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PROJECT ADMINISTRATION DATA SHEET

[X] ORIGINAL [ ] REVISION NO. _____

Project No. G-33-686 (Continuation of G-33-645) GTRI/~~GIT~~ DATE 3 / 30 / 84

Project Director: Dr. Herbert O. House School/~~Lab~~ Chemistry

Sponsor: DHHS/PHS National Institute of General Medical Science

Type Agreement: Grant No. 5 R01 GM30735-03

Award Period: From 6/1/84 To 5/31/85 (Performance) _____ (Reports)

Sponsor Amount:	This Change	Total to Date
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Funded:	$	$ 99,460

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Title: "Special Structrual Features to Control Reactions"

ADMINISTRATIVE DATA OCA Contact John W. Burdette ext. 4820

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Defense Priority Rating: N/A Military Security Classification: N/A

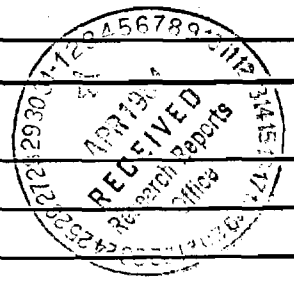
(or) Company/Industrial Proprietary: N/A

RESTRICTIONS

See Attached NIH Supplemental Information Sheet for Additional Requirements.

Travel: Foreign travel must have prior approval – Contact OCA in each case. Domestic travel requires sponsor approval where total will exceed greater of $500 or 125% of approved proposal budget category.

Equipment: Title vests with Georgia Tech



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SPONSORED PROJECT TERMINATION/CLOSEOUT SHEET

Date 12/5/86

Project No. G-33-686 School/~~XXX~~ Chem.

Includes Subproject No.(s) N/A

Project Director(s) H. O. House GTRC / ~~XXX~~

Sponsor DHHS/PHS National Institute of General Medical Science

Title "Special Structrual Features to Control Reactions"

Effective Completion Date: 5/31/85 (Performance) 8/31/85 (Reports)

Grant/Contract Closeout Actions Remaining:

- [ ] None
- [X] Final Invoice or Final Fiscal Report
- [ ] Closing Documents
- [ ] Final Report of Inventions - already submitted.
- [ ] Govt. Property Inventory & Related Certificate
- [ ] Classified Material Certificate
- [ ] Other

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JOURNAL OF CHEMICAL AND ENGINEERING DATA

Synthesis of Certain Cyclic Silanes

Herbert O. House, Joseph A. Hrable, and S. Lakshmi Narasimhan

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Synthesis of Certain Cyclic Silanes

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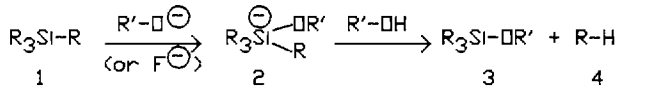
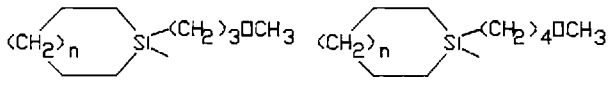
The chlorotrialkylsilanes 21–24 have been synthesized as precursors to potential steric blocking groups for alkanes and cycloalkanes. Reaction of these chlorosilanes with one of the organometallic reagents methyllithium, methylmagnesium chloride, *n*-octylmagnesium bromide, or *p*-chlorobenzylmagnesium chloride formed the silanes 25–34.

As part of our continuing interest (*1–4*) in the use of sterically bulky substituents to control reactant conformation and, in some cases, reaction stereochemistry, we initiated a study of certain trialkylsilyl substituents, R_3Si–. Such substituents, R_3Si–, have sufficient steric bulk (*5–9*) to exert control over reactant conformation in a manner similar to bulky alkyl substituents (*10*). Thus, a conformational *A* value of 2.4–2.6 kcal/mol is reported for the trimethylsilyl group (*8*, *9*). Furthermore, the susceptibility of tetraalkylsilanes **1** (Scheme I) to attack by hard nucleophiles such as F^- or $R'-O^-$ to form successively pentacoordinate intermediates **2** and cleavage products **3** and **4** (*11–16*) suggests that selective cleavage of certain steric blocking groups, R_3Si–, might be possible. In order to investigate this possibility, we have studied synthetic routes to silanes incorporating the trisubstituted silyl groups **5–8**. This paper describes the synthesis and characterization of these silanes.

Scheme I





5, n=1
7, n=0

6, n=1
8, n=0

The syntheses began with the conversion of each dibromide **9** or **10** to the corresponding bis-Grignard reagent followed by reaction with trichlorosilane (Scheme II). Subsequent orienting experiments were performed in which 1-octene (**13**) was converted to the silane **14** via either of the hydrosilation (*17*, *18*) products **15** or **16** without rearrangement of the carbon skele-

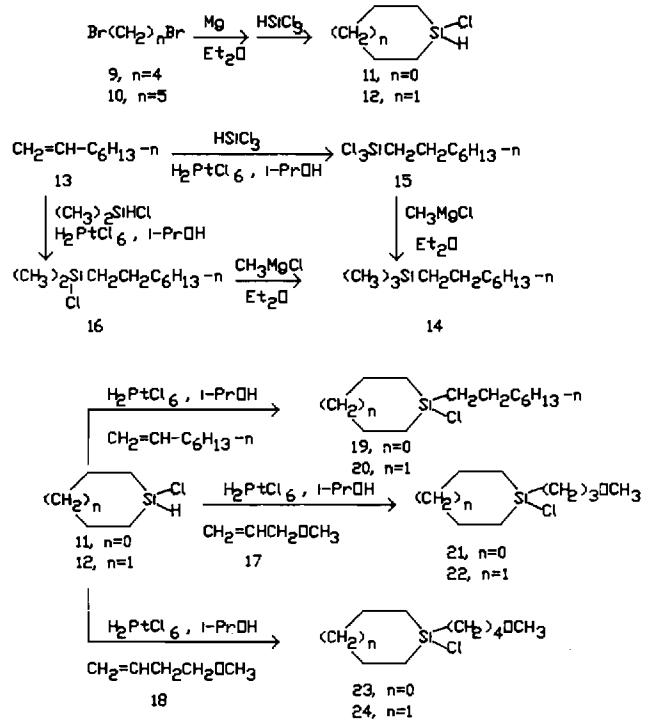
0021-9568/86/1731-0124$01.50/0

Table I. Physical Properties[a] of Compounds Prepared

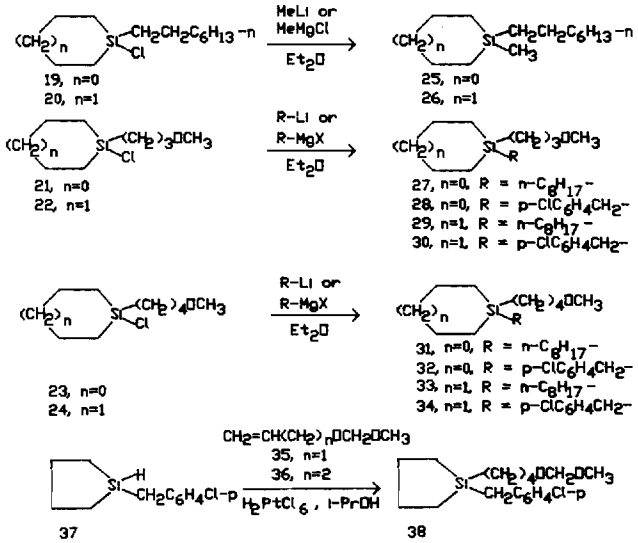
cmpd	formula	yield, %	bp (press.)	n_D(temp)	[ref] bp(press.), n_D (temp)	analyses	MS	(EI/CI) M(Int)	IR data,[b] cm^{-1}
15	$C_8H_{17}Cl_3Si$	96	57–58(1.2)	1.4463(25)	[19] 68(1.6), 1.4458(25)		(EI)	246 (M, 1)	
14	$C_{11}H_{26}Si$	88	89–90(9)	1.4222(25)	[20] 63(1.2), 1.4272(25)	C, H	(EI)	186 (M, 1)	
16	$C_{10}H_{23}ClSi$	69	65–66(1.5)	1.4341(25)	[21] 215–218(740), 1.4390(20)		(EI)	206 (M, 0.3)	
12	$C_5H_{11}ClSi$	69.4	142–143	1.4683(25)	[22] 143(760), 1.467(25)		(EI)	134 (M, 25)	2180 (SiH)
20	$C_{13}H_{27}ClSi$	80	134–136(0.6–0.7)	1.4702(25)			(EI)	248 (M, 2)	
26	$C_{14}H_{30}Si$	78	71–73(0.15–0.16)	1.4588(25)		C,H	(EI)	226 (M, 2)	
17	C_4H_8O	70	41.5–42.5	1.3744(25)	[23] 42–42.3, 1.3759(25)				1645(C=C), 914(CH=CH_2)
22	$C_9H_{19}ClOSi$	53	55(0.05)	1.4701(25)			(EI)	206 (M, 1.7)	
29	$C_{17}H_{36}OSi$	63	ca. 100(0.05)	1.4656(25)		C, H	(EI)	284 (M, 1.4)	
30	$C_{16}H_{25}ClOSi$	67	ca. 170–175(0.5)	1.5295(25)		C, H, Cl	(CI)	297 (M + 1, 40)	no C=O or OH
11	C_4H_9ClSi	45	114–116	1.4614(25)			(EI)	120 (M, 13)	2185 (Si–H)
19	$C_{12}H_{25}ClSi$	81	73(0.02)	1.4650(25)			(EI)	232 (M, 7)	
25	$C_{13}H_{28}Si$	77	ca. 70(0.07)	1.4552(25)		exact mass	(EI)	212 (M, 2)	
21	$C_8H_{17}ClOSi$	52	38–40(0.05)	1.4622(25)			(EI)	no M+, 165 (32)	no C=C
27	$C_{16}H_{34}OSi$	84	ca. 80–95(0.2–0.8)	1.4624(25)		C, H	(EI)	270 (M, 0.5)	no OH or C=O
28	$C_{15}H_{23}ClOSi$	69	ca. 160–163(0.5)	1.5315(25)		C, H, Cl	(EI)	282 (M, 0.1)	no OH or C=O
18	$C_5H_{10}O$	62	71–72	1.3890(25)	[24] 71–72, 1.3910(22)				1645(C=C), 920(CH=CH_2)
24	$C_{10}H_{21}ClOSi$	81	60–62(0.03)	1.4710(25)			(EI)	220 (M, 0.3)	no CH=CH
33	$C_{18}H_{38}OSi$	69	125–130(0.9–1.1)	1.4670(25)		C, H	(EI)	298 (M, 2)	
34	$C_{17}H_{27}ClOSi$	24	ca. 145(0.3)	1.5278(25)		C, H, Cl	(CI)	310 (M + 1, 27)	no OH or C=O
23	$C_9H_{19}ClOSi$	62	68–70(0.45)	1.4675(25)			(CI)	207 (M + 1, 54)	
31	$C_{17}H_{36}OSi$	58	ca. 150 (0.4)	1.4635(25)		C, H	(EI)	284 (M, 2)	no OH or C=O
32	$C_{16}H_{25}ClOSi$	30	ca. 168–171(0.5)	1.5279(25)		C, H, Cl	(CI)	297 (M + 1, 90)	no OH or C=O
35	$C_5H_{10}O_2$	40.1	90.5–91.5	1.3957(25)	[25, 26] 96–97		(CI)	103 (1.4, M + 1)	1645(C=C), 920(CH=CH_2)
36	$C_6H_{12}O_2$	68.1	116–117	1.4026(25)		C, H	(CI)	117 (28, M + 1)	1640(C=C), 918(CH=CH_2)
37	$C_{11}H_{15}ClSi$	72	74–75(0.05)	1.5520(25)		C, H, Cl	(EI)	no M+,211 (4)	2140 (Si–H)
38	$C_{17}H_{27}ClO_2Si$	85	165(0.2)	1.5221(25)		C, H, Cl	(CI)	327 (1.3, M + 1)	no OH or C=O

[a] Boiling point, bp, in °C. Pressure in mm. Temperature in °C. [b] In CCl_4.

Scheme II



Scheme III



ton. Corresponding hydrosilation reactions (*17*, *18*) employing the cyclic chlorosilanes **11** or **12** with one of the olefins **13**, **17**, or **18** yielded the set of trisubstituted chlorosilanes **19–24**.

Each of these water-sensitive chlorosilanes **19–24** was characterized by its NMR and mass spectra and by reaction with an organolithium or organomagnesium compound to form a tetrasubstituted silane (Scheme III). The ^{1}H and ^{13}C NMR spectra of these tetrasubstituted silanes **25–34** were used to establish that these products have been formed without rearrangement of the carbon skeletons. A related tetrasubstituted silane **38** was obtained by a hydrosilylation reaction of the trialkylsilane **37** with the terminal olefin **36**.

