Circular Dichroism Dependence on α-Methyl Configuration in Cyclohexanones. Experiments and RPA Calculations[1]

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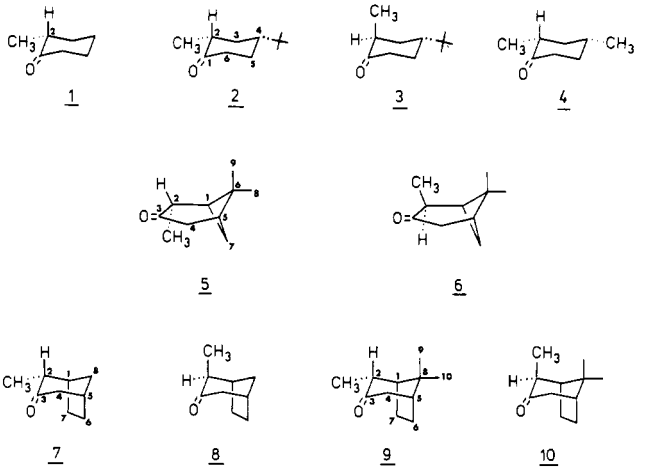
Abstract: The conformational structures and α-methyl orientations of 2-methylcyclohexanone (**1**), 2(e)-methyl-4-*tert*-butylcyclohexanone (**2**), 2(a)-methyl-4-*tert*-butylcyclohexanone (**3**), α- and β-pinanones (**5** and **6**), *exo*- and *endo*-2-methylbicyclo[3.2.1]octan-3-ones (**7** and **8**), and *exo*- and *endo*-2,8,8-trimethylbicyclo[3.2.1]octan-3-ones (**9** and **10**) were studied by molecular mechanics calculations and by analysis of ^{1}H NMR vicinal H|H coupling constants. Slightly flattened chair cyclohexanone conformations are predicted for **1-3** and **7-9**, with corresponding equatorial (**1**, **2**, **7**, **9**) or axial (**3**, **8**) α-CH_3 groups, but sofa-like cyclohexanone conformations are predicted for **5**, **6**, and **10**, with corresponding quasiequatorial or quasiaxial α-CH_3 groups. Their circular dichroism n → π* Cotton effects are interpreted in terms of the electronic effects of the lone dissymmetric α-CH_3 perturbers. Ab initio calculations in the random-phase approximation in extended basis sets reproduce the experimental rotatory strengths quite well, and a localized orbital analysis of these intensities in terms of bond couplings suggests a change in intensity mechanism as the CH_3—C—C=O torsion angle is varied. The "anti-octant" behavior of **5**, **6**, and **10** is accounted for by the analysis.

For more than 25 years, the octant rule[3] has played a major role in the determination of absolute configuration and in conformational analysis.[4] In this simple rule, the signed magnitude of the contribution made by an atom (or group) to the n → π* Cotton effect (CE) of a carbonyl chromophore is assumed to be determined by the atom's position in one of eight regions, or octants, surrounding the chromophore. The nodal surfaces separating these regions are the two symmetry planes of the isolated (C_{2v}) carbonyl group and a third (non-symmetry-determined) surface intersecting the other two.[5] Atoms lying in nodal surfaces are assumed to make no contribution to the CE, and pairs of atoms related by reflection across the symmetry planes exert no net contribution to the circular dichroism (CD) due to cancellation.

Occasionally, alkyl octant perturbers have been found to behave anomalously and yield an antioctant (dissignate[6]) rather than the expected octant (consignate[6]) signed contribution.[5b,7-9] Anomalies associated with groups placed on the carbon β to the C=O group have been resolved with a more accurate depiction of the third nodal surface that places erstwhile back-octant perturbers in front octants.[5b,7] A substituent attached to the α carbon of a ketone, on the other hand, is expected to exhibit a CE contribution that is strongly dependent on the R—C_α—C=O twist angle. A 0° twist corresponds to a fully equatorial conformation, and in the simple octant rule picture, it should lie in the *YZ* nodal plane and hence make no contribution to the CE. An α-axial substituent, however, juts directly into one of the back-octant regions, with concomitant large signed contribution. In substituted cyclohexanones, however, the *YZ* plane is no longer strictly a symmetry plane; thus even an α-equatorial methyl group might be expected to contribute to the CE.

Our interest in the octant behavior of such groups focused first on the α-equatorial methyl of 2-methylcyclohexanone (**1**) and its polycyclic analogues,[3] where the methyl group is located close to a carbonyl symmetry plane (*YZ*). At that time, there were very few known optically active α-methylcyclohexanones (**1-4**) that were achiral in the absence of the α-methyl group. These proved, however, to be only a qualified success as reliable models for chiroptical analysis. Since **1** was thought to contain a small amount of the conformer with an α-axial methyl configuration, and the presence of twist conformations had been suspected for all,[10] the CD data of **1-4** could not necessarily be viewed as an accurate indicator of the octant contributions of 2-equatorial or even 2-axial CH_3 perturbers.



The first hint that twist conformers might contribute to the stereochemistry of cyclohexanones **1-4** came from an ORD study in which Djerassi et al.[10b] attempted to define the magnitude of the CE contribution from 2-equatorial and 2-axial perturbers. Much later, the previously reported,[10b] unexpectedly large n → π* CEs for **2** and **3** were confirmed by CD, where the CE

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magnitudes of **2** were found to be essentially temperature invariant down to 77 K, and those of **3** decreased by only 15–25%. The chiroptical behavior of **2** was interpreted in terms of the predominance of a distorted chair conformation, calculated by the Boyd (MOLBD2) empirical force field,[11] that placed the α-CH_3 perturber essentially on an octant plane, with the major contributions to the CE coming from ring distortion. The calculated ring distortion is surprising because a 4-*tert*-butyl group was assumed to be a conformational anchor that at worst caused slight, yet symmetric flattening of the cyclohexanone ring, and the α-equatorial methyl configuration had not been expected to distort the chair cyclohexanone conformation. The chiroptical behavior of **3**, on the other hand, was interpreted in terms of a major contribution from the α-axial CH_3 weighed in with solvation effects and the presence of a small amount of twist boat conformer.[11]

However, it was not only the lack of suitably reliable models for α-equatorial and α-axial methyl ketones but especially the octant-dissignate CD behavior of the α-methylcyclohexanone moiety of α- and β-pinanone (**5** and **6**)[12] that prompted our detailed investigation into correlating the angular dependence (from equatorial to axial) of CH_3 orientation in cyclohexanones with octant contribution.

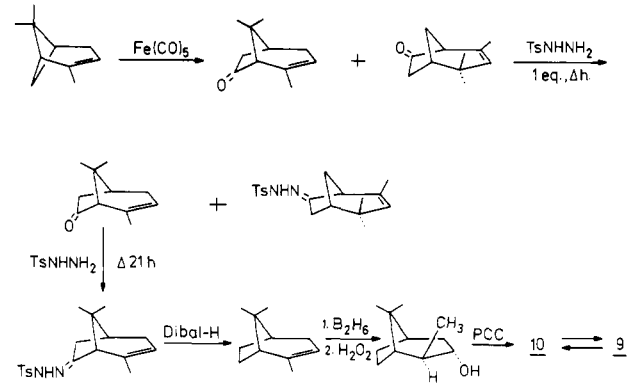
In the present work, we have reexamined the ring stereochemistry of cyclohexanones **1–3** and focussed particularly on alternative models for α-equatorial and α-axial methyl groups, viz., bicyclic ketones **5–10** in which the cyclohexanone moiety is constrained to adopt a symmetric chair, sofa, or boat conformation but cannot achieve a significant twist conformation. Ketones **1–10** also have the highly desirable property of being achiral in the absence of the α-CH_3 group; thus, other octant contributions are held to a minimum. Throughout the work, it is especially important to know (1) whether the inherent symmetry of the carbocyclic skeletons of **1–10** was retained and (2) the relative orientations of the C=O and its lone dissymmetric α-CH_3 perturber for each ketone. The latter is in major part dictated by whether ketones **1–10** assume a chair-, sofa- or boat-like cyclohexanone ring conformation. Those conformations were investigated by a combination of molecular mechanics (MM2[13]) calculations and Karplus-type equation treatment of vicinal H|H NMR coupling constants.

In the following, we report on the syntheses, conformational analysis, CD, and NMR of **1–10** and we follow this with a set of ab initio calculations of the rotatory strengths of these compounds in the random phase approximation (RPA), which partially includes electron correlation effects on excitation properties. These results will be analyzed in a localized orbital scheme that relates contributions to the CD to molecular structural features. This recently developed approach allows for the first time a detailed analysis of the mechanisms responsible for the CD intensity.[5a,14] The analysis will focus on the angular dependence of the CH_3 octant contribution, with angles varying from equatorial through axial.

Experimental Results and Discussion

Synthesis and Absolute Configuration. 2(*R*)-Methylcyclohexanone (62% ee) was obtained following asymmetric hydroboration of 1-methylcyclohexene with monoisopinocampheylborane prepared from (−)-α-pinene.[15] The corresponding 4-*tert*-butyl derivative (**2**) was prepared in racemic form by epimerization of 2(a)-methyl-4-*tert*-butylcyclohexanone (racemic **3**). The latter was prepared stereoselectively from 4-*tert*-butylcyclohexanone *N*,*N*-dimethylhydrazone[16] by reaction with lithium diisopropylamide and then quenching with CH_3I followed by KIO_4 cleavage of the hydrazone[17] to give a 91:9 mixture of racemic **3**:racemic **2**. In both cases, pure material was obtained by preparative gas chromatography. Pinanones **5** and **6** were prepared[12] from 100% ee (−)-α-pinene:[18] hydroboration of the pinene was followed by oxidation to give ketone **6**, and base-catalyzed epimerization of **6** gave a 4:1 mixture of **5**:**6**, from which pure **5** was isolated by preparative gas chromatography. Bicyclo[3.2.1]octan-3-one (**7**) was synthesized by diazoethane ring expansion[19] of 44% ee (−)-norcamphor;[20] its exo-epimer **8** was obtained by base-catalyzed epimerization of **7**, or directly by diazomethane ring expansion of the *exo*-3-methylnorcamphor obtained from essentially stereospecific *exo*-methylation[21] of 44% ee (+)-norcamphor. Ring expansion occurred on both sides of the carbonyl group to give the desired ketone (**7**) as well as the isomer, *exo*-2-methylbicyclo[3.2.1]octan-2-one, in the diazoethane ring expansion of norcamphor. Ketone **7** was separated by preparative gas chromatography.

Scheme I



The syntheses of **9** and **10** are outlined in Scheme I; thus, insertion of CO into 90% ee (−)-α-pinene with $Fe(CO)_5$ at high pressure[22] afforded a 70% yield of a 1:1 mixture of two ketones, which was separated by taking advantage of the differing rates of reaction of the ketones with *p*-toluenesulfonylhydrazine. The less hindered ketone reacted essentially exclusively under mild reaction conditions and was removed by crystallization. After the remaining ketone, 2,8,8-trimethylbicyclo[3.2.1]oct-2-en-7-one, was purified by distillation, it was derivatized as the tosylhydrazone under forcing conditions, and the resulting tosylhydrazone was reduced with DIBAL to give 2,8,8-trimethylbicyclo[3.2.1]oct-2-ene. Hydroboration of the latter followed by oxidation gave the *exo*-2-methyl ketone **10**, which could be epimerized easily to the *endo*-2-methyl isomer **9**. The pure ketones were obtained by preparative gas chromatography.

The absolute configurations of ketones **1–3** and **5–10** were known from previous work: **1**,[15,23] **2**, and **3**[10b,11] followed from known reaction stereochemistry and the absolute configuration of their precursors; **5**, **6**, **9**, and **10** followed from (−)-α-pinene;[15,24a] and **7** and **8** followed from (−)- or (+)-norcamphor.[20,24b] The enantiomeric excess (ee) in each instance could be related to previously determined ees: **1**,[15,25] **2**, and **3**[10,11] or precursors to **5**, **6**, **9**, and **10**,[12,24a] and **7** and **8**[15,19,24b,26] assuming no racemization or enantiomeric fractionation during their syntheses.

