Tetrahedron Vol. 43, No. 21, pp. 4905 to 4916, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

THE OCTANT RULE. XX.[1] SYNTHESIS AND CIRCULAR DICHROISM OF (1S,5S)-DIMETHYLADAMANTAN-2-ONE -- PREDICTED TO HAVE ZERO COTTON EFFECT

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(*Received in UK* 6 *February* 1987)

Abstract - The title compound was synthesized in optically active form from adamantane. Although the methyl perturbers lie in the extended local symmetry planes of the carbonyl chromophore, and octant and quadrant rules therefore predict they should make no contributions to the Cotton effect (CE), weak negative CEs are found in cyclopentane ($\Delta\varepsilon_{293}^{max} = -0.03$) and in CF_3CH_2OH ($\Delta\varepsilon_{288}^{max} = -0.02$) solvents.

For more than 25 years, the octant rule of Djerassi et al.[2] (Fig. 1) has been the subject of considerable interest by both experimentalists and theorists and has enjoyed wide application in interpreting details of absolute configuration and conformation from the circular dichroism (CD) and optical rotatory dispersion spectra.[3] In its simplest form, the rule states that the space surrounding the carbonyl group in an optically active ketone is divided into eight regions by (a) the two symmetry planes (XZ and YZ) of the isolated (C_{2v}) chromophore, and (b) by a third, non-symmetry-derived plane (A) perpendicular to and bisecting the C=O bond. If these three planes are taken to define a Cartesian coordinate system, then the sign of the contribution made by an alkyl substituent to the observed circular dichroism (CD) of the $n \rightarrow \pi^*$ transition varies as the sign of the product X·Y·Z of the atomic coordinates. Atoms having counterparts symmetrically placed across the carbonyl symmetry planes and atoms lying in symmetry planes will exert no effect on the CD.

Dedicated to Professor Hans Wynberg on the occasion of his 65th birthday.

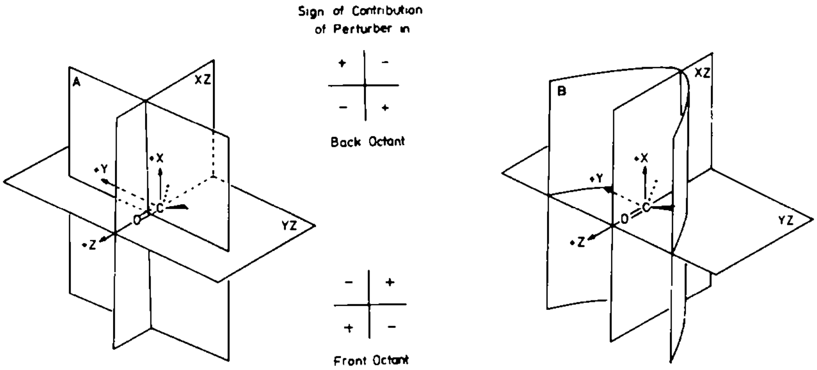


Figure 1. (Left) Classical octant rule diagram (ref 2) for the ketone carbonyl $n \to \pi^*$ transition. Local symmetry-derived, orthogonal octant planes XZ and YZ divide all space into quadrants, and a non-symmetry-derived third nodal surface (A) is approximated by an orthogonal plane bisecting the C=O bond. "Front" octants are those nearer an observer along the +Z axis, while "back" octants lie towards -Z. (Middle) Octant contribution signs that perturbers make in back and front octants. (Right) Revised octant rule (ref 7) with octant planes XZ and YZ unchanged and the third modal surface defined theoretically as a concave surface (B). Reprinted with permission from J. Am. Chem. Soc., 108, 4485 (1986). Copyright 1986 American Chemical Society.

This geometrical rule, so simple and straightforward to apply, has become invaluable for establishing the absolute configuration of a large number of compounds.[4] And since its conception, the octant rule for the ketone $n \to \pi^*$ transition has been probed and evaluated by theory and experiment. Quite early, Moffitt et al.[2b] recognized several potential problems in applying the rule, including the undefined shape of the third nodal surface (approximated as a plane) and the effect of unforeseen distortions from the "idealized" geometries typically employed. The former has generated considerable interest. Schellman[5] showed that a quadrant rule is the minimum sector rule for the carbonyl chromophore, where the quadrants are defined by the intersecting (local) symmetry planes (XZ and YZ, Fig. 1) which are coincident with the symmetry-determined nodal surfaces of the n and π^* orbitals. An octant rule was required to account for the behavior of alkyl perturbers lying in front of the carbonyl oxygen.[6] And the shape of the third octant surface was described by theory[7] and experiment[8] as concave and cutting behind the carbonyl carbon (B, Fig. 1) -- a surface which divides quadrant space into octant space and explains many previously noted "anti-octant" contributions of normal perturbers.

Problems with distortion from the "idealized" geometry have been less well recognized or investigated. In particular, it may be noted that the octant symmetry planes (XZ and YZ, Fig. 1) are derived from the local symmetry (C_{2v}) of the C=O chromophore and are therefore only approximations when the molecular symmetry does not coincide to the local symmetry of the chromophore. Thus, for chair cyclohexanone only the XZ octant plane coincides with both a C=O local symmetry plane and the molecular symmetry plane. In contrast, the YZ octant plane is no longer a molecular symmetry plane; thus, the C=O local symmetry begins to break down, and the surface YZ is only approximated by a plane. Similarly, for

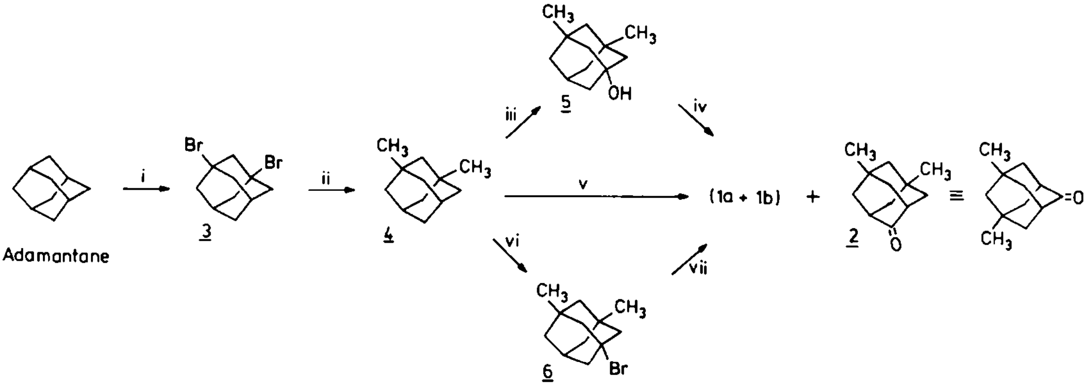
3(e)-methylcyclohexanone, which has no planes of symmetry (and therefore no molecular symmetry coincident with the local symmetry of the C=O group), the XZ octant surface is, strictly speaking, only approximately a plane. Distortion from planarity of the C=O local symmetry-derived octant surfaces (XZ and YZ, Fig. 1) attends all chiral molecules, but the octant rule works because most perturbers lie far from the octant "planes". When a perturber lies close to an octant surface, then "anomalous" behavior can be anticipated.[7]