Table II. NMR Spectra of Compounds Prepared

cmpd	(solv[a]) H NMR data	(solv[a]) C NMR data
15	(Car) 0.5–2.2 (m)	
14	(Car) 0.2–1.7 (17 H, m), –0.02 (9 H, s)	(Chl) 33.6 (t), 32.0 (t), 29.3 (t, 2 C), 24.0 (t), 22.7 (t), 16.8 (t), 14.2 (q), –1.6 (q, 3 C)
16	(Car) 0.6–1.7 (17 H, m), 0.37 (6 H, s)	
12	(Car) 4.87 (1 H, br s), 0.2–2.3 (12 H, m)	(Chl) 29.0 (t), 23.1 (t, 2 C), 14.8 (t, 2 C)
20	(Car) 0.2–2.2 (m)	
26	(Car) 0.2–2.4 (27 H, m), –0.02 (3 H, s)	(Chl) 33.7 (t), 32.0 (t), 30.2 (t), 29.4 (t, 2 C), 24.6 (t, 2 C), 23.8 (t), 22.8 (t), 14.1 (t, q, 2 C), 13.0 (t, 2 C), –4.8 (q)
17	(Car) 4.9–6.3 (3 H, m), 3.84 (d, of m), 3.23 (3 H, s)	
22	(Car) 3.30 (2 H, t), 3.25 (3 H, s), 0.4–2.2 (14 H, m)	(Chl) 74.3 (t), 58.2 (q), 29.2 (t), 23.5 (t, 2 C), 22.8 (t), 15.4 (t, 2 C), 13.1 (t)
29	(Car) 3.24 (2 H, t), 3.22 (3 H, s), 0.2–2.0(31 H, m)	(Chl) 75.5 (t), 58.2 (q)8 33.7 (t), 31.9 (t), 30.1 (t), 29.3 (t, 2 C), 24.5 (t, 2 C), 24.0 (t), 23.8 (t), 22.7 (t), 14.1 (q), 12.5 (t), 11.2 (t, 2 C), 8.5 (t)
30	(Car) 6.8–7.4 (4 H, m), 3.20 (5 H, s and t), 2.10 (2 H, s), 0.3–1.8 (16 H, m)	(Chl) 138.0 (s), 128.9 (s), 128.6 (d, 2 C), 127.6 (d, 2 C), 75.1 (t), 58.1 (q), 29.7 (t), 24.2 (t, 2 C), 23.6 (t), 22.1 (t), 10.6 (t, 2 C), 8.0 (t)
11	(Car) 5.13 (1 H, br), 0.4–2.0 (8 H, m)	(Chl) 25.7 (t, 2 C), 14.1 (t, 2 C)
19	(Car) 0.2–2.2 (m)	(Chl) 32.9 (t), 31.9 (t), 29.2 (t, 2 C), 26.0 (t, 2 C), 23.4 (t), 22.7 (t), 17.4 (t), 14.6 (t, 2 C), 14.1 (q)
25	(Car) 0.2–2.0 (25 H, m), 0.05 (3 H, s)	(Chl) 33.5 (t), 31.9 (t), 29.3 (t, 2 C), 27.3 (t, 2 C), 24.3 (t), 22.7 (t), 15.1 (t), 14.1 (q), 11.8 (t, 2 C), –3.2 (q)
21	(Car) 3.28 (2 H, t), 3.20 (3 H, s), 0.5–2.0 (12 H, m)	(Chl) 74.1 (t), 58.2 (q), 26.0 (t, 2 C), 23.5 (t), 14.6 (t, 2 C), 13.8 (t)
27	(Car) 3.28 (2 H, t), 3.23 (3 H, s), 0.2–2.0 (29 H, m)	(Chl) 75.4 (t), 58.1 (q), 33.6 (t), 31.9 (t), 29.2 (t, 2 C), 27.4 (t, 2 C), 24.4 (t, 2 C), 22.6 (t), 14.1 (t), 13.7 (q), 10.2 (t, 2 C), 9.8 (t)
28	(Chl) 6.8–7.4 (4 H, m), 3.25 (5 H, s and t), 2.10 (2 H, s), 0.3–1.8 (14 H, m)	(Chl) 138.1 (s), 129.1 (s), 128.6 (d, 2 C), 127.7 (d, 2 C), 74.9 (t), 58.1 (q), 27.1 (t, 2 C), 24.2 (t), 23.1 (t), 9.8 (t, 2 C), 9.5 (t)
18	(Car) 4.7–6.2 (3 H, m), 3.35 (2 H, t), 3.23 (3 H, s), 2.0–2.6 (2 H, m)	
24	(Car) 3.2–3.5 (5 H, m with s at 3.28), 0.3–2.1 (16 H, m)	(Chl) 72.0 (t), 58.2 (q), 32.8 (t), 29.2 (t), 23.4 (t, 2 C), 19.5 (t), 16.7 (t), 15.4 (t, 2 C)
33	(Car) 3.25 (2 H, t), 3.22 (3 H, s), 0.1–2.0 (33 H, m)	(Chl) 72.4 (t), 58.2 (q), 33.7 (t), 33.6 (t), 31.9 (t), 30.2 (t), 29.3 (t, 2 C), 24.5 (t, 2 C), 23.8 (t), 22.7 (t), 20.5 (t), 14.1 (q, ?), 12.4 (t, 2 C)8 11.3 (t, 2 C)
34	(Car) 6.6–7.4 (4 H, m), 3.0–3.4 (5 H, m with s at 3.22), 2.07 (2 H, s), 0.4–2.0 (16 H, m)	(Chl) 138.9 (s), 129.6 (s), 129.3 (d, 2 C), 128.3 (d, 2 C), 72.4 (t), 58.5 (q), 33.5 (t), 29.9 (t), 24.4 (t, 2 C), 22.3 (t), 20.3 (t), 11.8 (t), 10.8 (t, 2 C)
23	(Car) 3.30 (2 H, t), 3.23 (3 H, s), 0.2–2.0 (14 H, m)	(Chl) 72.0 (t), 58.2 (q), 32.6 (t), 26.0 (t, 2 C), 20.1 (t), 17.2 (t), 14.5 (t, 2 C)
31	(Car) 3.1–3.4 (5 H, m with s at 3.22), 0.3–1.7 (31 H, m)	(Chl) 72.4 (t), 58.2 (q), 38.5 (t, 2 C), 31.9 (t), 29.3 (t, 2 C), 27.4 (t, 2 C), 24.3 (t), 22.7 (t), 20.9 (t), 14.1 (q, ?), 13.7 (t, 2 C), 10.3 (t, 2 C)
32	(Chl) 6.8–7.4 (4 H, m), 3.2–3.6 (5 H, m with s at 3.25), 2.10 (2 H, s), 0.3–1.8 (16 H, m)	(Chl) 138.8 (s), 129.8 (s), 129.3 (d, 2 C), 128.3 (d, 2 C), 72.4 (t), 58.5 (q) 33.4 (t), 27.2 (t, 2 C), 23.3 (t), 20.8 (t), 13.2 (t), 10.0 (t, 2 C)
35	(neat) 4.9–6.3 (3 H, m), 4.59 (2 H, s), 4.05 (2 H, d of t), 3.30 (3 H, s)	(Chl) 134.6 (d), 116.9 (t), 95.8 (t), 68.3 (q), 55.2 (t)
36	(neat) 4.8–6.2 (3 H, m), 4.50 (2 H, s), 3.45 (2 H, t), 3.25 (3 H, s), 2.0–2.4 (2 H, m)	(Chl) 135.2 (d), 116.4 (t), 96.4 (t), 67.1 (t), 55.1 (q), 34.3 (t)
37	(Chl) 6.8–7.3 (4 H, m), 4.05 (1 H, m), 2.15 (2 H, d), 1.2–1.7 (4 H, m), 0.4–0.8 (4 H, m)	(Chl) 138.4 (s), 130.1 (s), 129.4 (d, 2 C), 128.5 (d, 2 C), 27.1 (t), 21.7 (t, 2 C), 8.7 (t, 2 C)
38	(Car) 6.8–7.2 (4 H, m), 4.60 (2 H, s), 3.50 (2 H, t), 3.30 (3 H, s), 2.15 (2 H, s), 1.3–1.8 (6 H, m), 0.4–0.8 (4 H, m)	(Chl) 138.7 (s), 129.7 (s), 129.1 (d, 2 C), 128.3 (d, 2 C), 96.4 (t), 67.3 (t), 55.0 (q), 33.4 (t), 27.2 (t, 2 C), 23.3 (t), 20.8 (t), 13.1 (t), 9.9 (t, 2 C)

[a] Car = carbon tetrachloride; Chl = deuteriochloroform.

Experimental Section

All melting points are corrected and all boiling points are uncorrected. The IR spectra were determined with a Perkin Elmer, Model 299, infrared recording spectrophotometer fitted with a grating. 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 chemical shift values are expressed in 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.

Preparation and Characterization of the Silanes and Related Compounds. The chlorosilane intermediates whose preparations are summarized in Scheme II were characterized by their physical and spectral properties (Tables I and II), but no effort was made to obtain analytical samples of these water-sensitive materials. The silanes prepared as summarized in Scheme III were fully characterized as indicated in Tables I and II. Descriptions of the preparation and purification of each of the compounds listed in Table I are available in the supplementary material.

Registry No. **9**, 110-52-1; **10**, 111-24-0; **11**, 55437-96-2; **12**, 18339-91-8; **13**, 111-66-0; **14**, 3429-76-3; **15**, 5283-66-9; **16**, 18162-84-0; **17**, 627-40-7; **18**, 4696-30-4; **19**, 99165-24-9; **20**, 99165-25-0; **21**, 99165-28-1; **22**, 99165-27-2; **23**, 99165-28-3; **24**, 99165-29-4; **25**, 99165-30-7; **26**, 99165-31-8; **27**, 99165-32-9; **28**, 99165-33-0; **29**, 99165-34-1; **30**, 99165-35-2; **31**, 99165-36-3; **32**, 99165-37-4; **33**, 99165-38-5; **34**, 99165-39-6; **35**, 62322-45-6; **36**, 99165-40-9; **37**, 99165-41-0; **38**, 99165-42-1; H_2PtCl_6, 16941-12-1; $HSiCl_3$, 10025-78-2; MeCl, 74-87-3; Me_2SiHCl, 1066-35-9; $CH_2{=}CHCH_2OH$, 107-18-6; n-$C_8H_{17}Cl$, 111-85-3; n-$C_{16}H_{33}Li$, 65018-38-2; n-$C_{16}H_{34}$, 544-76-3; p-$ClC_6H_4CH_2Cl$, 104-83-6; MeLi, 917-54-4; n-$C_8H_{17}Br$, 111-83-1; CH_3OCH_2Cl, 107-30-2; $CH_2{=}CHCH_2Br$, 106-95-6; $CH_2{=}CH(CH_2)OH$, 627-27-0; HCHO, 50-00-0; p,p'-dichlorobibenzyl, 5216-35-3.

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(25) Taskinen, E.; Laehteenmaeki, H. *Tetrahedron* **1978**, *32*, 2331.
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Supplementary Material Available: Descriptions of the preparation and purification of each of the compounds listed in Table I (22 pages). Ordering information is given on any masthead page.

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Unsymmetrically Substituted 1,8-Diarylanthracenes

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Unsymmetrically Substituted 1,8-Diarylanthracenes[1]

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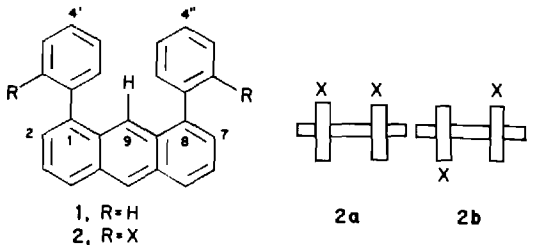
Unsymmetrically substituted 1,8-diarylanthracenes where the aryl rings are *m*-tolyl (**5**), *o*-tolyl (**6**), and 2,3-dimethylphenyl (**7**) have been synthesized; the barriers to aryl ring rotation in these hydrocarbons were found to be 5.3, 10.4, and 16.3 kcal/mol, respectively. Addition of either an acetoxyl (**14**) or a methyl (**15**) substituent at C-9 of the dixylylanthracene gave mixtures of cis and trans isomers that also exhibited rotation of an aryl ring within the temperature range 25–120 °C. X-ray crystal structures for the *cis*- (**14b**) and *trans*- (**14a**) 9-acetoxydixylylanthracenes demonstrated significant distortion in the geometry of the anthracene ring, permitting rotation of the aryl rings with unexpected ease in solutions at temperatures above 100 °C.

Our studies of 1,8-diphenylanthracene (**1**, Scheme I) and its derivatives have provided evidence that these molecules exist largely in conformations with the two phenyl rings approximately parallel and approximately perpendicular to the plane of the anthracene ring.[2,3] Such conformers possess a molecular cavity bounded on the bottom by the anthracene ring and on two sides by phenyl rings. This cavity is of sufficient size to allow reagents to enter and engage in chemical reactions at the bottom of the cavity, namely, at the C-9 position of the anthracene ring.

Scheme I



1, R = H
2, R = X

2a 2b

Consideration of this geometry leads to the conclusion that 1,8-diarylanthracene derivatives **2** with unsymmetrically substituted aryl rings will exist as two geometrical isomers, a cis form (**2a**) and a trans form (**2b**). Furthermore, the trans form **2b** would be composed of two nonsuperimposable mirror images (enantiomers). Resolution of an appropriate set of enantiomers possessing a functional group at C-9 would provide two molecules, each with

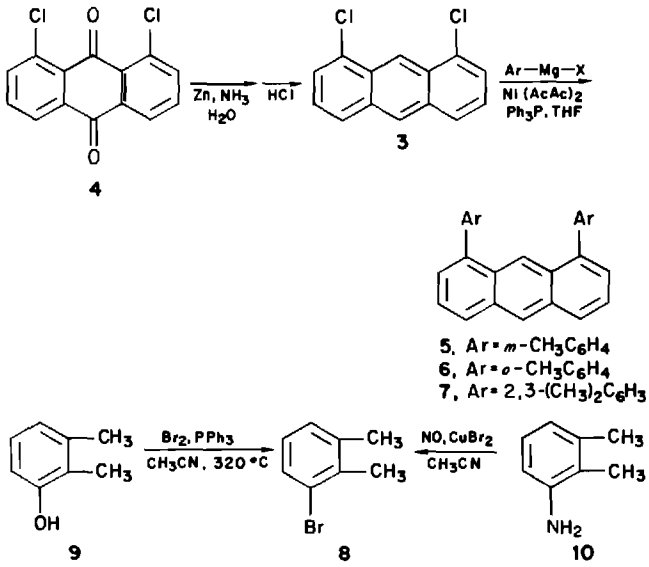
(1) A portion of this research was supported by Public Health Service Grant R01-GM-30735 from the National Institute of General Medical Science. The execution of this research was also aided by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer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

(2) (a) House, H. O.; Koepsell, D.; Jaeger, W. *J. Org. Chem.* **1973**, *38*, 1167. (b) House, H. O.; Koepsell, D. G.; Campbell, W. *Ibid.* **1972**, *37*, 1003.

(3) House, H. O.; Ghali, N. I.; Haack, J. L.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 1807.

0022-3263/86/1951-0921$01.50/0

Scheme II



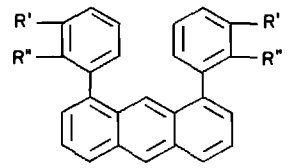
a chiral cavity and a functional group at the bottom of this cavity. Such molecules have the potential to serve as "synthetic enzymes" that could convert achiral substrates to chiral products or could discriminate between the two enantiomers of a racemic substrate.[4]

To explore this possibility we needed information about the rotation barrier for substituted phenyl rings in various 1,8-diarylanthracenes. Since rotation of an aryl ring would both interconvert cis and trans isomers **2a** and **2b** and would also allow racemization of the trans enantiomers, any diarylanthracene that was to be useful as a "synthetic enzyme" would need to have a sufficient barrier to rotation to be configurationally stable at the temperature where it was to be used. In this paper we describe the preparation and properties of several unsymmetrically substituted 1,8-diarylanthracenes that have provided information about the rotation barrier for aryl rings.

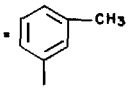
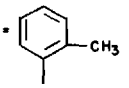
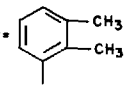
Our syntheses involved several modifications (see Experimental Section) of previous procedures[2,3] in which 1,8-dichloroanthraquinone (**4**) was reduced to 1,8-chloroanthracene (**3**, Scheme II), and this dihalide was coupled with various aryl-Grignard reagents in the presence of a nickel catalyst.[5] A particularly helpful modification involved the addition of a 2:1 molar ratio of Ph_3P and $Ni(AcAc)_2$ to the reaction mixture so that the nickel intermediates could be stabilized as $Ni(PPh_3)_4$ or $NiX_2(PPh_3)_2$.[5] With the present modifications, these syntheses provided very satisfactory routes to the three substituted 1,8-diarylanthracenes **5–7** as well as the parent hydrocarbon **1**.

Although the aryl halide precursors for Grignard reagents used to prepare anthracenes **5** and **6** were commercially available, it was necessary to prepare the xylyl bromide **8** from either the phenol **9** or the aniline **10**. Conversion of the aniline **10** to the bromide **8** by a conventional procedure involving diazotization in aqueous solution gave a rather poor yield of the bromide (typically 35%) accompanied by comparable amounts of the phenol **9**, a byproduct from solvolysis of the diazonium salt intermediate. This difficulty was avoided by employing an alternative procedure[6] in which the amine was treated with a stoichiometric amount of copper(II) bromide and excess nitric oxide in acetonitrile. This procedure offered a particularly convenient route to the bromide **8**.

Scheme III



rotation barriers

	Energy	coalesc temp	solvent
5, Ar = 	5.3 (0.5) kcal	−55 °C	CD_2Cl_2
6, Ar = 	10.4 (1.0) kcal	124 °C	DMF-d_7
7, Ar = 	16.3 (2.0) kcal	>170 °C	$C_6D_5NO_2$

The energy barriers for rotation of an aryl ring in the diarylanthracenes **5–7**, summarized in Scheme III were determined by standard NMR techniques (see Experimental Section). The data presented include the energies,[7] the solvents used for the NMR measurement, and the estimated coalescence temperatures. The barrier (5.3 kcal/mol) observed for anthracene **5** with no ortho substituent larger than hydrogen was approximately doubled (10.4 kcal) when one *o*-methyl substituent was present. The effective steric bulk of this *o*-methyl substituent was significantly enhanced (16.3 kcal) by the buttressing effect of a second methyl added to the **3** position of each phenyl ring in anthracene **7**. The cis (**2a**) and trans (**2b**) isomers of anthracene **7** were separated by HPLC techniques; these geometrical isomers interconverted only slowly at 25 °C so that reequilibration of solutions of the partially separated isomers was complete after 24 h. These results led us to anticipate that derivatives of the anthracene **7** with an additional hindering substituent larger than hydrogen at C-9 might be sufficiently stable to interconversion to be useful as potential "synthetic enzymes".

