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THE OCTANT RULE. XIV.[1] SYNTHESIS AND CIRCULAR DICHROISM OF α-exo and endo-DEUTERIOBICYCLO[3.2.1]OCTAN-3-ONE AND 6,6-DIMETHYBICYCLO[3.1.1]HEPTAN-3-ONE

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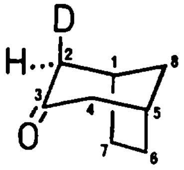
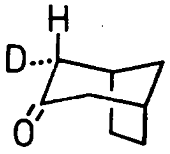
Abstract - (1R,5S)-2S-Deuteriobicyclo[3.2.1]octan-3-one (1) and (1R,5S)-2R-Deuteriobicyclo[3.2.1]octan-3-one (2), prepared by diazomethane ring enlargement of (1S,4R)-2(exo)-deuteriobicyclo-[2.2.1]heptan-2-one and (1S,4R)-2(endo)-deuteriobicyclo[2.2.1]-heptan-2-one respectively, both gave (-) n-π* circular dichroism (CD) Cotton effects, $\Delta\varepsilon_{294}^{max}$ = -0.05 and $\Delta\varepsilon_{294}^{max}$=-0.1, respectively, in hydrocarbon solvent. (1S,5R)-2S-Deuterio-6,6-dimethyl-bicyclo[3.1.1]heptan-3-one (3) and (1S,5R)-2R-deuterio-6,6-dimethylbicyclo[3.1.1]heptan-3-one (4), prepared from (-) myrtenal, both exhibited extraordinary vibrational fine structure for the n-π* CD transitions observed in hydrocarbon solvent and oppositely-signed CEs, $\Delta\varepsilon_{282}^{max}$ = -0.01 and $\Delta\varepsilon_{279}^{max}$ = +0.01 respectively in CF_3CH_2OH solvent.

Considerable recent attention has been drawn to circular dichroism (CD) due to isotopic substitution.[2] In particular, deuterium has been widely studied as an octant[3] perturber of the ketone carbonyl n-π* transition, with the observations that it generally makes a reversed-octant (or dissignate[4]) contribution.[2,5] These studies, especially those with conformationally immobile ketones, led to the determination of both signs and magnitudes of the perturber's contribution to the CD Cotton effect (CE) for deuterium in the axial and equatorial configurations at the α and β positions of chair cyclohexanone. And those data, when applied to conformationally mobile systems, led to interesting stereochemical conclusions regarding the preferred configuration of deuterium (vs H). For example, deuterium prefers the more sterically crowded axial configuration in 3-deuteriocyclohexanone.[2,6] Although deuterium is generally a dissignate octant perturber, the most notable exception to this trend is the consignate[4] contribution of an α-equatorial deuterium,[2,7] which is located close to an octant nodal plane, a region of sign change.[3,5] In order to explore this behavior, we prepared four α-deuterioketones (1 - 4) with the deuterium configuration ranging from quasi-equatorial (2) to bisected (3 and 4) to quasi-axial (1) and report on their CD behavior in this work.



1



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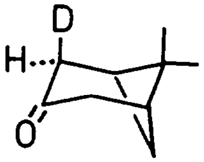

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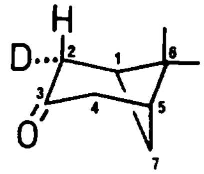
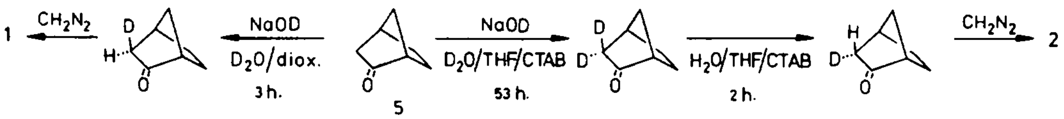