Conformational Analysis and α-CH_3 Configuration. In order

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(24) (a) See Klyne W.; Buckingham, J. "Atlas of Stereochemistry", vol 1, Oxford University Press, NY, 1974; page 84. (b) *ibid*, page 40.
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Table I. Comparison of Cyclohexanone Ring Torsion Angles and Selected Internal Angles for Energy-Minimized Ketone Structures by Molecular Mechanics (MM2)[a] Calculations

Compound[b]	Ring Torsion Angles, deg						Internal Angles (deg)		Actual Conformation[c]	Total Steric E (Kcal/mole)
	φ(1,2) (6-1-2-3)	φ(1,6) (2-1-6-5)	φ(2,3) (1-2-3-4)	φ(5,6) (1-6-5-4)	φ(3,4) (2-3-4-5)	φ(4,5) (3-4-5-6)	(2-1-6)	(3-4-5)		
	51.49	-51.48	-53.32	53.30	57.52	-57.52	115.3	110.9		5.73
	52.36	-52.84	-53.46	53.69	57.48	-57.18	115.5	111.0		6.23
	51.71	-51.71	-54.43	54.43	57.04	-57.04	114.7	108.5		12.58
	52.41	-53.03	-54.41	54.89	56.97	-56.79	114.8	108.6		13.01
	49.49	-51.32	-52.11	54.46	56.09	-56.55	115.8	108.5		15.17
	39.38	-39.38	-57.35	57.34	72.31	-72.31	116.1	100.4		17.16
	43.42	-42.65	-59.90	57.95	72.71	-71.42	115.6	100.6		18.67
	38.63	-40.77	-55.48	58.67	70.86	-71.56	116.5	100.5		19.99
	33.68	-33.67	-55.11	55.09	71.24	-71.22	117.4	98.58		22.75
	38.88	-37.95	-58.55	55.91	71.80	-69.89	116.8	98.61		24.92
	- 7.83	+ 3.46	-31.51	40.19	69.98	-74.10	120.0	98.29		28.24
	0.18	- 0.18	-47.42	47.42	82.69	-82.69	117.6	85.96		35.07
	2.79	- 2.80	-48.85	48.89	80.85	-80.87	117.6	85.28		39.99
	11.66	-11.09	-54.07	52.63	81.68	-80.47	117.7	85.34		42.08
	-15.90	+14.13	-37.27	41.00	78.84	-79.84	117.1	85.43		42.63

[a] See ref 13. Limited certainty begins with fourth significant figure. [b] Numbering system based on that shown for cyclohexanone is used throughout. [c] Viewed edgewise.

to learn whether the presence of an α-methyl group causes serious ring deformation in the cyclohexanone moiety of ketones **1–3** and **5–10**, we applied MM2[13] molecular mechanics to an investigation of their structures. Our previously reported MM2 calculations of the stereochemistry of cyclohexanone, 4-*tert*-butylcyclohexanone, and bicyclo[3.2.1]octan-3-one show the expected result in each case that chair cyclohexanone conformation is favored.[27] These results and those of Fournier[28] both agree that the cyclohexanone ring of bicyclo[3.2.1]octan-3-one is flattened in the vicinity of its C=O group due to the anti-reflex effect of the C_6–C_7 bridge, which compresses the ordinary 3,5-diaxial positions of cyclohexanone and causes local ring puckering (near C_8 of, e.g., **7–10**). Molecular mechanics (MOLBD2) calculations have also been reported for **2** and **3**, which indicate a preference for a distorted chair conformation in **2** but not in **3**.[11] This result is puzzling because one might think that the axial epimer (**3**) should suffer the greater distortion from a chair cyclohexanone conformation. Some of the results of our MM2 calculations on **1–3** and **5–10**, and their parent ketones, cyclohexanone, 4-*tert*-butylcyclohexanone, bicyclo[3.2.1]heptan-3-one, bicyclo[3.2.1]octan-3-one, and 8,8-dimethylbicyclo[3.2.1]octan-3-one, are summarized in Table I. The ring torsion angles presented are diagnostic of the symmetry of the cyclohexanone moiety, and for the energy-minimized geometries, the data show at most only minor distortion of their C_s symmetry. Distortion (or lack thereof) can be recognized most easily by comparing the pairs of torsion angles $\phi(1,2)$ and $\phi(1,6)$, $\phi(2,3)$ and $\phi(5,6)$, and $\phi(3,4)$ and $\phi(4,5)$. Introduction of an α-equatorial CH_3 group (as in **1**, **2**, **5**, **7**, and **9**) leaves the original C_s ring symmetry of the parent essentially unperturbed. But introduction of an α-axial CH_3 group leads to somewhat larger distortions, as noted especially in **10**,

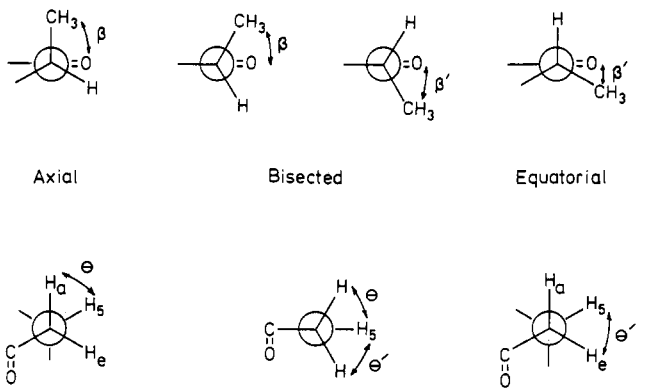

Figure 1. Newman projections for (upper) the β,β′ torsion angles that the C=O group makes with axial, bisected, and equatorial α-CH_3 groups and (lower) the β,β′ torsion angles that the axial (a) and equatorial (e) α-hydrogens make with the vicinal bridgehead (H_5) or equatorial H.

where a severe 1,3-diaxial $CH_3|CH_3$ interaction is relieved by ring twisting. The MM2-predicted skeletal desymmetrization of cyclohexanone C_s symmetry is not viewed, however, as large enough to generate a significant net octant contribution from the ring atoms, and our MM2 results stand in contrast to earlier predictions of larger ring distortions from application of the Boyd MOLBD2 empirical force field.[11] The differences in calculated geometries probably reflect the choices in parametrization made in each method; we believe that MM2 more accurately predicts the geometry, for reasons discussed above.

From the perspective of locating the position of the lone dissymmetric CH_3 perturbers relative to the C=O group (Figure 1), the cyclohexanone ring conformations of **1–3** and **5** and **10** are of special relevance. The data of Table I clearly show that the chair conformation obtains for **1** and **3** and their parent ketones. As expected, and in keeping with previous investigations,[27-29] the chair is somewhat flatter near C_1 than C_4 due to

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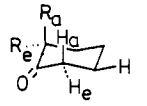
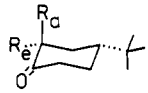
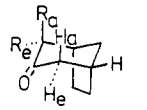
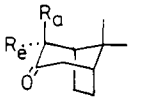
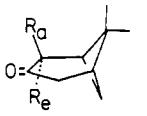
(28) (a) Fournier, J. *J. Mol. Struct.* **1975**, *27*, 177–183. (b) Reise, J.; Piccini-Leopardi, C.; Zahra, J. P.; Waegell, B.; Fournier, J. *J. Org. Magn. Res.* **1977**, *9*, 512–517.

Table II. Comparison of Methyl Group Orientation (β',β)[a] and Other Torsion Angles (θ,θ')[b] Derived from *vicinal* H|H NMR Coupling Constants[c] with Those Calculated by MM2[d] Molecular Mechanics for Energy-Minimized Cyclic Ketone Conformations

Ketone	Method	R_e=CH_3, R_a=H				R_a=CH_3, R_e=H			
		β'	θ	θ'	(|θ|+|θ'|)[e]	β	θ	θ'	(|θ|+|θ'|)[e]
	MM2:	- 5.09	56.19	-62.50	118.7	102.7	55.61	-62.70	118.3
	MM2:	- 5.02	57.90	-60.81	118.7	102.2	56.83	-61.41	118.2
	NMR:	-10.6	60.2	-63.5	123.7	90.6	62.1	-62.1	124.2
	MM2:	-10.6	57.33	-60.92	118.4	91.0	57.53	-61.23	118.8
	NMR:	-13.9	59.5	-58.9	118.4	39.1	f	-41.9	—
	MM2:	-14.1	57.59	-59.29	116.8	40.8	72.90	-43.25	116.2
	NMR:	-43.3	62.0	-58.9	120.9	34.7	57.0	-60.2	117.2
	MM2:	-42.0	64.0	-53.75	117.8	34.43	55.12	-62.96	118.1

[a] Torsion angle (in degrees) for the "axial" methyl ($R_a = CH_3$) $\beta = R_a—C_\alpha—C{=}O$; for the "equatorial" methyl ($R_e = CH_3$) $\beta' = R_e—C_\alpha—C{=}O$ (see Figure 1). [b] H–C–C–H torsion angles (in degrees) $\theta' = H_e–C_\alpha–C–H$ (see Figure 1). [c] ^3J determined by 360-MHz NMR (values reported in the Experimental Section) and used in the Karplus-type equation, $^3J(Hz) = 9.3\cos^2\theta + \cos\theta$ (ref 27 and 32), where θ (or θ') is defined in footnote *b*. The NMR derived β,β' values come from using NMR derived θ,θ' values in the MM2 program. [d] See ref 13. Limited certainty begins with the fourth significant figure. [e] The idealized value would be 120°. [f] $J_{H,He}$ could not be determined in the 360-MHz NMR spectrum.

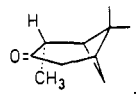
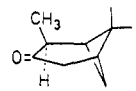
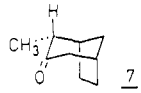
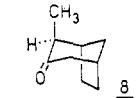
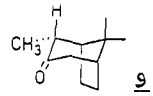
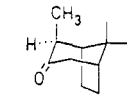
the sp^2 hybridization of the C=O carbon vs. sp^3 at C_4, but the α-methyl groups are taken to be essentially in the classical equatorial (**1** and **2**) and axial (**3**) configurations with $\beta' \simeq -5°$ and $\beta \simeq 102°$, respectively (Figure 1). Ring flattening near the C=O is increased in **7** and **8** and their parent ketone: $\phi(1,2)$ is closed from ~51° in cyclohexanone to ~39° in bicyclo[3.2.1]-octan-3-one due to the anti-reflex effect[27,28] of the ethano bridge, a bridge that also significantly closes the (3–4–5) internal angle. The consequences of this slightly increased ring flattening are to open the equatorial $CH_3—C_\alpha—C{=}O$ torsion angle (β') by ~6° and close the axial $CH_3—C_\alpha—C{=}O$ torsion angle (β) by ~11° in **7** and **8**—relatively small deformations from the standard equatorial and axial configurations (Table II). Addition of the *gem*-dimethyl group, as in **9** and its parent 8,8-dimethylbicyclo-[3.2.1]octan-3-one, leads to further ring flattening in the region of the C=O group—a response to alleviate newly introduced 1,3-diaxial CH_3|H interactions in the cyclohexanone ring. The importance of 1,3-diaxial interaction is strikingly illustrated by introduction of the *gem*-dimethyl group to **8** (to yield **10**), which causes a major conformational response to alleviate the newly introduced $CH_3|CH_3$ 1,3-diaxial repulsion: the cyclohexanone ring of **10** moves far from the (flattened) chair conformation to adopt an essentially sofa-like structure that is tilted slightly (3–8°) toward a boat. The changes in cyclohexanone ring conformation in the 8,8-dimethylbicyclo[3.2.1]octan-3-one system produce a relatively small opening of the β' angle (Figure 1) for the ψ-equatorial CH_3 of **9** (Table II)—a change in the direction of making the CH_3 configuration somewhat less equatorial-like. However, with the adoption of a near sofa cyclohexanone ring conformation in **10**, the erstwhile axial CH_3 group assumes a bisected or quasi-axial configuration, with a β angle (~41°) far from that (~102°) associated with the axial CH_3 configuration, e.g., of **3**.

The moderate ring flattening predicted for the carbonyl region of the cyclohexanone moiety of bicyclo[3.2.1]octan-3-one becomes even more exaggerated when the C_6–C_7 ethano bridge is replaced by the even more constraining one-carbon bridge of bicyclo-[3.1.1]heptan-3-one. This results in a conformation with five of the six cyclohexanone ring atoms lying in a plane which bisects the cyclobutane ring ($\phi(1,2) = 0.18°$, Table I). In fact, the trend toward a ring-flattened sofa conformation can be seen (Table I) to correlate with a reduction in size of the internal angle at C_4 of the cyclohexanone from ~111° to ~86°. Introduction of a *gem*-dimethyl group at C_7 leads to a slight bending of the sofa conformation ($\phi(1,2) \simeq 5°$, Table I) to move the C=O group *away* from the *syn*-CH_3. Our prediction, based on MM2 calculations, differs from that of Bessière-Chrêtien and Grison,[30a] who predict a slight (3°) tilting of the C=O group *toward* the *syn*-CH_3 (boat-leaning sofa conformation) on the basis of a ^{1}H NMR coupling constant analysis. Our prediction also differs from the calculation of Fournier[30b] in that the boat-leaning sofa conformation is 1.5 kcal/mol more stable than the chair-leaning sofa. The origin of this discrepancy is unclear but it may be due to a balance between (1) alleviation of electron repulsion between the C=O π-system and the *syn*-CH_3 group and (2) 1,3-diaxial *syn*-CH_3|H repulsions. The former will tend to bend the C=O away from the *syn*-CH_3; the latter will tend to bend it toward the *syn*-CH_3. The sofa-like conformation seen in the parent ketone is carried over to α- and β-pinanones (**5** and **6**). In **5**, the sofa is tilted slightly (~12.7°) toward the chair, possibly to reduce a nonbonded α-$CH_3|C_7$ gauche interaction. And in **6**, the sofa is tilted slightly (14–17°) toward the boat in order to alleviate a severe 1,3-diaxial repulsion between the α-CH_3 and the *syn*-CH_3 at C_6. Qualitatively similar conclusions on pinanone ring conformations were reached by Hirata[12] by comparing the *syn*-CH_3 ^{1}H NMR chemical shifts in the ketone and the parent hydrocarbon (anisotropic effect). These conformations lead to quasi-equatorial and quasi-axial β angles of nearly equal magnitude but opposite sign (Table II)—both far from the standard equatorial and axial torsion angles. In sum, the methyl ketones (**1–3** and **5–10**) present a full range of β and β' torsion angles ranging between equatorial ($\beta' \simeq 5°$) and axial ($\beta \simeq 103°$), as determined by MM2. It should be noted, however, that the energy minima obtained in

(29) (a) Abraham, R. J.; Bovill, M. J.; Chadwick, D. J.; Griffiths, L.; Sancasson, F. *Tetrahedron* **1980**, *36*, 279–285. (b) Abraham, R. J.; Bergen, H. A.; Chadwick, D. J. *Tetrahedron Lett.* **1981**, *22*, 2807–2810.

