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# Optical Rotatory Dispersion Studies. 128.[1] Octant Contributions of Methyl Groups in 4-*tert*-Butylcyclohexanones

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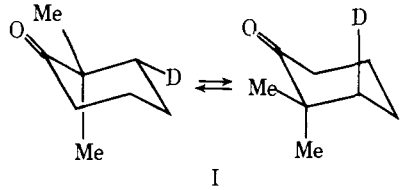
**Abstract:** A number of methyl-substituted 4-*tert*-butylcyclohexanones have been synthesized with high optical purity from naturally occurring chiral molecules of known absolute configuration. The circular dichroism spectra of these compounds were measured at both room temperature and 77 K in polar and nonpolar solvents, and empirical force field calculations were carried out to determine the energy difference between the chair and twist-boat conformations. Of particular interest was the discovery that the *trans*-3-methyl-4-*tert*-butylcyclohexanone (+)-**4** exists mainly in the twist-boat form. In addition, the apparent antioctant behavior of the β-axial methyl group in compound (−)-**5** at low temperature and in a polar solvent is interpreted as arising from solvation of the molecule.

## Introduction

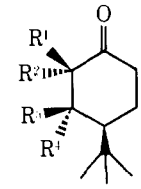
We reported in two recent communications[2,3] that variable-temperature circular dichroism measurements of monodeuterio substituted α,α-dimethylcyclohexanones (e.g., compound I) can be used to determine the energy difference




I

between the chair conformations with the deuterium in the equatorial and axial position, respectively. For the quantitative calculation of the energy difference it was necessary to make assumptions about the absolute magnitude of the rotational strengths ([*R*] values) of both conformers involved in the equilibrium. These values were obtained by adding the partial octant contributions of an α-equatorial and an α-axial methyl group as they have been reported in the literature[4,5] for a variety of model compounds, including steroids. A more direct method, which has been widely employed in the investigation of conformational equilibria by various physical methods,[6,7] is to introduce substituents into the conformationally flexible molecule so as to lock it into one or the other conformation. Ideally this conformational blocking group should have no effect on the physical property under investigation (in this study, the rotational strength). Cyclohexanones substituted with a γ-*tert*-butyl group are well suited for this type of study, since such molecules are known to function as conformationally rigid systems.[8] Also, the 4-*tert*-butyl group is located in a nodal plane in the octant diagram and should not contribute to the rotational strength.

In a previous paper,[9] we presented the synthesis of (*R*)-(+)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**3**). We have now extended the methodology used in the synthesis of (+)-**3** to the synthesis of (2*R*,4*R*)-(+)-2-methyl-4-*tert*-butylcyclohexanone (**1**), (3*R*,4*R*)-(+)-3-methyl-4-*tert*-butylcyclohexanone (**4**), (3*S*,4*R*)-(−)-3-methyl-4-*tert*-butylcyclohexanone (**5**), and (*S*)-(−)-3,3-dimethyl-4-*tert*-butylcyclohexanone (**6**), and report the CD spectra of ketones **1**–**6** together with the CD




**1**, $R^1$ = Me; $R^2$ = $R^3$ = $R^4$ = H
**2**, $R^2$ = Me; $R^1$ = $R^3$ = $R^4$ = H
**3**, $R^1$ = $R^2$ = Me; $R^3$ = $R^4$ = H
**4**, $R^4$ = Me; $R^1$ = $R^2$ = $R^3$ = H
**5**, $R^3$ = Me; $R^1$ = $R^2$ = $R^4$ = H
**6**, $R^3$ = $R^4$ = Me; $R^1$ = $R^2$ = H

spectra of several of the synthetic intermediates to these compounds. Ketone (+)-**3** is closely related to the conformationally mobile cyclohexanone I and the measurement of the CD spectrum of (+)-**3** will help to evaluate the conformational effects, if any, of the α,α-dimethyl "chiral probe".[2] Ketones (+)-**1** and (+)-**2** have been prepared previously,[10] although only their optical rotatory dispersion (ORD) spectra have been reported. By measuring their CD spectra, it can be determined if the partial methyl contributions are additive (i.e., is the α,α-dimethyl group contribution simply an algebraic sum of the individual methyl group contributions?). Also, these compounds can furnish additional chiroptical reference values

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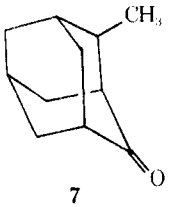
for the equatorial and axial α-methyl substituents in cyclohexanones. Similarly, compounds (+)-**4**, (−)-**5**, and (−)-**6** could be compared to other reference molecules with β-methyl substituents. Of particular interest is a comparison of the octant contribution for a β-axial methyl group, as obtained from compounds (−)-**5** and the β-axial methyladamantanone (**7**)



**7**

prepared and reported by Snatzke et al.,[11] since the antioctant behavior (in ethanol) of the latter compound has been interpreted as resulting from the location of the methyl group in a front octant.[12]

Meaningful group octant contributions can only be obtained experimentally if the conformation of the chosen molecule is known with certainty. Whereas in the adamantanones there is no ambiguity with respect to this question, cyclohexanones with a bulky C-4 substituent (e.g., *tert*-butyl) can possibly exist in other conformations (e.g., twist-boat forms) in addition to the most likely chair form. This is conceivable since the energy difference between these conformations in cyclohexanones is significantly lower as compared to the equivalent cyclohexane derivatives.[13] This question of conformational mobility was tested by measuring the circular dichroism spectra of **1**–**6** at low temperatures and in two solvent systems of different polarity. The problems associated with the interpretation of the intensity changes observed in going from room temperature to 77 K are discussed in more detail below. To obtain estimates of the energy differences between the chair and twist-boat conformations, we carried out empirical force field (EFF)[14] calculations on compounds **1**–**6** and compared them with the results from the low-temperature CD studies.

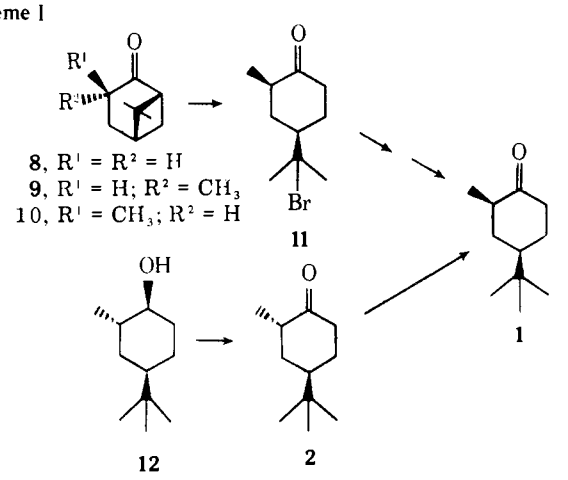
## Synthesis

The synthesis of the cis ketone (+)-**1** was similar to that reported for (+)-**3**[9] (Scheme I). (+)-Nopinone (**8**), prepared from (−)-β-pinene by ozonolysis, was alkylated (under kinetic control) with methyl iodide to give (+)-**9**. Treatment with 5% KOH/MeOH gave the thermodynamically more stable epimer (+)-**10**,[15] which was treated with $BBr_3$[16] to give the bromo ketone (+)-**11**. Reduction of the ketone functionality with $NaBH_4$, followed by replacement of the bromine atom with methyl using $Al(Me)_3$[17] and oxidation, led to (+)-**1**.