4

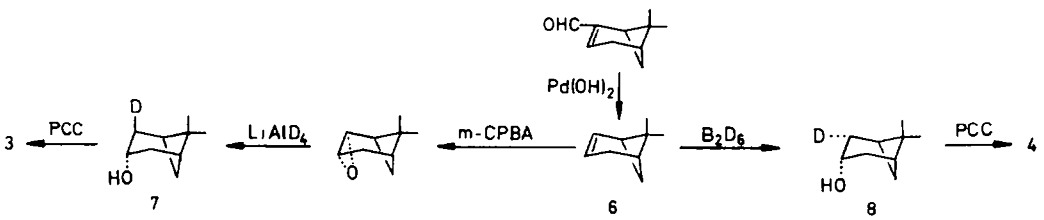
Syntheses. The syntheses of ketones 1 and 2 (Scheme 1) depend on the stereospecific introduction of deuterium (or its removal) from the α-exo position of norcamphor (5). The rate factor for exo vs endo exchange has been determined to be very large: k_{exo}/k_{endo} = 650[8a] or 715.[8b] Thus ketone 1 was prepared from (5) of known absolute configuration and enantiomeric excess (e.e.) by stereospecific base-catalyzed exchange of the exo-hydrogen for deuterium,[8a] then ring expansion with diazomethane. Similarly, ketone 2 was synthesized from 5 by (1) α,α-dideuteration using more forcing base-catalyzed exchange, then (2) stereospecific back exchange of the exo deuterium for hydrogen[5] followed by (3) ring expansion with diazomethane. Diazomethane ring expansion in both instances led to formation of isomeric bicyclo[3.2.1]octan-2-ones as well as over expansion.[9] However, the desired ketones (1 and 2) could be separated cleanly by preparative GC.

SCHEME 1



Deuterio-isonopinones 3 and 4 were prepared (Scheme 2) from a common intermediate, apopinene (6), which was obtained via $Pd(OH)_2$-catalyzed decarbonylation of myrtenal.[9] Their syntheses depend on the well-known, highly stereoselective reactions at the C=C face opposite to the gem-dimethyl bridge.[10,11] Thus, 6 gave exclusively the α-epoxide upon treatment with m-chloroperbenzoic acid,[11a] and the epoxide was opened stereospecifically[10b] with $LiAlD_4$ to give alcohol 7 with deuterium syn to the gem-dimethyl bridge. Oxidation of 7 with pyridinium chlorochromate gave 3. Ketone 4 was prepared from 6 first by stereospecific[9] deuterioboration (B_2D_6) to give alcohol 8 with deuterium anti to the gem-dimethyl bridge, then by oxidation of 8 with pyridinium chlorochromate.

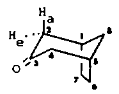
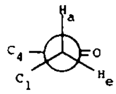
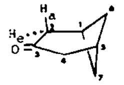
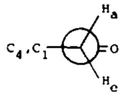
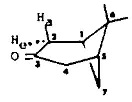
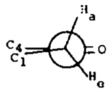
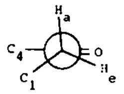
SCHEME 2



Molecular Geometry. In earlier work on conformational analysis of the bicyclo[3.2.1]octan-3-one system,[12] we used molecular mechanics (MM2)[13] calculations to provide an insight into cyclohexanone ring deformation from ideal chair geometry, with cyclohexanone and 4-tert-butylcyclohexanone as references. MM2 calculations predict an $H_e-C_\alpha-C=O$ torsion angle of ~9° and and $H_a-C_\alpha-C=O$ torsion angle of ~108°

for chair cyclohexanone and 4-*tert*-butylcyclohexanone. With more ring flattening near the C=O group of bicyclo[3.2.1]octan-3-one due to the anti-reflex action of the C_6-C_7 belt that pinches C_1 and C_5 together, the corresponding H_e-C_α-C=O torsion angle (~20°) is enlarged and the H_a-C_α-C=O torsion angle (~96°) is reduced. These findings and those for the even more severely pinched bicyclo[3.1.1]heptan-3-one system are given in Table 1. The data indicate a tendency toward ring flattening near the carbonyl group as C_1 and C_5 are brought closer together with two then one carbon chains. The consequence of this flattening is to open the H_e-C_α-C=O angle and close the H_a-C_α-C=O angle relative to those of chair cyclohexanone. Thus, the equatorial and axial positions begin to lose their distinction as they progress to the bisected geometry ($\beta = -\beta'$) of bicyclo[3.1.1]heptan-3-one, for which MM2 calculations predict (Table 1) a sofa conformation with carbons 1,2,3,4,5 lying nearly in a plane. Introduction of the gem-dimethyl group at C-6 causes only a slight deviation of the flattening calculated for the parent ketone, with a tilting of the C=O group away from C_6.[14] Thus, the deuterium atom of 3 departs significantly ($\beta' \cong 60°$) from the axial configuration and assumes a nearly bisected configuration, but that of 1 departs only slightly ($\beta' \cong -96°$). On the other hand, the erstwhile equatorial deuterium of 2 deviates significantly ($\beta \cong -20°$) from the equatorial configuration and in 4 assumes a nearly bisected configuration ($\beta \cong -57°$).