In what follows we will describe such a situation. The target molecule is 1,5-dimethyladamantanone (1a or 1b, Fig. 2) a chiral molecule which has both methyl perturbers lying on octant planes (XZ and YZ, Fig. 1) and attached to a molecular framework (adamantanone) which possesses the "idealized" (C_{2v}) octant symmetry.

Figure 2. (Left) (1S,5S)-Dimethyladamantanone (1a). (Right) (1R,5R)-Dimethyladamantanone (1b). (Middle) Octant projection diagrams for 1a (left) and 1b (right).

Synthesis and Stereochemistry. 1,5-Dimethyladamantan-2-one is readily prepared, albeit in low yield, from adamantane in four steps as outlined in Scheme I.

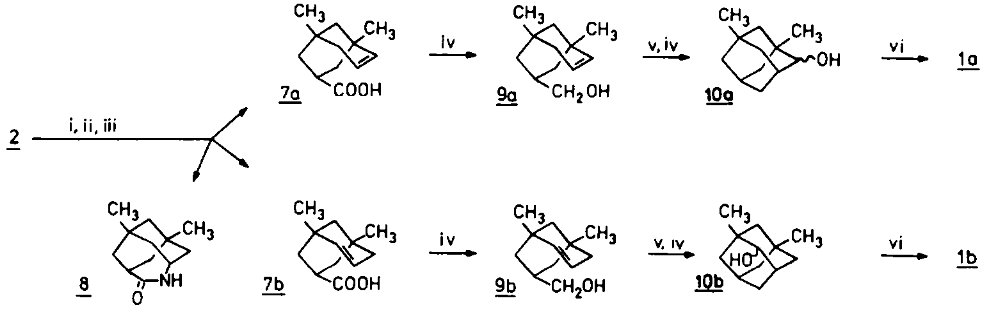
SCHEME I



(i) Br_2/Fe, 64%; (ii) $Me_2Zn/TiCl_4/CH_2Cl_2$, 78%; (iii) fuming H_2SO_4, 58%; (iv) conc. H_2SO_4/Δ 12.5-15% of 2, 5.3% of (1a + 1b), 12.5% of 4, 11% of 5; (v) conc. H_2SO_4/Δ, 7% of 1 + 2; (vi) Br_2/Δ, 85%; (vii) 1 equiv. Ag_2SO_4 in conc. H_2SO_4/Δ, 10% of 1 + 2.

Thus, adamantane brominates smoothly[9] to afford the known 1,3-dibromo derivative (3), which is converted in high yield to 1,3-dimethyladamantane (4) by application of the Reetz procedure.[10] The latter could be converted directly to racemic 1, *inter alia*, by heating in conc. H_2SO_4, according to Schleyer *et al.*[11] However, because we required optically active ketone and a resolution of the racemic mixture appeared problematic, we turned to the preparation of 1 from an achiral reaction by-product (2). The rationale for this interconversion is based on the elegant method of Wynberg et al[12] for the synthesis of optically active 4-deuterio-adamantan-2-ones and 4,4-dimethyladamantan-2-one. It involves ring opening of 2 to give a mixture of endo-1,5-dimethylbicyclo[3.3.1]non-6-ene-3-carboxylic acid enantiomers (7a and 7b, Scheme II). Since large quantities of 2 were required we sought for an optimal preparation of it from 4 and found it best to proceed via alcohol 5[13] according to the method of Farcasiu et al.[14] (Scheme I). An alternative method[15] via bromodimethyladamantane 6 proved less satisfactory.

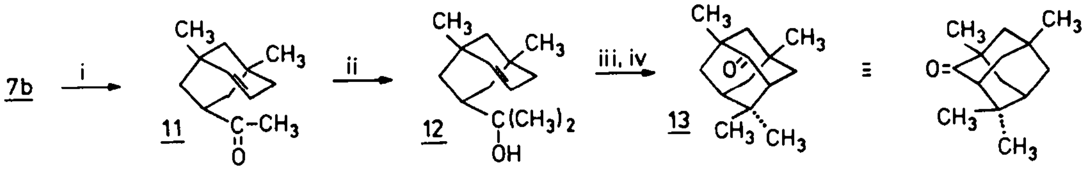
SCHEME II



(i) Anh. MeSO$_3$H, NaN$_3$; (ii) KOH/EtOH/Δ, 60% of 7a + 7b; (iii) resolution via quinine and cinchinodine salts; (iv) LiAlH$_4$/Et$_2$O; (v) 98% HCOOH/Δ; (vi) CrO$_3$/Me$_2$CO.

Conversion of achiral 5,7-dimethyladamantan-2-one (2) into optically active 1a and 1b was accomplished via the enantiomeric carboxylic acid derivatives 7a and 7b, as outlined in Scheme II. The synthesis of 7 from 2 has its analogy in reactions of the parent ketone, adamantanone, which has been shown to undergo an abnormal Schmidt reaction (e.g. as in step i) to give 4(e)-methanesulfonoxy-adamantan-2-one, which in turn gives (±)-endo-bicyclo[3.3.1]non-6-ene-3-carboxylic acid via a quasi-Favorskii reaction (e.g. as in step ii).[16] These reactions proceeded with 2, as expected, to afford 7 as well as the normal Schmidt product, 8. Although the parent (desmethyl) acid could be resolved easily with dehydroabietylamine,[3,12] this amine proved unsatisfactory for the resolution of 7. Rather, resolution of 7 was accomplished with quinine, giving (+)-acid (7b) as the most crystallizable salt, and (-)-acid (7a) (from the mother liquor) as the most crystallizable salt with cinchonidine. The (-)-acid had the larger magnitude rotation and was used in this work for the synthesis of 1a, first by reduction to 9a using LiAlH$_4$ then solvolytic ring closure to afford 10a, followed by Jones oxidation. The oily product, (-)-1 (assigned structure 1a) was identical to racemic material (Scheme I) in every measurement, except chiroptical.