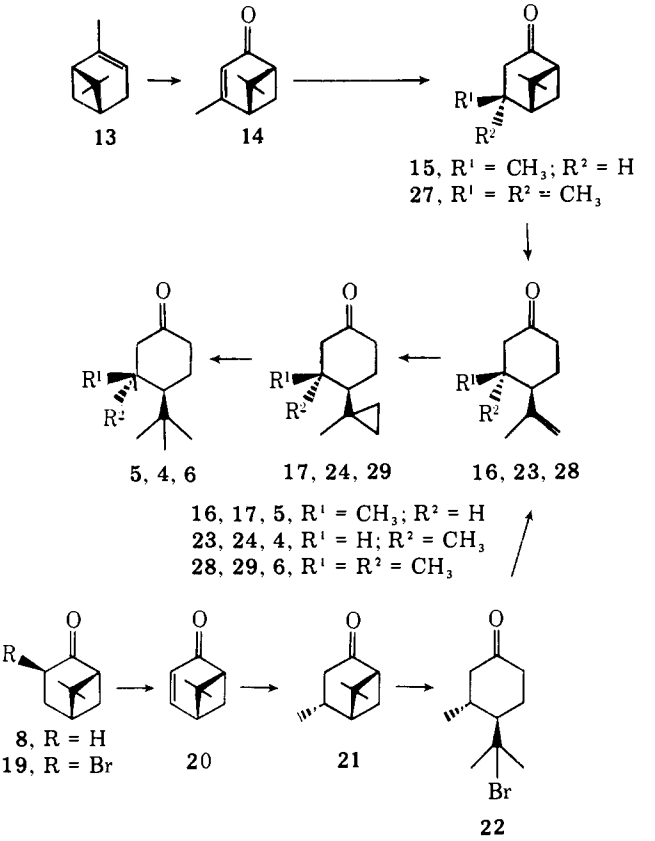
Both (+)-**1** and the trans ketone (+)-**2** were prepared previously (via resolution) in our laboratory.[10] A sample of resolved (+)-**12** from this earlier work was oxidized to (+)-**2**, treated with base to give (+)-**1**, and compared, by CD spectrum and rotation, with a sample of (+)-**1** from the current synthesis (Scheme I). Using a value of 88% enantiomeric excess (ee) (as determined by NMR methods in the synthesis of the related ketone (+)-**3**)[9] for the sample of (+)-**1** synthesized by the present methodology, the optical purity of (+)-**1** from the resolution was determined to be 100%, within experimental error. This places the optical purity of (+)-**2** also at 100%, and makes an independent synthesis of (+)-**2** by our present method unnecessary.

(+)-α-Pinene (**13**) (90% optical purity)[18] was used as starting material for the synthesis of the cis ketone (−)-**5** (Scheme II). Allylic oxidation[19] of (+)-α-pinene gave (+)-verbenone (**14**), which was hydrogenated to (+)-*cis*-verbanone (**15**).[20] Pyrolysis[21,22] of (+)-**15** gave the olefin (−)-**16** in low yield, which was treated with $CH_2I_2$ and Zn–Cu couple formed in situ[23] to afford (−)-**17**. Hydrogenation using $PtO_2$ in AcOH resulted in the cleavage of the least substituted bond of the cyclopropane ring[24] and the reduction of the ketone to a mixture of alcohols. Oxidation, without purification of the intermediate alcohol mixture, led to (−)-**5**.

Scheme I



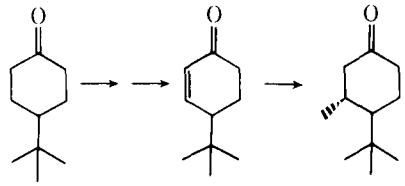

Scheme II




Scheme II also outlines the synthesis of the trans ketone (+)-**4**. Bromination/dehydrobromination of (+)-nopinone (**8**) gave (+)-apoverbenone (**20**)[25] contaminated with a small amount of starting material. Since it proved difficult to separate (+)-**8** from (+)-**20**, it was decided to carry the mixture through the next reaction before rigorous purification. Treatment of the mixture with $Me_2CuLi$ gave (+)-*trans*-verbanone (**21**)[26] together with a small amount of unreacted (+)-**20** and (+)-**8**. Purification by preparative LC provided (+)-**21**.

Opening of the cyclobutane ring in (+)-**21** was effected by $BBr_3$.[16] The resulting bromo ketone (+)-**22** proved to be somewhat unstable and, upon chromatography on silica gel, eliminated HBr to give the olefin (−)-**23**. Cyclopropanation (to give (−)-**24**) followed by hydrogenolysis and oxidation (as in (−)-**5**) gave (+)-**4**.

Scheme III



**25** **26** **4**

Owing to the unusual nature of the CD spectrum of (+)-**4** (vide infra), racemic **4** was synthesized as follows in order to confirm the chemical structure (Scheme III).

Bromoketalization of 4-*tert*-butylcyclohexanone (**25**), followed by dehydrobromination and deketalization, gave 4-*tert*-butyl-2-cyclohexen-1-one (**26**).[27] Treatment of **26** with $Me_2CuLi$,[28] followed by preparative gas chromatography, gave racemic **4** identical with (+)-**4** in all respects except for optical rotation.

The synthesis of the 3,3-dimethyl ketone (−)-**6** followed the synthesis of (−)-**5** very closely (Scheme II). Treatment of (+)-verbenone (**14**) with $Me_2CuLi$ according to the literature procedure[28] gave (+)-4,4-dimethylnopinone (**27**). The remaining steps in the synthesis of (−)-**6** from (+)-**27** proceeded exactly as in the synthesis of (−)-**5**.

## Results and Discussion

Determination of the partial octant contribution of a methyl group located at various positions with respect to a carbonyl chromophore has played an important role in the development of the octant rule.[12,29,30] From a large variety of conformationally (more or less) well-defined molecules such as steroids, decalones, adamantanones, etc., these contributions have been shown to be quite reproducible and independent of the particular molecular system from which they were derived.[4,5]

However, as pointed out above, the principal problem in this approach is the knowledge of the precise molecular conformation. Several studies[31-36] have applied the sensitivity of circular dichroism toward conformational changes to determine conformational energy differences by measuring the rotational strength over a certain temperature range. However, the interpretation of these CD data can meet with several difficulties, and, since these are also encountered in the present study, we will discuss them briefly here.

Strictly speaking, energy differences can be calculated only if no more than two conformations participate in the equilibrium under investigation. However, it has been demonstrated[37] that ketones can undergo temperature-dependent solvation equilibria even with such apparently inert and nonpolar solvents as hydrocarbons. The solvated and unsolvated species can have distinctly different rotational strengths, sometimes even of opposite sign. It is not possible a priori to distinguish such solvational equilibria from conformational changes that take place with temperature variation. Sometimes investigation in solvent systems of different polarity permits a differentiation of these effects; e.g., if no changes of the rotational strength are observed in a nonpolar solvent but large changes in a polar one (or vice versa), it might reasonably be concluded that these changes are associated with solvational effects. Difficulties can also arise from the operation of a dimerization equilibrium, which has been observed to take place with ketones at low temperatures.[38] Finally, there is the possibility of an interrelation of these effects in that solvation can affect the energy difference between various conformers. Thus, caution has to be exercised in the interpretation of variable-temperature CD measurements; one will often be left with a degree of uncertainty as to the origin of the observed changes and it is desirable to obtain independent information through other methods.