TABLE 1. Comparison of Selected Internal and Torsion Angles Calculated for Energy-Minimized Structures of Bicyclo[3.2.1]octan-3-ones[a] (1) and (2), 6,6-Dimethylbicyclo[3.1.1]heptan-3-ones (3) and (4), Bicyclo[3.1.1]heptan-3-one and Cyclohexanone[b,c] as obtained from MM2[d] Molecular Mechanics Calculations.

Structure	Newman Projection From C_α to C(=O)	Torsion Angle, deg.					Internal Angle, deg.	
		β	β'	(2,3)				
		H_e-C_α-C_3=O	H_a-C_α-C_3=O	C_1-C_2-C_3-C_4	C_2-C_1-C_n-C_5		C_1-C_n-C_5	C_2-C_3-C_4
		-20.43	96.40	39.39	72.30	(n=8)	100.4	116.1
		-58.73	58.92	0.177	82.69	(n=6)	85.96	117.6
		-57.07	59.97	2.81	80.87	(n=6)	85.29	117.6
		-8.91	108.2	51.48	57.51	(n=6)	110.9	115.4

[a] The molecular geometry calculated by MM2 has been confirmed by a determination and Karplus type analysis of the vicinal coupling constants $J_{H_1,H_{2a}}$ and $J_{H_1,H_{2e}}$ obtained from 360 MHz NMR (ref. 12).

[b] Arbitrary numbering system for cyclohexanone to conform to bicyclic numbering.

[c] The relevant torsion angles of 4-*tert*-butylcyclohexanone are very nearly the same as those of cyclohexanone (ref. 12).

[d] See ref. 12. Limited certainty begins with the fourth significant figure.

Circular Dichroism. Both bicyclo[3.2.1]octan-3-one and bicyclo[3.1.1]heptan-3-one are symmetric (C_s) compounds, as confirmed in our MM2 calculations, and substitution of hydrogen by deuterium is not expected to lead to skeletal distortions from this symmetry. Consequently, the deuterium atom of 1 - 4 can be viewed as the lone dissymmetric perturber (in the otherwise symmetric and achiral ketones); hence, it controls the sign and magnitude of the CD CE. Viewed as an octant perturber,[2,3,5] deuterium is weighed against hydrogen in a nearly equivalent site found by reflection across a carbonyl local symmetry derived octant surface.[3,5] The CD spectra of 1 and 3 (Fig. 1) show (-) CEs for both, indicating that the quasi-axial deuterium in an upper left or lower right back octant[2,3] makes a reversed octant or dissignate[4] contribution. Thus, as the D_a-C_α-C=O (β', Table 1) torsion angle closes from 108° of, e.g. 2S(e)-deuterio-4R-isopropylcyclohexanone ($\Delta\varepsilon_{298}^{max}$ -0.09),[7a] to 96° of 1 ($\Delta\varepsilon_{298}^{max}$ -0.05) to 60° of 3 ($\Delta\varepsilon_{282}^{max}$ -0.01) an α deuterium remains a dissignate perturber, although with a reduced magnitude for the smallest torsion angle (Table 2).