Since we have thus far[2,3] found no satisfactory method to effect selective, direct substitution at C-9 in 1,8-diarylanthracenes, we choose an alternative indirect route involving formation of the intermediate quinone **11** that could be selectively reduced to the 9-anthrone **12** (Scheme IV). Although preliminary small-scale experiments suggested that photosensitized oxidation of the dixylylanthracene **7** with oxygen in the presence of methylene blue might be part of a useful route for the formation of the quinone **11**, we were unsuccessful in efforts to use this reaction on a preparative scale.[8] After considerable experimentation with various oxidation procedures, we selected a two-phase oxidation with chromic acid in a water–chlorobenzene mixture that would regularly produce the desired quinone **11** in 50% yield. The major byproduct in this reaction was the keto lactone **13** that we presume was formed via the intramolecular attack of a phenoxy radical on one of the *o*-methyl groups.

(4) For recent reviews of this general concept, see: (a) Tabushi, I. *Tetrahedron* **1984**, *40*, 269–292. (b) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161–170. (c) Rebek, J., Jr. *Ibid.* **1984**, *17*, 258–264. (d) Cram, D. J. *Science* (*Washington, D.C.*) **1983**, *219*, 1177–1183. (e) Lehn, J.-M. *Ibid.* **1985**, *227*, 849–856.

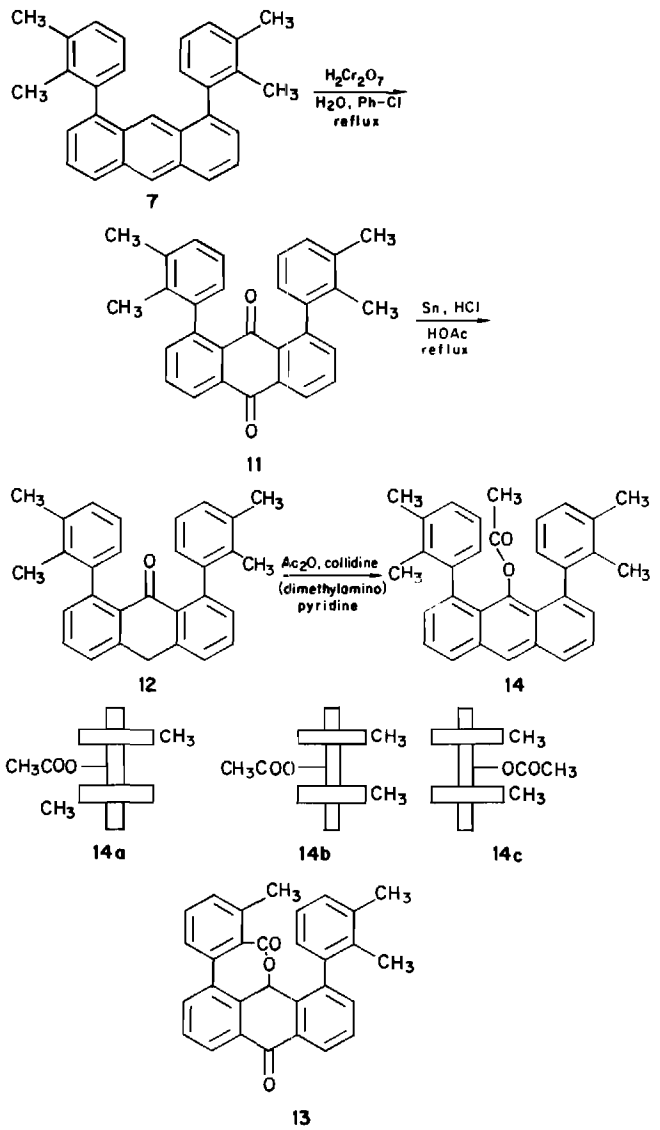
(5) For a recent review of this coupling procedure, see: Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340–348.

(6) (a) Brackman, W.; Smit, P. J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 857. (b) For a typical procedure to diazotize an anime and convert it to a bromide in aqueous solution, see: Hartwell, J. L. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. 3, p 185.

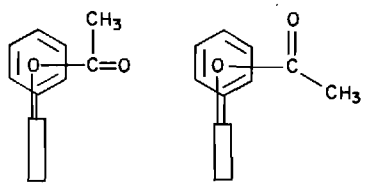
(7) Values in parentheses here and elsewhere in this paper indicate estimated standard deviations in the least significant digit(s).

(8) For a review of this reaction, see: Denny, R. W.; Nickon, A. *Org. React.* (*N.Y.*) **1973**, *20*, 133–336.

Scheme IV



Reaction of the anthrone **12** with a solution of acetic anhydride in collidine containing a catalytic amount of 4-(dimethylamino)pyridine produced a mixture of three 9-acetoxydixylylanthracenes **14**. Although all three compounds were interconverted when solutions of the products were heated above 100 °C, at room temperature HPLC techniques separated the mixture into the pure trans isomer **14a** and a rapidly equilibrating mixture of the cis isomer **14b** and a second component (minor) tentatively assigned the structure of the cis isomer **14c**. The major components **14a** and **14b** could also be separated from the mixture by recrystallization from a mixture of acetone and chloroform. The structures of these two materials were confirmed by obtaining an X-ray crystal structure for each compound as illustrated in Figures 1 and 2. The NMR spectra of solutions of these materials (see Experimental Section) were fully consistent with the solid state structures.



14b **14d**

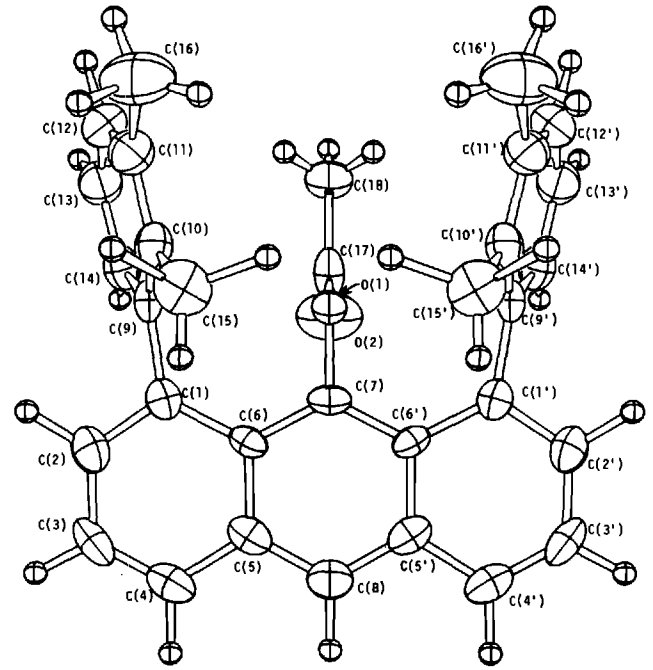


Figure 1. Perspective view of the molecular structure of *anti*-9-acetoxy-*cis*-1,8-dixylylanthracene.

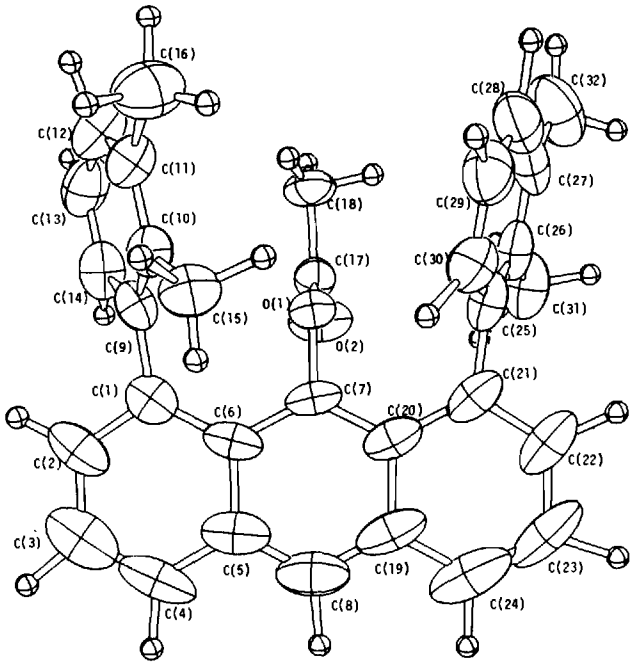
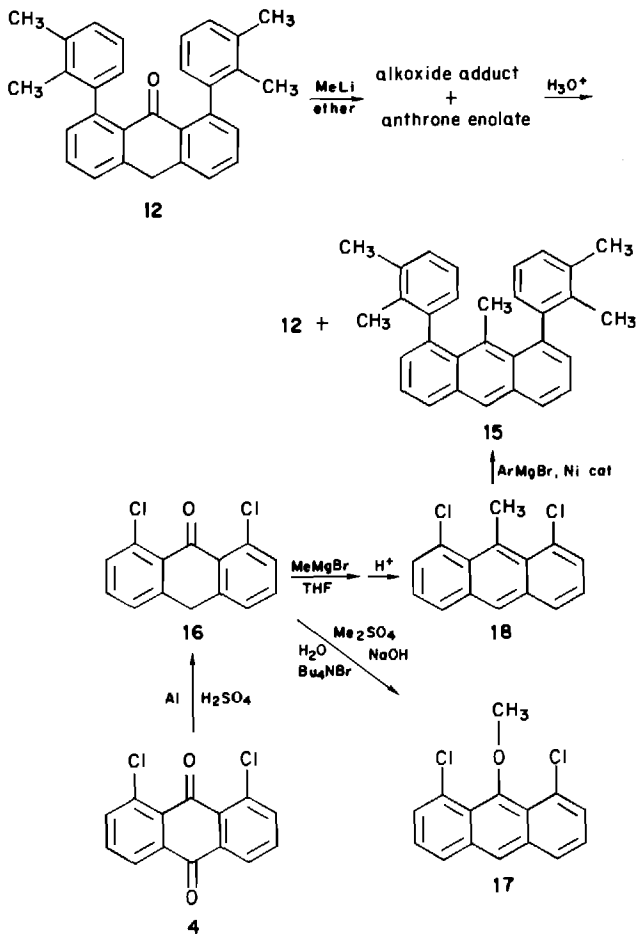


Figure 2. Perspective view of the molecular structure of 9-acetoxy-*trans*-1,8-dixylylanthracene.

The third product, present in solution as about 10% of a rapidly interconverting mixture with **14b**, has NMR absorption compatible with its tentative assignment as the cis-syn acetate **14c**. Presumably the two materials **14b** and **14c** are interconverting either by rotation about the C-9 C–O bond or by an inversion at oxygen involving a transition state with a linear C–O–C bond. Since this linear inversion at divalent oxygen is estimated to have an energy barrier greater than 18 kcal/mol,[9] it seems likely that the

(9) (a) Kessler, H.; Rieker, A.; Rundel, W. *Chem. Commun.* **1968**, 475. (b) Raban, M.; Kenney, G. W. *J. Tetrahedron Lett.* **1969**, 1295. (c) Gordon, A. J.; Gallagher, J. P. *Ibid.* **1970**, 2541. (d) For a review, see: Lambert, J. B. In "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Eds.; Wiley-Interscience: New York, 1971; Vol. 6, pp 19–105.

Scheme V



facile interconversion we are observing should be attributed to rotation and not a linear inversion process. Although we favor structure **14c** for the minor cis isomer present, we cannot exclude the possibility that the minor product has structure represented in part by formula **14d** and is interconverting with **14b** by rotation about the O–CO bond of the ester.

Another dixylylanthracene derivative with a substituent at C-9 was obtained by the reaction of the anthrone **12** with ethereal methyllithium. This reaction formed a mixture of the alkoxide precursor of hydrocarbon **15** (minor) and the enolate of anthrone **12** (major, Scheme V). However, when the crude reaction mixture was acidified, isolated, and treated with methyllithium repeatedly, a reasonable yield of the 9-methyl derivative **15** was obtained. This material proved to be a 2:1 mixture of trans (**15a**) and cis (**15b**) isomers that was interconverting slowly at 25 °C. In an alternative synthetic approach to 9-substituted diarylanthracenes, the dichloro quinone **4** was selectively reduced to the dichloroanthrone **16**. Subsequent methylation with dimethyl sulfate formed the 9-methoxy dichloride **17** and addition of methylmagnesium bromide to the anthrone afforded the 9-methyl dichloride **18**. Efforts to couple the 9-methoxy dichloride **17** with either phenylmagnesium bromide or the Grignard reagent from bromide **8** in the presence of various Ni or Pd catalysts were uniformly unsuccessful. However, reaction of the 9-methyl dichloride **18** with the *o*-xylyl-Grignard reagent in the presence of the catalyst from $Ni(AcAc)_2$ and Ph_3P did form the 9-methyl derivative **15** in low yield.

It is apparent that 1,8-dixylylanthracenes, even with additional substituents at C-9, have relatively low energy barriers to rotation of an aryl ring contrary to our expectation. The reason for the relatively low energy barriers became apparent when the crystal structures (Figures 1 and 2) for the 9-acetates **14a** and **14b** were examined. In both cases the two aryl rings are no longer parallel but are bent away from one another as a result of a series of small distortions in bond lengths and bond angles of the anthracene system. The extent of this distortion may be seen by using crystal structure data to compare the distance between the 4′ and 4″ positions of the two phenyl rings in various derivatives (see structure **1**). For the relatively uncongested molecule, 10-bromo-1,8-diphenylanthracene[3] with hydrogen at C-9, the distance is 5.485 Å (the calculated distance with no distortion should be 5.0 Å). The distance found for the *trans*-dixylyl acetate **14a** is 6.468 Å and the even more congested cis isomer **14b** has a distance of 6.833 Å. A view of the *trans*-dixylyl acetate **14a** from above the top edge of the anthracene ring in Figure 3 also provides an indication of the extent of distortion in these molecules. Thus, to achieve a significant increase in the barrier to aryl ring rotation it will be necessary to add substituents that oppose this distortion of the anthracene ring. We believe that addition of substituents at the C-2 and C-7 positions of the anthracene ring should be most effective and plan to explore the preparation and properties of such materials.

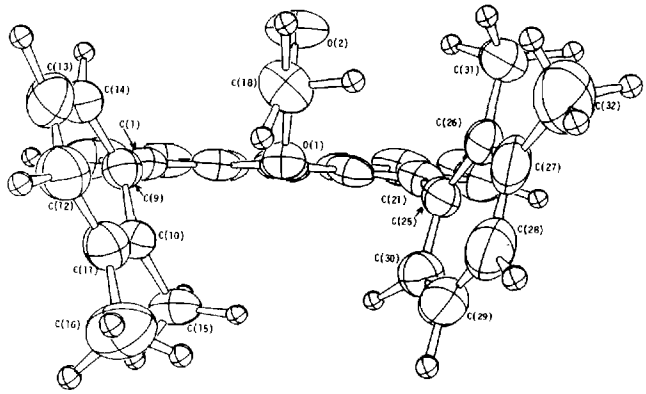


Figure 3. Perspective view of the molecular structure of 9-acetoxy-*trans*-1,8-dixylylanthracene as seen from the edge of the anthracene ring.