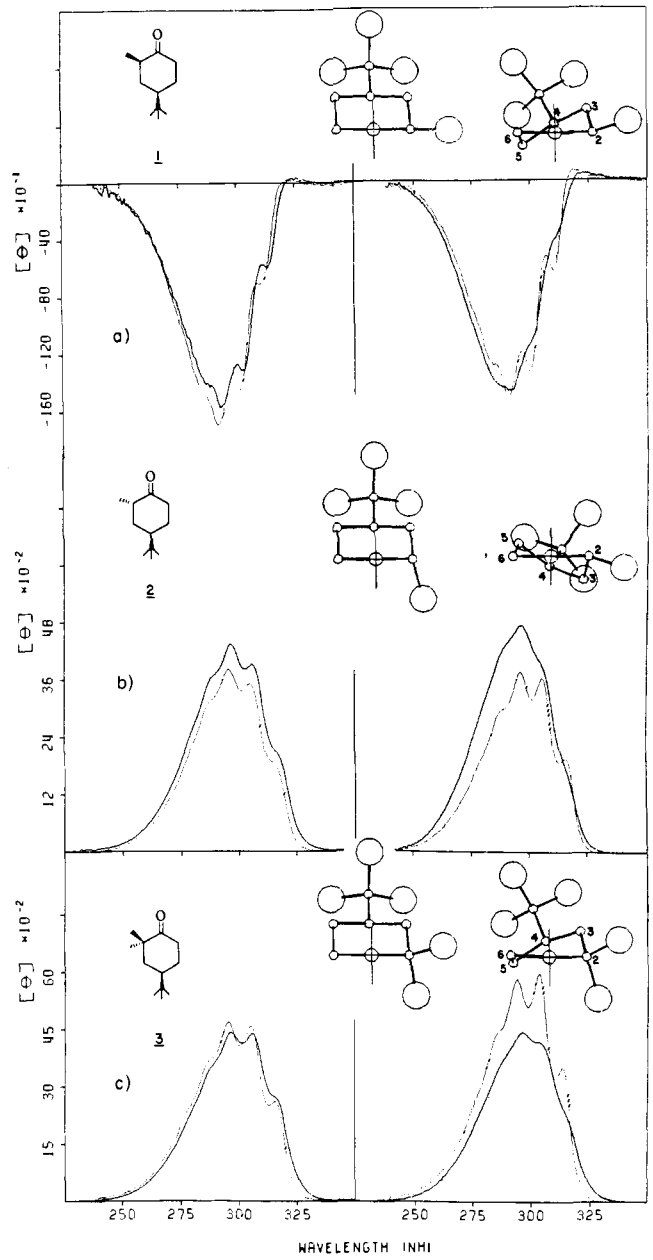



**Figure 1.** Circular dichroism spectra of (a) (2*R*,4*R*)-(+)-2-methyl-4-*tert*-butylcyclohexanone (**1**); (b) (2*S*,4*R*)-(+)-2-methyl-4-*tert*-butylcyclohexanone (**2**); (c) (*R*)-(+)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**3**) in IPM (isopentane-methylcyclohexane, 4:1 v/v) (left-side spectra) and EPA (ether-isopentane-ethanol, 5:5:2 v/v) (right-side spectra) at room temperature (heavy line) and 77 K (thin line). The structures, viewed along the C=O bond, of the chair and twist-boat conformations as obtained by the EFF calculations are given alongside the CD spectra (the methyl groups are symbolized by large circles).

The circular dichroism spectra of compounds **1–6** measured in EPA (isopentane-ether-ethanol, 5:5:2) and IPM (isopentane-methylcyclohexane, 4:1) at room temperature and 77 K are shown in Figures 1 and 2, and their rotational strengths are listed in Table I. In addition, this table contains the [*R*] values measured in methanol and isooctane. The last entry in each column of Table I is the [*R*] value for that methyl substituent as it appears in two recent review articles on the subject.[4,5]

Empirical force field (EFF) calculations have been shown to yield quite reliable values for conformational energy differences,[13,39-41] although exceptions are known.[42] We have carried out such calculations for compounds **1–6** in their chair and twist-boat conformations and list the calculated energy differences in Table II. The structures corresponding to these