SCHEME III



(i) MeLi, THF; (ii) MeLi, Et$_2$O, 12h; (iii) 98% HCOOH/Δ; (iv) LiAlH$_4$, Et$_2$O; (v) CrO$_3$/Me$_2$CO.

The absolute configuration of (<u>1a</u> or <u>1b</u>) of the ketone product [(−)-<u>1</u>] was determined in two ways. In the first, (+)-acid (<u>7b</u>) was converted to tetramethyladamantanone <u>13</u> as outlined in Scheme III. The reaction sequence has its analog in the synthesis of 4,4-dimethyladamantan-2-one (<u>14</u>, Fig. 3) by Wynberg *et al.*[12b] Since the angular methyl groups at C-1 and C-7 in <u>13</u> are predicted by the octant rule to make no contribution to the Cotton effect (CE), (they lie on octant symmetry planes), the gem-dimethyl perturbers at C-4 should determine its CE sign, which we find to be positive [$\Delta\varepsilon_{303}^{max}$ = +0.32, cyclopentane]. According to the octant rule, therefore, the absolute configuration of <u>13</u> is (1*R*), as drawn. Here, as in the parent (1*S*)-4,4-dimethyladamantan-2-one (<u>14</u>) [$\Delta\varepsilon_{303}^{max}$ = +0.61, isooctane] of Wynberg *et al*,[12b] the sign of the $n\rightarrow\pi^*$ CE is determined by the equatorial methyl group,[3,12b] which lies in an upper left or lower right back octant (Fig. 3). The absolute configuration and enantiomeric excess (e.e.) of <u>14</u> (77 ± 3% e.e.) and its precursors and derivatives have been established independently by NMR methods.[3,12b] So the assignments of absolute configuration for <u>13</u>, and thus <u>1a</u> and <u>1b</u> appear to be unambiguous. By comparing the magnitudes of the $\Delta\varepsilon$ values of <u>13</u> and <u>14</u>, we calculate an e.e. of ~40% for <u>13</u> and hence for its precursor acid (<u>7b</u>) with $[\alpha]_{589}^{20}$ = +8.2°.

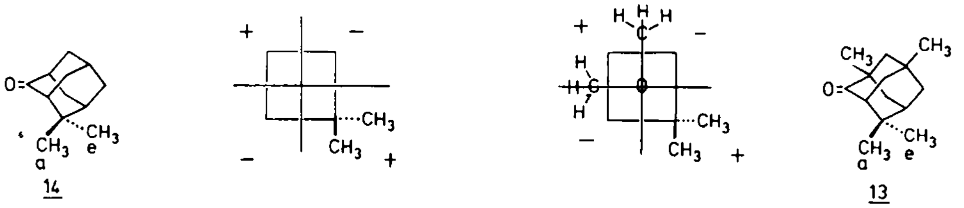
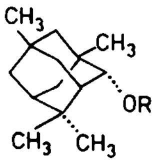


Figure 3. (Left) (1*S*)-4,4-Dimethyladamantan-2-one (<u>14</u>). (Right) (1*R*)-1,4,4,7-Tetramethyladamantan-2-one (<u>13</u>). (Middle) Octant projection diagram for <u>14</u> (left) and <u>13</u> (right).

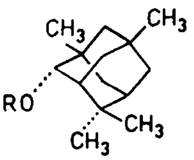
In the second, both the absolute configuration of <u>13</u> and its e.e. were determined from NMR[17] studies of the Mosher ester of its alcohol derivative. Steric hindrance guides the reduction of <u>13</u> by $LiAlH_4$ to give stereospecifically the product (<u>15b</u>) with the OH group *syn* to the axial CH_3 at C-4, as predicted on the basis of previously reported parallel studies of 4(a)-methyladamantan-2-one, which gives only <u>17</u> on reduction with $LiAlH_4$.[3] In that study the Mosher ester (<u>18</u>), formed by reaction of alcohol <u>17</u> with the acid chloride of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-(+)-MTPA],[18] was found to exhibit two ^{19}F-NMR signals for the diastereomeric CF_3 groups at δ 35.12 and δ 34.92 downfield from $CFCl_3$ internal standard, with the more shielded signal moving downfield faster upon the addition of $Eu(fod)_3$, as predicted[17] for <u>18b</u>. In the current study, racemic <u>16</u> (<u>16a</u> + <u>16b</u>) exhibited two equal intensity ^{19}F-NMR signals, one at δ 35.85, the other at δ 35.56, downfield from $CFCl_3$ internal standard; whereas, the ratio of these signals in the Mosher ester derived from <u>13</u>

gave the same two signals in the ratio 69:31, for the lower field:higher field resonances. These findings allow us to determine an e.e. of 38% for 13 and its precursor acid 7b, in good agreement with the e.e assigned above by CD. Addition of Eu(fod)$_3$ to the Mosher ester of racemic 15 or that derived from 13 caused the more deshielded resonance to move downfield faster, as predicted[17] for the assigned absolute configuration. We conclude, therefore, that the optically active acid precursor (7b) of 13 had an e.e. of 38% and that both 1a and its optically active precursor 7a ($[\alpha]_{589}^{20}$ -15.5°) have an e.e. of 72%.