(30) (a) Bessière-Chrêtien, Y.; Grison, C. *Bull. Soc. Chim. Fr.* **1971**, 1454–1468. (b) Fournier, J. *J. Chem. Res. (M)* **1977**, 3440–3456.

Table III. H-C-C-H Torsion Angles (θ,θ')[a] Calculated from ^3J Coupling Constants of Bicyclic Ketones and Karplus-Type Equations

Structure	Experimental[b] $^3J_\theta$	$^3J_{\theta'}$	(1)[c] θ	θ'	θ_T	(2)[d] θ	θ'	θ_T	(3)[e] θ	θ'	θ_T	(4)[f] θ	θ'	θ_T	(5)[g] θ	θ'	$\theta\theta_T$	(6)[h] θ	θ'	θ_T
 5	3.3	2.8	57.0	-60.2	117.2	58.8	-61.3	120.1	49.5	-53.0	102.5	51.6	-54.8	106.4	54.9	-58.1	113.0	48.8	-52.2	101.0
 6	2.5	3.0	62.1	-58.9	121.0	62.9	-60.3	123.2	55.1	-51.6	106.7	56.8	-53.5	110.3	60.0	-56.8	106.8	54.3	-50.8	105.1
 7	2.8	2.3	60.2	-63.5	123.7	61.3	64.0	125.3	53.0	-56.6	109.9	54.8	-58.2	113.0	58.1	-61.3	119.4	52.2	-55.7	107.9
 8	2.5	2.5	62.1	-62.1	124.2	62.9	-62.9	125.8	55.1	-55.1	110.2	56.8	-56.8	113.6	60	-60	120	54.3	-54.3	108.6
 9	2.9	3.0	59.5	-58.9	118.4	60.8	-60.3	121.1	52.3	-51.6	103.9	54.1	-53.5	107.6	57.4	-56.8	114.2	51.5	-50.8	102.3
 10	<1[i]	5.9	[i]	-41.9	120.9[j]	[i]	-47.0	123.1[j]	[i]	-31.5	106.6[j]	[i]	-35.3	110.2[j]	[i]	-39.8	116.7[j]	[i]	-34.0	105.0

[a] See Figure 1, $\theta_T = |\theta| + |\theta'|$. [b] Determined on $CDCl_3$ solvent at 360 MHz. [c] (1) $^3J = 9.3\cos^2\theta + \cos\theta$ from ref 27 and 32. [d] (2) $^3J = 13.86\cos^2\theta - 0.81\cos\theta$, abbreviated form from: Haasnoot, C. A. G.; DeLeeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792. [e] (3) $^3J = 8.5\cos^2\theta - 0.28$, from: Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15. [f] (4) $^3J = 9.27\cos^2\theta - 0.28$, from: Abraham, R. J.; Cooper, M. A.; Salmon, J. R.; Whittaker, D. *Org. Magn. Reson.* **1972**, *4*, 489–507. [g] (5) $^3J = 10\cos^2\theta$, from: Williamson, K. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 4623–4627. [h] (6) $^3J = 4.22 - 0.5\cos\theta + 4.5\cos^2\theta$, from: Karplus, M. *J. am. Chem. Soc.* **1963**, *85*, 2870–2871. [i] Could not be determined or calculated. [j] Average value of θ_T.

MM2 are in some cases quite shallow, e.g., in **5** and **6**. Conformations with β differing by 15° or so from the value at the minimum lie within 0.5 kcal of each other.

Because of the importance of knowing molecular geometry when interpreting CD spectra, we sought an independent determination of the β',β torsion angles (Figure 1) by analysis of vicinal H|H coupling constants (^3J). To do this, we identified and measured the ^3J coupling between hydrogens adjacent to the C=O group (at the α' carbon) and their vicinal bridgehead hydrogen (at the β' carbon) for ketones **5** and **10**.[31] In most cases the coupling could be clarified and identified with decoupling techniques or by taking advantage of aromatic solvent-induced shifts (in C_6D_6 solvent vs. $CDCl_3$). Having measured the relevant ^3J values, we examined the various Karplus-type equations (Table III) available for calculating the associated H-C-C-H torsion angles (θ,θ', Figure 2). One of these (eq 1, $^3J = 9.3\cos^2\theta + \cos\theta$)[27] was derived especially for bicyclic systems akin to ours[32] and more consistently gave θ,θ' torsion angles whose sums, $\theta_T = |\theta| + |\theta'|$, met the idealized geometry conditions, $\theta_T \simeq 120°$ (Table III). It was used in generating sets of "experimental" θ,θ' angles for **5–10** and also the corresponding β angles (Table II) by fixing the θ,θ' angles as nonvariable parameters in the MM2 program. This use of MM2 to generate β and β' angles from NMR-derived θ and θ' angles was checked, with good agreement, using Dreiding models and with θ and θ' held to the determined values. The β, β', θ, and θ' values of Table II show that the two methods of stereochemical analysis, experimental (NMR) and molecular mechanics calculation (MM2), give a satisfyingly consistent picture of bicyclic ketone stereochemistry—a picture that will become important to understanding their chiroptical properties. But first we turn to our attempt to correlate the equatorial or axial nature of the α-methyl groups with their ^1H and ^{13}C resonances.

Earlier workers noted that, for cyclohexanones in a chair conformation, an axial α-CH_3 was more deshielded (by $\delta \sim 0.1$) than an equatorial α-CH_3 in the ^1H NMR spectra.[33] This stereochemical information proved to be valuable in assigning the cyclohexanone ring stereochemistry of cycloheximide and its isomers.[33] For our ketones, we sought and found a rough correlation between the α-CH_3 configuration, as determined by its β or β' torsion angle, and its ^1H NMR chemical shift. As shown in Table IV, all of the equatorial or ψ-equatorial CH_3 groups (of **1**, **2**, **7** and **9**) appear at higher field (δ 0.99–1.05) than their axial or ψ-axial counterparts (in **3** and **9**), which appear at $\delta \sim 1.15$. The quasi-axial CH_3 (of **5**) falls at an intermediate chemical shift, albeit much closer in value (δ 1.12) to axial than to equatorial. And the quasi-axial CH_3 (of **6** or **10**) shows an even larger chemical shift (δ 1.21, 1.24) than does axial. How much of the quasi-axial chemical shift is due to steric deshielding by the *syn*-CH_3 of the *gem*-dimethyl is unclear. But it is clear that for CH_3 configurations far from equatorial or axial, one cannot reliably resort to the CH_3 ^1H NMR chemical shift as an indicator of its configuration.

Qualitatively similar results are found in the ^{13}C NMR shieldings of α-CH_3 groups, with equatorial and ψ-equatorial CH_3 resonances falling at higher field than those of axial or ψ-axial CH_3 resonances. However, the ^{13}C chemical shifts are also influenced by gauche interaction effects,[34] which may account for the large deshieldings (δ-deshielding[34b]) of the α-CH_3 groups in **6** and **10**. No better correlation could be found with the α-carbon resonance of the ketones of Table IV.

Circular Dichroism and Molecular Structure. In the previous section, we have shown that large distortions from the inherent C_s symmetry of the chair cyclohexanone moiety of **1–3** and **5–10** are not expected. The major ring distortion is one which moves

(31) Previous workers have assigned the ^1H NMR resonances of: (a) Bicyclo[3.2.1]octan-3-one: Baretta, A. J.; Jefford, C. W.; Waegell, B. *Bull. Chim. Soc. Fr.* **1970**, 3895–3993. (b) The methyl groups of α- and β-pinanone: refs. 12, 30a and Nakagawa, N.; Saito, S.; Suzuki, A.; Itoh, M. *Tetrahedron Lett.* **1967**, 1003–1006. Assignments in 7 and 10 followed from these data and those of ref. 27.

(32) Teisseire, P.; Galfre, A.; Plattier, M.; Corbier, B. *Recherches* **1966**, *15*, 52–82. Cited in ref. 31a.

(33) Johnson, F.; Starkovsky, N. A.; Gurowitz, W. D. *J. Am. Chem. Soc.* **1965**, *87*, 3492–3500.

(34) (a) Stothers, J. B.; Marr, D. H.; Grover, S. H.; Tan, C. T. *Can. J. Chem.* **1975**, *53*, 1351–1361. (b) Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1976**, *54*, 917–925.

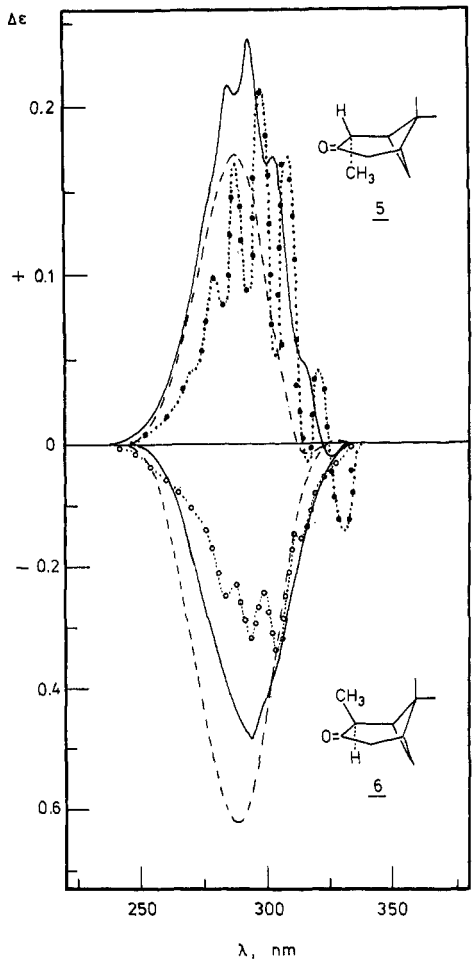


Figure 2. Circular dichroism spectra run at 24 °C on 0.005 M concentrations of (1) α-pinanone (**5**) in TFE (---), methanol (—), and perfluoropentane (●···●) (the gas-phase spectrum has the same profile as that in PFP) and (2) β-pinanone (**6**) in TFE (---), methanol (—), and *n*-heptane (○···○).

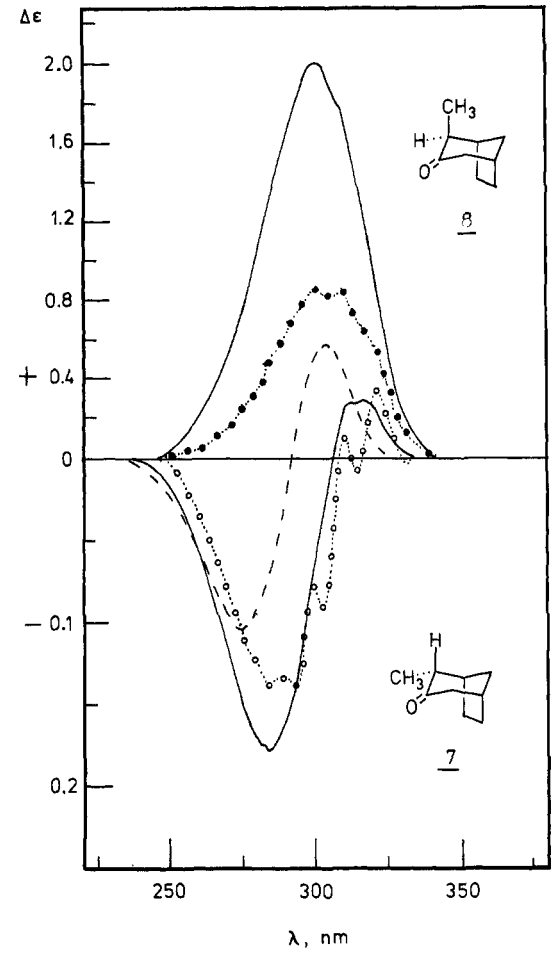


Figure 3. Circular dichroism spectra run at 24 °C on 0.005 M concentrations of (1) *exo*-2-methylbicyclo[3.2.1]octan-3-one (**8**) in methanol (—) and isopentane (●···●) and (2) *endo*-2-methylbicyclo[3.2.1]octan-3-one (**7**) in trifluoroethanol (---), methanol (—), and isopentane (○···○). Values are corrected to 100% ee.

the cyclohexanone moiety from chair to slightly flattened chair to the considerably flattened sofa conformation—all of which retain near-C_s symmetry. Hence, the lone dissymmetric perturber, the α-CH_3 group, is expected to be the major contributor to the ketone n → π* circular dichroism CE. The CD spectra of **5–10** are shown in Figures 2–4, and the CD spectra of **1–3** have been reported previously.[10,11] Pinanones **5** and **6** show (Figure 2) the previously recognized[12] vibrational fine structure for spectra run in hydrocarbon solvents. The ~1150 cm^{-1} vibronic spacing expected for C=O stretching vibrations in the n → π* excited state is strongly developed in CD spectra run in perfluoropentane solvent and in the gas phase (Figure 2). Solvent broadening in more polar solvents such as methanol or 2,2,2-trifluoroethanol results in a smooth CD profile, and none of the CD spectra of **5** and **6** showed bisignate character. Spectra run in $CHCl_3$ are similar to those run in hydrocarbon solvents but do not show the same degree of vibrational fine structure. It is important to note that the (+) CEs of **5** and (−) CEs of **6** are opposite to the signs predicted by the octant rule,[3] as has been reported earlier.[12] This contradicts the assumption that the position of the α-CH_3 groups is the controlling influence and points to a role played by the conformation of the ring (see Tables II and IV).