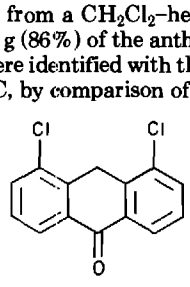
Experimental Section[10]

Preparation of 1,8-Dichloroanthracene (3). The following modifications in earlier directions[2,3] are an improved procedure for the preparation of this dihalide on a large scale. A slurry of 100.0 g (361 mmol) of the quinone **4** in 1.2 L of aqueous 28% NH_3 and 900 mL of H_2O was cooled to 10 °C (ice bath) and then 500 g (7.65 mol) of Zn dust was added, portionwise with stirring during 15 min. The resulting red slurry, which warmed to 30 °C when the cooling bath was removed, was heated to 75 °C on a steam bath and then held at this temperature with stirring for 4 h. During this period the color of the solution changed from red to light brown and a white precipitate separated. The mixture was

(10) 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.

allowed to stand and cool to room temperature and then the supernatant liquid was filtered from the mixture of white and grey (excess Zn) solids. The filtrate was extracted with two 200-mL portions of CH_2Cl_2 while the solids were separately extracted with several portions of boiling CH_2Cl_2. After the combined extracts had been concentrated, the residual off-white solid (85 g) was suspended in a mixture of 400 mL of aqueous 12 M HCl and 4.4 L of *i*-PrOH. The resulting suspension was refluxed for 3 h during which time all the solid dissolved to give a pale yellow solution. This solution was allowed to cool and stand overnight and then filtered with suction. The collected product was allowed to dry in the air for 2 days to leave 67.65 g (75.7%) of the dichloride **3** as yellow needles, mp 156.5–157 °C. Concentration of the mother liquor to one-third of its original volume followed by cooling, filtration, and drying separated an additional 8.07 g of product (total yield 75.72 g or 84.7%), mp 154–156 °C. This product was identified with previously described material, mp 156–157 °C, by a mmp determination and by comparison of IR and NMR spectra.

Preparation of 1,8-Dichloro-9-methoxyanthracene (17). In a modification of a previously described reduction procedure,[3] 100 g (361 mmol) of the quinone **4** was dissolved in 1.1 L of concentrated sulfuric acid with vigorous mechanical stirring. Then 30.0 g (1.11 mol) of Al powder was added and the mixture was stirred for 8 h while the temperature of the mixture was maintained at 25–30 °C by intermittent use of a cold water bath. The resulting yellow suspension was poured onto 3 L of ice and, after standing for 30 min, was filtered. The residual brown solid was extracted with eight 150-mL portions of CH_2Cl_2 and the combined extracts were washed with aqueous $NaHCO_3$, dried, and concentrated. The resulting tan solid (86.6 g or 90%) could be analyzed for the amounts of isomeric anthrones **16** (major) and **19** (minor) by examining the NMR signals ($CDCl_3$) for the benzylic methylene groups (δ 4.23 for anthrone **19** and δ 4.16 for anthrone **16**). Recrystallization from a CH_2Cl_2–hexane mixture very efficiently separated 82.3 g (86%) of the anthrone **16** as tan needles, mp 166–168 °C, that were identified with the previously described sample, mp 167–168 °C, by comparison of IR and NMR spectra.



19

To a solution of 160 g (4.0 mol) of NaOH and 7.1 g (22 mmol) of $(n\text{-Bu})_4NBr$ (a phase-transfer agent) in 500 mL of H_2O was added, dropwise and with vigorous stirring during 1 h, a solution of 20.0 g (76 mmol) of the anthrone **16** and 38 g (300 mmol) of dimethyl sulfate in 400 mL of CH_2Cl_2. The resulting mixture was stirred at 25 °C for an additional 2 h and then partitioned between water and CH_2Cl_2. The combined organic layers were dried and concentrated to leave 17.55 g (83%) of the crude methoxy dichloride **17** as a dark yellow-orange powder, mp 167–170 °C. Recrystallization from an acetone–chloroform mixture afforded 17.05 g (81%) of the methoxy derivative **17** as bright yellow prisms, mp 170–171 °C. A 2.00-g sample of the product was chromatographed on silica gel with a methylene chloride–hexane eluent (1:4 v/v) and the appropriate fractions were combined and recrystallized from a chloroform–acetone mixture to separate 1.80 g of the pure methyl ether **17**, mp 172–173 °C. The spectral properties follow: IR ($CHCl_3$), no absorption corresponding to OH or C=O groups in the 3-μm or 6-μm region; ^1H NMR (60 MHz, $CDCl_3$) δ 8.22 (1 H, s, aryl CH), 7.2–7.9 (6 H, m, aryl CH), 3.92 (3 H, s, methoxyl); ^{13}C NMR [$CDCl_3$, multiplicity determined by a DEPT (Distortionless Enhancement by Polarization Transfer)], 153.6 (s), 134.2 (2 C, s), 129.3 (2 C, s), 129.1 (2 C, d), 127.8 (2 C, d), 125.5 (2 C, d), 124.1 (d), 122.9 (2 C, s), 65.0 ppm (q); mass spectrum, *m/e* (relative intensity), 278 (51), 276 (82, M^+), 263 (65), 261 (100), 235 (16), 233 (24), 163 (18); UV maxima, nm (cyclohexane, ϵ), 260 (123 000), 347 (3090), 365 (6520), 385 (10 100), 402 (shoulder, 6030), 407 (8750).

Anal. Calcd for $C_{15}H_{10}Cl_2O$: C, 65.01; H, 3.64; Cl, 25.58. Found: C, 65.10; H, 3.68; Cl, 25.56.

Preparation of 1,8-Di-*o*-tolylanthracene (6). A solution of 94.9 g (0.75 mol) of *o*-chlorotoluene and 5.0 mL of 1,2-dibromoethane (to clean Mg surface) in ca. 600 mL of THF was added, dropwise and with stirring during 1 h, to 19.45 g (0.80 mol) of Mg turnings. After the addition was complete, the reaction mixture was refluxed for 15 h and then cooled. Analysis[11] of an aliquot of the solution (total volume 680 mL) indicated the concentration of the aryl-Grignard reagent to be 0.50 M corresponding to a 45% yield. This Grignard reagent solution (680 mL or 340 mmol) was added, dropwise and with stirring during 1 h, to a solution of 20.0 g (72.2 mmol) of the dichloride **3**, 100 mg (0.39 mmol) of nickel(II) acetylacetonate, and 205 mg (0.78 mmol) of Ph_3P in 200 mL of anhydrous THF.

During this addition a cold water bath was used periodically to keep the temperature of the reaction mixture below 50 °C. The resulting black (colloidal Ni) reaction mixture was stirred overnight (10 h) at 25 °C and then quenched with aqueous 3 M HCl and partitioned between water and methylene chloride. The organic phase was dried and concentrated to leave 26.1 g of crude product as a brown liquid. The product was crystallized from a methylene chloride–acetone mixture to separate 15.6 g (54%) of the hydrocarbon **6** as an off-white powder, mp 189–196 °C. A 2.00-g sample of this material was recrystallized again to separate 1.12 g of the pure hydrocarbon **6** as fine colorless needles, mp 200–201 °C: IR ($CHCl_3$), no absorption attributable to OH or C=O groups in the 3- or 6-μm regions; ^1H NMR (60 MHz, CCl_4) δ 7.0–8.6 (16 H, m, aryl CH), 1.92, and 1.89 (6 H, 2 s, Me groups and cis and trans isomers); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling) (double peaks for cis and trans isomers present are listed together), 140.3 and 140.2 (2 C, s), 139.7 (2 C, s), 136.5 and 136.3 (2 C, s), 131.62 and 131.57 (2 C, s), 130.7 and 130.6 (2 C, s), 130.12 and 130.10 (2 C, d), 129.6 and 129.4 (2 C, d), 127.4 and 127.3 (4 C, d), 126.5 and 126.4 (1 C, d), 125.53 and 125.48 (2 C, d), 125.3 and 125.2 (2 C, d), 125.1 (2 C, d), 124.2 and 124.0 (1 C, d), 19.9 ppm (2 C, q); mass spectrum, *m/e* (relative intensity), 359 (30), 358 (100, M^+), 357 (20), 343 (12), 265 (12), 252 (6), 170 (15), 101 (6); UV maxima, nm (cyclohexane, ϵ), 243 (48 100), 249 (86 700), 254 (123 000), 261 (136 000), 332 (3240), 349 (6630), 366 (10 100), 386 (8890). When this product was subjected to HPLC analysis employing a 0.46 × 25 cm column packed with 10-μm silica gel and eluted with hexane, only a single peak (13.98 min) was observed for the two equilibrating isomers present.

Anal. Calcd for $C_{28}H_{22}$: C, 93.81; H, 6.19. Found: C, 93.82; H, 6.17.

NMR Study of the Equilibration of the Two Stereoisomers of 1,8-Di-*o*-tolylanthracene (6). The ^1H NMR (300 MHz) of the hydrocarbon **6** in $CDCl_3$ at 35 °C exhibited peaks at δ 7.07–8.51 (16 H, m, aryl CH), 1.90, and 1.87 (6 H, 2 s, Me groups of cis and trans isomers) with a peak area ratio of ca. 1:1 for the two Me peaks. The ^1H NMR (300 MHz) of a 0.010 M solution of the hydrocarbon **6** in DMF-d_7 at 35 °C exhibited corresponding peaks at δ 7.12–8.77, 1.919, and 1.903 with a Me peak area ratio of ca. 1:1. The solution in DMF-d_7 was measured at each of the following temperatures: 373, 383, 393, 403, and 413 K. At each temperature below the estimated coalescence temperature (397 K), the chemical shifts and peak widths at half height for each of the Me peaks was measured. The spectrum measured in DMF-d_7 at 35 °C was used to measure the separation between Me peak A (571.22 Hz) and Me peak B (576.06 Hz) in the "nonexchange" limit. Using standard relationships,[14] a computer program was written to simulate the spectra of the two Me groups for various preexchange lifetimes, τ and various mole fractions[14c] of the two isomers responsible for peaks A and B. At each temperature these two quantities were varied to obtain the best match between the simulated and observed spectra. The values for τ (in ms) and the mole fraction of the isomer exhibiting peak A at various temperatures were 373 K, 125 and 0.51; 383 K, 91 and

(11) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
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(13) Blanchard, A. A. *Inorg. Synth.* **1946**, *2*, 126.
(14) (a) Gutowsky, H. S.; Holm, C. H. *J. Phys. Chem.* **1956**, *25*, 1228. (b) Pople, J. A.; Schneider, W. G.; Bernstein, H. J. "High-Resolution Nuclear Magnetic Resonance"; McGraw-Hill: New York, 1959; pp 218–224. (c) Drago, R. S. "Physical Methods in Chemistry"; W. B. Saunders: Philadelphia, 1977; pp 252–259.

0.52; 393 K, 62 and 0.51. From these data the Arrhenius activation energy for the interconversion of the two isomers was calculated to be 10.4 (ca. 1.0)[7] kcal/mol.

Preparation of 1,8-Di-*m*-tolylanthracene (5). A solution of 20.0 g (0.117 mol) of *m*-bromotoluene in 150 mL of THF was added, dropwise and with stirring during 1 h, to 5.0 g (0.020 mol) of Mg turnings with cooling to maintain the reaction temperature at 25 °C. After the addition was complete, the mixture was refluxed for 1 h and then cooled to room temperature. Analysis[11] of an aliquot of the reaction solution (total volume 155 mL) indicated the concentration of Grignard reagent to be 0.62 M corresponding to an 82% yield. The Grignard reagent solution (155 mL or 95.9 mmol) was added, dropwise and with stirring during 1 h, to a solution of 4.76 g (19.2 mmol) of the dichloride **3**, 50 mg (0.20 mmol) of nickel(II) acetylacetonate, and 102 mg (0.39 mmol) of Ph_3P in 50 mL of THF. The resulting black (colloidal Ni) mixture was refluxed for 2 h and then poured into 50 mL of aqueous 3 M HCl and partitioned between water and CH_2Cl_2. The organic layer was dried and concentrated to leave 6.2 g of light tan solid. Recrystallization from a $CHCl_3$–acetone mixture afforded 5.91 g (86.0%) of the hydrocarbon **5** as a colorless powder, mp 128–129 °C: IR ($CHCl_3$), no absorption corresponding to OH or C=O groups in the 3- or 6-μm region; ^1H NMR (60 MHz, $CDCl_3$) δ 8.46 (1 H, s, aryl CH), 8.73 (1 H, s, aryl CH), 7.2–8.1 (14 H, m, aryl CH), 2.32 (6 H, s, Me); ^{13}C NMR [$CDCl_3$, multiplicity determined by a DEPT], 140.7 (2 C, s), 140.5 (2 C, s), 137.5 (2 C, s), 131.9 (2 C, s), 130.6 (2 C, s), 130.1 (2 C, d), 127.9 (2 C, d), 127.8 (2 C, d), 127.5 (2 C, d), 127.1 (2 C, d), 126.7 (1 C, d), 126.0 (2 C, d), 125.2 (2 C, d), 124.0 (1 C, d), 21.4 ppm (2 C, q); mass spectrum, *m/e* (relative intensity) 359 (31), 358 (100, M^+), 342 (5.6), 327 (2.9), 265 (1.9), 252 (2.0), 179 (4.1), 163 (4.2); UV maxima, nm (cyclohexane, ϵ), 257 (shoulder, 81 100), 263 (151 000), 340 (4120), 358 (7460), 375 (10 800), 395 (9260).

Anal. Calcd for $C_{28}H_{22}$: C, 93.81; H, 6.19. Found: C, 93.68; H, 6.31.

NMR Study of the Equilibration of the Two Stereoisomers of 1,8-Di-*m*-tolylanthracene (5). The ^1H NMR (300 MHz) of the hydrocarbon **5** in CD_2Cl_2 at 27 °C exhibited a single peak at δ 2.38 for the 6 H atoms of the methyl groups in the rapidly equilibrating cis and trans isomers. The ^1H NMR (300 MHz) of a 0.010 M solution of the hydrocarbon **5** in CD_2Cl_2 was cooled slowly and spectra were obtained at the following temperatures: 260, 250, 240, 235, 230, 225, 220, 215, 210, 205, and 200 K. Line broadening became a sufficiently serious problem below 200 K to prevent collection of data below this temperature. At each temperature below the estimated coalescence temperature (218 K), the chemical shifts, peak widths at half height, and "depth of valley" for each of the Me peaks was measured. The spectrum measured 200 K was used to measure the separation between Me peak A (703.90 Hz) and Me peak B (724.50 Hz) in the "slow-exchange" limit. Previously described techniques were used to simulate the spectra of the two Me groups for various preexchange lifetimes, τ, and various mole fractions[14c] of the two isomers responsible for peaks A and B. The values for τ (in ms) and the mole fraction of the isomer exhibiting peak A at various temperatures were 200 K, 46.8 and 0.427; 205 K, 39.4 and 0.405; 210 K, 29.4 and 0.394; 215 K, 21.3 and 0.390; 220 K, 13.7 and 0.390. From these data the Arrhenius activation energy for the interconversion of the two isomers was calculated to be 5.3 (ca. 0.5)[7] kcal/mol.

