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THE OCTANT RULE. XVI[1]. CONFORMATION AND CIRCULAR DICHROISM OF SYN AND ANTI 2-METHYLBICYCLO[3.1.0]HEXAN-3-ONES, THUJONE AND ISOTHUJONE

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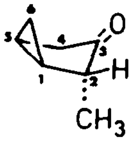
Abstract - (1S,5S)-exo-2(R)-Methylbicyclo[3.1.0]hexan-3-one (1) and (1S,5S)-endo-2(S)-methylbicyclo[3.1.0]hexan-3-one (2) were synthesized and their circular dichroism (CD) spectra run. Conformational analysis based on molecular mechanics calculations and Karplus equation analyses of vicinal H|H NMR coupling constants indicate boat-like sofa conformations for both 1 and 2, with very little ring distortion from the symmetry of the parent bicyclo[3.1.0]hexan-3-one. The lone dissymmetric ψ-axial and ψ-equatorial methyl groups of 1 and 2, respectively, are both octant consignate. The natural product analogs of 1 and 2, (-)-3-isothujone (3) and (+)-3-thujone (4) were prepared and examined similarly. Their α-methyl perturbers dominate the CD n-π^* Cotton effects.

The stereochemistry of bicyclo[3.1.0]hexane has been of interest because it has an unusual, conformationally restrained cyclohexane ring and because of the common occurrence of its skeletal framework among (thujane[2]) natural products.[3] Most investigations have concluded in favor of a boat-like conformation for the cyclohexane ring,[4] although introduction of sp^2 hybridized carbons into the 3-carbon belt leads to flattening of the 5-membered ring and a sofa-like cyclohexane conformation. When a ketone carbonyl is introduced at C-3, the resulting bicyclo[3.1.0]hexan-3-one has been shown to favor a boat-like sofa conformation with the C=O tilted toward C-6 (and out of co-planarity with carbons 1, 2, 4 and 5) by 15-19°. Thus, microwave spectral analysis gave a puckering angle



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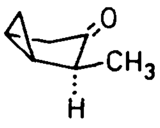

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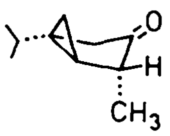

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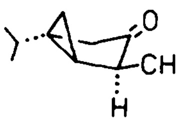
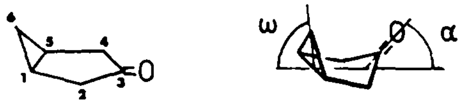


4

(α, Fig. 1) of 18.8°,[5] LIS-NMR analyses gave $\alpha \approx 15°$,[6] and analysis of vicinal H|H NMR coupling constants gave $\alpha \approx 17°$.[4] Microwave data also indicated that alkyl substitution causes only small changes in α, e.g. for isothujone (3) $\alpha = 15°$, for thujone (4) $\alpha = 25°$,[7] but an ^{1}H-NMR analysis gives $\alpha = -3°$ for isothujone, suggesting a chair-like sofa conformation.[4]



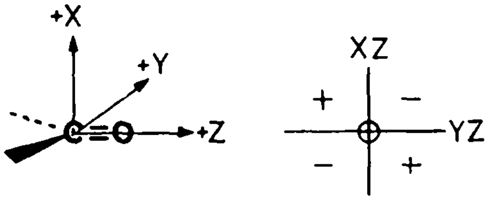


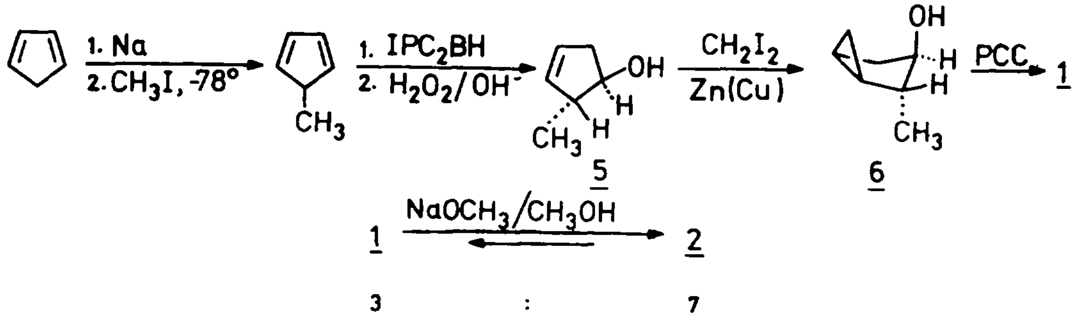
Figure 1. (left) Sofa conformation of bicyclo[3.1.0]hexan-3-one with carbons 1-5 lying in a plane. (right) Boat conformation showing interplanar angles α and ω. The puckering angle α measures the distortion from sofa coplanarity caused by tilting C-3 above or below the plane of atoms 1, 2, 4 and 5, while ω measures the tilting of C-6. Both α and ω are measured from appropriate ring torsion angles (Table 1).

Figure 2. (left) Coordinate system used in defining the carbonyl C_{2v} symmetry planes which form the "symmetry-derived" nodal planes (XZ and YZ) of the octant rule (ref. 9) for the ketone carbonyl n-π^* transition. (right) Octant projection diagram for back octants (as viewed from oxygen to carbon). The sign of the contribution to the Cotton effect due to a back octant perturber is given by the sign of the product of its coordinates (X.Y.Z). Perturbers lying on an octant nodal plane make no contribution.