In contrast to the CD spectra of **5** and **6**, ketones **7**, **9**, and **10** all exhibit bisignate CEs (Figures 3 and 4); however, the bisignate character is not particularly pronounced for **7** and **9** (except in alcoholic solvents), or for **8** in alcoholic solvents. The tendency to give bisignate CEs here is probably due to solvation effects,[35,36] although bisignate CEs have also been observed for compounds undergoing dynamic conformational changes where the contributing forms have oppositely signed CEs.[37] For 1,8,8-trimethylbicyclo[3.2.1]octan-3-one, whose cyclohexanone ring adopts a slightly flattened chair conformation[27] akin to that in **7**, **8**, and **9**, we observed a temperature-dependent bisignate n → π* CE.[27] This we interpreted in terms of summed, oppositely signed contributions from boat-like and chair conformers, but we did not exclude the possibility of CE control by solvent effects—an interpretation subsequently favored by others on the basis of their molecular mechanics calculations.[38] Low-temperature CD spectra of **7**, **8**, and **9** in MI and EPA show only minor changes in CE profiles and relatively small changes in the rotatory strengths in going from room temperature to −175 °C. In contrast, the bisignate CD of **10** determined at room temperature in MI becomes nearly completely (−) monosignate between −150° and −175°—a behavior very much like that of 1,8,8-trimethylbicyclo[3.2.1]octan-3-one in MI.[27] Whether this behavior reflects a temperature-dependent conformational equilibrium in **10** (where we calculate[37a] $\Delta G^\circ \simeq 0.56$ kcal/mol for a two-conformer equilibrium) or temperature-dependent solvation effects[27,35,36,38] is as yet unclear. As with **7–9**, the CD spectra profiles of pinanones **5** and

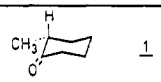
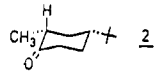
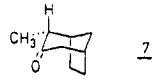
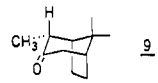
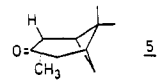
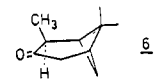
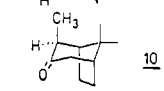
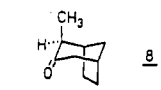
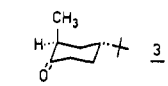
(35) Moscowitz, A.; Wellman, K. M.; Djerassi, C. *Proc. Natl. Acad. Sci. U.S.A.* **1963**, *58*, 799–804.

(36) (a) Rassat, A. In "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Snatzke, G., Ed.; Heyden: London, 1967; pp 314–328. (b) Colombeau, C.; Rassat, A. *Bull. Soc. Chim. Fr.* **1963**, 2673–2674.

(37) (a) Moscowitz, A.; Wellman, K. M.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 3515–3516. (b) Wellman, K. M.; Lauer, P. H. A.; Briggs, W. S.; Moscowitz, A.; Djerassi, C. *J. Am. Chem. Soc.* **1965**, *87*, 66–72.

(38) Jaime, C.; Buda, A. B.; Osawa, E. *Tetrahedron Lett.* **1984**, *25*, 3883–3886.

Table IV. Correlation of CH_3 Group Orientation (β,β') with NMR Chemical Shifts and Rotatory Strengths for Cyclohexanones and Bicyclic Ketones

Structure	Torsion Angle[a] β or β'	CH_3 Configuration	CH_3 Chemical Shift[b] ^1H	^{13}C	Rotatory Strength, R[c]	Octant Rule[d] Prediction
 1	- 5	equatorial	1.01	14.3	-0.44	(-)
 2	- 5	equatorial	1.03	14.5	-1.29[c]	(-)
 7	- 11	ψ-equatorial	1.01	12.7	-0.37, +0.03[f]	(-)
 9	- 14	ψ-equatorial	0.99	13.0	-0.19, +0.049[f]	(-)
 5	- 43	quasi-axial	1.12	15.1	+.59	(-)
 6	+ 35	quasi-axial	1.21	16.7	-1.30	(+)
 10	+ 39	quasi-axial	1.24	20.2	-1.16, +0.074[d]	(+)
 8	+ 91	ψ-axial	1.16	17.5	+2.74	(+)
 3	+102	axial	1.15	16.8	+4.91[e]	(+)

[a] Torsion angles in degrees: β = CH_3(ax)—C_α—C=O and β' = CH_3(eq)—C_α—C=O (see Figure 1 and Table II). [b] In δ downfield from $(CH_3)_4Si$. [c] R = rotatory strength (cgs) × 10^{40}; measured in methanol solvent for the n-π^* Cotton effect. [d] Reference 3. [e] Data from ref 11. [f] Bisignate Cotton effect, with the smaller R value appearing at longer wavelengths.

6[12] as well as cyclohexanones **1**[10c], **2**, and **3**[11] exhibit no large changes in shape or sign and show little change in their rotatory strengths down to −192°. At room temperature **1–3** and **5–10** are all largely in their most stable conformations (Tables I and II).

For **7–10** as for **5** and **6**, the lone dissymmetric α-CH_3 perturber is predicted by the octant rule to control the sign and magnitude of the CE. Consequently, it is not surprising that **8**, with its ψ-axial α-CH_3, is octant consignate,[6] as are **7** and **9**, with their ψ-equatorial α-CH_3 groups. The deviation from true axial or equatorial is small (Table II)—far smaller than for the bisected geometry quasi-axial α-CH_3 groups of **5** and **6**. Ketone **10**, however, with its sofa-boat conformation (akin to **6**, Table II) and quasi-axial α-CH_3 does not obey the octant rule—an observation supporting the notion that for CH_3—C_α—C=O torsion angles (β and β', Figure 1) $\simeq \pm 40°$ the simple octant rule picture is not adequate.

Although the equatorial and axial α-CH_3 groups of **1–3** and **7–9** are all octant consignate, the magnitudes of their contributions to the n → π^* CE differ considerably, with axial groups contributing more strongly (R, Table IV). However, the magnitudes are not the same for all equatorial groups, nor are they the same for the axial groups. In fact, the 2-methyl-4-*tert*-butylcyclohexanones, which might have been viewed as the best models from which to determine α-CH_3 group values,[10] give R values nearly twice as large as those of their close analogues (**1**, **7**, **8**, and **9**). Djerassi et al.[11] have explained the essentially solvent-independent and anomalously high R values of **2** (−1.29, methanol; −1.31, EPA; −1.35, isooctane; −1.41 MI) in terms of the stable deformed chair conformer predicted by their molecular mechanics calculations. The large magnitude of the room temperature R values of **3** (+4.91, methanol; +4.36, EPA; + 4.56, isooctane; +4.08, EPA) may be due to the intrusion of a twist boat conformer and/or to solvation effects.[11] Our MM2 calculations do not predict as strong a deformation of the chair conformation (Table I). However, even slight twisting of the ring near the C=O group can produce a large relative displacement of the distal *tert*-butyl group, throwing it off a C=O (octant) symmetry plane and thus making it a back-octant contributor, albeit distant from the C=O group. Alternatively, symmetry breaking within the ring could spoil the cancellation of pairs of contributions from ring atoms or bonds. In estimating the inherent R contributions of axial and equatorial α-CH_3 groups,[39] the lower values (Table IV) are recommended—values which are in better accord with those ($R_{eq} \simeq 0.2$, $R_{ax} \simeq 1.2$) derived from steroid CD spectra.

Theory and Analysis

The rotatory strength R_{0q} for a transition from the ground state $|0\rangle$ to an excited state $|q\rangle$ is given by the expression (in atomic units)[40]

$$R_{0q} = (2c\Delta E_{0q})^{-1}\langle 0|\nabla|q\rangle\cdot\langle 0|\mathbf{r} \times \nabla|q\rangle \qquad (1)$$

where ΔE_{0q} is the excitation energy, and where $\langle 0|\nabla|q\rangle$ and $\langle 0|\mathbf{r} \times \nabla|q\rangle$ are respectively the electric and magnetic dipole transition moment vectors. Other equivalent expressions exist but lend themselves less readily to subsequent analysis.

The transition moments and excitation energies in eq 1 are computed in the random phase approximation (RPA),[41,42] which is discussed extensively elsewhere;[14,40,43] here we present only the

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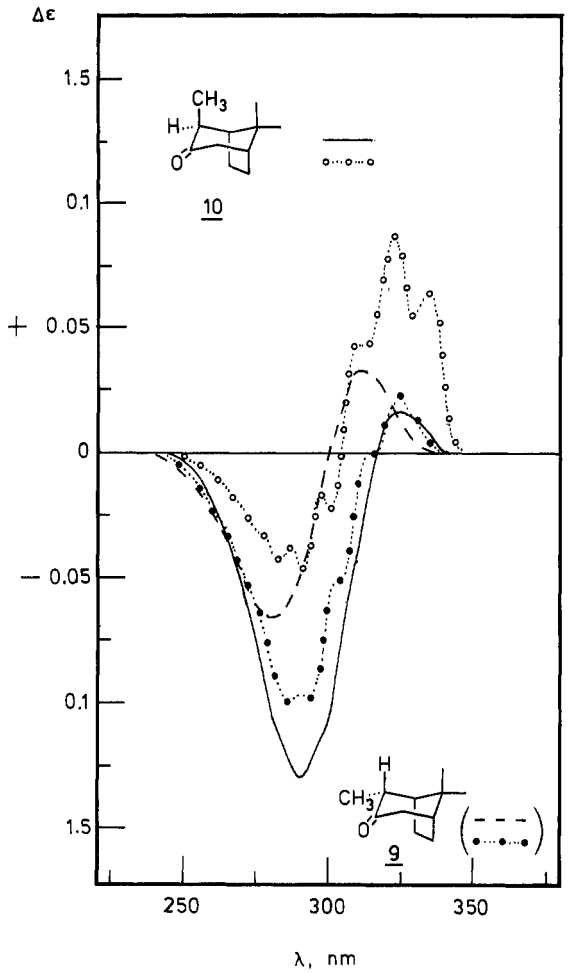

Figure 4. Circular dichroism spectra run at 24 °C on 0.005 M concentrations of (1) *exo*-2,8,8-trimethylbicyclo[3.2.1]octan-3-one (**10**) in methanol (—) and isopentane (O···O) and (2) *endo*-2,8,8-trimethylbicyclo[3.2.1]octan-3-one (**9**) in methanol (- - -) and isopentane (●···●). Values are corrected to 100% ee.

relations needed to define our notation. In a basis of occupied (ϕ_a, ϕ_b, ...) and virtual (ϕ_m, ϕ_n, ...) Hartree–Fock molecular orbitals, the RPA prescription for a transition moment of a Hermitian one-electron operator (such as **r**) may be written

$$\langle 0|\mathbf{r}|q\rangle = 2^{1/2}\sum_a\sum_m \langle\phi_a|\mathbf{r}|\phi_m\rangle S_{am,q} \quad (2)$$

While the relevant anti-Hermitian one-electron operators yield

$$\langle 0|\nabla|q\rangle = 2^{1/2}\sum_a\sum_m \langle\phi_a|\nabla|\phi_m\rangle T_{am,q} \quad (3)$$

and

$$\langle 0|\mathbf{r}\times\nabla|q\rangle = 2^{1/2}\sum_a\sum_m \langle\phi_a|\mathbf{r}\times\nabla|\phi_m\rangle T_{am,q} \quad (4)$$

The coefficients $S_{am,q}$ and $T_{am,q}$, together with the excitation energies ΔE_{0q}, are obtained as solutions of the RPA equations, which are easily solved by standard methods.[43] The (generally small) differences between the S and T coefficients incorporate electron correlation effects and turn out to be crucial for an adequate description of electronic intensities.