Preparation of 1,8-Diphenylanthracene (1). This procedure differs from that described earlier[3] in the addition of a relatively small amount of Ph_3P to help keep the Ni(0) species in solution. To a solution of 80.0 g (289 mmol) of the dichloride **3**, 818 mg (3.12 mmol) of Ph_3P, and 400 mg (1.56 mmol) of $Ni(acac)_2$ in 750 mL of THF was added, dropwise and with stirring during 2 h, 850 mL of a THF solution containing[11] 1.12 mol of PhMgBr. During the addition the temperature of the reaction mixture was maintained below 50 °C by intermittent cooling with a water bath. The resulting black colored reaction mixture (colloidal Ni) was stirred at 25 °C for an additional 10 h and then quenched by the addition of 150 mL of aqueous 3 M HCl. The reaction mixture was partitioned between water and CH_2Cl_2 and the organic layer was dried and concentrated to leave 92.5 g of the crude product as a brown solid, mp 170–182 °C. Recrystallization from a CH_2Cl_2–hexane mixture separated 79.16 g (83%) of the hydrocarbon 1 as colorless needles, mp 191–193 °C. This material was identified with a previously described sample (mp 191.5–193 °C) by a mmp determination and by comparison of IR and NMR spectra.

Preparation of 2,3-Dimethylbromobenzene (8). A. From the Aniline 10. Following a general procedure described previously,[6a] a cold (0 °C) slurry of 268.2 g (1.20 mol) of $CuBr_2$ in 1.5 L of acetonitrile was saturated with NO.[13] Then the ice cooling bath was replaced with a dry ice–CCl_4 bath, and a solution of 145.3 g (1.20 mol) of the aniline **10** in 300 mL of acetonitrile was added, dropwise and with stirring during 20 min. The resulting mixture was allowed to warm to 25 °C with stirring during the next 1.5 h while a slow stream of NO was continually passed through the solution. The resulting mixture was allowed to stand overnight and then it was poured into 2.5 L of water and extracted with five 200-mL portions of pentane. After the combined organic extracts had been washed with aqueous 10% NaOH and with aqueous NaCl, they were dried and then decolorized by filtration through a short column of alumina. The resulting pentane solution was distilled to separate 162.1 g (73%) of the bromide **8** as a colorless liquid, bp 101–103 °C (20 mm); n^{25}_D 1.5576. Redistillation through a Vigreux column afforded a sample of the xylyl bromide **8** as a colorless liquid with the same boiling point, n^{25}_D 1.5588 [lit.[12] n^{25}_D 1.5605]: NMR (neat) δ 6.5–7.5 (3 H, m, aryl CH), 2.15 (3 H, s, methyl), and 2.02 (3 H, s, methyl); IR (CCl_4), no bands in the 3- or 6-μm regions attributable to OH or C=O.

In a typical experiment involving diazotization of the aniline **10** in aqueous solution,[6d] a cold (0–3 °C) solution of 30.3 g (250 mmol) of the aniline **10** and 49 g (500 mmol) of sulfuric acid in 200 mL of water was treated with a solution of 17.5 g (250 mmol) of $NaNO_2$ in 30 mL of water while the temperature was kept at 0–3 °C by addition of ice and external cooling. This solution of the diazonium salt was added, slowly and with stirring, to a cold (0 °C) solution of 80 g (560 mmol) of CuBr in 180 mL of aqueous 48% HBr. The resulting solution was allowed to warm to 25 °C and then it was steam distilled. The bromide **8**, isolated from the steam distillate in the usual way, amounted to 16.0 g (34.5%), bp 210–214 °C, n^{25}_D 1.5721; the other major product present in the crude reaction mixture was the phenol **9**.

B. From the Phenol 9. Following a general procedure for the conversion of phenols to aryl bromides,[15] 176 g (1.1 mol) of Br_2 was added, dropwise and with stirring during 1.5 h, to a cold (0 °C) suspension of 288 g (1.1 mol) of Ph_3P in 250 mL of acetonitrile. After the resulting suspension had been stirred in an ice bath for an additional 30 min, a solution of 122.2 g (1.0 mol) of the phenol **9** in 125 mL of acetonitrile was added, dropwise and with stirring during 30 min. Then the slurry was allowed to warm to 25 °C and stirring was continued for 48 h. The acetonitrile was removed by distillation under reduced pressure (water aspirator) and the temperature of the residue in the stillpot was rapidly raised to 320 °C (voluminous evolution of HBr occurred at ca. 300 °C) resulting in distillation of the crude product, by 200–225 °C. The crude liquid product was washed successively with aqueous 20% NaOH and with aqueous NaCl and these aqueous washes were each extracted with pentane. The combined organic phases were dried, decolorized by filtration through a short column of alumina, and distilled to separate 76.6 g (41.1%) of the bromide **8**, bp 212–214 °C; n^{25}_D 1.5585.

Preparation of 1,8-Bis(2,3-dimethylphenyl)anthracene (7). A solution of 150.0 g (0.81 mol) of 2,3-dimethylbromobenzene in 1.0 L of THF was added, dropwise and with stirring during 5 h, to 23.09 (0.95 mol) of Mg turnings. During the addition, the temperature of the reaction mixture was kept at 25–30 °C by intermittent cooling with a water bath. After the addition was complete, the reaction mixture was allowed to stir overnight and then analyzed.[11] The solution (total volume 1.23 L) was 0.52 M in Grignard reagent corresponding to a 80% yield. This solution of Grignard reagent (0.648 mol) was added, dropwise and with stirring during 3 h, to a refluxing solution of 32.19 g (0.130 mol) of the dichloride **3**, 250 mg (0.96 mmol) of $Ni(acac)_2$, and 505 mg (1.92 mmol) of Ph_3P in 500 mL of THF. After the addition was complete, the black (colloidal Ni) reaction mixture was refluxed

(15) Typical procedures for the conversion of a phenol to an aryl bromide are given by Schaefer, J. P.; Higgins, J. *J. Org. Chem.* **1967**, *32*, 1607.

for an additional 3 h, stirred at 25 °C for 10 h, and then quenched by the addition of excess aqueous 3 M HCl. The reaction mixture was partitioned between water and CH_2Cl_2 and the combined organic layers were dried and concentrated. The residual brown solid (44 g, mp 201–210 °C) was recrystallized from a CH_2Cl_2–acetone mixture to separate 35.05 g of the hydrocarbon **7**; concentration of the mother liquors afforded an additional 6.45 g (total yield 41.50 g or 83%), mp 219–220 °C. The spectral properties of the hydrocarbon **7** (a slowly equilibrating mixture of cis and trans isomers) follow: IR ($CHCl_3$), no OH or C=O absorption in the 3- or 6-μm regions; ^1H NMR (60 MHz, $CDCl_3$) δ 6.8–8.6 (14 H, m, aryl CH), 2.17 and 2.25 (6 H, pair of singlets, Me groups of two isomers), 1.67 and 1.75 (6 H, pair of singlets, Me groups of two isomers); ^{13}C NMR ($CDCl_3$, multiplicity on off-resonance decoupling, pairs of peaks for cis and trans isomers listed together) 141.1 and 140.9 (s, 2 C), 139.9 (s, 2 C), 136.6 and 136.1 (s, 2 C), 135.2 and 134.7 (s, 2 C), 131.5 and 131.4 (s, 2 C), 130.9 and 130.6 (s, 2 C), 128.7 (d, 2 C), 128.1 and 128.0 (d, 2 C), 127.2 (d, 2 C), 126.3 (d), 125.3 and 125.2 (d, 2 C), 125.1 and 125.0 (d, 2 C), 124.91 and 124.89 (d, 2 C), 124.5 (d), 20.3 and 20.2 (q, 2 C), 17.0 and 16.7 ppm (q, 2 C); mass spectrum, *m/e* (relative intensity) 387 (33), 386 (100, M^+), 371 (13), 193 (9), 170 (8), 169 (8); UV maxima, nm (cyclohexane, ε), 253 (shoulder, 76 700), 260 (114 000), 332 (3310), 348 (6670), 366 (10 200), 386 (8980). HPLC analysis of this sample employing a 0.46 × 25 cm column packed with 10-μm silica gel and eluted with an ether–hexane mixture (1:99 v/v) showed two well-resolved peaks for the two isomers with retention times of 9.86 and 12.70 min. The relative areas for the two peaks varied from ca. 1:3 immediately after preparation of the solution to ca. 2:1 after the solution had been allowed to stand for 24 h. Similar changes in area were observed in the pairs of Me peaks in the NMR spectrum.

Anal. Calcd for $C_{30}H_{26}$: C, 93.22; H, 6.78. Found: C, 92.90; H, 6.95.

NMR Study of the Equilibration of the Two Diastereoisomers of 1,8-Bis(2,3-dimethylphenyl)anthracene (7). The ^1H NMR (300 MHz) spectrum of the hydrocarbon **7** as a 0.010 M solution in nitrobenzene-d_5 at 27 °C exhibited peaks at δ 6.89–8.53 (14 H, m, aryl CH), 2.08 and 2.19 (6 H, s, Me groups of two isomers), and 1.68 and 1.75 (6 H, s, Me groups of two isomers). Each of the sets of Me peaks exhibited an area ratio of 5:4 (high field:low field) at 27 °C. ^1H NMR spectra (300 MHz) of this solution were obtained at the following temperatures: 413, 423, 433, 438, and 443 K. Instrumental limitations prevented us from collecting data above this temperature; at this upper temperature limit each of the pairs of methyl peaks had broadened but had not yet coalesced. As the temperature was raised from 27 °C to 170 °C (443 K) the peak separation changed from 22.99 Hz to 18.15 Hz for the higher field pair of peaks and from 31.94 Hz to 22.94 Hz for the lower field pair of peaks. At each temperature studied, the chemical shift differences, the peak widths at half height, and the "depth of valley" for each pair of Me peaks was measured. The spectrum measured at 27 °C (300 K) was used to measure the "slow-exchange" limit; the higher field pair of methyl groups were located at 503.57 Hz (A) and 526.47 Hz (B) and the lower field pair of methyl groups were at 624.98 Hz (A) and 656.92 Hz (B). Previously described techniques were used to simulate the spectra of each pair of methyl groups for various preexchange lifetimes, τ, and various mole fractions[14c] of the two isomers responsible for each pair of peaks. The values for τ (in ms) and the mole fraction of the isomer exhibiting peak A of the higher field pair of methyl peaks at various temperatures were 413 K, 90.2 and 0.477; 423 K, 50.0 and 0.456; 433 K, 35.2 and 0.4597; 438 K, 31.03 and 0.4594; 443 K, 27.52 and 0.4617. The values for τ (in ms) and the mole fraction of the isomer exhibiting peak A of the lower field pair of methyl peaks at various temperatures were 413 K, 91.1 and 0.4547; 423 K, 55.8 and 0.4612; 433 K, 31.73 and 0.4622; 438 K, 26.42 and 0.4619; 443 K, 23.54 and 0.4633. From these data the average Arrhenius activation energy for the interconversion of the two isomers was calculated to be 16.3 (ca. 2.0)[7] kcal/mol.

Preparation of 1,8-Bis(2,3-dimethylphenyl)-9,10-anthraquinone (11). A mixture of 20.0 g (51.8 mmol) of the 1,8-dixylylanthracene **7**, 80.0 g (272 mmol) of potassium dichromate, 500 mL of chlorobenzene, 250 mL of water, 200 mL of HOAc, and 50 mL of concentrated sulfuric acid was refluxed with stirring for 10 days. After the resulting mixture had been cooled and extracted with three 100-mL portions of CH_2Cl_2, the combined organic extracts were washed with water, dried, and concentrated to leave 20.5 g of dark yellow solid, mp 235–260 °C. This crude product was chromatographed on silica gel with CH_2Cl_2–hexane eluent (1:1 v/v) to separate early fractions containing the quinone **11** and later fractions containing the more polar oxidation product, lactone **13**. The very polar products were not eluted from the chromatography column.

Concentration of the appropriate early chromatography fractions and subsequent recrystallization from a $CHCl_3$–acetone mixture separated 11.2 g (52.1%) of the anthraquinone **11** as a yellow solid, mp 269.5–270.5 °C. The spectral properties of the quinone **11** follow: IR ($CHCl_3$) 1674 cm^{-1} (quinone C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 8.3–8.5 (2 H, m, aryl CH), 6.8–7.9 (10 H, m, aryl, CH), and 4 methyl signals (ca. 3 H each corresponding to two isomers) at 2.25, 2.23, 1.95, and 1.88; ^{13}C NMR ($CDCl_3$, multiplicity measurement prevented by insolubility of sample, the number of peaks observed suggests that the material is a mixture of cis and trans isomers) 184.6, 184.0, 143.2, 140.8, 140.4, 137.5, 137.4, 136.5, 134.5, 134.2, 134.0, 133.9, 133.4, 133.1, 132.1, 131.8, 128.8, 128.7, 126.9, 126.2, 126.1, 125.8, 124.9, 124.8, 20.4, 17.0, 16.9 ppm; mass spectrum, *m/e* (relative intensity) 417 (15), 416 (46, M^+), 401 (74), 399 (42), 398 (100), 383 (15), 369 (5), 208 (14), 193 (11), 179 (11), 178 (15), 165 (7); UV maxima, nm (cyclohexane, ε), 258 (51 000), 332 (4200).

Anal. Calcd for $C_{30}H_{24}O_2$: C, 86.51; H, 5.81. Found: C, 86.54; H, 5.89.

Concentration of the appropriate later chromatographic fractions followed by recrystallization from a $CHCl_3$–ether mixture afforded 4.3 g (19%) of the keto lactone **13** as fine colorless needles, mp 261.8–262.5 °C. The spectral properties of the product follow: IR ($CHCl_3$), 1720 (γ-lactone), 1666 cm^{-1} (conjugated ketone); ^1H NMR (60 MHz, $CDCl_3$) δ 8.3–8.5 (2 H, m, aryl CH), 6.7–7.9 (10 H, m, aryl CH), 5.95 (1 H, s, benzylic CH-O), three 3 H singlets (aryl methyl) at 2.38, 2.15, 2.08; ^{13}C NMR ($CDCl_3$, multiplicity determined by DEPT), 182.8 (s), 167.1 (s), 144.4 (s), 139.5 (s), 138.7 (s, 2C), 137.6 (s), 136.8 (s), 136.5 (s), 135.8 (s), 135.5 (d), 133.9 (s), 133.6 (d), 132.0 (s), 131.2 (d), 131.0 (d), 130.1 (d, 2 C), 129.7 (d), 129.5 (d), 129.1 (s), 127.5 (d), 126.9 (d), 126.3 (d), 125.6 (d), 124.8 (d), 67.3 (d), 20.6 (q), 20.5 (q), 17.3 ppm (q); mass spectrum, *m/e* (relative intensity) 431 (21), 430 (81, M^+), 412 (47), 386 (29), 385 (23), 369 (39), 51 (24), 49 (100); UV maxima, nm (cyclohexane, ε), 230 (31 800), 248 (24 500), 283 (shoulder, 12 500), with intense end absorption (22 200 at 210 nm).

Anal. Calcd for $C_{30}H_{22}O_3$: C, 83.70; H, 5.15. Found: C, 83.46; H, 5.30.