Our concern with the ring conformation of bicyclo[3.1.0]hexan-3-one stems from an interest in stereochemically well-defined symmetric ketones with very limited conformational flexibility that can serve as model systems for an examination[8] of the boundaries of the octant rule[9] (Fig. 2). With addition of a CH_3 group to an α-carbon of bicyclo[3.1.0]hexan-3-one, we hoped to introduce little or no distortion of the inherent C_2 ring symmetry of the parent (XZ symmetry plane) and thus leave the CH_3 group as the lone dissymmetric perturber of the ketone carbonyl. Any electronic interaction between the cyclopropane moiety and the C=O group is expected to be of a symmetric nature, not effecting the XZ symmetry plane, but probably perturbing the erstwhile YZ nodal plane (Fig. 2). This concept is supported by optical rotatory dispersion studies of thujone (4) and isothujone (3), which show apparently no unusual effects due to the presence of the cyclopropane group:[10] 4 (with its methyl and possibly its isopropyl perturber both lying in (+) back octants) gives a (+) Cotton effect (CE); whereas, 3 gives a (−) CE. In the latter, the α-CH_3 lies in a (−) back octant and apparently dominates any possible (+) back octant contribution of the isopropyl perturber. In order to explore the importance of the angular configuration (relative to the C=O group) of the α-CH_3 perturber in determining the sign and magnitude of its contribution to the CE, we synthesized optically active ketones 1 and 2, which are analogs of isothujone (3) and thujone (4) but do not have their potentially complicating isopropyl groups. The circular dichroism spectra of 1-4 were recorded and analyzed in terms of molecular geometries obtained from molecular mechanics (MM2[11]) and Karplus-type[12] ^{1}H-NMR vicinal coupling constant computations.

Synthesis and Sterochemistry. Optically active bicyclic ketone 1 was prepared (Scheme 1) from the known (1R, 2R)-2-methylcyclopent-3-enol (5),[13] first by

SCHEME 1



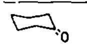
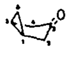
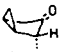
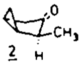
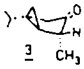
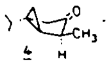
Simmons-Smith cyclopropanation[14] to give (1S,5S)-2(R)-methylbicyclo[3.1.0]hexan-3(R)-ol (6) then pyridinium chlorochromate oxidation. Epimerization of 1 afforded a 3:7 mixture of 1 and 2, from which pure 2 could be isolated by preparative gas chromatography. (Analogously, thujone (4) is epimerized in base to a 3:7 mixture of 3 and 4.[2]) The OH group of 5 directs the cyclopropanation stereospecifically syn, as expected for homoallylic alcohols.[14] If the cyclopropanation reaction had given some anti alcohol, oxidation of 6 would lead to a mixture of 1 contaminated with the enantiomer of 2. Since we are able to detect 2 in the presence of 1 by analytical gas chromatography, and we see much less than 1% of 2 (or its enantiomer) in unepimerized 1, we conclude that the cyclopropanation reaction went with >99% stereoselectivity and that oxidation of the resulting alcohol (6) gave no epimerization. These conclusions are supported by the fact that both 1 and 2 had the same infrared and NMR spectral data as their corresponding racemic counterparts prepared by an independent route.[15] Since the absolute configuration and enantiomeric excess (e.e.) of 5 had been determined previously,[13,16] the absolute configuration and e.e. shown for 1 and 2 follow from the facts that they are derived from 5 either by stereospecific reactions (5 → 6) or reactions that do not alter the absolute stereochemistry of 6 (6 → 1, 1 → 2), and work-up procedures that avoid enantiomeric fractionation.

(+)-3-Thujone (4) was isolated and purified by formation and crystallization of its bisulfite addition product -- a procedure which allows its separation from (-)-3-isothujone (3), an epimeric ketone which does not form a bisulfite addition product.[17] Pure (-)-3-isothujone (3) was obtained following Jones oxidation of (-)-3-neoisothujanol.[14b] The absolute configurations and e.e.'s of (3) and (4) follow from the work of previous investigators.[2,3,10b,17b]

Ring Conformation and α-CH_3 Configuration. The ring conformations of ketones 1 - 4 were investigated by MM2[11] molecular mechanics calculations and by analysis[12] of the vicinal $H_{2x}|H_1$ and/or $H_{4x}|H_5$ NMR coupling constants determined at 360 MHz. The results of MM2 calculations are given in Table 1 and include data for the parent, bicyclo[3.1.0]hexan-3-one, as well as cyclohexanone. Using MM2, we calculate a boat-like sofa conformation for bicyclo[3.1.0]hexan-3-one, with puckering angle $\alpha \simeq 16°$ -- a conformation and α angle in good agreement with those derived from (1) NMR methods (boat, $\alpha \simeq 15°$)[6] for $CDCl_3$ solutions, and (2) microwave spectroscopy (boat, $\alpha \simeq 19°$)[5] for the gas phase. In contrast with chair cyclohexanone, the α and ω puckering angles (Fig. 1) have the same sign, and whereas the ω angle magnitudes are comparable, the α angle is much smaller. The conformation of bicyclo[3.1.0]hexan-3-one, with its small α angle, is thus closer to a sofa than a boat. Introduction of an α-CH_3 group results in only slight distortion of the C_s ring skeletal symmetry of 1 and 2, as judged from comparing the magnitudes of the pairs of torsion angles (Table 1): $\phi(2,3)$ vs $\phi(3,4)$, $\phi(1,2)$ vs $\phi(4,5)$, and $\phi(1,6)$ vs

$\Phi(5,6)$. The boat-like sofa conformation is retained in both 1 and 2. In the former the α ($\approx 15°$) angle is essentially the same as that of the parent bicyclo-[3.1.0]hexan-3-one ($\alpha \approx 16°$), but in the latter the α angle ($\approx 25°$) is enlarged, and the skeleton is more boat-like. With 2 assuming a more boat-like conformation, the CH_3 group moves farther away from the cyclopropane CH_2 in order to minimize the inherent $CH_3 | CH_2$ gauche interaction which attends the introduction of a ψ-equatorial CH_3 group to bicyclo[3.1.0]hexan-2-one. The (MM2) calculated retention of C_s skeletal symmetry in 2 is supported by the observation that the vicinal coupling constants $^3J_{2x,1}$ and $^3J_{4x,5}$ are equal (≈5.5 Hz). Only one of these coupling constants, $^3J_{4x,5} = 5.0$ Hz, can be measured for 1 since position 2x is substituted by a CH_3 group, and the corresponding endo coupling constants, $^3J_{2n,1}$ and $^3J_{4n,5}$ are both <1 Hz and difficult to measure accurately. However very similar (boat-like) conformations for 1 and 2 are supported by their $^3J_{4x,5}$ values, and the fact that $^3J_{4x,5}$ of 1 is slightly less than $^3J_{4x,5}$ of 2 is consistent with a smaller α angle for 1.