Analysis of Intensities. We are free to choose the occupied molecular orbitals, ϕ_a, ϕ_b, ... as either localized or canonical; making the former choice, we define an excitation-characteristic "bond" (bond or lone pair) electric dipole transition moment from eq 3 by summing over all the virtual orbitals:[14]

$$\mathbf{p}_{a,q} = 2^{1/2}\sum_m \langle\phi_a|\nabla|\phi_m\rangle T_{am,q} \quad (5)$$

Table V. Overall Results of RPA Rotatory Strength Calculations

		rotatory strength R^a			
	β	R^∇(MIN)	R^∇(DZ)^b	$R^{[r]}$(DZ)^{b,c}	exptl
5	−43	−0.44	+3.87	+1.69	+0.59
9	−14	−0.28	−0.13	−0.02	−0.19, +0.05
7	−11	−0.44	−0.43	−0.02	−0.37, +0.03
1	−5	−0.32	−0.95	−1.00	−0.44
2	−5	−0.28			−1.29
6	+35	+0.18	−3.39	−1.67	−1.30
10	+39	+0.72	−5.00	−2.25	−1.16, +0.07
8	+91	+3.81	+1.73	+1.60	+2.74
3^d	+102	+4.26	+4.06	+3.92	+4.91

^{a} (cgs) × 10^{10}; MIN = minimal basis, DZ = split-valence basis. ^{b} 3-Methylcyclohexanone fragment only. ^{c} Defined as $R^\nabla(f^{r\nabla}/f^\nabla)$; see ref 40. ^{d} *tert*-Butyl group excluded in all calculations.

with a similar definition for the magnetic dipole transition moment, eq 4

$$\mathbf{l}_{a,q} = 2^{1/2}\sum_m \langle\phi_a|\mathbf{r}\times\nabla|\phi_m\rangle T_{am,q} \quad (6)$$

Substituting eq 2–6 into eq 1 yields

$$R_{0q} = \sum_a\sum_b R^q_{ab} = (4c\Delta E_{0q})^{-1}\sum_a\sum_b\{\mathbf{p}_{a,q}\cdot\mathbf{l}_{b,q} + \mathbf{p}_{b,q}\cdot\mathbf{l}_{a,q}\} \quad (7)$$

Each term is origin-independent and so can be assigned a physical meaning. These terms can be regrouped into three sets, each corresponding to one of the mechanisms outlined by Kirkwood.[14] Thus,

$$R_{0q} = R_{0q}(\text{intr.}) + R_{0q}(\mu - m) + R_{0q}(\mu - \mu) \quad (8)$$

where

$$R_{0q}(\text{intr.}) = (4c\Delta E_{0q})^{-1}\sum_a \mathbf{p}_{a,q}\mathbf{l}'_{a,q} \quad (9a)$$

$$R_{0q}(\mu\text{–}m) = (4c\Delta E_{0q})^{-1}\sum_a\sum_b(\mathbf{p}_{a,q}\cdot\mathbf{l}'_{b,q} + \mathbf{p}_{b,q}\cdot\mathbf{l}'_{a,q}) \quad (9b)$$

and

$$R_{0q}(\mu\text{–}\mu) = (4c\Delta E_{0q})^{-1}\sum_a\sum_b(\rho_a - \rho_b)\cdot(\mathbf{p}_{a,q}\times\mathbf{p}_{b,q}) \quad (9c)$$

The quantity $\mathbf{l}'_{a,q}$ is the "bond" magnetic transition moment defined relative to an origin at the centroid position ρ_a of localized orbital a:

$$\mathbf{l}'_{a,q} = 2^{1/2}\sum_m \langle\phi_a|(\mathbf{r} - \rho_a)\times\nabla|\phi_m\rangle T_{am,q} \quad (10)$$

Computations and Results

We chose compounds **1**, **2**, and **5–10** and **3** without the *tert*-butyl group, for computation and analysis of rotatory intensities. SCF molecular orbitals were generated with use of GAUSSIAN 80[44] on the structures resulting from the MM2 calculations. These orbitals were used as input to Program RPAC,[43] which carried out the RPA calculations and intensity calculations.

We initially used only a minimal STO-5G atomic orbital basis due to the size of the molecules; our earlier results indicated that this basis set yielded satisfactory results for the n → π* excitation,[5a] even though most other types of excitation are not well described. All singly excited configurations arising from the valence occupied MOs were included in the RPA calculations; the largest such set included 1224 configurations.

The computed n → π* rotatory strengths for the chosen molecules are shown in Table V; the minimal-basis excitation energies were all within 0.1 eV of 4.2 eV, in agreement with experiment. For the molecules whose cyclohexanone ring is basically in a chair conformation (**1–3**, **7–9**) the computed rotatory

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Table VI. Mechanistic Analysis of the Calculated n → π* Rotatory Strength R^{∇}_{0q} for the Methylcyclohexanone Fragments, in the DZ Basis Set

	R^{∇}_{0q}	R(intr.)[a]	R(μ-m)[b] (%)	R(μ-μ)[c]	total $-CH_3$[d]	|β|
1	−0.95	−0.38	−0.38 (40)	−0.19	−0.51	5
3	+4.06	+0.45	+2.82 (69)	+0.80	+11.64	102
5	+3.87	+0.24	+3.08 (80)	+0.55	−0.45	43
6	−3.39	−0.18	−2.71 (80)	−0.50	+0.22	35
7	−0.43	−0.50	+0.17 (−40)	−0.10	−0.39	11
8	+1.73	+0.11	+1.24 (72)	+0.37	+9.68	91
9	−0.13	−0.47	+0.40 (−308)	−0.06	−0.26	14
10	−5.00	−0.82	−3.38 (68)	−0.79	−0.21	39

[a] Equation 9a. [b] Equation 9b, with percent of total R in parentheses. [c] Equation 9c. [d] Total contribution from localized orbitals corresponding to methyl group C–C and 3 C–H bonds.

strengths are in quite good agreement with the experimental values, and in fact they obey the octant rule. The sofa-like conformations of **5**, **6**, and **10**, on the other hand, yield results opposite in sign to the experimental ones, although the computed results obey the octant rule in all cases.

In order to see whether an extended basis set could resolve the discrepancies in our minimal-basis calculations, we repeated the calculations on the same molecules using Dunning's [3s 2p/2s] split-valence basis set.[45] The methylcyclohexanones could be handled as is, with 96 orbitals in the atomic basis set, giving rise to 1495 configurations in the RPA. The other molecules, however, were too large to be treated at this level; they were modeled by their chair (or sofa) methylcyclohexanone fragments with all remaining atoms clamped in their positions appropriate for the full molecule. In the case of the "classic" octant rule for molecules **1** and **3**, with an α-axial methyl perturber, the computed extended-basis ("DZ") results in Table V are quite similar to the minimal-basis ones, and to the experimental rotatory strengths, whereas the resulting R values for the hitherto anomalous compounds now agree with experiment as well.

For purposes of analysis, the occupied MOs were localized by using the Foster-Boys criterion,[46] and the resulting "banana" double bonds in the C=O groups were re-transformed to recover local σ and π bonds.[47] The virtual orbitals were not localized, since the summation over m in eq 5–7 makes it immaterial whether the virtual orbitals are localized or not.

Table VI shows the decomposition of the computed DZ n → π* rotatory strengths into the three mechanisms of eq 9. It is seen that the μ–m mechanism dominates the description to the extent of 68–80% for all but molecules **1**, **7**, and **9**, where the methyl group is nearly equatorial. In these molecules, the contributions from the intrinsic mechanism are equally important. In all cases, the intrinsic mechanism yields the same sign as the overall rotatory strength, but only small magnitudes. The μ–μ mechanism appears not to be important for the n → π* excitation in these molecules.

Table VI also shows the total contribution of the four localized MOs making up the methyl group to the overall rotatory strength. In contrast to our initial assumption that the methyl group controlled the sign and magnitude of R, the numbers show this to be partially true only for the "classic" octant rule positions based on a chair cyclohexanone skeleton. For the sofa conformers, the methyl group itself plays only a minor role, and in all cases the numerical differences from the total R value imply that framework contributions are also significant.

The distinctive behavior of the sofa conformers is evident in Table VII, which displays the distribution of R_{ab} terms (eq 7) in order of increasing absolute magnitude for representatives of each of the three ranges of β angle (~90°, ~0°, ~45°). For the fully

Table VII. Distribution of R_{ab} Contributions for Conformations Corresponding to $\beta \simeq 90°$, 0°, and 45° (Calculations as in Table VI)

$\|R^{q}_{ab}\|$[a]	ax **3** $\sum R^{q}_{ab}$ (n)[b]	eq **1** $\sum R^{q}_{ab}$ (n)[b]	sofa **6** $\sum R^{q}_{ab}$ (n)[b]
<1.000	+1.486 (255)	−0.505 (259)	−1.393 (258)
1.000–1.999	−1.421 (5)	−0.892 (3)	−1.936 (5)
2.000–2.999	0.0 (0)	0.0 (0)	3.056 (7)
3.000–3.999	0.0 (0)	0.0 (0)	3.855 (1)
4.000–4.999	+13.196 (3)	−5.405 (3)	4.100 (1)
5.000–5.999	+5.533 (7)	+5.721 (5)	−4.441 (3)
≥6.000	−14.730 (6)	+0.131 (6)	−6.631 (1)
total R^{∇}	+4.064 (276)	−0.950 (276)	−3.390 (276)

[a] Equation 7. For $a \neq b$, the sum of $R_{ab} + R_{ba}$ is displayed. [b] Sum of all R^{q}_{ab} in designated range, with number of terms in parentheses.

axial and equatorial methyl groups, corresponding to a chair cyclohexanone framework, there are a number of large terms and a host of small ones, but none of intermediate size. The large terms are mostly couplings between the nonbonding orbital and bonds along the well-established zigzag pattern extending away from the C=O group.[5a] The large net magnitudes of the groups of terms in the axial case indicate symmetry breaking within the cyclohexanone framework, as well as an uncompensated methyl C–H zigzag coupling to the nonbonding orbital. The much smaller net terms in the equatorial case show that framework symmetry is less distorted by the methyl group. Indeed, the overall rotatory strength is a result of a delicate balance among the many small contributions.

The pattern exhibited by **6**, representative of the sofa conformation with $\beta \sim 45°$, is qualitatively different. The erstwhile large contributions have weakened, giving a much more even distribution of magnitudes. Not only are the zigzag couplings weakened by the distortion of the ring, but there is substantial symmetry breaking in the ring orbitals as well.

Concluding Discussion

What emerges from the above analysis is the following: Although the overall rotatory strengths vary in a regular way with the CH_3—C_α—C=O angle β (or β′), it is misleading to ascribe this dependence in any simple way to the position of the methyl group vis-a-vis the carbonyl group. As the conformation changes from axial to equatorial, there are changes in the intensity mechanism as well as changes in the relative importance of "perturber" and framework couplings. An analysis of the sort presented here can help focus on the structural features of a molecule that actually do dominate the observed CE in different cases. Empirical rules that emerge will likely not have the simple elegance of the original Octant Rule, but they will include structural features of the "symmetric" framework as well as the "dissymmetric perturber".

Experimental Section

General. Circular dichroism (CD) spectra were recorded on a JASCO J-40 instrument equipped with a photoelastic modulator and a J-DPY data processor and a spectroscopic Dewar for variable-temperature CD measurements. Ultraviolet (UV) spectra were recorded on a Cary 219 spectrophotometer, and rotations were determined in chloroform, unless otherwise indicated, on a Perkin-Elmer 141 polarimeter. All nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$ and reported in δ downfield from tetramethylsilane unless otherwise indicated on a JEOL FX-100 or Brucker 360 instrument. Abbreviations used are x = exo, n = endo, a = anti, s = syn. For ketones **5** and **6**, x and n are relative to C_6, and for **7**–**10**, they are relative to C_8. Mass spectra (MS) were recorded at 70 eV ionizing voltage on a JEOL JMS-07 mass spectrometer. Infrared (IR) spectra were measured on a Perkin-Elmer Model 599 instrument. All melting points are uncorrected and were determined on a Thomas-Hoover capillary apparatus. Combustion analyses were performed by Micro-Analytical Lab, Mountain View, CA. Analytical gas chromatography (GC) was performed on a Varian-Aerograph Model 2400 F/I instrument on 6 ft × $^1/_8$ in. diameter columns with the indicated stationary phases that were adsorbed on 80/100 Chromosorb W-AW-DMCS: column A (25% FFAP), column B (15% QF-1), or column C (5% SE-30). Preparative gas chromatography (GC) was performed on 5 ft × $^3/_8$ in. diameter column D (12% FFAP) or 6

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(47) Hartman, W. W.; Brethen, M. R. *Org. Synth. Coll. vol II* **1943**, 278 and 464–465. We used 70% ethylamine in place of 33% methylamine.

ft × 3/8 in. diameter column E (15% QF-1), using a Varian-Aerograph Model 1720 T/C instrument. Spectral data were obtained with use of spectral grade solvents (MCB): methanol, trifluoroethanol (TFE), isopentane, isooctane, *n*-heptane, chloroform, methylcyclohexane–isopentane [4:1 (v/v)] (MI), ethyl ether–isopentane–ethanol [5:5:2 (v/v/v)] (EPA), and perfluoropentane (PFP). The last was a gift from 3M Corp, St. Paul, MN. Other solvents were distilled and dried before use: benzene, pentane, chloroform, and dichloromethane from P_2O_5; acetone from $KMnO_4$; and diethyl ether from $LiAlH_4$ under N_2. The solvents were used freshly distilled or stored over 4A molecular sieves (Linde). The $LiAlD_4$ used in this work was 99.8%, from Alfa-Ventron. Column chromatography was accomplished on act. II or III Woelm neutral alumina or on Florisil (Floridin Corp.).