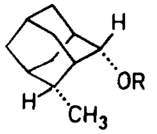


15a

R = H

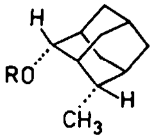


15b



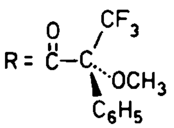
17a

R = H



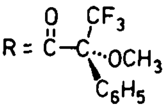
17b

16a



16b

18a



18b

Circular Dichroism Spectra. The circular dichroism (CD) spectra (Fig. 4) of 1a were run in cyclopentane and 2,2,2-trifluoroethanol (TFE) solvents. Although the octant rule predicts no $n \to \pi^*$ CD, the data clearly reveal a weak monosignate (-)-CE, with the expected vibrational fine structure in cyclopentane solvent. Since the CD spectrum of racemic 1 serves as the baseline, any observed CD for 1a must be due to uniquely to this optically active ketone. The CE remains (-) with an essentially invariant rotatory strength at -150° C in isopentane-methylcyclohexane and in EPA glasses. CEs are also observed between 180 and 210 nm, apparently due to overlapping (or mixed) σ-π^*, n-σ^* (n-3S) and π-π^* transitions.[4,20] The stereochemical significance of the far UV CD transitions is still under investigation.[4]

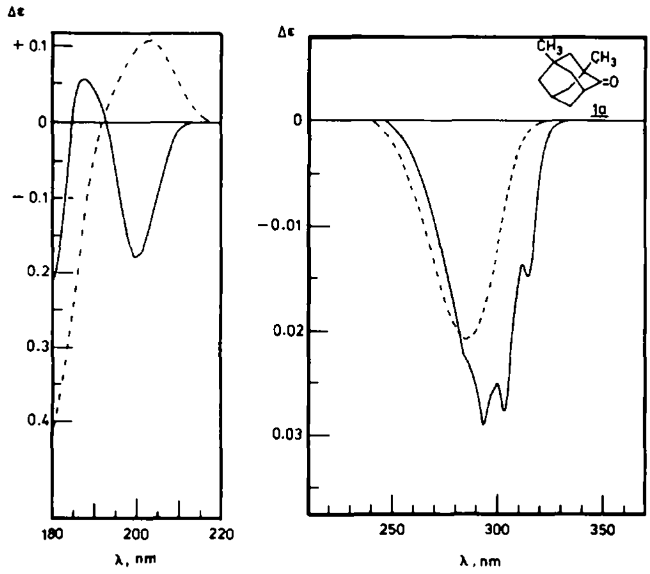


Figure 4. Circular dichroism spectra of 1a in cyclopentane (———) and 2,2,2-trifluoroethanol (- - - -) at 18°C, run on a JASCO J-600 instrument, with the Δε =0 baseline being the CD of racemic ketone. Sample concentrations are 0.03 - 0.04 M (1 cm cell pathlength) for the region 220 - 370 nm. Sample concentrations are 0.003 M (0.05 cm pathlength) for the region 180- 220 nm for 72% e.e. samples. Curves are smoothed for this region of the spectrum. All data are corrected to 100% e.e.

DISCUSSION

In order to explore possible ring skeletal distortions due to methyl substitution in 1, molecular mechanics calculations were run using the Allinger force-field (MM2). The calculations reveal (1) a broad energy minimum with no strong preference for ring skeletal distortion from the adamantanone C_{2v} symmetry and (2) staggered rotamers for the angular CH_3 groups. Consequently, all atoms of 1, be either on octant symmetry planes (XZ or YZ, Fig. 1), or they have mirror image counterparts across the symmetry planes. The CD data therefore appear to be real and attributable to the CH_3 substituents as opposed to other factors.

This apparent discrepancy with the predictions of the octant rule was anticipated ten years ago in a theoretical paper of Yeh and Richardson.[21] These authors provided an analysis and insight into how 1 and related adamantanones, e.g. 4(e),8(e),9(e)-trimethyladamantan-2-one, might be reconciled with the octant rule. They pointed out that the one electron perturbation model of $n \rightarrow \pi^*$ optical activity in chiral ketones, which provides the simplest and most direct rationalization for the octant rule, may be insufficient to account for optical activity when carried out only to first order. In first order perturbation only (additive) pairwise interactions between the C=O group and dissymmetric perturbers are considered, and in this sense the octant rule lacks qualitative completeness. When the one electron model is carried to higher order perturbation, multiplicative terms contribute to the $n \rightarrow \pi^*$ rotatory strength. Thus ketones such as 1, which in first order one electron perturbation theory are predicted (by the simple octant rule) to have zero optical activity, are in fact predicted to be optically active in second order perturbation, which accounts for three-way interactions among the two CH_3 perturbers and the C=O chromophore. Qualitatively, this means that each CH_3 group of 1 destroys a plane of symmetry in the C_{2v} C=O chromophore, hence an octant symmetry plane. Thus, the octant or quadrant symmetry planes are, except for molecules with C_{2v} symmetry, e.g. adamantanone, only approximately planes. The deviation from planarity will depend on the location and nature of the perturbation. And while such deviations are not important for more qualitative applications of the octant rule, they can in fact be detected and analyzed in molecules like 1.

Concluding Comments. (1*S*,5*S*)-Dimethyladamantan-2-one (1a) is observed to exhibit a weak ($\Delta\varepsilon \sim -0.02$) negative $n \rightarrow \pi^*$ CE; whereas, the symmetry-derived octant rule predicts $\Delta\varepsilon = 0$. The observation of a non-zero CE is in fact in accord with a breakdown in the extended local symmetry of the C=O group and the octant symmetry surfaces no longer being exactly the planes (XZ and YZ) of Fig. 1, and with second order perturbation theory. We observe that the CH_3 perturbers of 1a flank the sign-determining octant, but a fuller explanation of the CE awaits a detailed theoretical analysis.

EXPERIMENTAL

General: Circular dichroism (CD) spectra were recorded on a JASCO J-600 instrument, or 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 rotations were determined in 95% ethanol, 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 JEOL FX-100 or IBM NR80-AF instrument. Infrared (IR) spectra were measured on a Perkin-Elmer Model 599 instrument. All melting points are uncorrected and were determined on a Thomas-Hoover or Mel-Temp capillary apparatus. Combustion analyses were carried out by MicAnal, Tucson, AZ. Analytical gas chromatography (GC) was performed on a Varian-Aerograph model 2400 F/I instrument on 6 ft. x 1/8 in. diam. columns with the indicated stationary phases that were adsorbed on 80/100 Chromosorb W-AW-DMCS: column A (12% QF-1) and column B (20% FFAP). Column chromatography was accomplished on Baker silica gel, 60-200 mesh. Spectral data were obtained using spectral grade solvents (MCB): n-pentane, cyclopentane and 2,2,2-trifluoroethanol (TFE). Other solvents were distilled and dried before use: petroleum ether, pentane, 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). Quinine, $[\alpha]^{25}_{589}$ = -154° (c. 2) and cinchonidine, $[\alpha]^{25}_{589}$ = -109.2° (c. 1.5), and R-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid were from Aldrich.