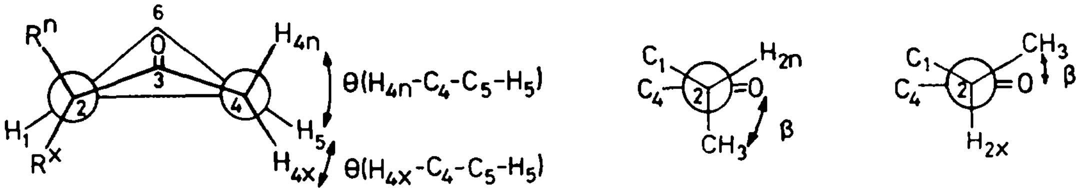
TABLE 1. Comparison of Ring Torsion, Puckering and Internal Angles for Energy-Minimized Conformations of Cyclohexanone, Bicyclo[3.1.0]hexan-3-one and its 2-CH_3 Derivatives, and Isothujone and Thujone as Determined by (MM2) Molecular Mechanics Calculations.[a]

Compound[b]	Ring Torsion Angle, (φ), deg. φ(2,3) (1-2-3-4)	φ(3,4) (2-3-4-5)	φ(1,2) (3-2-1-6)	φ(4,5) (3-4-5-6)	φ(1,6) (2-1-6-5)	φ(5,6) (1-6-5-4)	(2-1-5-6)	(4-5-1-6)	(1-2-3-O)	(5-4-3-O)	Internal Angles (deg) (2-3-4)	(1-6-5)	Interplanar Ring Puckering Angles deg[c] α	β	Total Steric Energy (kcal/mole)
	51.49	-51.49	-53.32	53.30	57.52	-57.52	-	-	-131.1	131.1	115.3	110.9	-48.9	60	5.73
	-16.11	16.11	-55.39	55.39	95.78	-95.78	-112.7	112.7	164.1	-164.1	110.1	60.28	15.9	67.3	18.81
	-14.9[d]	14.9[d]	-56.5[d]	56.8[d]	97.1[d]	-97.2[d]	-110.5[d]	110.5[d]	165.1[d]	-165.1[d]	106.1[d]	57.9[d]	14.9[d]	69.5[d]	
													(17)[e]		
											104.1[f,g]	60.4[f]	18.8[f]	66.9[f]	
 1	-15.93	16.30	-56.03	54.86	96.46	-95.54	-112.2	112.8	165.1	-164.6	110.3	60.25	14.9-15.4	67.2-67.8	20.61
 2	-24.03	22.54	-48.96	52.91	94.02	-96.17	-114.5	112.2	154.2	-155.7	109.1	60.35	24.3-25.8	65.5-67.8	19.93
 3	-15.75	14.06	-54.09	58.02	96.68	-97.04	-112.1	109.2	165.2	166.9	110.5	60.12	13.1-14.8	67.9-70.8	25.79
													25[h]	66.93[g]	
 4	-24.42	20.79	-46.62	55.73	94.03	-97.53	-114.7	108.8	153.8	157.4	109.1	60.22	22.6-26.2	65.3-71.2	25.41
													~3[e]		
													15[h]	66.93[g]	

[a] See ref. 11. Limited certainty begins with the fourth significant figure. [b] Numbering system used throughout conforms to that of bicyclo[3.1.0]hexan-3-one. [c] Puckering angle $\alpha = 180° - \phi(1\text{-}2\text{-}3\text{-}O)$; $\beta = 180° - \phi(2\text{-}1\text{-}5\text{-}6)$. [d] Data from ref. 6; derived from LIS-NMR analysis. [e] Data from ^{1}H-NMR vicinal H|H coupling constant analysis of ref 4. [f] Data derived from microwave spectroscopy in ref. 5. [g] Assumed value, not calculated. [h] α-angle for the corresponding thujone isomer, determined by microwave spectroscopy assuming $\beta = 66.9°$, ref. 7.

As with 1 and 2, isothujone (3) and thujone (4) show very little distortion of their skeletal (C_s) symmetry (Table 1). In fact, the calculated boat-like sofa ring geometries of 1 and 3 are very similar, as are those of 2 and 4 -- an indication that the isopropyl groups of isothujone and thujone do not play a significant role in determining their conformations.[7] Our calculated α-puckering angles for 3 and 4 are very similar to those of 1 and 2, and they are also in rough qualitative agreement with those determined from microwave studies.[7] They differ from those derived from microwave studies in that 3 is predicted by MM2 to have a smaller α angle than 4. But both methods agree on a boat conformation; whereas, an analysis of vicinal H|H NMR coupling constants indicated a chair-like sofa conformation for 4 with twisting of the ring skeleton ascribed to the presence of bridgehead isopropyl substituent.[4]

Conformational analysis using vicinal H|H NMR coupling constants (^3J) depends on an accurate determination of ^3J values and, critically, on the choice of (Karplus-type) equation relating H-C-C-H dihedral angle (θ, Fig. 3) to ^3J. Our

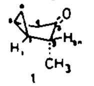
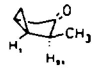
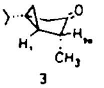
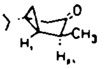