FIGURE 1

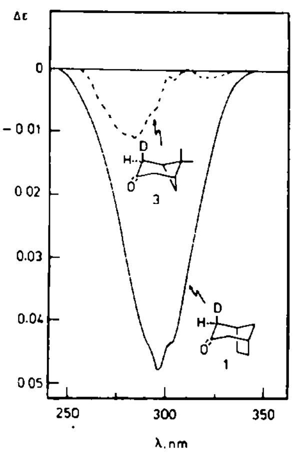


FIG. 1. Circular dichroism of 0.01 M 1 and 3 at 23°C in CF_3CH_2OH, corrected to 100% e.e. and d_1.

FIGURE 2

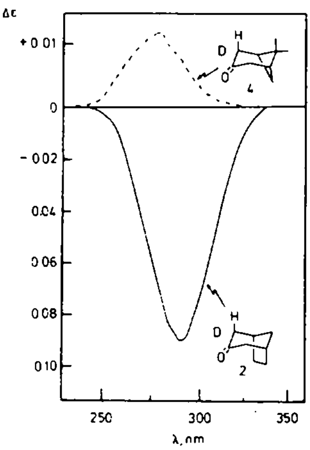


FIG. 2. Circular dichroism of 0.01 M 2 and 4 at 23°C in CF_3CH_2OH, corrected to 100% e.e. and d_1.

FIGURE 3

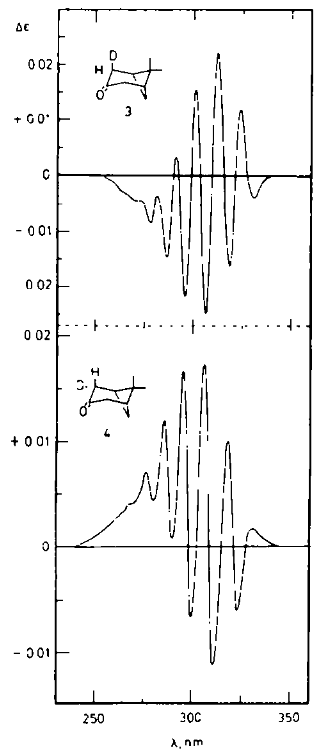
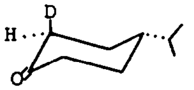
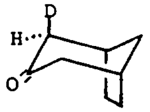
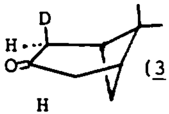
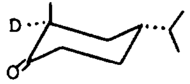
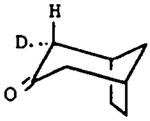
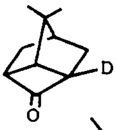
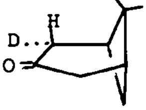


FIG. 3. (far right) Circular dichroism of 3 and 4 in n-heptane at 24°C, corrected to 100% e.e. and d_1.

The CD spectra of the erstwhile α-equatorial deuterioketones (Fig. 2) show a (-) CE for 2 and a (+) CE for 4. Thus, as the D_e-C_α-C=O torsion angle (β', Table 1) opens from ~9° of, e.g. 2R(e)-deuterio-4R-isopropylcyclohexanone ($\Delta\varepsilon_{299}^{max}$ -0.009),[7b] to ~20° of 2 ($\Delta\varepsilon_{290}^{max}$ -0.04) to 57° of 4 ($\Delta\varepsilon_{279}^{max}$ +0.01), deuterium moves from equatorial to quasi-equatorial and changes from a consignate to a dissignate perturber at large torsion angles. Since the deuterium of 4 assumes a nearly mirror image location relative to that of 3 (β ≈ -β', Table 1) it is not surprising that the CEs are of opposite sign and nearly equal magnitude. Data for a torsion angle (β'=37°) intermediate between that of 2 and 4 can be found in (1R,6S)-3(S)-deuterio-6,7,7-trimethyltricyclo[3.2.1.0^{6,7}]octan-4-one[15] (Table 2), whose lone dissymmetric (deuterium) perturber makes a dissignate contribution. Therefore, it would appear that an "equatorial" deuterium is a consignate perturber up to β' angles of between 20 and 37° where it becomes a dissignate perturber. The reason for this is not yet clear.