1,3-Dibromoadamantane (3):[9] In a 1L round bottom flask were placed adamantane (Aldrich 99%) (54.4 g, 0.4 mol) and 100 mL of bromine (312 g, 1.96 moles). After cooling to 0°C, 1.5 g of iron powder (wetted with a few drops of water) were added carefully while stirring. A vigorous reaction occurred, with evolution of HBr. After 3 h at room temperature, the solid mass was dissolved in 200 mL of methylene chloride. The organic phase was washed successively with 10% aq. sodium bisulfite (until bromine disappearance), sat. aq. $NaHCO_3$, and sat. brine; then it was dried ($MgSO_4$). After solvent removal, recrystallization of the residue in ether-methanol gave 75.4 g (64%) of 1,3-dibromoadamantane (3) as colorless prisms, m.p. 110-115°C, [lit.[9] 112-113 °C]. A second crop of crystals, 16.0 g, m.p. 105-110°C consists probably of a mixture of mono and dibrominated adamantanes. It had IR (KBr) ν: 2970, 2940, 2880, 1460, 1350, 1325, 1300, 1250, 1030, 960, 830, 700 cm^{-1} and ^1H-NMR δ : 1.65 (2H, s), 2.25 (10H, s), 2.80 (2H, s) ppm.

1,3-Dimethyladamantane (4): This reaction was carried out under a nitrogen atmosphere until hydrolysis of the product. To 113 g (0.9 mol) of a 90% solution of dimethylzinc[22] in 100 mL of dichloromethane at -30° C, were added (by syringe) 10 mL (17.2 g, 0.10 mol) of $TiCl_4$. After 30 min, the dark orange solution of titanium reagent[10] was allowed to warm up to 5°C, then a solution of 69.0 g (0.23 mol) of 1,3-dibromoadamantane (3) in 100 mL of dichloromethane were added via a dropping funnel. The temperature was kept under 15 °C. After 3 h at 5°C, the mixture was poured over 300 g of ice, acidified with concentrated HCl, and extracted with 200 mL of methylene chloride. The organic phase was washed with 5% aq. $NaHCO_3$, sat. brine solution, then dried ($MgSO_4$). After removal of the solvent, distillation in a Claisen flask afforded 30.0 g (78%) of 1,3-dimethyladamantane (4) as a colorless oil, b.p. 90°C/15 mm. This material was identical with an authentic sample from Aldrich and had IR ν : 2900, 1460, 1380, 1360, 1350, 1175, 1110, 950 cm^{-1} and ^1H-NMR δ: 0.74 (6H, s), 1.07 (2H, s), 1.30 (8H, m), 1.45 (2H, m), 1.90 (2H, m) ppm.

3,5-Dimethyladamantane-1-ol (5): This alcohol was prepared by the method described by Moore.[13] 1,3-Dimethyladamantane (4) (12.0 g, 0.073 mol) was dissolved in 120 mL of fuming sulfuric acid (30% SO_3) at 0° C by vigourous stirring during 25 min to give a dark brown solution. The solution was poured immediately onto 1000 g of ice and extracted with ether. The ether solution was washed with 5% aq. $NaHCO_3$, sat brine sol., then dried (Na_2SO_4). After removal of the solvent, recrystallization of the residue in petroleum ether (b.p. 40-60°) gave 7.7 g (58%) of 3,5-dimethyladamantan-1-ol (5) as colorless needles m.p. 94-98°C [lit.[13] mp 97°]. It had IR (KBr) ν: 3300, 2900, 2840, 1450, 1350, 1320, 1190, 1060, 1030 cm^{-1} and ^1H-NMR δ: 0.86 (6H, s), 1.05 (2H, s), 1.20 (8H, m), 1.45 (3H, m), 2.08 (1H, m) ppm.

3,5-Dimethyl-1-bromoadamantane (6): A mixture of 3.6 g (22 mmol) of 1,3-dimethyladamantane (4) and 20 mL of bromine was maintained under reflux at 80°C during 5 h after which time the excess bromine was removed by distillation. The cooled residue was diluted with methylene chloride (80 mL), washed with 10% aq. sodium bisulfite, sat. $NaHCO_3$ sol., sat. brine sol. then dried ($MgSO_4$). After removal of the solvent, distillation of the residue afforded 4.52 g (85%) of 3,5-dimethyl-1-bromoadamantane (6) as a colorless oil, b.p. 95°C/0.45 mm [lit.[15] b.p. 67-69° C/0.03 mm]. It had IR (film) ν : 2940, 1460, 1330, 1180, 980, 940, 890, 825, 735, 670 cm^{-1} and ^1H-NMR δ : 0.85 (6H, s), 1.15 (2H, s), 1.40 (4H, br.s.), 1.95 (4H, br.s.), 2.13 (3H, s) ppm.

5,7-Dimethyladamantan-2-one (2) and (±)-1,5-dimethyladamantan-2-one (1a + 1b): A solution of 3,5-dimethyladamantan-1-ol (5) (19.1 g, 106 mmol) in 200 mL of 92% H_2SO_4 was kept at 30°C for 5 days. The dark brown solution was then poured onto 1500 g of ice, extracted with 2 x 200 mL of ether, washed successively with water, 5% aq. $NaHCO_3$, sat. aq. NaCl, then dried ($MgSO_4$). Removal of the solvent then distillation afforded 8.7 g of distillate, b.p. 50-80°C/0.5 mm and 4.3 g of pot residue. Chromatography of the distillate on a column of silica gel 40-140 mesh (ø = 4 cm, h = 33 cm) and elution with petroleum ether - ether (85:15) gave successively:

(i) a first fraction of hydrocarbon, identified as 1,3-dimethyladamantane (4), 2.27 g (12.5%), and

(ii) a second fraction, which after crystallization in pentane, gave 2.6 g (12.5%) of 5,7-dimethyladamantan-2-one (2) as colorless prisms, m.p. 56-64 C. [lit.[14] m.p.: 64-65°C]. It had IR (KBr)ν : 2940, 2870, 1730, 1700, 1460, 1300, 1230, 1070, 900, 480 cm^{-1}; ^1H-NMR δ : 0.85 (6H, s), 1.44 (2H, s), 1.65 (8H, m), 2.39 (2H, br.s.) ppm; and ^{13}C-NMR δ: 28.8 (q), 30.7 (s), 44.9 (t), 46.2 (d), 50.5 (t), 218.7 (s) ppm.