(−)-2(*R*)-Methylcyclohexanone (1). This ketone was prepared as described previously via asymmetric hydroboration of 1-methylcyclohexene[15] followed by pyridinium chlorochromate oxidation of the resulting (1*R*,2*R*)-2-methylcyclohexanol, $[\alpha]^{20}_D$ −26.9° (neat), 62% ee[15] to afford ketone **1**, bp 160–161 °C. IR (film) ν 2940, 2850, 1710 cm^{-1}; ^1H NMR δ 1.01 (d, 3 H, J = 6.2 Hz), 1.4–2.5 (br m, 9 H); ^{13}C NMR δ 212.61 (C_1), 44.89 (C_2), 41.38 (C_6), 35.82 (C_3), 27.57 (C_5), 24.76 (C_4), 14.29 (CH_3).

(±)-*trans*-2(a)-Methyl-4-*tert*-butylcyclohexanone (3). A solution of 4-*tert*-butylcyclohexanone (Aldrich) (5.0 g, 32 mmol) and 7.9 g (132 mmol) of *N*,*N*-dimethylhydrazine (Aldrich) in 30 mL of absolute ethanol and 35 mL of toluene was heated by reflux with azeotropic removal of H_2O for a day. The solvents were removed (rotary evaporator), and the residue was distilled under vacuum to give, after a small forerun, 4.5 g (70% yield) of 4-*tert*-butylcyclohexanone dimethylhydrazone, bp 54–56 °C (0.15 mmHg), with purity 96% as determined by GC on column C. ^1H NMR δ 0.89 (s, 9 H, $-C(CH_3)_3$), 1.0–3.5 (m, 9 H), 2.40 (s, 6 H, $-N(CH_3)_2$). IR (neat) ν 2970, 2780, 1645, 1450, 1400, 1380, 1030, 1000, 970 cm^{-1}.

A cold (0 °C) solution of 4.5 g (23 mmol) of the dimethylhydrazone in 10 mL of tetrahydrofuran (THF) (distilled from $LiAlH_4$) was kept under N_2 and added to a magnetically stirred solution of 11 mL (25 mmol) of 2.4 M *n*-butyllithium in hexane and 3.6 mL (26 mmol) of diisopropylamine in 40 mL of THF at 0 °C. The solution was kept in a refrigerator (−10 °C) for 30 h and then cooled to −78 °C for the addition of 2.8 g (46 mmol) of CH_3I. Following stirring at −78 °C for 1 h, the solution was allowed to warm to room temperature and then poured into 40 mL of H_2O:CH_2Cl_2 (3:1). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried (Na_2SO_4). After concentration, the residue was dissolved in 130 mL of CH_3OH and 80 mL of a pH 7 aqueous buffered (Tris) solution. The mixture was then treated with a solution of 11.6 g (50.6 mmol) of KIO_4 in 30 mL of H_2O. After being stirred overnight, the reaction mixture was extracted (CH_2Cl_2) and dried ($MgSO_4$) to afford 1 g (18%) of mixed ketones, bp 69–71 °C (0.35 mmHg) determined by GC on column B to be 91% axial (**3**) and 9% equatorial (**2**) 2-methyl-4-*tert*-butylcyclohexanones. **3**: ^1H NMR δ 0.91 (s, 9 H), 0.9–2.4 (m, 8 H), 1.15 (d, 3 H, J = 7.1 Hz). ^{13}C NMR δ 216.00 (C_1), 44.30 (C_4), 42.84 (C_2), 41.08 (C_6), 37.87 (C_3), 32.84 ($-C(CH_3)_3$), 27.51 (C_5), 27.22 ($-C(CH_3)_3$), 16.75 (CH_3).

(±)-*cis*-2(e)-Methyl-4-*tert*-butylcyclohexanone (2). A 400-mg portion of axial ketone **3** in 30 mL of CH_3OH was stirred with 100 mg of sodium methoxide at 25 °C for 4 h. The solution was diluted with H_2O (100 mL) and extracted with ether (2 × 50 mL). The extract was dried ($MgSO_4$) and concentrated to give 300 mg (75% of mixed ketones: 90% of the desired equatorial epimer (**2**) and 10% of the axial (**3**)), as determined by GC on column B. **2**: ^1H NMR δ 0.91 (s, 9 H), 0.9–2.4 (m, 8 H), 1.01 (d, 3 H, J = 6.3 Hz). ^{13}C NMR δ 213.49 (C_1), 46.99 (C_4), 44.30 (C_2), 41.20 (C_6), 37.17 (C_3), 32.25 ($-C(CH_3)_3$), 28.51 (C_5), 27.51 ($-C(CH_3)_3$), 14.58 (CH_3).

(−)-(1*S*,5*R*)-2(*S*),6,6-Trimethylbicyclo[3.1.1]heptan-3-one (β-Pinanone (6)). β-Pinanone was prepared from >99% ee (−)-α-pinene,[18] $[\alpha]^{20}_D$ −51.3° (neat), by hydroboration and Jones oxidation, as described previously.[21] **6**: $[\alpha]^{25}_D$ −12.6° (neat); UV ϵ^{max}_{292} = 14 (*n*-heptane); ϵ^{max}_{288} = 21, ($CHCl_3$); ϵ^{max}_{288} = 30; CD $[R]^{25}_{294}$ = −0.92 (*n*-heptane); $[R]^{25}_{300}$ = −1.13 ($CHCl_3$); $[R]^{25}_{289}$ = −1.80 (TFE); $[rR]^{25}_{284}$ = −1.40 (CH_3OH); IR (neat) ν 2950, 1710 cm^{-1}; ^1H NMR δ 0.88 (s, 3 H, *syn*-CH_3), 1.20 (m, H_{7x}), 1.21 (d, 3 H, α-CH_3, J = 7.4 Hz), 1.32 (s, 3 H, *anti*-CH_3), 2.08 (ddd, H_1, $J_{1,7x}$ = 6.2 Hz, $J_{1,5}$ = 6.2 Hz, $J_{1,2n}$ = 2.3 Hz), 2.12 (ddt, H_5, $J_{5,1}$ = 6.3 Hz, $J_{5,7n}$, $J_{4,4x}$), 2.46 (br dq, H_{2n}, $J_{2n,CH}$ = 7.5 Hz, $J_{2n,4n}$ = 1.3 Hz), 2.53 (ddd, H_{4n}, $J_{4n,4x}$ = 19.0 Hz, $J_{4n,5}$ = 2.5 Hz, $J_{4n,2n}$ = 1.0 Hz), 2.62 (m, H_{7x}), 2.65 (dddd, H_{4x}, $J_{4n,4x}$ = 19.0 Hz, $J_{4x,5}$ = 3.0 Hz, $J_{4x,7x}$ = 3.0 Hz, $J_{4x,2x}$ = 1.0 Hz); ^{13}C NMR δ 214.76 (C_3), 51.25 (C_2), 45.05 (C_1), 44.69 (C_5), 39.20 (C_6), 39.02 (C_4), 34.34 (C_7), 27.03 (C_8), 21.88 (C_9), 16.79 (C_{10}); mass spectrum, m/z (rel. intensity) 152 [$M^{\cdot+}$] (20%), 110 (25%), 109 (11%), 97 (32%), 95 (58%), 83 (100%) amu. The CH_3 groups showed aromatic solvent-induced shifts in the ^1H NMR determined in perdeuteriobenzene, $\Delta\delta(CDCl_3-C_6D_6)$: C_8 (+0.27), C_9 (+0.22), C_{10} (+0.05).

(−)-(1*S*,5*R*)-2(*R*),6,6-Trimethylbicyclo[3.1.1]heptan-3-one (α-Pinanone (5)). α-Pinanone was prepared by base-catalyzed epimerization of β-pinanone (**6**), as described previously.[21] **5**: $[\alpha]^{25}_D$ −24° (neat); UV ϵ^{max}_{281} = 25 (CH_3OH); CD $[R]^{25}_{307}$ = +0.64 (CH_3OH); $[R]^{25}_{288}$ = +0.41 (TFE); $[R]^{25}_{299}$ = +0.41, $[R]^{25}_{322}$ = 0.015 (PFP); IR (neat) ν 2390, 1710 cm^{-1}; ^1H NMR δ 0.90 (s, 3 H, *syn*-CH_3), 1.12 (d, 3 H, α-CH_3, J = 7.2 Hz), 1.16 (d, H_{7n}, $J_{7n,7x}$ = 10.7 Hz), 1.34 (s, 3 H, *anti*-CH_3), 1.93 (ddd, H_1, $J_{1,7x}$ = 6.3 Hz, $J_{1,5}$ = 6.3 Hz, $J_{1,2x}$ = 2.3 Hz), 2.12 (dddd, H_5, $J_{5,7x}$ = 6.3 Hz, $J_{5,1}$ = 6.3 Hz, $J_{5,4x}$ = 3.1 Hz, $J_{5,4n}$ = 3.1 Hz), 2.41 (ddd, H_{4n}, $J_{4n,4x}$ = 19.0 Hz, $J_{4n,5}$ = 3.3 Hz, $J_{4n,2x}$ = 1.3 Hz), 2.46 (dt, H_{7x}, $J_{7x,1}$ = 6.2 Hz, $J_{7x,5}$ = 6.2 Hz, $J_{7x,4x}$ = 3.0 Hz, $J_{7x,2x}$ = 3.0 Hz), 2.62 (dddd, $J_{4x,4n}$ = 19.0 Hz, $J_{4x,5}$ = 2.8 Hz, $J_{4x,7x}$ = 2.8 Hz, $J_{4x,2x}$ = 1.0 Hz), 2.63 (qdm, H_{2x}, $J_{2x,CH}$ = 7.2 Hz, $J_{2x,1}$ = 2.0 Hz); ^{13}C NMR δ 215.27 (C_3), 46.67 (C_2), 44.74 (C_1), 44.56 (C_5), 38.65 (C_4), 38.59 (C_6), 29.29 (C_7), 26.54 (C_8), 19.93 (C_9), 15.19 (C_{10}). The CH_3 groups showed aromatic solvent-induced shifts in the ^1H NMR determined in perdeuteriobenzene, $\Delta\delta$ ($CDCl_3-C_6D_6$): C_8 (+0.27), C_9 (+0.29), C_{10} (+0.09).

(−)-(1*R*,5*S*)-*endo*-2(*R*)-Methylbicyclo[3.2.1]octan-3-one (7). A solution of 4 g (27.4 mmol) of *N*-ethyl-*N*-nitrosourethane[47] in 50 mL of absolute ethanol was added dropwise (45 min) to a magnetically stirred, cold (0 °C) solution of 200 mg of $LiOH\cdot H_2O$[48] and 2 g (18.2 mmol) of (−)-norcamphor,[21] $[\alpha]^{25}_D$ −9.2°, 32% ee,[26] in 40 mL of absolute ethanol. After 6 h, the reaction mixture was colorless and had warmed to 10 °C. The solution was then diluted with 100 mL of CH_2Cl_2, and the layers were separated. The organic layer was washed sequentially with 2 × 50 mL of H_2O, 50 mL of 2 N aqueous HCl, 50 mL of aqueous Na_2CO_3, and 50 mL of H_2O. Subsequent drying ($MgSO_4$) and solvent removal by fractional distillation afforded 1.76 g of crude products,[19] which were distilled, bp 30 °C (0.25 mmHg). Final separation of **7** from the isomeric ring expansion product *exo*-3-methylbicyclo[3.2.1]octan-2-one (with a longer retention time) and other products was achieved by preparative GC on column D. **7**: $[\alpha]^{25}_D$ −2.39°, $[\alpha]^{25}_{436}$ = −4.8° (*c* 1, ethanol); UV ϵ^{max}_{293} = 16 (MI), ϵ^{max}_{290} = 17 (PFP), ϵ^{max}_{286} = 20 ($CHCl_3$), ϵ^{max}_{286} = 17 (EPA), ϵ^{max}_{284} = 16 (CH_3OH); CD $[R]^{25}_{294}$ = −0.38, $[R]^{25}_{321}$ = +0.012 (MI); $[R]^{25}_{286}$ = −0.29, $[R]^{25}_{321}$ = +0.062 (PFP); $[R]^{25}_{289}$ = −0.41, $[R]^{25}_{319}$ = +0.041 ($CHCl_3$); $[R]^{25}_{280}$ = −0.44, $[R]^{25}_{307}$ = +0.025 (EPA); $[R]^{25}_{283}$ = −0.40, $[R]^{25}_{318}$ = +0.035 (CH_3OH); $[R]^{25}_{275}$ = −0.26, $[R]^{25}_{305}$ = +0.087 (TFE); $[R]^{25}_{293}$ = −0.36, $[R]^{25}_{322}$ = +0.027 (isooctane); $[R]^{25}_{293}$ = −0.41, $[R]^{25}_{321}$ = +0.024 (isopentane) (all $[R]$ values corrected to 100% ee); IR (CCl_4) ν 2923, 1710 cm^{-1}; ^1H NMR δ 1.01 (d, 3 H, J = 6.9 Hz), 1.43 (m, H_{6n}), 1.58 (m, H_{8a}), 1.61 (m, H_{7n}), 1.70 (m, H_{6x}), 1.78 (m, H_{7x}), 1.95 (br d, H_{8s}, $J_{8s,8a}$ = 11.5 Hz), 2.26 (ddd, H_{4n}, $J_{4n,4x}$ = 15.0 Hz, $J_{4n,5}$ = 2.8 Hz, $J_{4n,8a}$ = 2.8 Hz), 2.32 (br m, H_1), 2.43 (ddd, H_{4x}, $J_{4x,4n}$ = 16.0 Hz, $J_{4x,5}$ = 2.3 Hz, $J_{4x,6}$ = 3.5 Hz, $J_{4x,2x}$ = 1.7 Hz), 2.45 (ddq, H_{2x}, $J_{2x,CH}$ = 7.1 Hz, $J_{2x,7x}$ = 3.4 Hz, $J_{2x,4x}$ = 1.8 Hz), 2.54 (br m, H_5); ^{13}C NMR δ 213.24 (C_3), 51.37 (C_2), 49.79 (C_4), 42.65 (C_1), 39.78 (C_8), 36.51 (C_5), 29.08 (C_6), 24.28 (C_7), 12.81 (CH_3); mass spectrum, m/z (rel. intensity) 138 [$M^{\cdot+}$] (33%), 123 (6%), 109 (25%), 96 (7%), 95 (44%), 94 (33%), 82 (15%), 81 (100%) amu.