Preparation of 1,8-Bis(2,3-dimethylphenyl)-9-anthrone (12). To a refluxing mixture of 10.0 g (24.0 mmol) of the dixylyl quinone **11**, 10.0 g (84.3 mmol) of grannular tin, and 300 mL of HOAc was added, dropwise and with stirring during 2 h, a solution of 80 mL of aqueous 12 M HCl in HOAc. The resulting pale yellow solution was refluxed with stirring for an additional hour during which time some colorless precipitate formed. The resulting slurry was poured into an ice–water mixture and the crude product was collected on a filter. The crude anthrone **12** amounted to 9.6 g (98%) of off-white powder, mp 207–218 °C dec. The material was chromatographed on silica gel with a CH_2Cl_2–hexane eluent (2:3 v/v) to separate 0.4 g (5%) of the diarylanthracene **7** in the early fractions. Later fractions were combined and recrystallized from a $CHCl_3$–ether mixture to separate 8.60 g (89%) of the pure anthrone **12** as a colorless powder, mp 226.5–227.5 °C: IR ($CHCl_3$) 1670 cm^{-1} (conjugated C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 6.8–7.5 (12 H, m, aryl CH), 4.28 (2 H, s, methylene), 2.20 (6 H, s, Me), 1.95 (3 H, s, Me), 1.83 (3 H, s, Me); ^{13}C NMR ($CDCl_3$, multiplicity determined by a DEPT), both the cis and trans isomers are present in this sample) 187.2 (1 C, s) 185.7 (1 C, s), 142.8 (1 C, s), 142.5 (1 C, s), 141.7 (1 C, s), 141.1 (1 C, s), 139.7 (1 C, s), 139.5 (1 C, s), 136.1 (1 C, s), 135.9 (2 C, s), 134.0 (1 C, s), 133.6 (2 C, s), 133.4 (1 C, s), 133.3 (1 C, s), 130.7 (1 C, d), 130.3 (1 C, d), 130.1 (1 C, d), 130.0 (1 C, d), 128.2 (2 C, d), 127.1 (1 C, d), 126.7 (1 C, d), 126.4 (1 C, d), 126.0 (1 C, d), 124.5 (1 C, d), 124.3 (1 C, d), 34.4 (1 C, t), 34.3 (1 C, t), 20.4 (2 C, q), 17.1 (1 C, q), 17.0 ppm (1 C, q); mass spectrum, *m/e* (relative intensity) 403 (10), 402 (33, M^+), 388 (31), 387 (96), 385 (46), 384 (100), 370 (17), 369 (39), 355 (8), 353 (8), 282 (11), 279 (16), 201 (17), 193 (12), 186 (15), 185 (14),

178 (29); UV maxima, nm (cyclohexane, ϵ), 304 (shoulder, 10 500), 260 (26 900).

Anal. Calcd for $C_{30}H_{26}O$: C, 89.51; H, 6.51. Found: C, 89.85; H, 6.66.

Preparation of the 9-Acetoxy-1,8-dixylylanthracenes 14. To a slurry of 2.00 g (4.97 mmol) of the anthrone **12** in 30 mL of collidine was added 10 mL of acetic anhydride and 0.20 g (1.63 mmol) of 4-(dimethylamino)pyridine. The resulting mixture was heated to 95 °C for 15 min during which time the suspension first changed to a clear solution and then a colorless precipitate formed. The reaction mixture was poured into cold aqueous HCl and the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried and concentrated to leave a brown viscous liquid that was triturated with acetone. The residual pale brown solid (1.95 g) was extracted with 15 mL of chloroform to leave 0.60 g of mixture of the cis acetates **14b** and **14c**, mp 310–315 °C. The soluble material from this extraction was concentrated and chromatographed on silica gel with a hexane–CH_2Cl_2 eluent (1:1 v/v) to separate early fractions containing (NMR analysis) the minor cis acetate **14c**, middle fractions containing the trans acetate **14a**, and late fractions containing the major cis acetate **14b**. Within an hour the early and late fractions each contained an equilibrium mixture of the cis acetates **14b** and **14c**, yield 0.21 g (total yield 0.81 g or 37%) of pale yellow powder, mp 315–316 °C. The middle chromatographic fractions were concentrated to separate 0.48 g (22%) of the trans acetate **14a** as a yellow powder, mp 314.5–316 °C. Since all the isomers **14** interconvert readily when heated above 100 °C, the final melting point of any sample is the melting point of the high melting cis isomer **14b**. This cis (**14b**) and trans (**14a**) acetates could each be recrystallized from a warm mixture of acetone and $CHCl_3$ without cis–trans isomerization. Recrystallization of the cis material separated the more abundant (and less soluble) acetate **14b** as colorless needles, mp 315–316 °C, while recrystallization of the trans isomer gave the product **14a** as pale yellow prisms, mp 315–316 °C.

The spectral properties of the cis isomer **14b** (a mixture of **14b** and **14c** in solution) follow: IR (KBr pellet) 1760 cm^{-1} (acetate C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (1 H, s, aryl CH), 8.00 (2 H, d, J = 8.5 Hz, aryl CH), 7.44 (2 H, d of d, J = 6.8 and 8.5 Hz, aryl CH), 6.9–7.2 (8 H, m, aryl CH), 2.29 and 2.23 (6 H, 2 s in ratio 9:1, aryl Me), 1.88 and 1.87 (6 H, 2 s in ratio 1:9, aryl Me), 0.22 and 0.12 (3 H, 2 s in ratio 1:9, acetate Me); mass spectrum, m/e (relative intensity) 444 (9.2, M^+), 403 (34), 402 (100), 386 (9.2), 370 (4.1), 369 (4.1), 43 (6.6); UV maxima, nm (cyclohexane, ϵ), 257 (shoulder, 64 100), 264 (95 300), 326 (shoulder, 1410), 345 (3170), 358 (6210), 376 (9740), 397 (8500).

Anal. Calcd for $C_{32}H_{28}O_2$: C, 86.45; H, 6.35. Found: C, 86.33; H, 6.36.

The spectral properties of the trans isomer **14a** follow: IR ($CHCl_3$), 1760 cm^{-1} (acetate C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (1 H, s, aryl CH), 8.03 (2 H, d of d, J = 3 and 7 Hz, aryl CH), 7.47 (2 H, m, aryl CH), 7.0–7.2 (8 H, m, aryl CH), 2.31 (3 H, s, aryl Me), 2.28 (3 H, s, aryl Me), 1.99 (3 H, s, aryl Me), 1.87 (3 H, s, aryl Me), 0.24 (3 H, s, acetate Me); mass spectrum, m/e (relative intensity) 444 (9.7, M^+), 403 (33), 402 (100), 386 (11), 43 (22); UV maxima, nm (cyclohexane, ϵ), 258 (shoulder, 81 500), 264 (117 000), 327 (shoulder, 1570), 347 (3460), 360 (7100), 378 (10 900), 400 (9500); ^{13}C NMR [$CDCl_3$, multiplicity determined by a DEPT] 170.3 (s), 143.8 (s), 143.5 (s), 142.7 (s), 137.5 (s), 137.0 (s), 136.7 (s), 136.2 (s), 135.7 (s), 133.7 (s), 132.9 (s), 132.3 (s), 130.2 (d), 130.1 (d), 128.5 (d), 128.3 (d), 128.2 (d), 128.03 (d), 127.96 (d), 127.1 (d), 126.5 (d), 125.1 (s), 124.9 (d), 124.6 (d), 124.3 (d), 123.8 (d), 123.6 (s), 20.5 (q), 20.3 (q), 17.3 (q), 17.2 (q), 16.6 ppm (q).

Anal. Calcd for $C_{32}H_{28}O_2$: C, 86.45; H, 6.35. Found: C, 86.48; H, 6.36.

Preparation of 9-Methyl-1,8-dichloroanthracene (18). A cold (0 °C) solution of 15.00 g (57.0 mmol) of the anthrone **16** in 300 mL of THF was added, dropwise and with stirring during 30 min, to 50 mL (85 mmol) of a cold (0 °C) 1.70 M solution of MeMgBr in THF. The resulting deep red solution was stirred at 0 °C for 1 h and then hydrolyzed by the addition of aqueous 3 M HCl and extracted with CH_2Cl_2. After the organic extract had been washed with aqueous NaCl, dried, and concentrated, the residual off-white solid (14.1 g, mp 101–110 °C) was suspended in a solution of 1.0 mL of aqueous 12 M HCl in 100 mL of HOAc and the suspension was refluxed for 5 h. The mixture was partitioned between water and CH_2Cl_2 and the organic extract was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. Recrystallization from a $CHCl_3$–acetone mixture afforded 9.3 g (63%) of the dichloride **18** as yellow prisms, mp 125.5–127 °C (lit.[16] mp 127 °C); IR ($CHCl_3$) no absorption corresponding to OH or C=O groups in the 3- or 6-μm region; ^1H NMR (60 MHz, $CDCl_3$) δ 7.1–8.1 (7 H, m, aryl CH), 3.35 (3 H, s, aryl Me); ^{13}C NMR [$CDCl_3$, multiplicity determined by a DEPT], 133.8 (1 C, s), 133.1 (2 C, s), 131.4 (2 C, s), 131.2 (2 C, s), 129.3 (2 C, d), 128.0 (2 C, d), 126.3 (2 C, d), 124.8 (2 C, d), 26.8 ppm (1 C, q); mass spectrum, m/e (relative intensity) 264 (12, M^+), 262 (63, M^+), 260 (100, M^+), 227 (23), 225 (72), 189 (60), 95 (45), 94 (43); UV maxima, nm (cyclohexane, ϵ), 263 (113,000), 335 (shoulder, 1300), 350 (2610), 369 (5240), 389 (8090), 412 (6640).

Preparation of the 9-Methyl-1,8-dixylylanthracene 15. A. From the Anthrone 12. To a cold (0 °C) solution of 2.00 g (4.97 mmol) of the dixylylanthrone **12** in 80 mL of THF was added, dropwise with stirring and cooling during 30 min, 2.7 mL of an ethereal solution containing[11] 5.13 mmol of MeLi. After the resulting orange solution (contains the enolate of anthrone **12**) had been stirred at 0 °C for 1 h, it was acidified with aqueous 3 M HCl and the final two-phase mixture was refluxed for 30 min. Then the mixture was partitioned between water and CH_2Cl_2 and the organic layer was washed with aqueous NaCl, dried, and concentrated. The residual yellow solid (2.2 g) contained (TLC analysis) a mixture of the anthrone **12** (major) and the anthracene **15** (minor). The crude product was subjected to the same addition–dehydration procedure two more times employing 2.0-mL and 1.5-mL portions of ethereal MeLi. The resulting crude product, 1.9 g of yellow solid, was chromatographed on silica gel with hexane–CH_2Cl_2 eluents (4:1 and 1:1 v/v). Combination and concentration of the appropriate early fractions followed by recrystallization from an acetone–$CHCl_3$ mixture separated 0.82 g (41%) of the anthracene **15** as a pale yellow solid, mp 214–215 °C. Combination of the appropriate later chromatographic fractions afforded 0.98 g (49%) of the starting anthrone **12**, mp 228–229 °C.

The anthracene **15**, a slowly equilibrating mixture of trans (**15a**) and cis (**15b**) isomers, has the following spectral properties: IR ($CHCl_3$) no absorption corresponding to OH or C=O groups in the 3- or 6-μm region; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (1 H, s, aryl CH), 7.96 (2 H, d, J = 8.4 Hz, aryl CH), 7.40–7.45 (2 H, m, aryl CH), 6.96–7.08 (6 H, m, aryl CH), 2.28 (6 H, s, aryl Me), 1.96 and 1.95 (6 H total, 2 s, cis and trans aryl Me), 1.49 and 1.59 (3 H total, two s in ratio 1:2, cis and trans aryl Me); mass spectrum, m/e (relative intensity) 401 (32), 400 (88, M^+), 386 (35), 385 (100), 370 (26), 369 (18); UV maxima, nm (cyclohexane, ϵ), 262 (shoulder, 62 500), 270 (86 600), 350 (2740), 370 (5530), 390 (8510), 410 (7140).

Analysis of the mixture of stereoisomeric anthracenes **15** by HPLC employing a 120-cm column packed with 10-μm silica gel and eluted with an ether–hexane eluent (1:1200 v/v) showed two partially resolved peaks (75.06 and 79.13 min). The area ratio for these peaks varied from 3.5:1 immediately after a solution of the sample had been prepared to 1.8:1 after the solution had been allowed to stand for 48 h.

Anal. Calcd for $C_{31}H_{28}$: C, 92.95; H, 7.05. Found: C, 92.77; H, 7.08.

B. From the Dichloride 18. To a refluxing solution of 3.00 g (11.5 mmol) of the dichloride **18**, 25 mg (0.10 mmol) of $Ni(acac)_2$, and 50 mg (0.20 mmol) of Ph_3P in 100 mL of THF was added, dropwise and with stirring during 1 h, 110 mL of a THF solution containing 57.2 mmol of the Grignard reagent from 2,3-dimethylbromobenzene (**8**). The resulting dark brown reaction mixture was refluxed for an additional 4 h and then hydrolyzed by the addition of aqueous 3 M HCl and extracted with CH_2Cl_2. After the organic extract had been dried and concentrated, the residual brown liquid (3.2 g) was chromatographed on silica gel employing various mixtures of hexane and CH_2Cl_2 as eluents. The appropriate fractions were combined and recrystallized from an acetone–chloroform mixture to separate 1.29 g (28.1%) of the anthracene **15** as a yellow powder, mp 213.5–215 °C, that was

(16) Barnett, E. B.; Goodway, N. F.; Wiltshire, J. L. *Chem. Ber.* **1930**, *63B*, 472.

identified with the previously described sample by comparison of NMR spectra and by a mmp determination.

Crystal Structure of *anti*-9-Acetoxy-*cis*-1,8-bis(2,3-dimethylphenyl)anthracene (14b). A crystal of the acetate **14b** was mounted and data were collected by procedures described in the supplementary material. The crystal belonged to the orthorhombic system and the data collected were consistent only with space groups *Pnma* or $Pna2_1$ (No. 62 or 33).[17] The crystal was centrosymmetric. Assuming the space group *Pnma*, a successful refinement was obtained. From a total of 2195 reflections collected in a complete octant of data, 1415 were accepted as statistically above background. In the data refinement, described in the supplementary material, 178 parameters were varied for the 1415 observations. The full-matrix least-squares refinement converged at $R = 0.0897$ and $R_w = 0.0744$. A perspective view of the acetate **14b** 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 9-Acetoxy-*trans*-1,8-bis(2,3-dimethylphenyl)anthracene (14a). A crystal of the acetate **14a** 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).[17] From a total of 4249 reflections collected in a complete quadrant of data, 2594 were accepted as statistically above background. In the data refinement, described in the supplementary material, 335 parameters were varied for the 2594 observations. The full-matrix least-squares refinement converged at $R = 0.0789$ and $R_w = 0.0686$. A perspective view of the acetate **14a** 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.

Supplementary Material Available: Descriptions of the determination of crystal structures for the trans acetate **14a** and the cis acetate **14b**, including tables of atomic coordinates for each compound (10 pages). Ordering information is given on any current masthead page.

(17) "International Tables for X-Ray Crystallography," Vol. I, Kynoch Press: Birmingham, England, 1952.

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Perhydroazulenes. 6. 4-Keto Derivatives with Bridgehead Methyl Substituents

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

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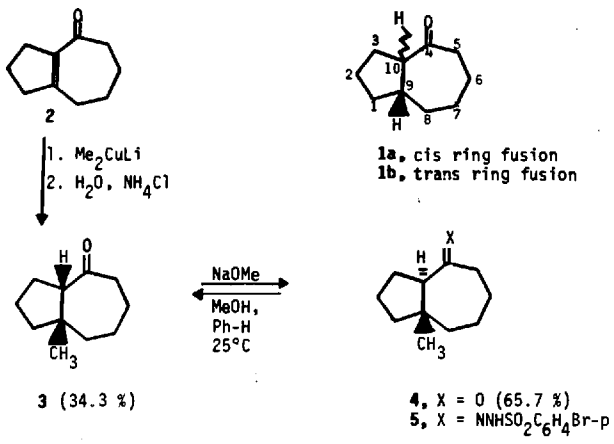
The two 9-methyl stereoisomers **3** and **4** and the two 10-methyl stereoisomers **8** and **9** of 4-ketoperhydroazulene have been prepared and fully characterized by means of spectra, analyses, and crystal structures. Several routes, including the selective methylation of the enone **2** to form 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% **4** 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.