(iii) Finally, the column was exhaustively eluted with ether to give 2.15 g (12.5%) of the starting tertiary alcohol 5, m.p. 80-85°C.

The mother liquor from the crystallization of 2 (above) was distilled to give 1.1 g (5.3%) of a mixture of 30% 2 and 70% (±)-1,5-dimethyladamantan-2-one (1a + 1b) as a colorless oil, b.p. 130-145°C/2 mm. Chromatography of 2.0 g of this mixture on a column of silica gel (60-200 mesh) (ø = 2 cm, h = 53 cm) with petroleum ether - ether (9:1) as eluant and collecting fractions of 50-60 mL, gave the following:

Fraction 9	100% (1a + 1b)
Fraction 10	100% (1a + 1b)
Fraction 11	70% (1a + 1b) + 30% 2

The purity was checked by analytical gas chromatography on column A. Redistillation of fractions 9 and 10 gave 0.64 g of (±)ketone (1a + 1b) as a colorless oil, b.p. 150°C/1mm. It had UV (n-heptane): $\varepsilon_{302}^{max} = 17.0$, $\varepsilon_{292}^{max} = 18.0$, $\varepsilon_{288}^{max} = 18.0$, $\varepsilon_{280}^{sh} = 15.3$; IR (film)ν : 2910, 2850, 1720, 1460, 1380 cm^{-1}; and ^1H-NMR δ: 0.87 (3H, s), 0.92 (3H, s); 1.36-2.00 (10H, m), 1.90-2.20 (1H, m), 2.30-2.60 (1H, m) ppm; and ^{13}C-NMR δ : 22.41 (q), 28.71 (q), 28.95 (d), 30.65 (s), 38.53 (t), 42.65 (t), 45.47 (t), 45.93 (t), 46.12 (s), 46.42 (d), 53.03 (t), 218.18 (s) ppm.

(±)-1,5-Dimethylbicyclo[3.3.1]non-6-en-3-endo-carboxylic acid (7a + 7b): 5,7-Dimethyladamantan-2-one (2) (5.8 g, 33 mmol) was dissolved in 60 mL of 98% methanesulfonic acid at 0°C under stirring. Sodium azide (3.0 g, 46 mmol) was added in small portions, and nitrogen evolution was observed. After 5 h at room temperature, the solution was poured onto 400 g of ice and water in a 2L beaker then neutralized by careful addition of Na_2CO_3. The organic material was extracted with 150 mL of dichloromethane, and this layer was washed with water and dried ($MgSO_4$). (Reacidification of the aqueous phase and extraction of any acid present is recommended.) Solvent removal (rotovap) gave 8.0 g of imine ester, which was treated with 8.0 g of KOH in 100 mL of 60% ethanol-water at reflux for 12 h. After cooling, the solvent was removed on a rotovap, and the residue was dissolved in 250 mL of water. Extraction with ether (100 mL) gave a neutral fraction (8).

The basic aqueous solution was acidified at 0°C using conc. HCl then extracted with ether. The extract was washed with water and dried ($MgSO_4$) to give the acid fraction. Evaporation of the ether gave 4.0 g of residue, which was recrystallized in pentane at -50°C to give 2.53 g (40%) of acid (7a + 7b) as colorless prisms, m.p. 103-108°C. It had IR (KBr) ν : 3040, 2970, 2920, 2880, 2800 (br), 1710, 1460, 1300, 1270, 1240, 1200, 930, 790, 720, 630 cm^{-1}; ^1H-NMR δ : 0.92 (3H, s), 0.98 (3H, s), 1.10-2.70 (9H, m), 5.26 (1H, d, J=6 Hz), 5.47 (1H, d, J=6 Hz), 11.7 (1H, s) ppm; and ^{13}C-NMR δ : 29.0 (q), 30.3 (q), 32.3 (t), 33.1 (t), 36.9 (t), 37.7 (t), 38.2 (s), 38.5 (s), 47.1 (d), 128.3 (d), 134.8 (d), 182.3 (s) ppm.

Anal. Calc. for $C_{12}H_{18}O_2$ (194.26): C, 74.19; H, 9.34.
Found: C, 74.20; H, 9.33.

The neutral fraction gave, after evaporation of the solvent and recrystallization in ether-pentane, 0.43 g (7%) of the amide (8) as colorless prisms, m.p. 117-126°C. It had IR (KBr) ν: 3200, 3040, 2920, 1670, 1490, 1450, 1380, 1360, 1350, 1330, 1270, 1210, 1190, 1110, 950, 820, 800, 560, 485, 415, 390 cm^{-1}; ^1H-NMR δ: 0.83 (6H, s), 1.00-1.70 (10H, m), 2.64 (1H, br.s.), 3.31 (1H, br.s), 7.22 (1H, br.s.) ppm; and ^{13}C-NMR δ : 30.9 (q), 31.7 (t), 37.0 (t), 42.4 (s), 42.5 (t), 46.5 (d), 49.3 (d), 181.3 (s) ppm.

Anal. Calc. for $C_{12}H_{19}NO$ (193.28): C, 74.57; H, 9.91; N, 7.25
Found: C, 74.52; H, 10.04; N, 7.11

Resolution of (±)-1,5-Dimethylbicyclo[3.3.1]non-6-en-3-endo-carboxylic acid (7a + 7b): Racemic acid (7a + 7b) (3.8 g, 20 mmol) and quinine (6.5 g, 20 mmol) were dissolved in 100 mL of ethyl acetate. Cooling to 0°C and filtration gave 9.5 g of the quinine salt of the (+)-acid. A second recrystallization gave 8.0 g of salt and a third recrystallization in 50 mL ethyl acetate at room temperature gave 4.4 g of salt, m.p. 82-85° C. This salt was dissolved in 150 mL of 2N HCl and stirred at room temperature for 2 h. Extraction with ether (80 mL), washing (successively with 50 mL of 2N HCl, 50 mL of sat. brine), drying (Na_2SO_4) and solvent evaporation gave 1.38 g (73%) of the (+)-acid, (7b), $[\alpha]_{589}^{20} = +8.2°$, $[\alpha]_{578}^{20} = +8.5°$ (c 1.32).