Deuteriated isonopinones 3 and 4 give nearly mirror image CD curves, which exhibit tremendous vibrational fine structure in hydrocarbon solvents (Fig. 3) and which are also nearly insensitive to temperature lowering. (The well-structured curves of Fig. 3 collapse to the typical bell-shaped curves of Figs. 1 and 2 when 3 and 4 are run in trifluoroethanol solvent.) Similar but less developed fine structure has been found previously, e.g. with the epimeric pinanones,[16] and very similar fine structure was observed with spiro-2-cyclopropane-isopinanone.[17] The CD curves with rotatory strengths of mixed sign in the vibrational substructure of a single electronic transition, represent almost perfect examples where the rotatory strength originates from second order (vibrational) contributions. In Fig. 3 (top) a (+) "allowed" vibrational progression of the 1200 cm^{-1} C=O stretch in the n-π* excited state based on a totally symmetric mode is superimposed on a (-) combination that takes it origin in odd quanta of a nontotally symmetric mode and quanta of a totally symmetric mode. In Fig. 3 (bottom) the "allowed" and "forbidden" vibrational progressions are of opposite sign, as one would expect from molecules of essentially mirror images types ($\beta = -\beta'$, Table 1). The origin of vibrational structuring in electronic CD transitions has been explained by Weigang,[18] and our results show that overlapping bands of mixed sign may originate from factors other than conformational and solvational effects.[12,19,20]

TABLE 2. n-π* Reduced Rotatory Strengths [R] and β,β' Torsion Angles for D-C_α-C=O of α-Deuterioketones.

Compound	Torsion Angle, deg.[a]			
	β	β'	[R][b]	Dissignate/Consignate[c]
 [d]	108	--	-0.25[e]	Dis.
 (1)	96	--	-0.14[f]	Dis.
 (3)	60	--	-0.029[g]	Dis.
 [d]	--	- 9	-0.03[h]	Cons.
 (2)	--	-20	-0.29[i]	Cons.
 [i]	--	-37	+0.078[j]	Dis.
 (4)	--	-57	+0.037[j]	Dis.

[a] See Table 1, here torsion angles $\beta = D_a-C_\alpha-C=O$ and $\beta' = D_e-C_\alpha-C=O$; [b] [R]=rotatory strength x 1.08 x 10^{-40}; corrected to 100% e.e. and 100% d_1 and measured at 25°C; [c] Definition in ref. 4; [d] Values from ref. 6; [e] Measured in isooctane solvent; the value in EPA (-0.3) is thought to be too low due to H exchange for D occurring during isolation (ref. 7a); [f] Measured in EPA solvent; [g] Measured in CF_3CH_2OH solvent; [h] Measured in isooctane solvent; [i] Value from ref. 15; [j] Measured in CF_3CH_2OH solvent.

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 unless otherwise indicated on a Perkin-Elmer R-24B or JEOL FX-100 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. All melting points are uncorrected and were determined on a Thomas-Hoover capillary apparatus. 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% FFAP (column B) stationary phases absorbed on 80/100 Chromosorb W AW, DMCS. Preparative gas chromatography (GC) was achieved on a 5 ft x 3/8 in diam. column (12% of QF-1 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): n-heptane, methanol, trifluoroethanol, chloroform, 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_2 and stored over 4A molecular sieves (Linde). Column chromatography was accomplished on Florisil (Floridin Co.).

(+)-(1S,4R)-exo-3S-Deuteriobicyclo[2.2.1]heptan-2-one:[8a] A solution of 2.4 g of (+)-(1S,4R)-bicyclo[2.2.1]heptan-2-one[21] (5) $[\alpha]_D$ +13.9° (c 2.76, $CHCl_3$), 44% e.e. [Lit[22] -28.7° (c 2.2, $CHCl_3$) for 100% e.e.], in 10 mL of p-dioxane was stirred at 25°C for 3 h with 4.3 mL of 0.35 N aqueous NaOD. After neutralization with 1.5 mL of 2 N aqueous HCl and evaporation of the dried ($MgSO_4$) ether extract, 1.2 g (50%) of deuterated ketone, m.p. 92-94°C, was obtained with 88% d_1, 12% d_0 by mass spectrometry.