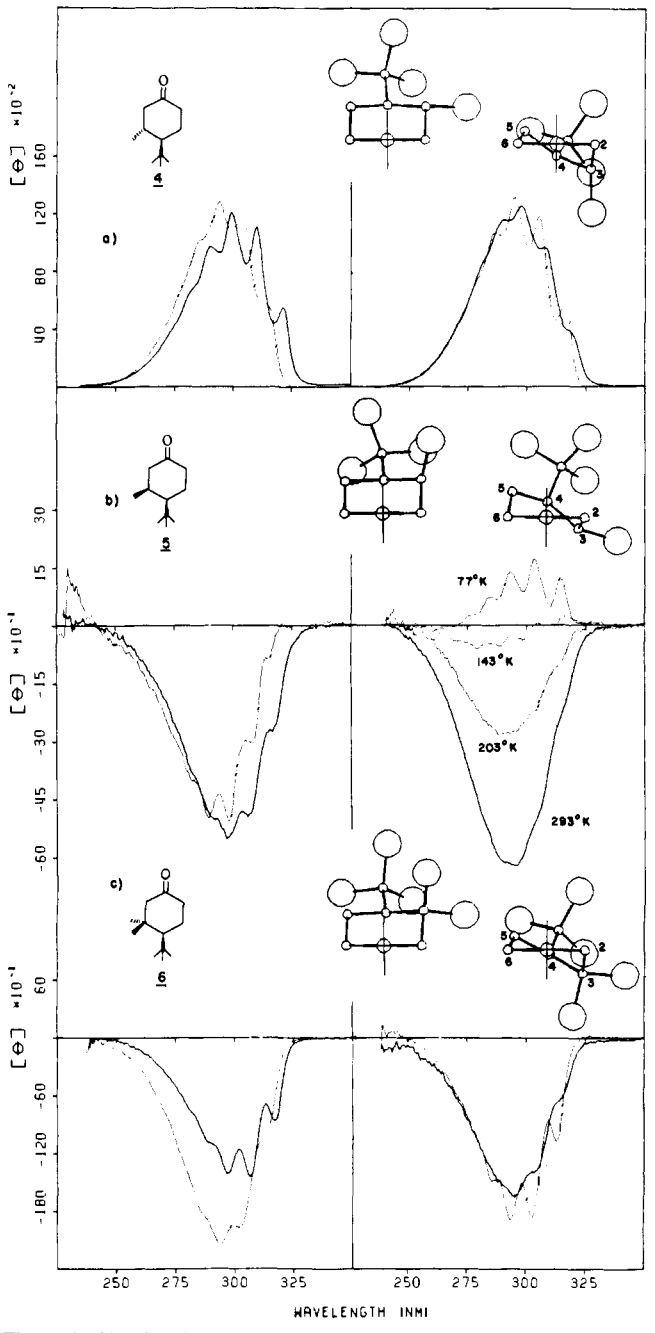



**Figure 2.** Circular dichroism spectra of (a) (3*R*,4*R*)-(+)-3-methyl-4-*tert*-butylcyclohexanone (**4**); (b) (3*S*,4*R*)-(−)-3-methyl-4-*tert*-butylcyclohexanone (**5**); (c) (*S*)-(−)-3,3-dimethyl-4-*tert*-butylcyclohexanone (**6**) in IPM (isopentane-methylcyclohexane, 4: 1 v/v) (left-side spectra) and EPA (ether-isopentane-ethanol, 5:5:2 v/v) (right-side spectra) at room temperature (heavy line) and 77 K (thin line). The structures, viewed along the C=O bond, of the chair and twist-boat conformations as obtained by the EFF calculations are given alongside the CD spectra (the methyl groups are symbolized by large circles).

energy minima are given in Figures 1 and 2 alongside their respective circular dichroism spectra.

The circular dichroism spectra of the cis ketone (+)-**1** (Figure 1a) exhibit a negative Cotton effect. Using the equations for converting ORD amplitudes $a$ to rotational strengths $[R]$ (see footnote *c*, Table I) we find that the results from the present study ($[R] = -1.39$, methanol, Table I) are in close agreement with those reported in the literature[10] ($a = -17.5$, $[R] = -1.44$, methanol). Treatment of (+)-**1** with dilute base results in a marked intensity reduction ($[R] = -0.80$, methanol) in the CD spectra, as was noted in the ORD report.[10] This results from the presence of approximately 6% of the trans ketone (+)-**2** (which has a large positive Cotton effect; see Figure 1b). The value of 6% axial methyl is also consistent with the results obtained from the CD spectra of the conformationally flexible analogue (*R*)-(−)-2-methylcyclohexanone,[43] which has an $[R]$ value similar ($[R] = -0.99$) to that measured for the base-equilibrated sample of (+)-**1**.

Inspection of Figure 1a and the $[R]$ values listed in Table I reveals that the Cotton-effect amplitudes are quite insensitive toward solvent polarity and temperature changes, thus indicating that solvent-solute equilibria are absent and that the molecule exists predominantly in the energetically most stable chair conformation. A feature which went unnoticed in the ORD spectra is the small positive CD band at the long-wavelength side, which is observed in all solvent systems investigated, making it unlikely that this band is due to the presence of a solvated species. Most probably it results from a separate vibrational progression with a different symmetry than that giving rise to the negative Cotton effect near the band center (around 290 nm) of the n→π* C=O transition. Such a situation has been observed in various other systems and the reader is referred to the theoretical interpretation of this effect by Weigang.[44] The α-equatorial methyl substituent has been labeled[4] as a consignate perturber based on the assumption that it is located slightly above the plane defined by the ring carbon atoms 1, 2, and 6. In cyclohexanone it has in fact been verified that the dihedral angle between the C=O and $C_2$–$H_{eq}$ bonds is approximately 6°;[45] experimental evidence that such an arrangement also persists for an α-equatorial methyl group seems to be lacking, however. Our EFF calculations on (+)-**1** (see diagram in Figure 1a) place the methyl group almost exactly in the symmetry plane of the octant diagram and, according to the postulates of the octant rule,[29] it should not make any contribution to the rotational strength; yet the observed rotational strengths (Table I) are of substantial magnitude. Assuming that the EFF calculations approximate the stereochemistry of this molecule correctly, these results suggest that the main contributing factor for the observed Cotton-effect amplitude is a small distortion of the cyclohexanone ring from the true chair form, an interpretation which has already been put forward.[10] This distortion may account for the large deviation of the $[R]$ value of (+)-**1** from the reported literature value (Table I). It is also worthwhile to mention that Richardson et al.[46] have shown that inclusion of higher than first-order terms in the derivation of the octant rule leads to nonzero rotational strengths in such cases where the octant rule would predict a zero result.

The circular dichroism spectra of the trans ketone (+)-**2** (Figure 1b) show an intense positive Cotton effect in both solvent systems, with rotational strengths which compare closely to those calculated from the previously reported ORD spectrum.[10] The octant contribution of the α-axial methyl group is also consistent with the values reported in the literature[4,5] (Table I). The low-temperature spectra, however, show a significant decrease in intensity (Figure 1b and Table I) amounting to 15% in IPM and 25% in EPA. This somewhat different behavior in the two solvent systems indicates that solvent-solute interactions are contributing to the observed decrease of amplitude at 77 K; whether they are the only cause remains uncertain. An axial methyl group is a sterically unfavored situation and, while the equatorial 4-*tert*-butyl substituent prevents the molecule from assuming the other chair conformation (with the α-methyl group in the equatorial position), a twist-boat conformation is accessible in which both alkyl groups assume a quasi-equatorial position. This conformation, shown in Figure 1b in its octant representation, would result in a large positive Cotton effect since the ring atoms 3 and 5 as well as the 2-methyl group fall into positive octants. Therefore the presence of a small percentage of this conformation at room temperature could account for the observed

**Table I.** Experimental Rotational Strengths[a]

| 4 substituent | solvent[b] | position of methyl group: cis-2 | trans-2 | 2,2 | trans-3 | cis-3 | 3,3 |
|---|---|---|---|---|---|---|---|
|  | ME | | | | −1.64 | | −1.49 |
| | IO | | | | −1.85 | | −1.34 |
| | EPA-RT | | | | −1.89 | −0.64 | −1.42 |
| | EPA-77 | | | | **23** −1.86 | **16** 0.21 | **28** −0.96 |
| | IPM-RT | | | 4.32 | −1.51 | −0.63 | −1.21 |
| | IPM-77 | | | 4.27 | −2.60 | 0.80 | −1.30 |
|  | ME | | | | | | −1.79 |
| | IO | | | | | | −1.76 |
| | EPA-RT | | | | | | −1.72 |
| | EPA-77 | | | | | **30** | **31** −1.46 |
| | IPM-RT | | | 4.16 | | −0.61 | −1.58 |
| | IPM-77 | | | 4.59 | | −0.01 | −1.57 |
|  | ME | | | | | | −2.62 |
| | IO | | | | | | −2.02 |
| | EPA-RT | | | | −2.26 | −0.76 | −2.23 |
| | EPA-77 | | | | **24** −2.50 | **17** 0.14 | **29** −1.92 |
| | IPM-RT | | | 3.64 | −2.33 | | −1.78 |
| | IPM-77 | | | 4.06 | −3.07 | | −1.84 |
|  Br | ME | | | 5.23 | | | |
| | IO | | | 4.45 | 8.87 | | |
| | EPA-RT | | | 4.76 | 9.37 | | |
| | EPA-77 | | | 5.90 | **22** 8.21 | | |
| | IPM-RT | | | 4.66 | 9.01 | | |
| | IPM-77 | | | 5.68 | 8.75 | | |
|  | ME | −1.39 | 5.30 | 5.27 | 12.08 | −0.66 | −1.61 |
| | IO | −1.46 | 4.93 | 4.59 | 10.81 | −0.59 | −1.33 |
| | EPA-RT | −1.42 | 4.71 | 4.47 | 12.27 | −0.66 | −1.65 |
| | EPA-77 | **1**[d] −1.34 | **2** 3.53 | **3** 5.53 | **4** 11.71 | **5** 0.10 | **6** −1.63 |
| | IPM-RT | −1.52 | 4.41 | 4.53 | 11.24 | −0.57 | −1.31 |
| | IPM-77 | −1.57 | 3.72 | 4.58 | 11.74 | −0.48 | −2.10 |
| lit. octant contributions[c] | | 0.50–0.66 con | 3.94–5.64 con | 4.81–4.98 con | 1.66–1.99 con | 0.33 dis | 1.33–1.66 con |