The mother liquors of the recrystallizations above were combined and evaporated to dryness. Recrystallization of the residue in 50 mL of ethyl acetate gave 8.0 g of quinine salt (wet) of the (-)-acid. Decomposition of this salt, as described above, gave 2.0 g of acid, $[\alpha]_{589}^{20} = -2.5°$, $[\alpha]_{578}^{20} = -2.6°$ (c 1.14). This material (2.1 g, 11 mmol) was dissolved in 75 mL of ethyl acetate containing 3.3 g (11 mmol) of cinchonidine. After cooling to 0°C, the precipitated salt (5.5 g) was removed by filtration. Recrystallization from 75 mL of ethyl acetate gave 4.0 g of salt, and a third recrystallization from 75 mL of ethyl acetate gave 2.8 g. Treatment of this salt with dilute HCl, then ether extraction as above gave 0.50 g (26%) of the (-)-acid (7a) as colorless prisms, $[\alpha]_{589}^{20} = -15.5°$, $[\alpha]_{578}^{20} = -16.2°$ (c. 1.12).

(-)-(3S)-1,5-Dimethyl-3-endo-hydroxymethylbicyclo[3.3.1]non-6-ene (9a): (-)-(3S)-1,5-Dimethylbicyclo[3.3.1]non-6-en-3-endo-carboxylic acid (7a) (0.50 g, 2.6 mmol) in 10 mL of ether was added to a suspension of 0.45 g (12 mmol) of $LiAlH_4$ in 40 mL of ether at 0°C with stirring. The solution was heated under reflux for 1 h cooled to 0°C and quenched by successive, careful addition of 0.45 mL of water, 0.45 mL of 15% NaOH and 1.3 mL of water. After stirring for 30 min., the white precipitate was filtered. The filtrate was concentrated and the residue was distilled (Kugelrohr) to give 0.45 g (96%) of the (-)-(3S)-alcohol 9a, as a colorless oil, b.p. 155-160°C/1 mm, $[\alpha]_{589}^{20} = -64.5°$, $[\alpha]_{578}^{20} = -67.5°$ (c 1.07). It had IR (film) ν: 3340, 3010, 2950, 2900, 1650, 1450, 1030, 740, 680 cm^{-1}

Anal. Calc. for $C_{12}H_{20}O$ (180.28): C, 79.94; H, 11.18.
Found: C, 79.54; H, 11.47.

(-)-(1S)-1,5-Dimethyladamantan-2-one (1a): A solution of 0.45 g (2.5 mmole) of (-)-(1S)-1,5-dimethyl-3-endo-hydroxymethylbicyclo[3.3.1]non-6-ene (9a), $[\alpha]_{589}^{20} = -64.5°$, (c 1.07) in 6 mL of 98% formic acid was kept at 110°C for 2 h. After cooling, the mixture was poured onto 100 g of ice water and extracted with 50 mL of ether. The extract was washed with 50 mL of 5% $NaHCO_3$, sat. brine and dried (Na_2SO_4). Evaporation of the solvent gave 0.50 g of crude formate ester diastereomers. This material, dissolved in 40 mL of ether was treated with 0.20 g (5.2 mmol) of $LiAlH_4$ in 10 mL of ether. After heating at reflux for 30 min., the mixture was quenched by the addition of 0.20 mL of water followed by 0.20 mL of 15% NaOH and 0.60 mL of water. After stirring for 30 min., a white precipitate was removed by filtration, and the solvent was evaporated to give 0.40 g of crude alcohol 10a, a colorless oil crystallizing at room temp. This alcohol was dissolved in 30 mL of acetone, and stirred magnetically with a suspension of 3.0 g of anhydrous $MgSO_4$. Jones reagent[23] (1 mL, 3M) was added until a red color persisted. After 20 min. at room temp., excess reagent was destroyed by the addition of a few drops of 2-propanol. The mixture was filtered and the filtrate evaporated (roto-vap). The residue was dissolved in ether, washed with water, dried ($MgSO_4$) and evaporated to give 0.37 g of crude ketone. The ketone was purified by column chromatography (ø = 1 cm, h = 45 cm) using silica gel with petroleum ether - ether (9:1) as eluant. Evaporation of the solvent and distillation (Kugelrohr) gave 0.26 g (56% from the starting alcohol 9a) of the ketone (-)-(1S)-1a as a colorless oil, b.p. 150°C/1mm. The material was >99.99% pure by analytical GC (columns A and B). The IR spectrum was identical with the racemic material independently prepared by oxidation of 5 with sulfuric acid. It had $[\alpha]_{589}^{20} = 0.0°$, $[\alpha]_{365}^{20} = -2.3°$ (c 0.98, heptane); UV (cyclopentane): $\varepsilon_{309}^{sh} = 17.4$, $\varepsilon_{293}^{max} = 18.7$, $\varepsilon_{289}^{max} = 18.7$, $\varepsilon_{280}^{sh} = 16.3$; CD (cyclopentane): $\Delta\varepsilon_{314}^{max} = -0.011$, $\Delta\varepsilon_{303}^{max} = -0.020$, $\Delta\varepsilon_{292}^{max} = -0.021$, UV (trifluoroethanol): $\Delta\varepsilon_{282}^{max} = 18$; CD (2,2,2-trifluoroethanol): $\Delta\varepsilon_{288}^{max} = -0.016$. (CD values for 72% e.e.).

(+)-(3R)-1,5-Dimethyl-3-endo-(2-hydroxy-2-propyl)bicyclo[3.3.1]non-6-ene (12): (The organometallic reactions were performed under nitrogen until hydrolysis). To a solution of 0.56 g (2.9 mmoles) of (+)-(3R)-1,5-dimethylbicyclo[3.3.1]non-6-en-3-endo-carboxylic acid (7b), $[\alpha]_{589}^{20} = +8.2°$ (c 1.32) in 15 mL of THF, were added at 0°C under stirring 10 mL (12 mmol) of a solution of 1.2 M CH_3Li in ether. After 4 h at room temperature, the solution was poured onto 100 g of ice water, acidified with 20 mL of 2 N HCl and extracted with ether (50 mL). The ether extract was washed with sat. brine, dried (Na_2SO_4) and evaporated to give the crude methyl ketone (11), 0.58 g, as a colorless oil. This material, dissolved in 15 mL of dry ether was treated with 20 mL of a solution of 1.2M (24 mmoles) CH_3Li in ether at room temperature for 12 h. The reaction mixture was poured onto ice water (100 g), acidified with 20 mL of 2N HCl and extracted with ether (50 mL). The ether extract was washed with sat. brine, dried (Na_2SO_4) and evaporated to afford 0.48 g (77% from the acid) of the (+)-alcohol (12b) as a colorless oil.