(-)-(1S,4R)-2S(a)-Deuteriobicyclo[3.2.1]octan-3-one (1): To deuterated norcamphor from above (628 mg, 5.7 mmol) in 30 mL of ether and 50 mL of CH_3OH at 0°C was added 100 mL of 0.4 M ethereal diazomethane (40 mmol), and the solution was placed in a freezer at -25°C for 30h. Further reaction does not increase yield.[9] Solvents were removed by careful distillation to a volume of 1 mL. Four major products were found as detected by analytical GC on column A: 20% of 1, 20% of its isomer, 4-deuteriobicyclo[3.2.1]octan-2-one, and their higher homologs.[9] The desired ketone (1) had a shorter retention time than its 4-deuterio-2-keto isomer and higher homologs. It was isolated in >99% purity by preparative GC and had: $[\alpha]^{25}_{365}$ -14.8° (c 0.13, MI); CD: $[R]_{293}$ = -0.14 (EPA), $[R]_{294}$ = -0.17 (MI) (values corrected to 100% e.e. and 100% d_1); IR (CCl_4) ν: 2940, 2870, 2240, 1703 cm^{-1}; ^1H-NMR δ: 1.51 (2H, m), 1.78 (4H, m), 2.30 (1H, m), 2.40 (1H, m), 2.53 (3H, m) ppm; MS m/z (rel. intens.): 125[$M^{+\cdot}$] (6.2%), 124 (1.5%) amu, corresponding to 80% d_1, 20% d_0. Some back exchange of hydrogen for deuterium occurs during the preparative GC.[7a]

(1S,4R)-endo-3R-Deuteriobicyclo[2.2.1]heptan-2-one: A solution of 1 g of ketone (5) (53% e.e.) in 20 mL of THF was stirred at room temperature for 8 h with 4 mL of 1 N aqueous NaOD in D_2O and ca. 10 mg of cetyltrimethylammonium bromide (CTAB) (phase transfer catalyst).[5] The aqueous NaOD was removed and 4 mL of fresh 1 N aqueous NaOD in D_2O was added along with ca. 10 mg of CTAB, and stirring was continued for 45 h more. Ether was added, and the ether extracts (3 x 50 mL) were washed with sat. aqueous NH_4Cl and dried (Na_2SO_4). The ether was carefully distilled affording 0.85 g of optically active dideuterated ketone, mp 92-94°, 100% d_2 by mass spectrometry. The exo-deuterium was selectively back exchanged[5] in the following. A solution of 850 mg of dideuterionorcamphor in 15 mL of THF was stirred vigorously with 4 mL of 1 N aqueous NaOH and a catalytic amount of cetyltrimethylammonium bromide (CTAB) for 2 h.[8a] The mixture was shaken with 100 mL of pentane and 50 mL of brine. After separation, the aqueous layer was extracted with pentane (2 x 70 mL), and the combined organic layers were washed with aq. sat. NH_4Cl solution then dried ($MgSO_4$). The solvent was evaporated to give 800 mg of the endo-deuterionorcamphor, mp 92-94°, 94% d_1 by mass spectrometry.

(-)-(1S,4R)-2R(e)-Deuteriobicyclo[3.2.1]octan-3-one (2): At 5°C, 1 g (9 mmol) of the endo-deuterionorcamphor from above in 30 mL of absolute ethanol was treated with 1.2 equivalents of ethereal diazomethane.[9] When the yellow color had faded nearly, another aliquot was added to the solution, while maintaining the temperature at 5°C. After the third addition, the solvents were removed to afford a solid residue containing 5 major components as found by analytical GC on column A. Purification by preparative GC gave 20% of the desired ketone (2), 20% of its isomer, 4-deuteriobicyclo[3.2.1]octan-2-one and the remainder higher boiling homologs. Ketone 2 had CD: $[R]_{289}$ = -0.29 (CH_3OH), $[R]_{294}$ = -0.30 (n-heptane) (values corrected to 100% e.e. and 100% d_1); IR (CCl_4) ν: 2940, 2870, 1715 cm^{-1}; ^1H-NMR δ: 1.50 (2H, m), 1.80 (4H, m), 2.30 (1H, m), 2.40 (1H, m), 2.50 (3H, m), ppm; MS m/z (rel. intens.): 125[$M^{+\cdot}$] (6.1%), 124 (1.8%) amu for 77% d_1. Some back exchange of deuterium occurs during the preparative GC.