1,3 2,4

Figure 3. (left half) Newman projection diagram for the boat-like sofa conformation of 1 (R^n = H, R^x = CH_3) and 2 (R^n = CH_3, R^x = H) showing H-C-C-H dihedral angles used in the vicinal H|H NMR coupling constant analysis. There are similar Θ angles across the ring for 1 [$\Theta(H_{2n}-C_2-C_1-H_1)$] and for 2 [$\Theta(H_{2x}-C_2-C_1-H_1)$]. Similar structures follow for 3 and 4 where H_5 is replaced by an isopropyl group, with the consequence of removing the H|H vicinal coupling for the Θ's shown. With changes in conformation from boat to sofa to chair, $\Theta(H_{4n}-C_4-C_5-H_5)$ opens and $\Theta(H_{4x}-C_4-C_5-H_5)$ closes. (right half) Newman projection diagrams for the C_2-C_3 bond of 1 - 4 showing the β torsion angles, β = ($CH_3-C_2-C_3$=O). As the conformation changes from boat to chair, β for 1 and 3 closes and β for 2 and 4 opens.

values of $^3J_{2x,1}$ for 1 and 3 are identical (5.5 Hz) and very nearly the same as that found previously for 3 (5.4 Hz).[4] The coupling constants $^3J_{2n,1}$ of 2 and 4 are too small to be determined accurately at present. However, $^3J_{4x,5}$ of 2 has been determined (5.0 Hz), and if the isopropyl group of 4 causes no large change in its ring geometry relative to that of 2, as is indicated by MM2 calculations (Table 1), then one might assume the same conformation obtains for 4 as for 2. The sensitivity of Θ to the choice of Karplus-type equation is illustrated in Table 2. The Θ, β and α angles obtained or derived from the equation $^3J = 9.3\cos^2\Theta + \cos\Theta$,[18] which has served well in strained bicyclic systems,[12,18,19] are compared with those from the original Karplus equation ($^3J = 8.5\cos^2\Theta - 0.28$)[20] and its variation ($^3J = 6.28\cos^2\Theta - 0.28$)[4] which was specifically modified to fit bicyclo[3.1.0]hexan-3-one. The first equation[18] consistently overestimates and the last equation[4] consistently underestimates the Θ calculated by MM2. The original Karplus equation,[20] on the other hand, gives Θ values in consistently closest agreement

TABLE 2. H-C-C-H Dihedral Angles (Θ), $CH_3-C_\alpha-C{=}C$ Torsion Angles (β) and Ring Puckering Angles (α) Derived from Karplus-Type Analysis of Vicinal H|H NMR Coupling Constants (^3J) and Their Comparison with those Derived from MM2 Molecular Mechanics Calculations.^{a}

Ketone	Coupling Constant (Hz)				H-C-C-H Dihedral Angle (deg)^b				Torsion Angle (deg)^b	Puckering Angle (deg)^c	Total Steric Energy
	$^3J_{2n,1}$	$^3J_{2x,1}$	$^3J_{4n,5}$	$^3J_{4x,5}$	$\Theta H_1-C_1-C_2H_{2n}$	$\Theta H_1-C_1-C_2-H_{2x}$	$\Theta H_{4n}-C_4-C_5-H_5$	$\Theta H_{4x}-C_4-C_5-H_5$	$(CH_3-C_\alpha-C{=}O)$	α	(kcal/mole)
 1	<1	--	<1	5.0	^{d} ^{d} ^{d} (-95.60)	-- -- -- --	^{d} ^{d} ^{d} (93.00)	-37.98^e -23.52^f -47.04^g (-29.29)	-78.07^h -70.24^h -80.06^h (-74.20)	18.6 11.3-12.[illegible] 20-20.5 (14.9-15.4)	20.70 20.64 21.02 $(20.61)^a$
 2	--	5.5	<1	5.5	-- -- -- --	34.45^e 16.39^f 44.18 (37.89)	^{d} ^{d} ^{d} (89.92)	-34.45^e -16.39^f -44.18^g (-32.67)	29.49^h 33.97^h 27.88^h (30.12)	24.8-26.5 20.0-21.7 26.5-28.0 (24.3-25.8)	19.34 20.29 20.12 $(19.93)^a$
 3	<1	--	--	--	^{d} (-89.84)	-- --	-- --	-- --	^{d} (-74.44)	^{d} (13.1-14.8)	^{d} $(25.79)^a$
 4	--	5.5	--	--	-- -- -- --	34.45^e 16.39^f 44.18^g (42.62)	-- -- -- --	-- -- -- --	31.31^h 38.51^h 29.82^h (29.71)	21-25 (14.5-18.5) 22.9-26.1 (22.6-26.2)	25.53 26.60 25.41 $(25.41)^a$

^{a} MM2-derived values are in parentheses. ^{b} See Fig. 3. ^{c} See Fig. 1. ^{d} Not determined. ^{e} Using $^3J = 8.5\cos^2\theta - 0.28$ (ref. 20) ^{f} Using $^3J = 6.28\cos^2\theta - 0.28$ (ref. 4). ^{g} Using $^3J = 9.3\cos^2\theta + \cos\theta$ (refs 12,18,19) ^{h} Obtained using the MM2 program with the θ angle held to the NMR-derived value.

with the MM2 values. The data of Table 2 indicate that as $\theta(H_{4x}-C_4-C_5-H_5)$ opens the ring conformation becomes more boat-like, e.g. the puckering angle α increases. However, the energy differences between the conformations defined by the variously derived Θ angles are usually small. The orientation of the CH_3 group relative to the C=O group (β torsion angle) can also be determined from the conformation defined by Θ and will become important in the following analysis of the circular dichroism spectra of 1 - 4.