(If the crude product still shows a strong C=O band in the IR spectrum, it is treated again with CH_3Li in ether, as before). It had IR (film): 3400, 3010, 2950, 1640, 1450, 1370, 1120, 940, 900, 730 cm^{-1}; and $[\alpha]^{20}_{589} = +29.2°$, $[\alpha]^{20}_{578} = +31.0°$, $[\alpha]^{20}_{546} = +35.4°$, $[\alpha]^{20}_{436} = +61.0°$ and $[\alpha]^{20}_{365} = +96.4°$ (c 0.62). The alcohol was used directly in the next step.

(+)-(1R)-1,4,4,7-Tetramethyladamantane-2-one (13): A solution of (+)-alcohol 12 from above, $[\alpha]^{20}_{589} = +29.2°$ (c 0.62), (0.48 g, 2.3 mmol) in 6 mL of 98% formic acid was heated at 100°C for 3 h. After cooling the solution was poured onto 100 g of ice water, extracted with ether (50 mL), washed successively with water, 5% $NaHCO_3$, sat. brine and dried ($MgSO_4$). Evaporation of the solvent gave 0.50 g of crude diastereomeric formate esters. This material was dissolved in ether (20 mL) and treated with 0.25 g of $LiAlH_4$ in 30 mL of ether at reflux for 1 h. The solution was cooled to 0 C and quenched successively with 0.25 mL of water, 0.25 mL of 15% NaOH and 0.75 mL of water. After stirring for 30 min., white precipitate was removed by filtration, and the ether was evaporated to give 0.37 g of crude tetramethyladamantanol. The latter was oxidized with 0.60 g (2.8 mmol) of pyridinium chlorochromate in 10 mL of dichloromethane at room temperature for 12 h. The solution was diluted with 50 mL of ether and decanted, and the residue washed with 3x10 mL of ether. The combined ethereal solution was passed through a column of silica gel (ø = 1 cm, h = 10 cm) collected and evaporated. The crude product, 0.34 g, was purified by column chromatrography on silica gel (ø = 1 cm, h = 40 cm) eluant: pentane-ether (9:1). The main fraction gave 0.195 g (41%) of the (+)-ketone 13, m.p. 63-68°C as pale yellow prisms. It had $[\alpha]^{20}_{589} = +10.0°$, $[\alpha]^{20}_{578} = +10.2°$, $[\alpha]^{20}_{546} = +11.2°$, $[\alpha]^{20}_{436} = +25.4°$ and $[\alpha]^{20}_{365} = +66.0°$ (c 0.41, cyclopentane); UV (cyclopentane): $\varepsilon^{sh}_{313} = 14.5$, $\varepsilon^{sh}_{303} = 24.6$, $\varepsilon^{max}_{293} = 27.6$, $\varepsilon^{max}_{289} = 27.6$, $\varepsilon^{sh}_{280} = 25.0$; CD (cyclopentane): $\Delta\varepsilon^{max}_{314} = +0.201$, $\Delta\varepsilon^{max}_{303} = +0.316$, $\Delta\varepsilon^{max}_{294} = +0.296$; IR (KBr) ν: 2950, 2910, 2870, 1710, 1450 cm^{-1}; ^1H-NMR δ: 0.81 (3H, s), 0.83 (3H, s), 0.87 (3H, s), 1.03 (3H, s), 1.30-1.70 (6H, m), 1.80-1.95 (2H, m), 1.95-2.15 (2H, m) ppm; ^{13}C-NMR δ : 22.19 (q), 25.36 (q), 27.42 (q), 28.56 (q), 30.43 (s), 38.40 (t), 38.78 (s), 39.01 (t), 41.02 (t), 41.49 (t), 45.20 (s), 54.22 (d), 56.62 (d), 206.13 (s) ppm.

Anal. Calc. for $C_{14}H_{22}O$ (206.32): C, 81.49; H, 10.75
Found: C, 81.53; H, 10.88

Enantiomeric Excess (e.e.) and Absolute Configuration of 1a and 1b. -- Ketone 13 obtained from above (100 mg, 0.48 mmol) was reduced quantitatively and stereospecifically to the syn alcohol (15a + 15b) with $LiAlH_4$ (40 mg) in 10 mL of diethyl ether. Analytical GC (cols A & B) indicated only one epimer, which was derivatized as its Mosher ester[18] with the acid chloride of R-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid as previously described.[17] In the ^{19}F-NMR spectrum run in $CDCl_3 + CFCl_3$, the diastereomeric CF_3 signals of the Mosher ester (16a + 16b) were split into two lines, δ 35.85 and 35.56 ppm downfield from $CFCl_3$ internal standard in the ratio 69:31, respectively. Accordingly, alcohol 15a + 15b (derived from 13 above) has an e.e. of 38% of one enantiomer. This means that ketone 13, with $[\alpha]^{20}_{589} = +10.0°$ (c 0.41, cyclopentane) and its parent acid 7b with $[\alpha]^{20}_{589} = +8.2°$ (c 1.32) also have an e.e. of 38%. Consequently, acid 7a with $[\alpha]^{20}_{589} = -15.5°$ (c 1.12) and its derived ketone 1a have an e.e. of 72%.

The absolute configuration of the predominant enantiomer of 13 is assigned 1R because the more intense resonance of the ^{19}F signals for the diastereomeric CF_3 groups of the derived Mosher ester (16a + 16b) was faster moving upon addition of $Eu(fod)_3$.[17] The shifts were 35.85 → 39.85 → 42.05 ppm for the more intense ^{19}F signal and 35.56 → 37.93 → 39.55 ppm for the less intense ^{19}F signal. (Similarly, the ^{19}F-NMR resonance of 18b was faster moving than that of 18a.[3]) This means that the structure shown for 13 represents the absolute configuration of its predominant enantiomer, and that of 1a is the absolute configuration of the predominant enantiomer of (-)-1. These conclusions independently confirm the absolute configurations assigned by CD.[1]

Acknowledgement - We thank the National Science Foundation (CHE 8218216) for generous support of this work. We acknowledge the assistance of Mr. J.W. Givens III with the MM2 calculations and Dr. W.M.D. Wijekoon with the LIS-NMR and for CD measurements.

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