(1S,5R)-6,6-Dimethylbicyclo[3.1.1]hept-2-ene (6):[10a] A slurry of 8 g (53 mmol) of (-)-myrtenal (Aldrich), $[\alpha]_D$ -15° (neat) 100% e.e. and 1 g of freshly made palladium hydroxide on barium sulfate was heated slightly above 140°C with magnetic stirring for 1.5 h. A Dean-Stark trap collected 6 mL (83%) of the desired apopinene (6). Its purity was determined to be 95% GC. It had IR (neat) ν: 3020, 2940, 2810, 1615, 710, 680 cm^{-1}.

(-)-Apopinene epoxide:[11a] A magnetically stirred solution of 1.4 g (11.5 mmol) of apopinene from above in 50 mL of CH_2Cl_2 at room temperature in 100 mL round-bottom flask equipped with condenser was treated portion-wise with 3.5 g (20 mmol) of 85% m-chloroperoxybenzoic acid (Aldrich). Exothermic activity and reflux occurred near the end of the addition. The solution was stirred for 14 h. The white floating solid (m-chlorobenzoic acid) was removed by filtration and was washed with 20 mL of pentane. After drying ($MgSO_4$) the combined CH_2Cl_2-pentane solution was concentrated to afforded 1.4 g (88% yield) of oily epoxide, which was 95% pure by analytical GC on column B. The epoxide had $[\alpha]_D^{25}$ -49.5° (c 3.0 ethanol); IR (neat) ν: 2980, 2910, 2870, 860, 800 cm^{-1}; ^1H-NMR δ: 0.90 (3H, s), 1.21 (3H, s), 1.5-2.3 (6H, m), 3.2 (2H, m) ppm; MS m/z (rel. intens.): 138 [$M^{+\cdot}$] (4%), 123 (31%), 105 (21%), 95 (76%), 94 (49%), 67 (100%) amu.

(1S,5R)-2S(a)-Deuterio-6,6-dimethylbicyclo[3.1.1]heptan-3(S)-ol:[10a,11b] A solution of 1.2 g (9.1 mmol) of apopinene epoxide from above in 5 mL of dry THF was added dropwise under a N_2 atmosphere via syringe to a magnetically stirred slurry of 0.35 g (8.3 mmol) of $LiAlD_4$ in 40 mL of cyclohexane and 10 mL of dry THF. Since GC analysis on column A showed only 50% reaction after 12 h of heating at reflux, more LiAlD (0.31 g, 7.4 mmol) was added and heating was continued for an additonal 13 h. The reaction was quenched with wet ether and water sequentially. The organic layer was collected, dried ($MgSO_4$) and concentrated to afford the crude trans-deuterio alcohol as 60% of a three component mixture (GC, column A). The crude product was oxidized directly in the following step.