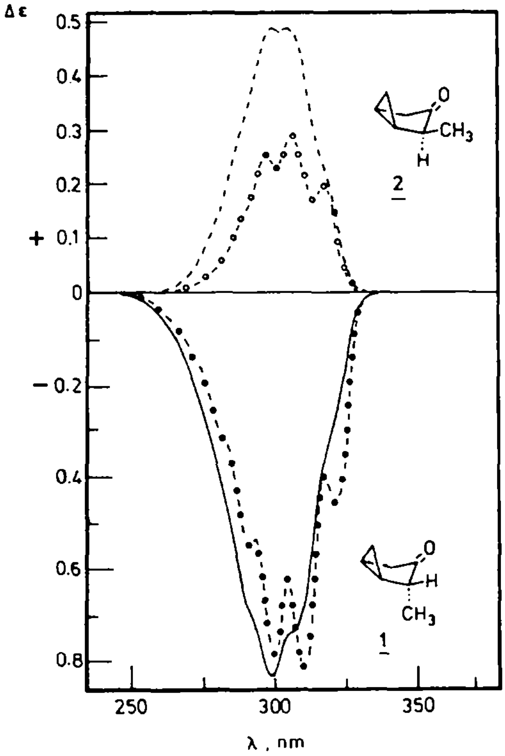


Figure 4. Circular Dichroism of 0.02 M 1 (———) and 2 (- - - - -) in methanol, and 1 (- ● - ● -) and 2 (- o - o -) in cyclopentane at 23°C. Data are corrected to 100% e.e.

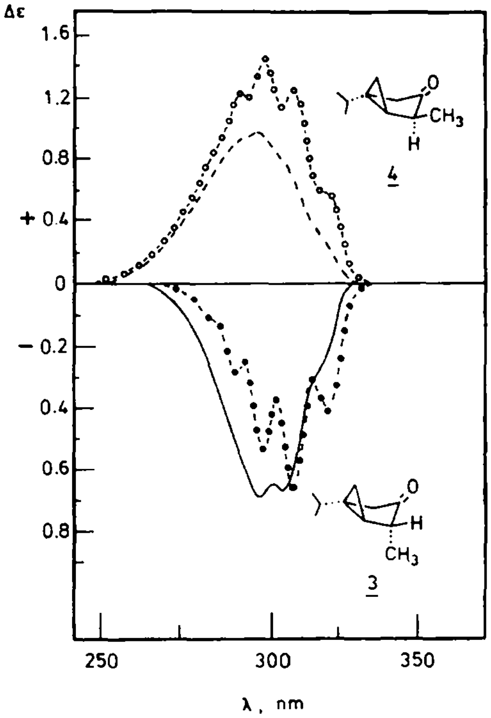
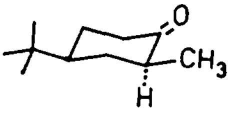
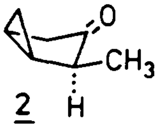
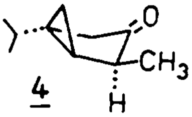
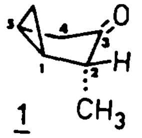
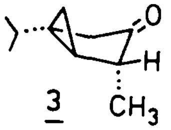
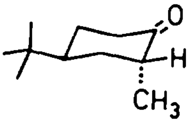


Figure 5. Circular dichroism of 0.01 M 3 (———) and 4 (- - - - -) in methanol, and 3 (- ● - ● -) and 4 (- o - o -) in isooctane at 25°C. Data are corrected to 100% e.e.

Circular Dichroism and CH_3 Configuration. The circular dichroism (CD) spectra of 1 - 4 (Figs. 4 and 5) all show monosignate Cotton effects (CEs) for the ketone carbonyl $n-\pi^*$ transition. The corresponding UV spectra show no unusual wavelength shifts or ε enhancements that might have been expected from electronic interaction between the C=O and the α,β-cyclopropane chromophore.[21] And in confirmation of earlier observations based on the optical rotatory dispersion spectra of 3 and 4,[10] we find no unusual effects in the CD spectra -- as one might expect from a symmetric disposition (Table 1) of the two chromophores. With the near retention in 1 - 4 of the C_s skeletal symmetry of the parent bicyclo[3.1.0]hexan-3-one, the ring atoms contribute very little to the CE, which is expected to be dominated in 1 and 2 by the lone dissymmetric α-CH_3 group or, in 3 and 4 by a combination of the α-CH_3 and β-isopropyl groups. In fact, the CE signs of 1 and 2 as well as 3 and 4 can be seen to be controlled by the configuration of the α-CH_3 group, and both the signs and the associated rotatory strengths change little upon temperature lowering to -175°C, e.g. 29% decrease for 4, 24% increase for 3, 24% decrease for 1 -- an indication that neither major conformational changes nor temperature-dependent solvational effects intervene. The β-isopropyl groups of 3 and 4 makes a (+) consignate[22] contribution, as predicted from the octant diagram,[10a,b] but the magnitude of its contribution is outweighed in 3 by the (-) consignate contribution of the α-CH_3 group.

TABLE 3. Correlation of CH_3 Group Configuration (β) with NMR Chemical Shifts and Rotatory Stengths for Methyl Ketones.

Structure	Torsion Angle β[a] (deg)	CH_3	CH_3 Chemical Shift[b] ^1H	^{13}C	Reduced Rotatory Strength [R][c] in: Methanol	Isooctane
	5.02	equatorial	1.03	14.5	+1.39[d]	+1.46[a]
 2	30.1 (29.5)	ψ-equatorial	1.05	12.2	+1.35	+0.678[e]
 4	29.7	ψ-equatorial	1.04	12.4	+3.24	+4.89
 1	-74.2 (-78.1)	ψ-axial	1.20	17.3	-2.65	-2.30[e]
 3	-74.4	ψ-axial	1.16	18.0	-1.98	-1.58
	-102	axial	1.15	16.8	-5.30[d]	-4.93[d]

[a] From the energy-minimized structure obtained in (MM2) molecular mechanics calculations. Values in parentheses come from the Karplus equation (ref. 20) and Table 2. β is defined in Fig. 3.