(−)-*exo*-2-Methylbicyclo[3.2.1]octan-2-one had $[\alpha]^{24}_D$ −23.4° (*c* 1.3, ethanol); UV ϵ^{max}_{288} = 21 (isopentane), ϵ^{max}_{278} = 23 (TFE); CD $[R]^{25}_{292}$ = −4.77 (isopentane), $[R]^{25}_{287}$ = −3.70 (TFE) (all $[R]$ values corrected to 100% ee); IR (CCl_4) ν 2970, 1713 cm^{-1}; ^1H NMR δ 1.00 (d, 3 H, α-CH_3, J = 6.1 Hz), 1.34 (dd, H_{4x}, $J_{4x,4n}$ = 12.5 Hz, $J_{4x,5}$ = 3.0 Hz), 1.67 (m, H_9), 1.73 (m, H_{4n}), 1.77 (m, H_8), 1.78 (m, H_6 or H_7), 2.05 (m, H_6 or H_7), 2.40 (m, H_5), 2.44 (ddq, H_{3n}, $J_{3n,CH}$ = 6.1 Hz, $J_{3n,4n}$ = 12.0 Hz, $J_{3n,4x}$ = 8.0 Hz), 2.75 (dd, H_1, $J_{1,7x}$ = 2.5 Hz, $J_{1,8a}$ = 2.5 Hz); ^{13}C NMR δ 214.59 (C_2), 50.60 (C_1), 42.00 (C_4), 38.90 (C_8), 37.79 (C_3), 34.34 (C_5), 27.85 (C_6), 27.47 (C_7), 14.04 (CH_3); mass spectrum, m/z (rel. intensity) 138 [$M^{\cdot+}$] (36%), 123 (9%), 110 (5%), 109 (18%), 107 (11%), 105 (8%), 96 (12%), 95 (25%), 94 (9%), 83 (11%), 82 (11%), 81 (62%), 80 (100%) amu.

(+)-(1*R*,5*S*)-*exo*-2(*S*)-Methylbicyclo[3.2.1]octan-3-one (8). A solution of 148 mg of ketone **7** (above) was epimerized in 3 mL of trifluoroacetic acid by heating at reflux under N_2 for 70 h. The cooled reaction mixture was diluted with 4 mL of H_2O and carefully neutralized to pH 7 with solid $NaHCO_3$. After extraction with ether (3 × 7 mL) and drying ($MgSO_4$), the products were freed of solvent by fractional distillation. Final purification was achieved by preparative GC on column D. **8**: $[\alpha]^{25}_D$ +7.0° (*c* 0.4, MI); UV ϵ^{max}_{293} = 34 (EPA), ϵ^{max}_{296} = 23 (MI); CD $[R]^{25}_{299}$ = +2.74 (EPA), $[R]^{25}_{302}$ = 2.37 (MI) ($[R]$ values corrected to 100% ee); ^1H NMR δ 1.16 (d, 3 H, α-CH_3, J = 7.3 Hz), 1.49 (dddd, H_{6n}, H_{7x}, $J_{6n,6x}$ = 11 Hz, $J_{6n,7n}$ = 10 Hz, $J_{6n,7x}$ = 3.4 Hz, $J_{6n,8s}$ = 1.7 Hz), 1.7–1.99 (m, H_{6x}, H_{7x}, H_{8a}), 2.02 (br d, H_{8s}, $J_{8s,8a}$ = 12.3 Hz), 2.18

(48) Lithium ion is reported to have a beneficial effect on ring expansions using diazomethane. Belikova, N. A.; Ordubadi, M.; Sitnikova, L. V.; Platé, A. F. *Zh. Org. Khim.* **1973**, *9*, 1880–1886. We used LiOH in place of LiCl.

(dddd, H_{4n}, $J_{4n,4x}$ = 16.0 Hz, $J_{4n,5}$ = 2.5 Hz, $J_{4n,8a}$ = 1.8 Hz, $J_{4n,2n}$ = 1.5 Hz), 2.22 (br m, H_1), 2.33 (qdm, H_{2n}, $J_{2n,CH}$ = 7.5 Hz), 2.46 (br m, H_5), 2.49 (ddd, H_{4x}, $J_{4x,5}$ = 2.5 Hz, $J_{4x,6x}$ = 1.7 Hz, $J_{4x,2x}$ = 1.3 Hz); ^{13}C NMR δ 216.50 (C_3), 53.06 (C_2), 47.68 (C_4), 41.36 (C_1), 35.10 (C_5), 32.06 (C_8), 30.01 (C_7), 28.31 (C_6), 17.55 (CH_3); mass spectrum, *m/z* (rel. intensity) 138 [$M^{\cdot+}$] (35%), 123 (5%), 109 (25%), 95 (38%), 94 (30%), 82 (12%), 81 (100%) amu.

Ketone **8** was also prepared by a second route from (+)-norcamphor: $[\alpha]^{25}_D$ +15.2° (*c* 2.2, $CHCl_3$), 53% ee,[26] as follows.

(1*R*,4*S*)-*exo*-3(*S*)-Methylbicyclo[2.2.1]heptan-2-one:[21] To a solution of 1.5 mL (11 mmol) of diisopropylamine (distilled from CaH_2) and 5 mL of THF (distilled from $LiAlH_4$) under N_2 at −78 °C was added (via syringe) 4.1 mL (10 mmol) of 2.4 M *n*-butyllithium in hexane. After 10 min, 1.1 g (10 mmol) of (+)-norcamphor, 53% ee, in 5 mL of THF (distilled from $LiAlH_4$) was added dropwise at −78 °C (via syringe). After 5 min, 1 mL (15 mmol) of iodomethane (passed through alumina) was added at −78 °C (via syringe), and the solution was stirred an additional 30 min (white precipitate appears, LiI). The solution was warmed to room temperature and saturated aqueous NH_4Cl was added. After ether extraction and drying ($MgSO_4$), the solvent was removed (rotary evaporator). Distillation gave 750 mg (60%) of *exo*-3-methylnorcamphor with bp 32–34 °C (0.9 mmHg) [lit.[21] bp 54–55 °C (9 mmHg) of >96% purity, determined by GC on column A.

Diazomethane Ring Expansion of *exo*-3-Methylnorcamphor. A heterogeneous mixture of 0.3 g (2.4 mmol) of *exo*-3-methylnorcamphor from above in 10 mL of CH_3OH and 0.5 g of $LiOH{\cdot}H_2O$ in 5 mL of H_2O was stirred magnetically and cooled to 0 °C. Small portions (0.5–1.0 g) of XR-101 (Aldrich) were added over 5 h until ca. 7 g had been added. Brine (50 mL) was added, and the reaction mixture was extracted with ether (2 × 25 mL) and then H_2O (25 mL) and dried ($MgSO_4$). After evaporation of solvents, a white salt appeared. The desired products were washed free from the salts with pentane to yield 0.25 g of crude products. Preparative GC showed a 35% yield of a 1:2 ratio of ketones **8** and **9**. Preparative GC on column D afforded both the exo (**8**) and endo (**9**) ketones.

(1*R*,5*S*)-2,8,8-Trimethylbicyclo[3.2.1]oct-2-en-7-one. A solution of 37 g (0.27 mol) of (−)-α-pinene, $[\alpha]^{20}_D$ −41.9° (neat), 81% ee,[18] and 55 g (0.28 mol) of $Fe(CO)_5$ (Alfa) was purged with argon for 5 min, capped, and heated at 175 °C for 53 h in a sealed pressure bottle (150 mL volume). The cooled, dark reaction mixture was suction filtered over a layer of alumina (black precipitate is flammable!). The orange filtrate was concentrated (rotary evaporator) to afford 36 g of crude material. Vacuum distillation afforded 21 g (70%) of a 1:1 mixture, bp 57–60 °C (0.6 mmHg) of the desired ketone and its isomer, (1*S*,5*S*)-2,4,4-trimethylbicyclo[3.2.1]oct-2-en-7-one. Removal of the latter was achieved by selective reaction with 1 equiv of *p*-toluenesulfonylhydrazone (Aldrich) under mild conditions. Thus, a 21-g (128 mmol) portion of the mixture of ketones in 250 mL of 95% ethanol was heated at reflux with 13.7 g (74 mmol) of tosylhydrazine for 1.5 h. Upon cooling the mixture to room temperature no crystals formed, and the solution was concentrated to half volume and placed in a freezer at −20 °C. This led to crystallization, and the (white) crystals were collected by suction filtration and rinsed with 250 mL of pentane and 100 mL of cold (0 °C) ether. The filtrates were *not* discarded but instead were combined and evaporated to afford a viscous oil, which was stirred vigorously with 300 mL of pentane to afford a second batch of white crystals. These crystals were collected by filtration and combined with the first crop to give 85% yield of the tosylhydrazone of (1*S*,5*S*)-2,4,4-trimethylbicyclo[3.2.1]oct-2-en-7-one, mp 159–163 °C dec. The desired ketone was recovered from the pentane filtrate by concentration and vacuum distillation, bp 55–59 °C (0.55 mmHg), 5 g (48%). A pure sample was obtained by preparative GC on column E. ^1H NMR δ 0.97 (s, 3 H), 1.00 (s, 3 H), 1.69 (s, 3 H), 1.8–2.7 (m, 6 H), 5.42 (m, 1 H); ^{13}C NMR δ 210.23 (C_7), 131.55 (C_2), 120.78 (C_3), 63.39 (C_1), 42.68 (C_6), 38.64 (C_5), 37.18 (C_8), 32.33 (C_4), 26.48 (C_{10}), 22.32 (C_{11}), 19.63 (C_9); mass spectrum, *m/z* (rel intensity) 164 [$M^{\cdot+}$] (21%), 149 (14%), 122 (22%), 121 (27%), 107 (100%) amu.

(1*R*,5*S*)-2,8,8-Trimethylbicyclo[3.2.1]oct-2-en-7-one *p*-Toluenesulfonylhydrazone. A solution of 10.5 g (64 mmol) of the above ketone and 11.5 g (62 mmol) of *p*-toluenesulfonylhydrazine in 200 mL of CH_3OH and 1.5 mL of concentrated HCl was heated at reflux for 21 h. Then a soxhlet extraction system, using 3A molecular sieves as the drying agent in the cup, was mounted to the reaction flask, and reflux was continued for an additional 9 h. Upon cooling, no crystals formed, but after 75 mL of solvent was removed (under vacuum) and 5 mL of water was added, crystals formed. The first (9.5 g, mp 110–115 °C) and second crops (2.5 g) gave a combined yield of 56%, with the remainder being unreacted starting material.

Anal. Calcd for $C_{18}H_{24}O_2N_2S$ (332.47): C, 65.03; H, 7.27; N, 8.43. Found: C, 64.95; H, 7.29; N, 8.43.

(−)-(1*S*,5*R*)-2,8,8-Trimethylbicyclo[3.2.1]oct-2-ene. A slurry of 8 g (24 mmol) of tosylhydrazone from above in 100 mL of freshly distilled CH_2Cl_2 was stirred magnetically at 25 °C and treated dropwise with 70 mL (70 mmol) of 0.9 M diisobutylaluminum hydride in hexane (Aldrich).[49] After the mixture was stirred an additional hour, 10 g (75 mmol) of sodium acetate trihydrate was added to quench the reaction, and the mixture was stirred overnight at room temperature. Then 10 mL of H_2O and 100 mL of 3 N aqueous NaOH were added followed by stirring for 30 min. Product was extracted with ether and dried ($MgSO_4$) and the solvent distilled fractionally at 1 atm. The residue was distilled under vacuum to afford 1.1 g (30% yield) of olefin, bp 55–57 °C (6.5 mmHg). The crude olefin could be purified by preparative GC on column D. Pure olefin: $[\alpha]^{25}_D$ −6.5° (*c* 1.08, ethanol); ^1H NMR δ 0.93 (s, 3 H), 1.03 (s, 3 H), 1.63 (s, 3 H), 1.2–2.5 (m, 8 H), 4.96 (m, 1 H); ^{13}C NMR δ 141.19 (C_2), 116.15 (C_3), 50.51 (C_1), 41.74 (C_8), 41.62 (C_5), 34.77 (C_7), 33.08 (C_4), 30.56 (C_6), 26.76 (C_{10}), 23.13 (C_9), 20.85 (C_{11}).