0022-3263/86/1951-2408$01.50/0

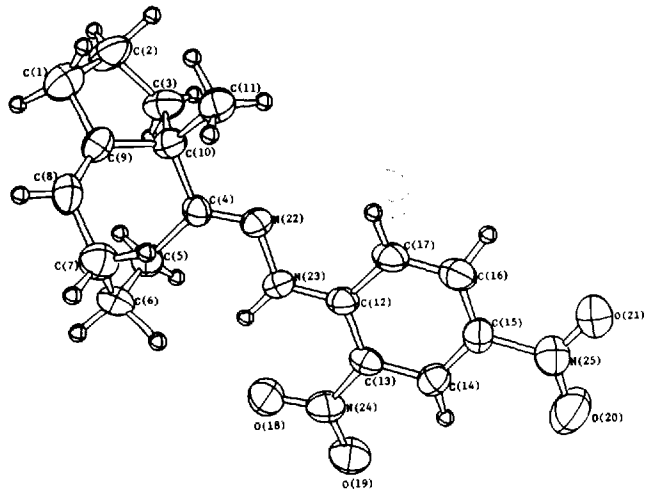


Figure 1. Perspective view of the molecular structure of the (2,4-dinitrophenyl)hydrazone of 10-methyl-4-keto-$\Delta^{8(9)}$-octahydroazulene. (The H atom thermal parameters have been reduced for clarity.)

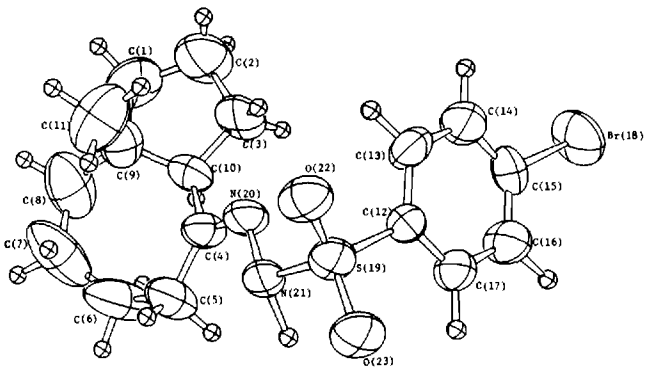


Figure 2. Perspective view of the molecular structure of the ((*p*-bromophenyl)sulfonyl)hydrazone of *trans*-9-methyl-4-ketoperhydroazulene. (The H atom thermal parameters have been reduced for clarity.)

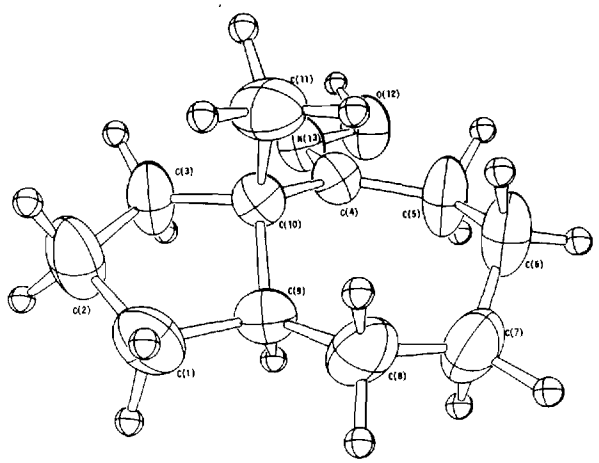


Figure 3. Perspective view of the molecular structure of the oxime of *trans*-10-methyl-4-ketoperhydroazulene. (The H atom thermal parameters have been reduced for clarity.)

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

(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**.

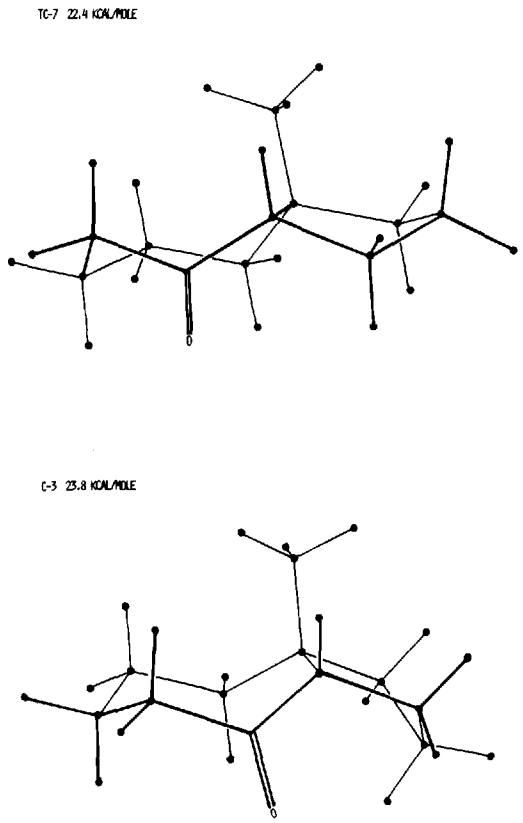


Figure 4. Low-energy conformers of *cis*-9-methyl-4-ketoperhydroazulene.

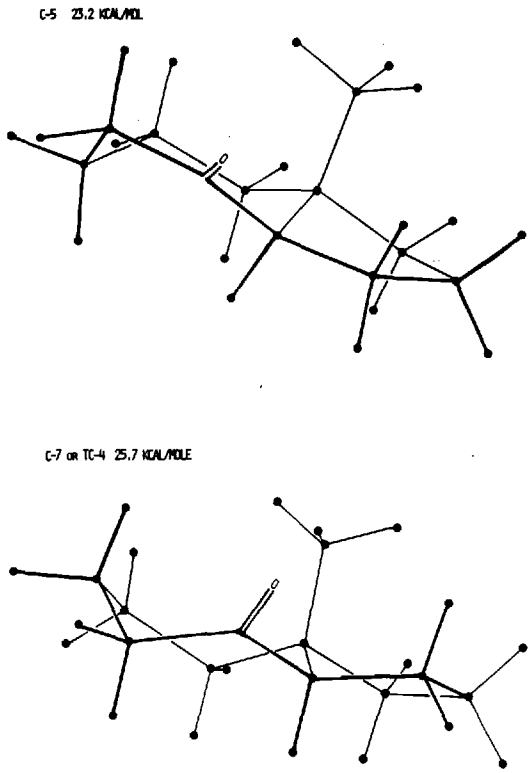
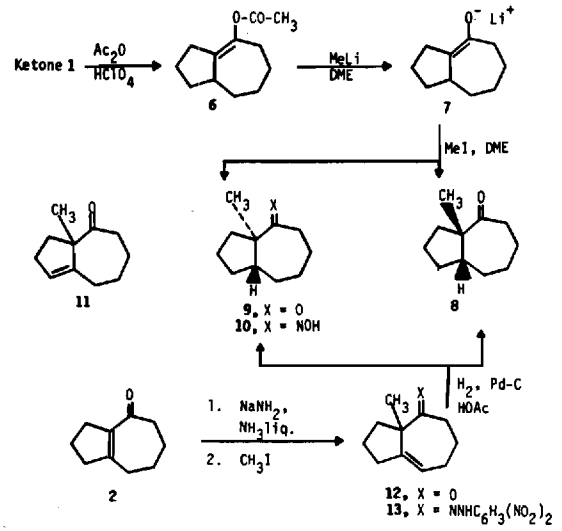


Figure 5. Low-energy conformers of *trans*-9-methyl-4-ketoperhydroazulene.

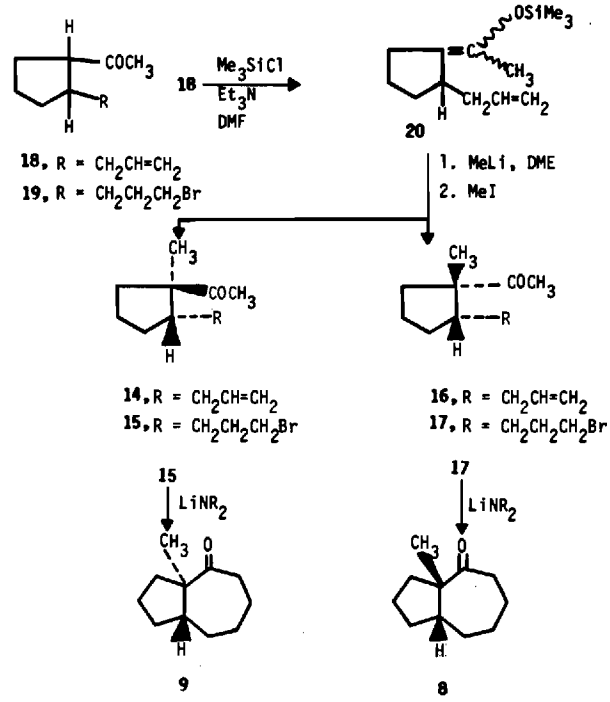
removed any ambiguity from these assignments by converting the trans ketone **4** to its sulfonylhydrazone derivative **5** and determining the structure by X-ray crystallography (see Figure 2).

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

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.

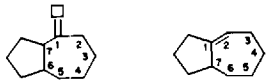
When the same reaction sequence was followed to convert the trans ketone **14** successively to the bromo ketone **15** and the trans bicyclic ketone **9**, we obtained the ketone **9** as a liquid product whose spectra did not correspond with the spectra of the product tentatively identified as the 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.

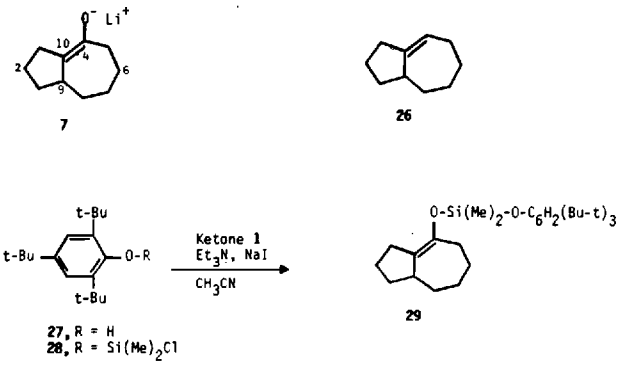
(8) (a) DeClercq, P. J. *J. Org. Chem.* **1981**, *46*, 667. (b) DeClercq, P. J. *Tetrahedron* **1981**, *37*, 4277. (c) DeClercq, P. J. *Tetrahedron* **1984**, *40*, 3717, 3729. We are grateful to Dr. DeClercq for providing us with complete listings for his current programs.

(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

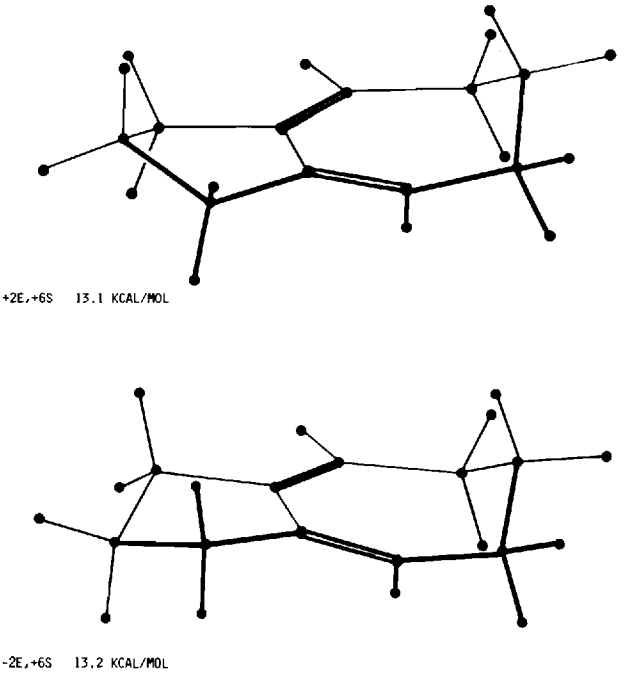


Figure 6. Low-energy conformations of $\Delta^{4(10)}$-, $\Delta^{8(9)}$-hexahydroazulene.

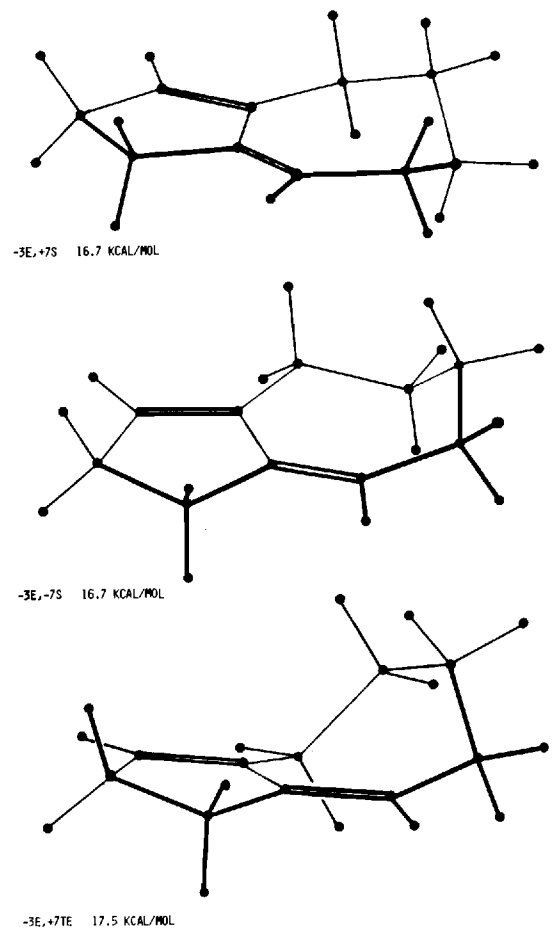


Figure 7. Low-energy conformations of $\Delta^{3(10)}$-, $\Delta^{8(9)}$-hexahydroazulene.

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.

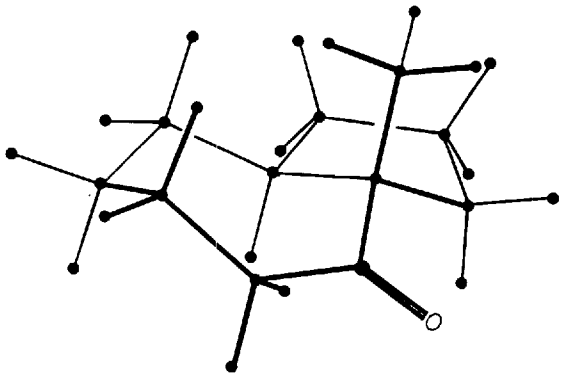
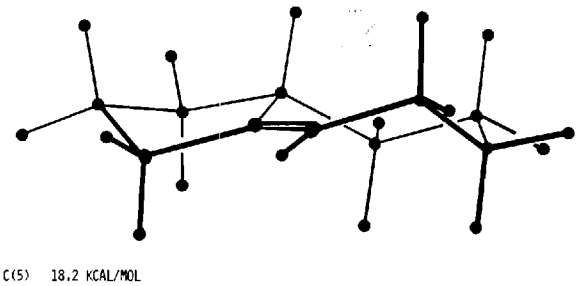
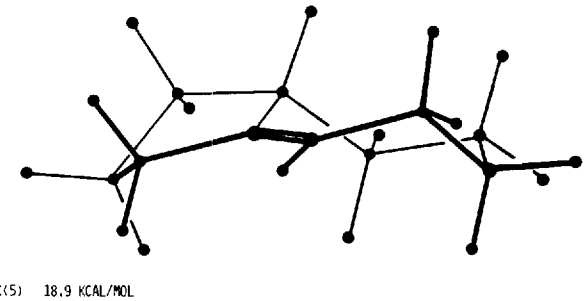


Figure 8. Perspective view of the *trans*-10-methyl-4-ketoperhydroazulene C(5) conformer present in a crystalline derivative.