[b] In δ, ppm downfield from $(CH_3)_4Si$.

[c] [R] = rotatory strength (cgs) x 1.08 x 10^{40} for the ketone n-π* Cotton effects.

[d] Values from ref. 23; data were obtained on the enantiomers. MM2 calculations on these ketones do not reveal the severe ring distortions predicted by the empirical force field of Boyd and used in ref. 23.

[e] Run in cyclopentane.

The relationship between α-CH_3 configuration and its CE contribution is important,[22b] and ketones 1 - 4, with their α-CH_3 configurations neither fully axial nor equatorial, offer insight into this stereochemical problem. As shown in Table 3, there is a qualitative correlation between α-CH_3 configuration and its ^1H and ^{13}C-NMR chemical shifts: the more shielded values correspond to the more equatorial-like configuration. As the α-CH_3 moves from equatorial to ψ-equatorial, as in 2(e)-methyl-4-tert-butylcyclohexanone[23] to 2 and 4, the β angle opens from

~5° to ~30°, but the inherent CE contribution of the α-CH_3 remains octant consignate[22] (cf. 2). Similarly, as the α-CH_3 moves from axial to ψ-axial, as in 2(a)-methyl-4-*tert*-butylcyclohexanone[23] to 1 and 3, the β angle closes from -102° to ~ -75°, but again the inherent contribution of the α-CH_3 remains octant consignate[23] (cf. 1). These results are important because the α-CH_3 groups of α- and β-pinanone were reported[24] to be octant dissignate[22] contributors. And, with the pinanone ring in a sofa conformation, the β angles ($\simeq$ 40°) lie intermediate between axial and equatorial. Apparently, as the equatorial β angle is opened past ~30° to ~40°, the α-CH_3 group changes over from an octant consignate to an octant dissignate perturber. A similar result occurs as the axial β angle is closed past ~-75° to ~-40°. Further work on clarifying the point of transition is underway.

EXPERIMENTAL

General: Circular dichroism (CD) spectra were recorded on a JASCO J-40 instrument equipped with a photoelastic modulator and a J-DPY data processor. Ultraviolet (UV) spectra were recorded on a Cary 219 spectrophotometer, and specific 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 ppm downfield from tetramethylsilane on a JEOL FX-100 or Bruker 360 instrument. Mass spectra (MS) were recorded at 70 or 30 eV ionizing voltage on a JEOL JMS-07, mass spectrometer. Infrared (IR) spectra were measured on a Perkin-Elmer Model 599 instrument. Analytical gas chromatography (GC) was carried out on a Varian-Aerograph model 2400 F/I instrument using a 6 ft x 1/8 in diam. column with 15% QF-1 (column A) or 5% SE-30 (column B) stationary phases absorbed on 80/100 Chromosorb W AW-DMCS. Preparative gas chromatography (GC) was achieved on a 6 ft x 3/8 in diam. column (C) packed with 15% QF-1 on 60/80 Chromosorb W AW-DMCS or on an 8 ft x 1/4 in diam column (D) packed with 9% carbowax 20M on 60/80 chromosorb W AW-DMCS using a Varian Aerograph model 1720 T/C instrument.

Spectral data were obtained using spectral grade solvents (MCB): methanol, cyclopentane, isooctane, methylcyclohexane-isopentane, 4:1, v/v (MI) and ether-isopentane-ethanol, 5:5:2, v/v/v (EPA). Other solvents were distilled and dried before use: pentane, cyclohexane, chloroform and dichloromethane all from P_2O_5; and diethyl ether and tetrahydrofuran from $LiAlH_4$ under N_2. The solvents were used freshly distilled or stored over 4A molecular sieves (Linde). Dioxane was distilled from CaH and stored over 4A molecular sieves (Linde).

(-)-(1R,2R)-trans-2-Methylcyclopent-3-en-1-ol (5): This alcohol was prepared as described by Partridge *et al.*[13] using diisopinocampheyl borane prepared from (-)-α-pinene, $[\alpha]_D^{25}$ = -47.5° (neat), 92+% e.e.[25] It had $[\alpha]_D^{25}$ = -169° (c 1.13 CH_3OH); ^1H-NMR (100 MHz) δ: 1.02 (d, 3H, J = 7.0 Hz), 1.6-2.8 (m, 3H), 3.8 (m, 1H), 4.3 (m, 1H), 5.5 (s, 2H) ppm; mass spectrum: 98 $[M^{+\cdot}]$ (48% rel. abund.) amu, [Lit.[13] $[\alpha]_D^{25}$=-175° for >99% e.e.].

(1S,2R,3R,5S)-exo-2-Methylbicyclo[3.1.0]hexane-endo-3-ol (6): A flame-dried 100 mL three-neck round-bottom flask, equipped with condenser, 10 mL addition funnel, argon inlet and rubber septa, was filled with 3.6 g (53 mmol) of freshly made Zn(Cu) couple[26] (flame dried under vacuum), 30 mg of iodine and 40 mL of anhydrous ether. Diiodomethane (11.5 g, 43 mmol) (distilled and dried over 4 A sieves) was added using a syringe, and the resulting slurry was heating at gentle reflux for 1.5 hours with magnetic stirring. A solution of 2 g (21 mmol) of 2-methylcyclopent-3-en-1-ol from above in 9 mL of anhydrous ether was added dropwise during 15 min. Vigorous reflux began and continued until all of the cyclopentenol had been added. The gray-black slurry was heated at reflux for an additional 15.5 hours, then was cooled to room temperature and treated dropwise with 8 mL of a saturated solution of aqueous ammonium chloride. The ether was decanted and the gray sludge rinsed with ether. The combined ether layers were washed with saturated aqueous potassium carbonate (4 x 20 mL). More ether (100 mL) was added and the ether layer was separated, dried ($MgSO_4$), and concentrated by rotary evaporation under vacuum to afford 2.1 g (89% yield) of 95% pure product. It had $[\alpha]_D^{25}$ = -54.3 (c 0.14); IR (film) ν: 3615, 3360, 1050 cm^{-1}; ^1H-NMR (100 MHz) δ: 0.58 (m, 2H), 0.93 (d, 3H, J=7.0 Hz), 1.12 (s, 2H), 1.5-2.3 (m, 4H), 3.84 (d, 1H, J=7 Hz) ppm; mass spectrum, *m/z* (rel. intens): 112 $[M^{+\cdot}]$ (2%), 94 (18%), 79 (31%), 71 (71%), 57 (100%) amu.