[a] Values are given in terms of reduced rotational strengths $[R] = 0.75 \times 10^{-2} \int([\theta]/\lambda)d\lambda$ (integration was carried out over the 340–240-nm range) and are corrected for 100% enantiomeric excess. [b] ME = methanol; IO = isooctane; EPA-RT = EPA at room temperature; EPA-77 = EPA at 77 K; IPM-RT = IPM at room temperature; IPM-77 = IPM at 77 K. [c] Taken from ref 4 and 5. The values given in these references are expressed in terms of $\delta\Delta\epsilon$ and have been converted to $[R]$ by using the empirical relationship $[R] = 3.32\,\Delta\epsilon$, which was found by comparing the rotational strength $[R] = 24.75 \int(\Delta\epsilon/\lambda)d\lambda$ with the $\Delta\epsilon_{max}$ value of cholestanone. The general applicability of this conversion depends on the assumption that the center frequency and half-bandwidth for the n→π* Cotton effect are the same for all ketones. [d] The boldface numbers in the table refer to the figure of that molecule as it appears in the text.

decrease of intensity at 77 K, at which temperature the equilibrium would be shifted completely to the chair conformation. The EFF calculations of these two geometries (chair and twist-boat) result in an energy difference of 2.4 kcal/mol (Table II), which would mean that the twist-boat form would be present to only 2% at room temperature. This value appears to be too small to account for the observed temperature changes of the rotational strength unless one assumes a very large ($[R] > 20$) rotational strength for the twist-boat conformation. It seems more likely that both solvation and conformational effects are responsible for these temperature-dependent amplitude changes.

The interpretation of the circular dichroism spectra (Figure 1c) of the 2,2-dimethyl ketone (+)-**3** is less ambiguous. Here a significant increase of $[R]$ (Table I) is observed in EPA (23%) at 77 K, whereas the rotational strength remains virtually unchanged (<1%) over this temperature range in IPM (Figure 1c and Table I). Therefore one can conclude with confidence that the changes observed in EPA are associated with the presence of a solvent–solute equilibrium. The calculated energy difference between the chair and twist-boat conformations (+)-**3** (Table II) also indicates that this molecule exists at room temperature predominantly in the chair conformation. The rotational strengths of (+)-**3** are found to be substantially larger (ca. 25% in methanol and isooctane) than the sum of the partial contributions for the α-axial ((+)-**2**) and α-equatorial ((+)-**1**) methyl groups, if one makes the additional assumption (see discussion above) that the room-temperature spectra of (+)-**2** are not perturbed by the presence of small amounts of twist-boat conformations. However, the predicted rotational strengths for (+)-**3** (calculated by taking the sum of the literature partial contributions for the α-axial and the α-equatorial methyl groups given in Table I) are in close agreement with the experimental results. This discrepancy is a result of the large deviation from the literature values for the cis ketone (+)-**1**, as discussed above.

**Table II.** Energy Differences between Chair and Twist-Boat Conformations Obtained by EFF Calculations[a]

| compd | $E_{twist\text{-}boat} - E_{chair}$, kcal/mol | % chair at 293 K | % chair at 77 K |
|---|---|---|---|
| **1** | 0.5 | 70 | 96 |
| **2** | 2.4 | 98 | 100 |
| **3** | 4.2 | 100 | 100 |
| **4** | −0.8 | 20 | 0.5 |
| **5** | 5.6 | 100 | 100 |
| **6** | 4.9 | 100 | 100 |
| *trans*-3-methyl-4-isopropylcyclohexanone | 3.2 | 99 | 100 |

[a] The atomic coordinates for the energy minima of the chair and twist-boat conformations are available on request from the authors.

The synthetic route (see ref 9) which led to (+)-**3** proceeded through a series of intermediates with various substituents in the 4 position. The rotational strengths of these molecules measured in IPM at room temperature and 77 K are given in Table I. In general the [*R*] values at room temperature for the 4-substituted 2,2-dimethylcyclohexanones are somewhat smaller than those found for (+)-**3**; in all instances except for the 4-isopropenyl substituted ketone a 10–20% increase of [*R*] is noted on lowering the temperature to 77 K. Since we observed no solvent–solute interactions for (+)-**3** in IPM, it appears reasonable to associate these changes with conformational equilibria. Aside from any different ring conformations, we have to consider various conformations resulting from the energetically nonequivalent rotamers of the 4 substituents with respect to the cyclohexanone ring, each of which may show somewhat different rotational strengths.

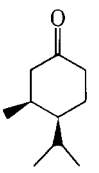
Of particular interest are the partially unexpected results obtained with the β-methyl substituted cyclohexanones. The CD spectra of the trans ketone (+)-**4** are shown in Figure 2a and are characterized by *positive* Cotton effects of unusually large ([*R*] = 10.81–12.08; see Table I) amplitude. This was a most surprising result, since from the well-established octant contributions of an equatorial β-methyl substituent (see Table I) one would have predicted a *negative* Cotton effect with a rotational strength of approximately [*R*] = −1.66 to −1.99 as was observed, for instance, in the adamantanone series[47] ([*R*] = −2.23). A reasonable explanation for this abnormal CD behavior of (+)-**4** is to assume a deviation from the normal chair conformation. An indication that this might be the correct interpretation was obtained from the CD data of the synthetic precursors of (+)-**4**. Compounds (−)-**23** (4-isopropenyl) and (−)-**24** (1-methyl-1-cyclopropyl at the 4 position) exhibit Cotton effects and rotational strengths of the expected sign and magnitude, whereas compound (+)-**22** (2-bromo-2-propyl substituent) again shows the unexpectedly large, *positive* Cotton effect (see Table I). These data seem to indicate that the steric interaction between the equatorial 4-*tert*-butyl and the trans (equatorial) 3-methyl groups must be such that the chair conformation becomes energetically less favorable than the most likely alternative, a twist-boat conformation. The unusually large CD amplitude is in agreement with this assumption, since only twist conformations exhibit rotational strengths of such magnitude.[48-50] Also, since the van der Waals radius for bromine is only slightly smaller (1.95 Å) than that for methyl (2.0 Å),[51] the 2-bromo-2-propyl substituent in (+)-**22** is subject to steric interactions similar to those of the *tert*-butyl group in (+)-**4**, resulting in a similar CD spectrum. The results of the EFF calculations for (+)-**4** confirm the above interpretation, since the twist-boat form of (+)-**4** shown in Figure 2a is calculated to be 0.8 kcal/mol lower in energy than the chair conformation (Table II). However, the EFF calculations for *trans*-3-methyl-4-isopropylcyclohexanone, which approximate the steric situation for compounds (−)-**23** and (−)-**24**, confirm that the energy relationship is reversed for these compounds as compared to (+)-**4**; i.e., the chair conformation is found to be more stable than the twist-boat conformation by 3.2 kcal/mol (Table II). Therefore, one of the rotamers of the isopropenyl (and 1-methyl-1-cyclopropyl) group in (−)-**23** (and (−)-**24**) must be able to minimize the steric interactions between it and the adjacent methyl group in the chair form, making this conformation the energetically most stable. The presence of only small intensity changes in the spectra of (+)-**22** and (+)-**4** indicates that, even at room temperature, the molecules are preferentially in the twist conformation. This result indicates that the EFF calculated energy difference of 0.8 kcal/mol is an underestimate and that this difference should be at least 1.5 kcal/mol.