Anal. Calcd for $C_{11}H_{18}$ (150.27): C, 87.93; H, 12.07. Found: C, 88.19, H, 11.96.

(1*S*,5*R*)-*exo*-2(*S*),8,8-Trimethylbicyclo[3.2.1]octan-*endo*-3(*S*)-ol. A magnetically stirred slurry of 1.0 g (6.7 mmol) of olefin from above and 0.3 g (8.0 mmol) of $NaBH_4$ in 50 mL of dry THF at 0 °C was treated dropwise with a solution of 1.4 mL (12 mmol) of $BF_3{\cdot}Et_2O$ in 30 mL of dry THF. The ice bath was removed, and the reactions mixture was stirred for 20 h. After dropwise quenching of the reaction mixture with H_2O (1 mL), 20 mL of 3 N aqueous NaOH was added. Then 20 mL of 30% aqueous H_2O_2 was added dropwise, and the mixture was stirred overnight. The solution was extracted with ether (200 mL), and the ether layer was separated and washed with brine and then dried (Na_2SO_4). Concentration afforded ca. 1 g of crude, low-melting alcohol, which was distilled under vacuum to give 600 mg, (43% yield) of 80% purity alcohol with bp 115–125 °C (7–8 mmHg) using a kugelrohr apparatus. It had IR (neat) ν 2950, 1440, 780 cm^{-1} and was taken directly to the next step.

(−)-(1*S*,5*R*)-*exo*-2(*S*),8,8-Trimethylbicyclo[3.2.1]octan-3-one (10). A slurry of 190 mg (1.1 mmol) of the above alcohol, 50 mg of anhydrous sodium acetate, and 550 mg (4.4 mmol) of pyridinium chlorochromate in 50 mL of CH_2Cl_2 was stirred magnetically for only 30 min. After dilution with 50 mL of anhydrous ether, the reaction mixture was decanted and passed quickly (pressure) through a short (2 cm × 10 cm) column of Florisil. Concentration of the eluents afforded 144 mg of crude product, which was purified by preparative GC on column D to afford 50 mg (27% yield) of pure **10**. This compound easily epimerizes on unsilanized glassware at room temperature; it should be kept cold until needed. $[\alpha]^{25}_D$ −4.4° (*c* 0.09, MI); UV ϵ^{max}_{284} = 16 (CH_3OH), ϵ^{max}_{296} = 16 (MI); CD $[R]^{25}_{291}$ = −1.25, $[R]^{25}_{323}$ = +0.080 (CH_3OH), $[R]^{25}_{291}$ = −0.23, $[R]^{25}_{322}$ = +0.27 (MI) ([*R*] values corrected to 100% ee, based on 81% ee of **10** prepared from 81% ee of (−)-α-pinene); IR ($CDCl_3$) ν 2950, 1705 cm^{-1}; ^1H NMR δ 1.02 (s, 3 H, *syn*-CH_3), 1.13 (s, 3 H, *anti*-CH_3), 1.24 (d, 3 H, α-CH_3, *J* = 7.7 Hz), 1.52 (m, H_{6n}, H_{7n}), 1.69 (d, H_1, $J_{1,7x}$ = 5.7 Hz), 1.89 (br t, H_5, $J_{5,4x}$ = 5.9 Hz), 2.05 and 2.19 (m, H_{6x}, H_{7x}), 2.18 (m, H_{2n}, $J_{2n,CH}$ = 7.5 Hz, $J_{2n,1}$ = 1.5 Hz), 2.20 (d, H_{4n}, J_{4n4x} = 20 Hz), 2.66 (ddd, H_{4x}, J_{4x4n} = 19.6 Hz, $J_{4x,5}$ = 5.95 Hz, $J_{4x,6x}$ = 2.2 Hz); ^1H NMR (C_6D_6) δ 0.72 (s, 3 H, *syn*-CH_3), 0.82 (s, 3 H, *anti*-CH_3), 1.14 (m, H_{6n}, H_{7n}), 1.18 (d, 3 H, α-CH_3, *J* = 7.6 Hz), 1.43 (m, H_5, $J_{5,7x}$ = 6.5 Hz), 1.74 (dd, H_1, $J_{1,6x}$ = 6.4 Hz, $J_{1,2n}$ = 2.0 Hz), 1.70 and 1.90 (m, H_{6x}, H_{7x}), 1.93 (q, H_{2n}, $J_{2n,CH}$ = 7.6 Hz), 2.00 (d, H_{4n}, $J_{4n,4x}$ = 19.6 Hz), 2.45 (ddd, H_{4x}, $J_{4x,4n}$ = 19.8 Hz, $J_{4x,5}$ = 5.65 Hz, $J_{4x,6x}$ = 2.0 Hz); ^{13}C NMR δ 213.36 (C_3), 53.24 (C_2), 49.03 (C_1), 46.92 (C_4), 42.47 (C_5), 42.30 (C_8), 31.59 (C_7), 29.54 (C_6), 27.73 (C_{10}), 22.34 (C_9), 20.18 (C_{11}). The CH_3 groups showed aromatic solvent induced shifts in the ^1H NMR determined in perdeuteriobenzene, $\Delta\delta(CDCl_3-C_6D_6)$ C_9 (+0.37), C_{10} (+0.31), C_{11} (+0.06).

Anal. Calcd for $C_{11}H_{18}O$ (166.26): C, 79.46; H, 10.91. Found: C, 79.22; H, 11.10.

(−)-(1*S*,5*R*)-*endo*-2(*R*),8,8-Trimethylbicyclo[3.2.1]octan-3-one (9). The endo ketone **9** was faster moving on GC than its epimer (**10**, above). The latter epimerized readily to **9** in normal glassware at room temperature as evidenced by GC studies on new and one week old samples of **10**. Preparative GC separation on column D gave pure **9**. $[\alpha]^{25}_D$ −2.08° (*c* 3.7, ethanol); UV ϵ^{max}_{297} = 19 (CH_3OH), ϵ^{max}_{287} = 21 (isopentane); CD $[R]^{25}_{281}$ = −0.20, $[R]^{25}_{311}$ = +0.053 (CH_3OH); $[R]^{25}_{286}$ = −0.31, $[R]^{25}_{324}$ = +0.027 (isopentane) ([*R*] values corrected to 100% ee, based on 81% ee of **9**, prepared from 91% ee of (−)-α-pinene); IR ($CDCl_3$) ν 2950, 1705 cm^{-1}; ^1H NMR δ 0.99 (d, 3 H, α-CH_3, *J* = 6.5 Hz), 1.06 (s, 3 H, *syn*-CH_3), 1.33 (s, 3 H, *anti*-CH_3) 1.36 (ddd, H_{6n}, $J_{6n,6x}$ = 12 Hz, $J_{6n,7}$ = 9.5 Hz, $J_{6n,7x}$ = 4.7 Hz), 1.51 (ddd, H_{7n}, $J_{7n,7x}$ = 14 Hz, $J_{7n,6n}$ = 9.5 Hz, $J_{7n,6x}$ = 4.7 Hz), 1.74 (br m, H_1, $J_{1,7x}$ = 7 Hz, $J_{1,2x}$ = 2.3 Hz), 1.81 (m, H_{6x}), 1.90 (br m, H_5, $J_{5,6x}$ = 6 Hz, $J_{5,4x}$ = 3 Hz), 1.98 (m, H_{7x}), 2.13

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(dd, H_{4n}, $J_{4n,4x}$ = 16.3 Hz, $J_{4n,5}$ = 2.86 Hz), 2.64 (dt, H_{4x}, $J_{4x,4n}$ = 16.3 Hz, $J_{4x,5}$ = 3.05 Hz), 2.72 (m, H_{2x}, $J_{2x,CH}$ = 6 Hz); ^{13}C NMR δ 213.24 (C_3), 50.72 (C_1), 46.56 (C_4), 45.92 (C_2), 44.46 (C_5), 42.58 (C_8), 28.13 (C_6), 26.38 (C_{10}), 22.87 (C_7), 20.94 (C_9), 12.98 (C_{11}); mass spectrum, m/z (rel. intensity) 166 [$M^{\cdot+}$] (38%), 109 (77%), 96 (36%), 95 (100%) amu. The CH_3 groups showed aromatic solvent-induced shifts in the ^1H NMR determined in perdeuteriobenzene, $\Delta\delta(CDCl_3-C_6D_6)$ C_9 (+0.30), C_{10} (+0.40), C_{11} (−0.03).

Anal. Calcd for $C_{11}H_{18}O$ (166.26): C, 79.46; H, 10.91. Found: C, 79.58; H, 10.86.

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Spectroscopic Identification of Formyl Cyanide (CHOCN) in the Flash Pyrolysis of Methoxyacetonitrile

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Abstract: The gas-phase infrared spectrum of the short-lived species formyl cyanide has been recorded at low resolution. Four of the nine fundamentals were oserved: ν_2(C≡N stretch) = 2229 cm^{-1}, ν_3(C=O stretch) = 1716 cm^{-1}, ν_5(C—C stretch) = 914 cm^{-1}, and ν_7(C—C≡N bend) = 230 cm^{-1}. Identification of the CHOCN bands among the numerous absorption bands of the pyrolysis products of methoxyacetonitrile was made by stop-flow techniques and by comparison to recent ab initio calculations.

Formyl cyanide is a species of considerable chemical interest for several reasons. It is the simplest combination of the aldehyde and cyano groups and forms the prototype for the acyl cyanides.[1] From the viewpoint of organic synthesis, formyl cyanide has a variety of potential uses as a formylating agent for nucleophilic species. The prevalence of carbonyl and cyano compounds in the interstellar medium[2] suggests the likelihood that acyl cyanides are of astrophysical importance. Finally, HCOCN is a small enough molecule to be attractive for high-resolution spectroscopic studies in the microwave, infrared, and ultraviolet regions of the spectrum.

Formyl cyanide was recently reported by one of us[3] as an unstable product of the flash pyrolysis of methoxyacetonitrile. This was the first laboratory identification of this species although attempts to synthesize it by classical preparative organic techniques have been reported.[4,5] Ultraviolet long path absorption spectroscopy was used to identify CHOCN by the characteristic n → π^* absorption bands found in the 350–390-nm region. Comparison of the band frequencies and rotational profiles to the well-known bands of propynal led to the firm conclusion that CHOCN was responsible for the new spectrum. Despite the substantial number of products anticipated from the thermal decomposition of CH_3OCH_2CN, the UV absorption technique provided a clear window for the observation of formyl cyanide in the pyrolysis mixture.

Since the initial discovery, a set of high-level ab initio calculations have been published[6] predicting the vibrational frequencies, rotational constants, and dipole moment of formyl cyanide. These calculations were motivated by an unsuccessful search for the microwave spectrum of CHOCN.[7] The reasons for the failure to observe a microwave spectrum are unclear. A large dipole moment (calculated to be 2.75 D[6]) is expected for the molecule and the pyrolysis conditions appeared well-established from previous experiments which monitored the electronic transition in the ultraviolet.[3] However, a variety of other stable products were identified by microwave and UV absorption techniques, proving that the pyrolysis did not lead solely to the production of CHOCN. Due to these complications, we felt it was necessary to establish the identity and relative abundance of formyl cyanide in the pyrolysis mixtures using independent spectroscopic methods. Gas-phase infrared and mass spectrometric measurements under optimized conditions are reported in this work.

Table I. Observed and Calculated Vibrational Frequencies for Formyl Cyanide (cm^{-1})

mode	description	3-21G scaled[a]	experiment
ν_1(a′)	CH stretch	2917	
ν_2(a′)	C≡N stretch	2309	2229
ν_3(a′)	C=O stretch	1691	1716
ν_4(a′)	CH rock	1385	
ν_5(a′)	C—C stretch	894	914
ν_6(a′)	C—C=O bend	637	
ν_7(a′)	C—C≡N bend	258	230, 227[b]
ν_8(a″)	CH wag	1026	
ν_9(a″)	C—C≡N bend	417	278[b]

[a] From ref 6. [b] From ref 3.

Experimental Section

Low-pressure gas-phase infrared spectra of methoxyacetonitrile pyrolysis streams were recorded on a Bomem DA3.02 FTIR. The modulated infrared beam was transferred from the evacuated interferometer into an external, 3 m long, 85 mm i.d. Pyrex absorption cell which it traversed twice before reentering the instrument and impinging on a liquid nitrogen cooled MCT detector (450–5000 cm^{-1}). Two CsI windows separated the cell from the interferometer and homebuilt, gold-coated beam steering optics were employed. For the mid-infrared a KBr beamsplitter was used. Far-infrared experiments, limited to the 200-cm^{-1} cutoff of the CsI windows, were done with use of a 3-μm Mylar beamsplitter and a DTGS detector.

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