(-)-(1S,5R)-2S(a)-Deuterio-6,6-dimethylbicyclo[3.1.1]heptane-3-one (3):[10] A magnetically stirred slurry of 1.0 g (7.1 mmol) of crude trans-deuterio-alcohol from above, 100 mg of anhydrous sodium acetate and 100 mL of dry CH_2Cl_2 was treated at room temperature with 4.5 g (33 mmol) of pyridinium chlorochromate.[23] After 2 h of stirring, 50 mL of pentane was added to precipitate the chromium salts. The supernatant was decanted and passed through a short (1 in. diam x 5 in. length) column of Florisil using pentane (ca. 50 mL) as the eluent. The solution was concentrated to afford a viscous residue, which was purified by preparative GC equipped with a silanized glass injection port to minimize exchange of deuterium for hydrogen. Pure 3 was obtained as a clear glassy solid, m.p. ~30°C. It had $[\alpha]_D^{25}$ -7.2° (c 0.86, $CHCl_3$); UV: ε_{290}^{max} 15 (n-heptane), ε_{290}^{max} 21 ($CHCl_3$), ε_{290}^{max} 17 (CH_3OH), ε_{282}^{max} 12 (trifluoroethanol); CD: $[R]_{282}$ -0.029 (trifluoroethanol); IR (CCl_4) ν: 2900, 1710 cm^{-1}; ^1H-NMR (360 MHz) δ: 0.88 (3H, s), 1.16 (H, d, J=10.6 Hz), 1.33 (3H, s), 2.12 (2H, d, J=6 Hz), 2.48 (1H, s), 2.48 (1H, d, J=19 Hz), 2.58 (1H, d, J=10.6 Hz), 2.67 (1H, d, J=19 Hz) ppm; ^{13}C-NMR δ: 19.94 (q, C_9), 25.91 (q, C_8), 32.11 (t, C_7), 37.67 (d, C_1, C_5), 38.54 (s, C_6), 44.1 (m, C_2), 44.45 (t, C_4), 211.13 (s, C_3) ppm; MS m/z (rel. intens.): 139 [$M^{+\cdot}$] (15.5%), 138 (0%), 71 (98%) amu.

(1S,5R)-endo-2R-Deuterio-6,6-dimethylbicyclo[3.1.1]heptan-endo-3(S)-ol:[10b] A magnetically stirred slurry of 1.0 g (8.1 mmol) of apopinene (above) and 0.11 g (3.0 mmol) of $NaBD_4$ in 10 mL of dry THF under argon at 0°C was treated dropwise with a solution of 0.55 mL (4.0 mmol) of BF_3 etherate in 5 mL of dry THF. The reaction mixture was stirred for 18 h at room temperature. The reaction was quenched by dropwise addition of 2 mL of wet ether and then 2 mL of H_2O. The resultant organoborane was oxidized by adding 2 mL of 3N aqueous NaOH and 2 mL of aqueous H_2O_2. This mixture was stirred 12 h and extracted with ether (3x50 mL). The dried ($MgSO_4$) ether layer was concentrated to give 1.1 g of crude liquid deuterio alcohol that was 85% pure by GC on column A. The alcohol was used directly in the next step.

(+)-(1S,5R)-2R(e)-Deuterio-6,6-dimethylbicyclo[3.1.1]heptan-3-one (4):[10] A magnetically stirred solution of 800 mg (5.7 mmol) of cis deuterio alcohol from above in 200 mL of CH_2Cl_2 was treated at room temperature with 6.6 g (22.7 mmol) of pyridinium chlorochromate[23] and was stirred for 2.75 h. Dry ether (100 mL) was added to precipitate chromium salts. The solution was decanted and washed briefly with 20 mL of 2 N aqueous HCl then with 10 mL of brine. The dried ($MgSO_4$) solution was concentrated to give a viscous residue, which was dissolved in a minimum amount of acetone then purified by preparative GC equipped with a silanized glass injection port to minimize exchange of deuterium for hydrogen. Ketone 4 was obtained as glassy solid, m.p. ~30°C. It had $[\alpha]_D^{25}$ +7.6° and $[\alpha]_{365}^{25}$ +27° (c 0.17, trifluorethanol); UV: ε_{294}^{max} 13 (n-heptane); CD: $[R]_{279}$ +0.037 (trifluorethanol); IR (CCl_4) δ: 2920, 2150, 1715 cm^{-1}; ^1H-NMR (360 MHz) ν: 0.88 (3H, s), 1.16 (1H, d, J=10.6 Hz), 1.33 (3H, s), 2.12 (2H, d, J=6Hz), 2.48 (1H, d, J=20 Hz), 2.58 (1H, d, J=10.6 Hz), 2.67 (1H, s), 2.67 (1H, d, J=20 Hz) ppm; ^{13}C-NMR δ: 19.94 (q, C_9), 25.91 (q, C_8), 32.11 (t, C_7), 36.67 (d, C_1, C_5), 38.54 (s, C_6), 44.04 (m, C_2), 44.45 (t, C_4) 211.30 (s, C_3) ppm; MS m/z (rel. intens.): 139 [$M^{+\cdot}$] (16%), 138 (0.3%) amu.

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