*Therefore, although the tert-butyl group is in general a good conformational anchoring group, the present observations indicate that in particular situations the twist conformation can become energetically more favored.* In such cases, another group (e.g., the isopropenyl or 1-methyl-1-cyclopropyl) would be a better choice as a "lock" for a chair conformation.

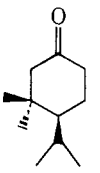
The foregoing discussion for (+)-**4** might indicate that a similar unusual conformational situation exists also for its cis analogue (−)-**5**. However, this is not the case. From model inspections and EFF calculations (Table II) it can be seen that the twist-boat form of this molecule cannot relieve the strain between the adjacent substituents and that the chair conformation remains the energetically preferred one. The calculated energy difference was found to be 5.6 kcal/mol (Table II).

The CD spectra of (−)-**5** are shown in Figure 2b. In IPM a comparatively small, negative Cotton effect is observed whose intensity is somewhat reduced (15%) at 77 K. In contrast the spectra measured in EPA undergo drastic changes with temperature, leading to a sign inversion at 77 K. Such a different behavior in both solvent systems is characteristic for the presence of a solvent–solute equilibrium.[37] The doubly signed CD spectrum at 143 K (positive at 319 and negative at 284 nm) seems to support this view, the solvated and unsolvated species having oppositely signed rotational strengths.

Our data for compound (−)-**5** are quite consistent with the data reported by Snatzke et al.[11] for the corresponding β-axial 4-methyladamantanone (**7**), i.e., a consignate behavior ([*R*] = −0.17) having been noted in isooctane and a dissignate behavior ([*R*] = 0.30) in ethanol. The difference from our data is that we observe a negative Cotton effect (consignate behavior) in both polar and nonpolar solvents at room temperature (Table I) and the sign inversion takes place only at lower temperature in the polar solvent mixture EPA. Therefore, we suggest that the apparent dissignate behavior in both the 4-*tert*-butylcyclohexanone and adamantanone systems is caused by a solvation effect which overrides the inherent consignate contribution of the β-axial methyl group. Whereas this appears to be a reasonable explanation of the CD temperature behavior of compound (−)-**5**, we point out that the appearance of two oppositely signed bands at low temperatures is observed in both IPM and EPA for compounds (−)-**16** and (−)-**30**, with an isopropenyl and isopropyl group in the 4 position. We suggest that the additional factor of rotamer conformation (i.e., the conformation of the substituent with respect to the cyclohexanone ring) is responsible for the observed temperature dependency of these CD spectra.



**30**



**31**

The circular dichroism spectra of the 3,3-dimethyl ketone (−)-**6** are shown in Figure 2c. In both solvent systems a negative Cotton effect is observed, as is the case for the synthetic precursors (−)-**28**, (−)-**31**, and (−)-**29** (with isopropenyl, isopropyl, and 1-methyl-1-cyclopropyl groups in the 4 position of the cyclohexanone ring, respectively (Table I)). Therefore, the energy inversion observed for (+)-**4** does not take place, and the chair remains the most stable conformation throughout the series. This is also substantiated by the EFF calculations, which predict the chair to be lower in energy by 4.9 kcal/mol as compared to the twist-boat conformation (Table II). A comparison of the temperature dependence of the rotational strengths (Figure 2c and Table I) reveals that [*R*] increases by ca. 60% in IPM but remains virtually unchanged in EPA on lowering the temperature to 77 K. The solvent dependency is therefore just the reverse of that observed for (+)-**3** (Figure

Ic). We also note that the resolution of the vibrational fine structure decreases in IPM but increases in EPA at 77 K. Such a behavior could possibly be caused by a dimerization equilibrium being present in the nonpolar (but not in the polar) solvent mixture. The rotational strengths for (−)-**6** are in agreement with those expected from the literature values (Table I).

## Summary

In summary, the presently recorded chiroptical results once again demonstrate the extraordinary sensitivity and utility of CD measurements for the detection of conformational changes. It is unlikely that other physical techniques would have demonstrated that the presence of an *equatorial* substituent adjacent to the 4-*tert*-butyl blocking group causes the twist-boat conformation to become the energetically preferred one, while as subtle a change as connecting two of the *tert*-butyl methyl groups to form a cyclopropane ring provides a suitable anchor for the chair conformation. The results of the EFF calculations are found to be in qualitative agreement with these experimental results.

## Experimental Section

**General Notes.** Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were determined on a Rudolph Autopol III polarimeter in thermostated 1.00-dm cells with removable endplates, for solutions in chloroform, unless otherwise noted. Ultraviolet (UV) spectra were obtained on a Cary 14 M spectrometer in a quartz cell of 1-cm path length. Infrared (IR) spectra were recorded either for neat liquid films between NaCl plates or for solutions in chloroform on either a Perkin-Elmer Model 700A spectrometer or a Nicolet Model 7199 Fourier transform spectrometer. Proton nuclear magnetic resonance (NMR) spectra were obtained on a Varian T-60 (60 MHz) spectrometer or by Dr. L. J. Durham on the Bruker HXS 360 (360 MHz) spectrometer of the Stanford Magnetic Resonance Laboratory using deuteriochloroform as solvent and tetramethylsilane as internal reference. Low-resolution mass spectra (MS) were obtained on a Varian MAT-44 spectrometer. High-resolution mass spectra were determined by Ms. A. Wegmann on a Varian MAT-711 spectrometer. Both spectrometers operated at 70 eV using a direct inlet system. Elemental analyses were determined by Mr. E. Meier of the Stanford Microanalytical Laboratory. The circular dichroism spectra were measured on a JASCO J-40 circular dichrometer, and the low-temperature spectra were obtained with a previously described cell.[52] The low-temperature CD spectra were corrected for solvent contraction using the values reported by Korvar and Bosma.[53] All temperatures are given in degrees Centigrade.