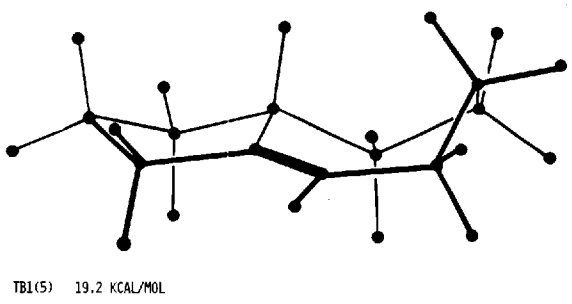
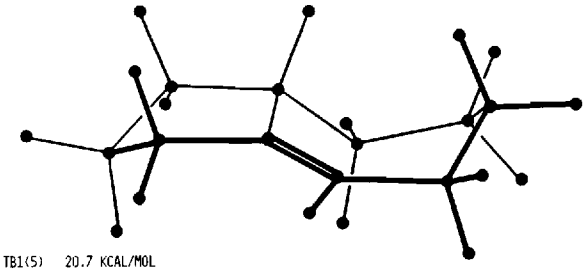


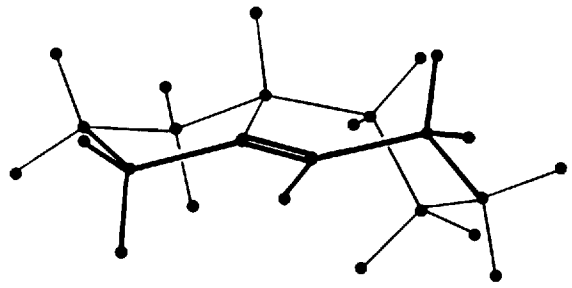
Figure 9. Low-energy conformations of $\Delta^{4(10)}$-octahydroazulene.

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

(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.





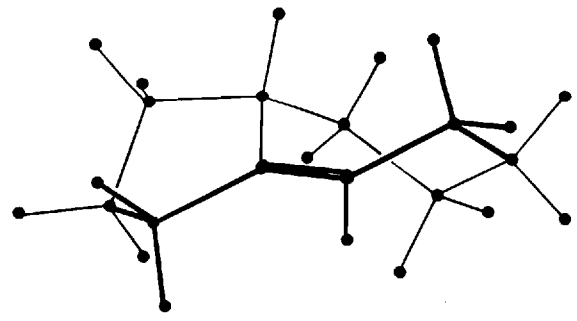
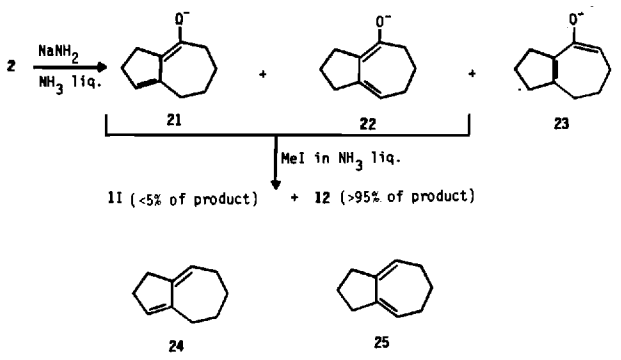


Figure 10. Low-energy conformations of $\Delta^{4(10)}$-octahydroazulene.

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

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.

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

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

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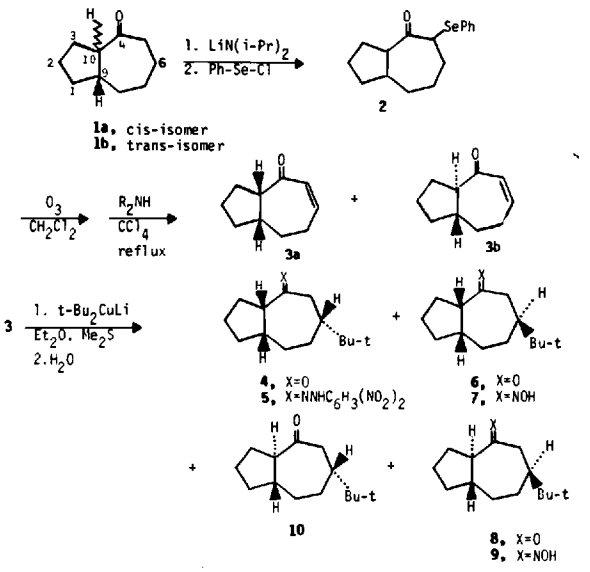
The four diastereoisomeric 6-*tert*-butyl-4-ketoperhydroazulenes **4**, **6**, **8**, and **10** have been prepared. The previously unknown cis-syn isomer **6** was characterized with spectra, an analysis, and a crystal structure of its oxime. The two stereoisomeric enol acetates **11** and **12** were 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

0022-3263/86/1951-2416$01.50/0

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

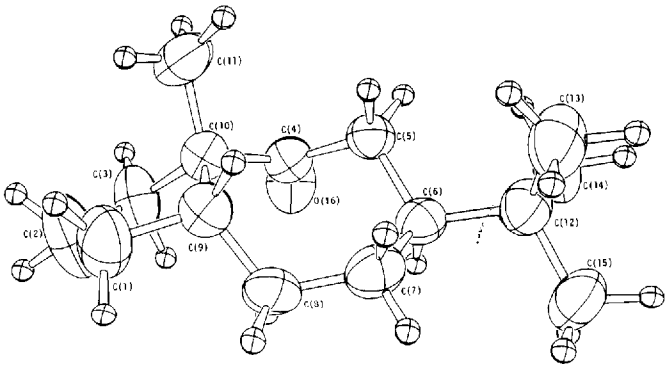


Figure 1. Perspective view of the molecular structure of 6-*syn-tert*-butyl-*cis*-10-methyl-4-ketoperhydroazulene.

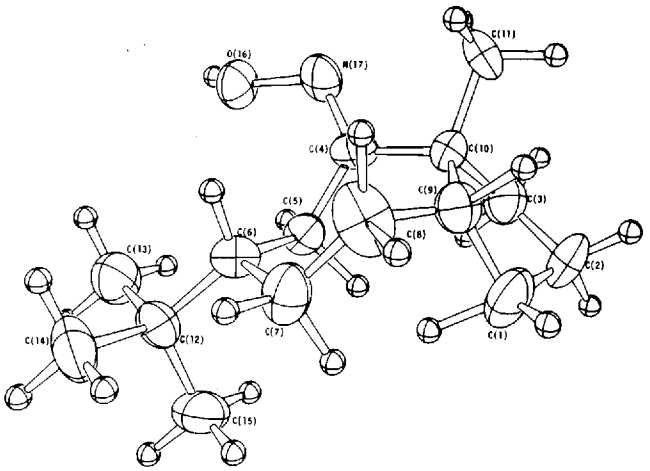


Figure 2. Perspective view of the molecular structure of 6-*anti-tert*-butyl-*cis*-10-methyl-4-ketoperhydroazulene oxime.

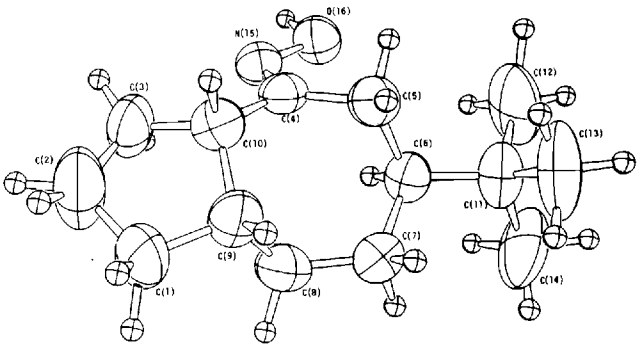


Figure 3. Perspective view of the molecular structure of 6-*syn-tert*-butyl-*cis*-4-ketoperhydroazulene oxime.

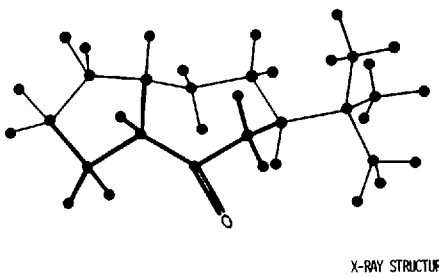


Figure 4. Perspective view of the 6-*syn-tert*-butyl-*cis*-4-ketoperhydroazulene conformer present in the oxime derivative.

(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.

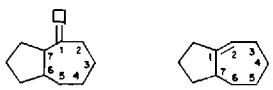
(2) House, H. O.; Gaa, P. C.; VanDerveer, D. *J. Org. Chem.* **1983**, *48*, 1661.

(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.

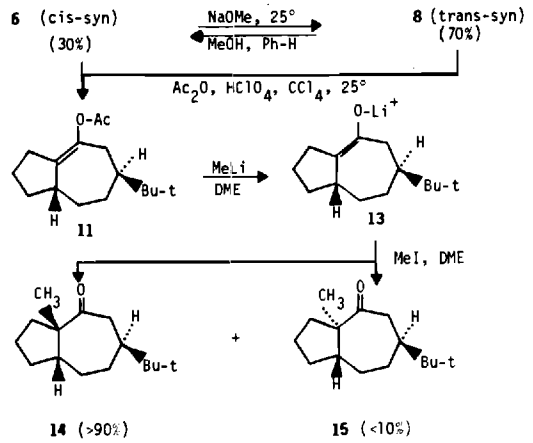
(5) Perspective drawings of the low-energy conformations of the ketones **4**, **6**, **8**, and **10** are presented elsewhere.[3] These conformers were derived from sets of possible conformations selected by the procedure of DeClercq[7] and then modified to minimize their conformational energies by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

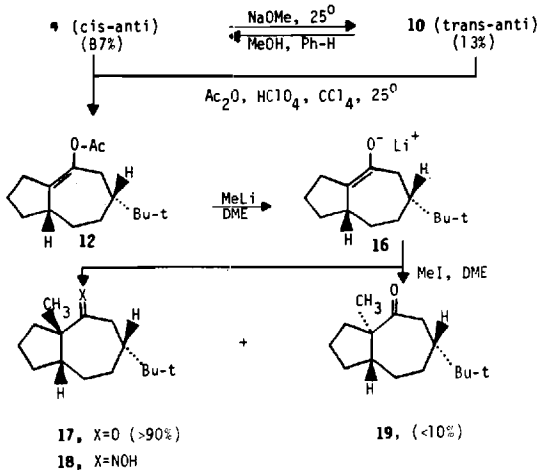


(7) (a) DeClercq, P. J. *J. Org. Chem.* **1981**, *46*, 667. (b) DeClercq, P. J. *Tetrahedron* **1981**, *37*, 4277. (c) DeClercq, P. J. *Ibid.* **1984**, *40*, 3717, 3729. We are grateful to Dr. Clercq for providing us with complete listings for his current programs.

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

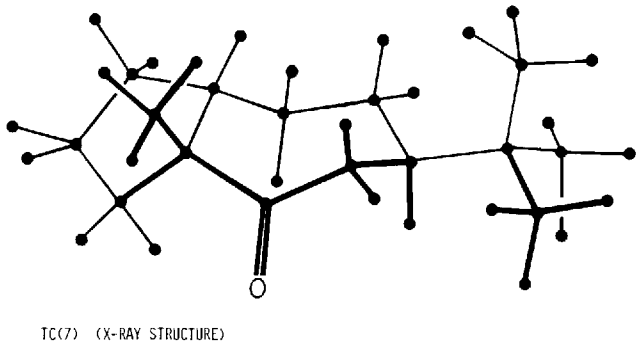


Figure 5. Perspective view of the 6-*syn*-*tert*-butyl-*cis*-10-methyl-4-ketoperhydroazulene conformer present in the crystal.

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.

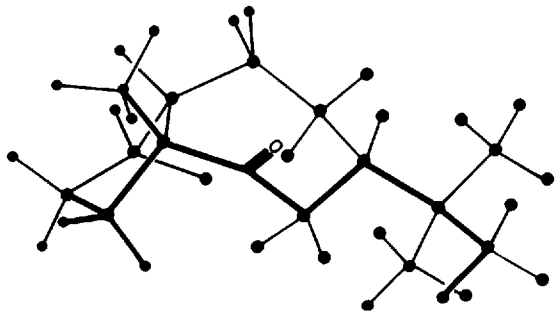
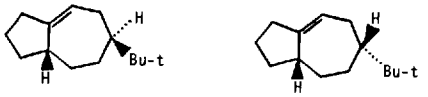


Figure 6. Perspective view of the 6-*anti-tert*-butyl-*cis*-10-methyl-4-ketoperhydroazulene conformer present in the crystalline oxime derivative.

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.

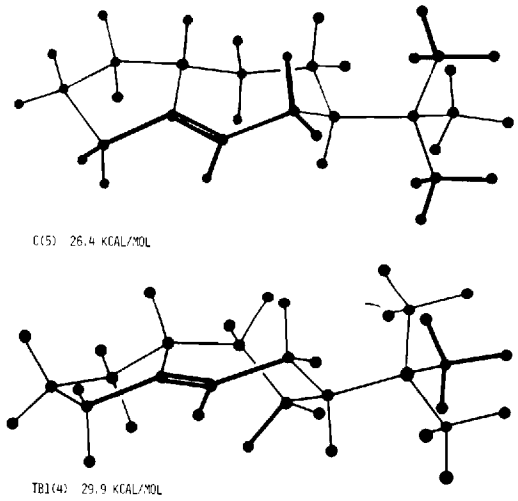


Figure 7. Low-energy conformers of 6-*syn-tert*-butyl-$\Delta^{4(10)}$-octahydroazulene.

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 ^{1}H 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.

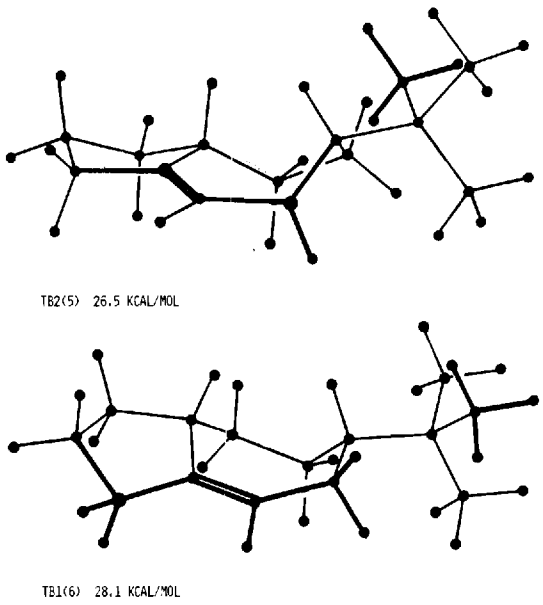


Figure 8. Low-energy conformers of 6-*anti*-*tert*-butyl-$\Delta^{4(10)}$-octahydroazulene.

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 $P1$ 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.

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FINAL SCIENTIFIC REPORT FOR THE NIH RESEARCH GRANT # RO1-GM-30735
(Grant Period 06/01/82 to 05/31/85)

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Completed publications resulting from the research grant, "Special Structural Features to Control Reactions," NIH # RO1-GM-30735, during the period June 1, 1982 to August 31, 1986 are listed below. Six sets of reprints of publications # 1-6 were mailed to the NIH Grants Officer in 1984 and six sets of reprints for publications # 7-10 are enclosed with this report. These publications describe all of the successfully completed research work that was supported by this NIH Research Grant during the active grant period (06/01/82 to 05/31/85).

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