(-)-(1S,2R,5S)-exo-2-Methylbicyclo[3.1.0]hexan-3-one (1): A slurry of 1.0 g (9.0 mmol) of the cyclopropyl alcohol from above and 100 mg of anhydrous sodium acetate in 100 mL of dichloromethane were treated with pyridinium chlorochromate at room temperature for 3.75 hours. Chromium salts were precipitated by adding 100 mL of anhydrous ether, and the brown supernatant was decanted and passed quickly over alumina (2 cm x 10 cm) using air pressure. The solution was concentrated to afford 700 mg of ketone 1, which was 80% pure as determined by analytical GC on column A. Purification by preparative GC on column C afforded pure 1. It had $[\alpha]_D^{25}$=-87.2° (c

0.33, CCl_4); UV: ε_{288}^{max} = 21 (CH_3OH), ε_{300}^{max} = 24 (cyclopentane); CD in Fig. 4 and Table 3; IR (CCl_4) ν: 1740 cm^{-1}; ^1H-NMR (360 MHz) δ: -0.025 (dt, H_{6n}, $J_{6n,6x}$ = 5.9 Hz, $J_{6n,5}$ = 4.0 Hz, $J_{6n,1}$ = 4.0 Hz), 0.905 (dtt, H_{6x}, $J_{6x,6n}$ = 5.9 Hz, $J_{6x,5}$ = 7.8 Hz, $J_{6x,1}$ = 7.8 Hz, $J_{6x,4x}$ =2.0 Hz, $J_{6x,2x}$ = 2.0 Hz), 1.198 (d, CH_3, J=7.6 Hz), 1.295 (dt, H_1) $J_{1,6n}$ = 4.0 Hz, $J_{1,6x}$ = 7.8 Hz, $J_{1,5}$ = 7.8 Hz), 1.535 (m, H_5), 2.150 (d, H_{4n}, $J_{4n,4x}$ = 19.3 Hz), 2.175 (q, H_{2n}, J=7.5 Hz), 2.643 (dtt, H_{4x}, $J_{4x,4n}$ = 19.1 Hz, $J_{4x,5}$ = 5.0 Hz, $J_{4x,6x}$ = 1.8 Hz) ppm; ^{13}C-NMR δ: 10.82 (C_5), 12.81 (C_6), 17.26 (CH_3), 18.95 (C_1), 39.02 (C_4), 45.51 (C_2), 220.50 (C_3) ppm; mass spectrum: m/z (rel. intens.): 110 [$M^{+\cdot}$] (10%), 82 (54%), 67 (100%) amu.

(+)-(1S,2S,5S)-endo-2-Methylbicyclo[3.1.0]hexan-3-one (2): A solution of ca. 600 mg of ketone (1) and 100 mg of sodium methoxide in 15 mL of methanol was stirred overnight at room temperature. Water (20 mL) was added and the products were extracted with ether (3 x 80 mL). The dried ($MgSO_4$) ether extracts were concentrated to afford 450 mg of a mixture of 1 and 2. Preparative GC on column D afforded pure 2. It had $[\alpha]_D^{25}$ = +50.0° (c. 0.38, CCl_4); UV: ε_{285}^{max} = 16 (CH_3OH), ε_{284}^{max} = 24 (cyclopentane); CD in Fig. 4 and Table 3; IR (CCl_4) ν: 1745 cm^{-1}; ^1H-NMR (360 MHz) δ: -0.161 (dt, H_{6n}, $J_{6n,6x}$ = 5.7 Hz, $J_{6n,5}$ = 4.3 Hz, $J_{6n,1}$ = 4.3 Hz), 0.733 (dtt, H_{6x}, $J_{6x,6n}$ = 5.7 Hz, $J_{6x,5}$ = 7.8 Hz, $J_{6x,1}$ = 7.8 Hz, $J_{6x,2x}$ = 1.7 Hz, $J_{6x,4x}$ = 1.7 Hz), 1.050 (d, CH_3 J= 6.9 Hz), 1.500 (m, H_1, $J_{1,2x}$ = 5.5 Hz, $J_{1,5}$ = 5.7 Hz, $J_{1,6n}$ = 4.3 Hz), 1.652 (m, H_5, $J_{5,4x}$ = 5.5 Hz, $J_{5,1}$ = 5.7 Hz, $J_{5,6n}$ = 4.3 Hz), 2.186 (d, H_{4n}, $J_{4n,4x}$ = 19.1 Hz), 2.680 (dtt, H_{4x}, $J_{4x,4n}$ = 19.1 Hz, $J_{4x,5}$ = 5.5 Hz, $J_{4x,6x}$ = 2.0 Hz, $J_{4x,2x}$ = 2.0 Hz), 2.685 (qdt, H_{2x}, J_{2x,CH_3} = 6.9 Hz, $J_{2x,1}$ = 5.5 Hz, $J_{2x,6x}$ = 2.0 Hz, $J_{2x,4x}$ = 2.0 Hz) ppm; ^{13}C-NMR δ: 9.30 (C_5 and C_6), 12.17 (CH_3), 18.54 (C_1), 40.83 (C_4), 43.76 (C_2), 217.75 (C_3) ppm; mass spectrum, m/z (rel. intens.): 110 [$M^{+\cdot}$] (29%), 82 (100%) amu.