High-pressure liquid chromatography (LC) was performed on either a Waters Associates Prep LC/System 500 using silica gel columns or a Waters Associates analytical high-pressure liquid chromatography system using a 100 cm × 4.5 mm column packed with Corasil II. Column chromatography was done using E. Merck silica gel 60 (230-400 mesh ASTM). Gas chromatography (GC) was performed on a Varian Aerograph 2700 with thermal conductivity detector on 1/4 in. × 10 ft aluminum columns of either 10% SE-30 on Chromosorb W or 15% Carbowax 20M on Chromosorb W.

The EFF calculations were carried out with a computer program (MOLBD2) reported by Boyd[54,55] which was modified to fit the memory requirements of a Data General NOVA 840 computer. The force constants for the bond deformation modes (stretch, bend, and twist) were taken from ref 13 and 56; for the nonbond interactions, the force constants reported by Bartell[40] were adopted.

**(+)-Nopinone (8) and (+)-*trans*-3-Methylnopinone (9).** The synthesis of these compounds has been described in the previous paper.[9]

**(+)-*cis*-3-Methylnopinone (10).** (+)-*trans*-3-Methylnopinone (**9**) was treated with 5% methanolic potassium hydroxide for 24 h at room temperature. The reaction mixture was poured into water and extracted with hexane. The hexane extracts were washed with brine to neutrality, dried over anhydrous $Na_2SO_4$, and distilled to give the ketone (+)-**10**: $[\alpha]^{20}_D$ +56.1° (*c* 1.25); IR (neat) 1710 $cm^{-1}$; NMR $\delta$ 0.72 (s, 3 H), 1.15 (d, 3 H, $J$ = 6 Hz), 1.32 (s, 3 H); MS *m/z* 152 (32, $M^+$), 110 (15), 109 (35), 95 (27), 83 (100), 55 (37); mol wt 152.121 12. (calcd for $C_{10}H_{16}O$, 152.120 11).

**(2*R*,4*R*)-(+)-2-Methyl-4-(2-bromo-2-propyl)cyclohexanone (11).** This procedure follows that of Levine and Gopalakrishnan.[16] Into a 25-mL two-neck round-bottom flask (argon inlet, serum stopper, and magnetic stirrer) were placed (+)-*cis*-3-methylnopinone (**10**, 263 mmol, 400 mg) and $CH_2Cl_2$ (8 mL, distilled from $P_2O_5$) under argon. The flask was cooled to −78 °C and $BBr_3$ (2.9 mmol, 270 μL) was added dropwise. The mixture was stirred for 30 min, and pyridine (8.7 mmol, 700 μL) was added, followed by methanol (26.3 mmol, 1.07 mL). The solution was poured into water and extracted with ether. The combined extracts were washed with 5% oxalic acid and brine, passed through a portion of anhydrous $Na_2SO_4$, concentrated, and chromatographed rapidly (eluting with 5% ethyl acetate–hexane) to give the bromide (+)-**11** (331 mg, 54%) as a colorless oil: $[\alpha]^{20}_D$ +7.94° (*c* 1.41); IR (neat) 1720 $cm^{-1}$; NMR $\delta$ 1.05 (d, 3 H, $J$ = 6 Hz), 1.8 (s, 6 H); MS *m/z* 234 (2, $M^+$ for Br = 81), 232 (2, $M^+$ for Br = 79), 153 (28), 97 (44), 69 (100), 55 (81).

Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.51; H, 7.35. Found: C, 52.17; H, 7.59.

**(2*S*,4*R*)-(+)-2-Methyl-4-*tert*-butylcyclohexanone (2).** A solution of alcohol (+)-**12**[10] ($[\alpha]^{20}_D$ + 28.8° (*c* 1.33), mp 85–85.5 °C, 0.3 mmol, 50 mg) in 2 mL of acetone (freshly distilled from potassium permanganate) was cooled to 0 °C and treated with Jones reagent[57] (1.76 mmol, 220 μL). The solution was stirred for 6 min, diluted with ether, and poured into cold saturated $NaHCO_3$ solution. The aqueous layer was washed with ether, and the combined ether extracts were washed with water, dried over anhydrous $Na_2SO_4$, and concentrated to give 42 mg (85%) of a colorless oil. Purification by LC (eluting with 0.5% ethyl acetate–hexane) provided the pure ketone (+)-**2**: $[\alpha]^{20}_D$ +140° (*c* 0.38); IR (neat) 1720 $cm^{-1}$; NMR $\delta$ 0.9 (s, 9 H), 1.14 (d, 3 H, $J$ = 7 Hz); MS *m/z* 168 (30, $M^+$), 112 (95), 57 (100); mol wt 168.152 13 (calcd for $C_{11}H_{20}O$, 168.151 41).

**(2*R*,4*R*)-(+)-2-Methyl-4-*tert*-butylcyclohexanone (1), Method I.** The bromide (+)-**11** (1.29 mmol, 300 mg) was added to a solution of $NaBH_4$ (1.93 mmol, 72 mg) in methanol (5 mL) at 5 °C and stirred for 25 min. The reaction mixture was diluted with ether, poured into 5% HCl, and extracted with ether. The ether extracts were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated. The resulting solid (242 mg) was added to a 100-mL three-neck round-bottom flask (argon inlet, serum stopper, dry ice condenser, and magnetic stirrer) under argon. The flask was cooled to −78 °C and $CH_3Cl$ (ca. 10 mL) was added, followed by $Al(Me)_3$ (14.4 mmol, 6.0 mL of a 2.41 M solution, Alfa-Ventron). The cooling bath was removed and the reaction mixture was allowed to reflux for 4 h. The flask was cooled to −78 °C and $CH_3Cl$ (ca. 10 mL) was added, followed by $Al(Me)_3$ (14.4 mmol, 6.0 mL of a 2.41 M solution, Alfa-Ventron). The cooling bath was removed and the reaction mixture was allowed to reflux for 4 h. The flask was cooled to −78 °C and cold methanol (6 mL) was added dropwise. The flask and dry ice condenser were warmed to room temperature and the $CH_3Cl$ was allowed to boil off. Dilute HCl (9 mL) was added dropwise and the mixture was extracted with ether. The combined ether extracts were washed with brine, dried over anhydrous $Na_2SO_4$, concentrated, and chromatographed (eluting with 6% ethyl acetate–hexane) to give a mixture of 2-methyl-4-*tert*-butylcyclohexanols. The alcohols (108 mg) were dissolved in 5 mL of acetone, treated with excess Jones reagent[57] (ca. 500 μL), and stirred for 30 min at room temperature. The reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous $Na_2SO_4$, and concentrated to give the ketone (+)-**1** (100 mg, 46% from (+)-**11**), $[\alpha]^{20}_D$ +12.2° (*c* 0.35).

**Method II.** The ketone (+)-**2** (0.3 mmol, 50 mg) was treated with 5% methanolic potassium hydroxide for 12 h at room temperature. The reaction mixture was poured into water and extracted with hexane. The combined hexane extracts were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated to give 48 mg (96%) of (+)-**1** as a colorless oil: $[\alpha]^{20}_D$ +14.1° (*c* 0.51); IR (neat) 1720, 1370 $cm^{-1}$; NMR $\delta$ 1.07 (s, 9 H), 1.17 (d, 3 H, $J$ = 6 Hz); MS *m/z* 168 (28, $M^+$), 112 (100), 57 (79); mol wt 168.151 90 (calcd for $C_{11}H_{20}O$, 168.151 41).

