which were the anti-cis ketone **17**, and a smaller amount of an isomeric material (*m/e* 222) that may be the anti-trans ketone **19**. Two other components present had *m/e* values of 182 and 208; the later component may be one of the unalkylated ketone isomers **4** or **10**.

Preparation of the Cis-anti Oxime 18. A solution of 4.5 mg (0.020 mmol) of the cis ketone **17** and 25 mg (0.36 mmol) of hydroxylamine hydrochloride in 0.75 mL of aqueous EtOH (2:1 v/v) was refluxed for 30 min and then cooled to separate 4.2 mg (87%) of the oxime **18** as colorless needles, mp 151–152 °C: IR (CCl_4) 3600, 3300 (free and associated OH), 1630 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$) δ 6.9 (1 H, br, OH), 2.80–2.86 (1 H, m, aliphatic CH), 1.2–2.0 (13 H, m, aliphatic CH), 1.17 (3 H, s, Me), 0.91 (9 H, s, *t*-Bu); mass spectrum, *m/e* (relative intensity) 237 (4, M^+), 220 (82), 206 (31), 196 (64), 180 (100), 149 (20), 107 (30), 95 (32), 93 (26), 86 (20), 81 (47), 79 (26), 73 (23), 69 (22), 67 (36), 57 (94), 55 (43), 43 (24), 41 (89), 39 (20).

Anal. Calcd for $C_{15}H_{27}NO$: M_r 237.2093. Found: M_r 237.2064.

Crystal Structure of 6-*syn*-*tert*-Butyl-*cis*-10-methyl-4-ketoperhydroazulene (14). A crystal of the ketone **14** 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 *P*1 or $P\bar{1}$ (No. 1 or 2).[20] Assuming the space group $P\bar{1}$, a successful refinement was obtained. From a total of 2448 reflections collected in a complete hemisphere of data, 1624 were accepted as statistically above background. In the data refinement, described in the supplementary material, 171 parameters were varied for the 1624 observations. The full-matrix least-squares refinement converged at R = 0.078 and R_w = 0.078. A perspective view of the ketone **14** 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 6-*anti*-*tert*-Butyl-*cis*-10-methyl-4-ketoperhydroazulene Oxime (18). A crystal of the oxime **18** 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 for $P2_1/c$ (No. 14).[20] From a total of 2533 reflections collected in a complete quadrant of data, 1007 were accepted as statistically above background. In the data refinement, described in the supplementary material, 181 parameters were varied for the 1007 observations. The full-maxtrix least-squares refinement converged at R = 0.122 and R_w = 0.089. A perspective view of the oxime **18** 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 6-*syn*-*tert*-Butyl-*cis*-4-ketoperhydroazulene Oxime (7). A crystal of the oxime **7** was mounted and data were collected by procedures described in the supple-

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

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

mentary material. The crystal belonged to the monoclinic system and the data collected were consistent only with space group $P2_1/c$ (No. 14).[20] From a total of 2735 reflections collected in a complete quadrant of data, 1317 were accepted as statistically above background. In the data refinement, described in the supplementary material, 170 parameters were varied for the 1317 observations. The full-matrix least-squares refinement converged at $R = 0.097$ and $R_w = 0.091$. A perspective view of the oxime 7 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.

Supplementary Material Available: Descriptions of the determination of crystal structures for the syn-cis ketone **14**, the anti-cis ketoxime **18**, and the syn-cis ketoxime **7**, including tables of atomic coordinates, bond distances, and bond angles for each compound and Figures 9 and 10, perspective drawings of additional low-energy conformers calculated with the MM2 program for the diastereoisomeric olefins **20** and **21** (14 pages). Ordering information is given on any current masthead page.

Chemistry of 1,3,5-Tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene, a β-Tricarbonyl Trianion Equivalent

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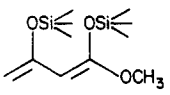
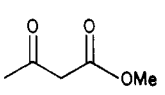
The title compound has been synthesized and its chemistry studied. Condensation with orthoesters, acid chlorides, or imidazolides gave aromatic compounds in a 5C + 1C condensation. A formal synthesis of lasiodiplodin has been completed.

It is well recognized that in nature condensation of poly-β-carbonyl compounds is a major pathway for the biogenesis of aromatic natural products.[1,2] Collie, as early as the 1890's, was the first to recognize the formation of benzenoid derivatives from polyketide acids.[3] Subsequently, numerous efforts to mimic this reaction in the laboratory have met with varying degrees of success.[1,2] The main difficulty has been to control the specificity of the direction of condensation.[2]

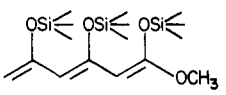
Recently the use of 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene (**1**) as the dianion equivalent of methyl acetoacetate (**2**) has been introduced.[4] The use of **1** as



1



2



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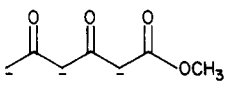

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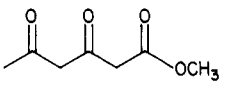
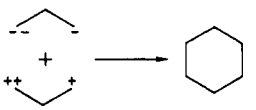


5

a dicarbonyl unit in forming benzenoid aromatic compounds has been quite successful. Specifically, a new cycloaromatization reaction was demonstrated on the basis of the reaction of **1** with various 1,3-dielectrophiles under Lewis acid catalyzed conditions.[5,6] Essentially, the reaction involves the union of two three-carbon units according to eq 1, and the regiochemistry is controlled by the different reactivities of the reaction sites.



(1)

We have demonstrated the utility of this approach by the synthesis of sclerin,[7] a plant growth promoter, and Δ^1-tetrahydrocannabinol,[8] the active component of marijuana.

In this paper, we report on the study of 1,3,5-tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene (**3**), the equivalent of the trianion **4** of the tricarbonyl compound methyl triacetate (**5**).

Results and Discussion

A. Preparation of 1,3,5-Tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene. The starting point was the synthesis of methyl triacetate (**5**) from dehydroacetic acid (**6**), which has been described in the literature.[9] Although **5** was reported to be indefinitely stable at room temperature, we have noted that crude **5** dimerizes after 2 to 3 months to give two aromatic compounds, **7** and **8**, in approximately a 1 to 1 ratio. These compounds may be separated easily by column chromatography.

The next step involved the conversion of **5** to the bis silyl enol ether **9** utilizing literature procedures with a slight variation.[6] The bis silyl enol ether **9** was then transformed into 1,3,5-tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene (**3**) through a minor modification of literature procedure.[6]

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(2) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.
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