(+)-3-Thujone[17] [(+)-(1R,4S,5S)-1-isopropyl-endo-4-methylbicyclo[3.1.0]hexan-3-one] (4): A 12 mL aliquot of a freshly made solution of sodium bisulfite (16.3 g, 0.130 mol), sodium bicarbonate (1.5 g, 0.018 mol) in 2 mL of 95% ethanol and 25 mL of water was mixed with 5 g (0.033 mol) of western red cedar leaf oil[17,27] by stirring for 17.5 hours at room temperature. The resulting syrup was rinsed with ether on a sintered glass funnel to yield white crystals, which were dried in air for 0.5 hours. This bisulfite adduct was then dissolved in 50 mL of water and heated at reflux for 3 hours. Extraction with ether (3 x 50 ml), subsequent drying ($MgSO_4$) and concentration afforded 1 g (20%) of (+)-3-thujone, >96% purity as determined by GC on column B). It had $[\alpha]_D^{20}$ +35.7° (neat) [Lit[2] $[\alpha]_D$=+72.46° (neat) for 100% e.e.]; UV: ε_{274}^{max} = 28 (methanol), ε_{274}^{max} = 26 (isooctane); CD in Fig. 5 and Table 3; IR (film) ν: 1740 cm^{-1}; ^1H-NMR (360 MHz) δ: -0.04 (dd, H_{6n}, $J_{6n,6x}$ = 4.0 Hz, $J_{6n,1}$ = 6.0 Hz), 0.59 (bt, H_{6x}), 0.95 (d, CH_3, J = 7.0 Hz), 1.01 (d, CH_3, J = 7.0 Hz), 1.04 (d, α-CH_3, J = 7.0 Hz), 1.45 (ddd, H_1, $J_{1,6n}$ = 6.0 Hz, $J_{1,2x}$ = 5.5 Hz, $J_{1,6x}$ = 8.0 Hz), 1.44 (sept, H_7, J = 7.0 Hz), 2.13 (d, H_{4n}, J = 18.5 Hz), 2.55 (ddd, H_{4x}, J = 18.5 Hz, $J_{4x,6x}$ = 2.0 Hz, $J_{4x,2}$ = 2.0 Hz), 2.71 (qdd, H_{2x}, J_{2x,CH_3} = 7.0 Hz, $J_{2x,1}$ = 5.5 Hz, $J_{2x,6x}$ = 2.0 Hz, $J_{2x,4x}$ = 2.0 Hz) ppm; ^{13}C-NMR δ: 12.42 (α-CH_3), 14.58 (C_6) 19.61 (2 x CH_3), 24.53 (C_1), 27.21 (C_5), 32.54 (C_7), 41.61 (C_2), 45.30 (C_4), 218.23 (C_3) ppm; mass spectrum, m/z (rel. intens.) 152 [$M^{+\cdot}$] (10%), 124 (10%), 110 (80%), 109 (54%), 96 (10%), 95 (60%), 82 (26%), 81 (100%) amu.

(-)-3-Isothujone[17][(-)-(1R,4R,5S)-1-isopropyl-exo-4-methylbicyclo[3.1.0]hexan-3-one (3): A solution of 1.5 g (9.7 mmol) of pure (-)-3-neoisothujanol[27] in 25 mL of acetone at 0°C was treated with 3 mL of Jones reagent while being magnetically stirred. After 5 min of continued stirring, the solution was diluted with 150 mL of water, and the product was extracted with ether (2 x 50 mL). The dried ($MgSO_4$) ether extract was concentrated on a rotary evaporator to give 1.2 g (78%) of ketone 3 of >96% purity as determined by GC on column B. It had $[\alpha]_D^{20}$ = -18.4° (neat) [Lit.[2] $[\alpha]_D$ = -19.94° (neat) for 100% e.e.]; UV; ε_{288}^{max} = 32 (methanol), ε_{298}^{max} = 27 (isooctane); CD in Fig. 5 and Table 3; IR (film) ν: 1738 cm^{-1}; ^1H-NMR (360 MHz) δ: 0.13 (dd, H_{6n}), 0.76 (ddd, H_{6x}, $J_{6x,1}$ = 8.2 Hz, $J_{6x,6n}$ = 5.8 Hz, $J_{6x,4x}$ = 2.5 Hz), 0.95 (d, CH_3, J = 6.7 Hz), 1.01 (d, CH_3, J = 6.7 Hz), 1.09 (dd, H_1, $J_{1,6x}$ = 8.9 Hz, $J_{1,6n}$ = 4.5 Hz), 1.16 (d, α-CH_3, J = 7.5 Hz), 1.36 (sept., H_7, J = 6.3 Hz), 2.22 (dq, H_{2n}, J_{2n,CH_3} = 7.5 Hz, $J_{2n,4n}$ = 1.0 Hz), 2.07 (dd, H_{4n}, $J_{4n,4x}$ = 19.0 Hz, $J_{4n,2n}$ = 1.0 Hz), 2.55 (ddd, H_{4x}, $J_{4x,4n}$= 19.0 Hz, $J_{4x,6x}$ = 2.5 Hz, $J_{4x,1}$ = 1.4 Hz) ppm; ^{13}C-NMR δ: 17.99 (α-CH_3), 18.58 (C_6), 19.51 (CH_3), 19.81 (CH_3), 25.56 (C_1), 29.46 (C_5), 32.74 (C_7), 39.46 (C_4), 47.13 (C_2), 220.76 (C_3) ppm; mass spectrum, m/z (rel. intens.): 152 [$M^{+\cdot}$] (7%), 124 (9%) 110 (68%), 109 (43%), 95 (45%), 82 (25%), 81 (100%) amu.

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