**(+)-Verbenone (14).** This is the procedure of Dauben et al.[19] A solution of $CrO_3(py)_2$ complex was prepared by adding anhydrous $CrO_3$ (0.495 mol, 49.5 g) to a solution of pyridine (0.991 mol, 78.3 g) in $CH_2Cl_2$ (ca. 1200 mL). The solution was stirred for 15 min and (+)-α-pinene (**13**, 10.0 g, $[\alpha]^{25}_D$ 47.2° (neat), 90% optical purity)[18] was added. After stirring for 24 h at room temperature, the reaction

mixture was filtered, concentrated, and passed through a column of Florisil. The resulting solution was washed with 5% HCl, saturated $NaHCO_3$ solution, water, and brine, dried over anhydrous $Na_2SO_4$, concentrated, and distilled to give 1.05 g of starting material and 4.0 g (40%) of (+)-verbenone (**14**): $[\alpha]^{20}_D$ +247.8° (*c* 3.23); UV $\lambda_{max}$ 252 nm (log $\epsilon$ 3.97); IR (neat) 1680, 1620 $cm^{-1}$; NMR $\delta$ 1.0 (s, 3 H), 1.5 (s, 3 H), 2.02 (d, 3 H, $J$ = 2 Hz); MS *m/z* 150 (100, $M^+$), 135 (82), 107 (82), 91 (41), 80 (58); mol wt 150.103 90 (calcd for $C_{10}H_{14}O$, 150.104 46).

**(+)-*cis*-Verbanone (15).** The catalytic hydrogenation of (+)-verbenone (**14,** 0.12 mol, 18 g) with $PtO_2$ (0.04 g) in cyclohexane (20 mL) at room temperature and 1 atm was completed overnight. The reaction mixture was filtered, concentrated, and distilled to give (+)-*cis*-verbanone (**15,** 14 g, 77%): $[\alpha]^{20}_D$ +56.5° (*c* 1.0); IR (neat) 1705 $cm^{-1}$; NMR $\delta$ 1.0 (s, 3 H), 1.17 (d, 3 H, $J$ = 7 Hz), 1.34 (s, 3 H); MS *m/z* 152 (19, $M^+$), 109 (30), 95 (54), 83 (100), 55 (52); mol wt 152.120 12 (calcd for $C_{10}H_{16}O$, 152.120 11).

**(3*S*,4*R*)-(−)-3-Methyl-4-Isopropenylcyclohexanone (16).** (+)-*cis*-Verbanone (**15,** 0.092 mol, 14 g) was pyrolyzed at 450 °C in a Pyrex tube (25-mm diameter, 30-cm length) pack with glass beads (5-mm diameter) at a rate of 375 $\mu$L/min. The crude product (13.3 g) was purified using LC (eluting with 5% ethyl acetate-hexane), which provided the pure unsaturated ketone (−)-**16** (2.75 g, 20%): $[\alpha]^{20}_D$ −0.5° (*c* 1.38); IR (neat) 1710, 1650, 880 $cm^{-1}$; NMR $\delta$ 0.77 (d, 3 H, $J$ = 7 Hz), 1.8 (s, 3 H), 4.65 (bs, 1 H), 4.88 (bs, 1 H); MS *m/z* 152 (23, $M^+$), 110 (19), 82 (33), 68 (100), 67 (43), 67 (43); mol wt 152.119 76 (calcd for $C_{10}H_{16}O$, 152.120 11).

**(3*S*,4*R*)-(−)-3-Methyl-4-(1-methyl-1-cyclopropyl)cyclohexanone (17).** A mixture of zinc dust (2.57 mmol, 167 mg) and cuprous chloride (2.57 mmol, 254 mg) in anhydrous ether (1 mL) was heated to reflux for 30 min with stirring under nitrogen. Methylene diiodide (1.28 mmol, 103 $\mu$L) was added, and the mixture was heated at 40 °C until bubbles appeared and the solution turned dark. The olefin (−)-**16** (0.99 mmol, 150 mg) and 500 $\mu$L of $CH_2I_2$ were added and the mixture was kept at 40 °C with stirring for 20 h. The solution was diluted with ether and filtered through Celite, washed with 5% HCl, water, and brine, dried over anhydrous $Na_2SO_4$, concentrated, and chromatographed on silver nitrate impregnated silica gel (eluting with 5% ethyl acetate-hexane) to give the cyclopropane (−)-**17** (130 mg, 79%): $[\alpha]^{20}_D$ −19.3° (*c* 0.71); IR (neat) 3100, 1720, 1180 $cm^{-1}$; NMR $\delta$ 0.28 (m, 2 H), 0.45 (m, 2 H), 1.0 (d, 3 H, $J$ = 8 Hz), 1.05 (s, 3 H); MS *m/z* 166 (1, $M^+$), 138 (45), 111 (75), 96 (56), 82 (53), 67 (47), 55 (100); mol wt 166.135 43 (calcd for $C_{11}H_{18}O$, 166.135 76).

**(3*S*,4*R*)-(−)-3-Methyl-4-*tert*-butylcyclohexanone (5).** The catalytic hydrogenation of the cyclopropane (−)-**17** (0.21 mmol, 35 mg) with 2 mg of $PtO_2$ in 1 mL of acetic acid at room temperature and 4 atm (Parr hydrogenation apparatus) was completed overnight. The reaction mixture was poured into water and extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution, water, and brine, dried over anhydrous $Na_2SO_4$, and concentrated to give 32 mg of a mixture of 3-methyl-4-*tert*-butylcyclohexan-1-ols. A solution of the alcohol mixture in 1 mL of acetone was treated with excess Jones reagent[57] (ca. 50 $\mu$L) and stirred at room temperature for 30 min. Normal workup (as described in the synthesis of the ketone (+)-**1**) gave the ketone (−)-**5** (30 mg, 95%): $[\alpha]^{20}_D$ −3.4° (*c* 0.53); IR (neat) 1715 $cm^{-1}$; NMR $\delta$ 0.97 (s, 9 H), 0.97 (m, 3 H); MS *m/z* 168 (10, $M^+$), 112 (32), 57 (100); mol wt 168.152 10 (calcd for $C_{11}H_{20}O$, 168.151 41).

**(+)-*cis*-3-Bromonopinone (19).** This procedure follows that of Grimshaw et al.[25] A solution of (+)-nopinone (**8**, 14 mmol, 2.0 g) in $CCl_4$ (20 mL) was treated with *N*-bromosuccinimide (18 mmol, 3.2 g) and benzoyl peroxide (0.1 g) and refluxed for 3 h. The mixture was filtered and the filtrate was concentrated, diluted with ether, and passed through a column of alumina (activity I). The resulting solution was concentrated and recrystallized from pentane to give 1.11 g (37%) of the bromide (+)-**19** as a white, crystalline solid: mp 111–112 °C; $[\alpha]^{20}_D$ +15.3° (*c* 1.77); IR (solution) 1720 $cm^{-1}$; NMR $\delta$ 0.87 (s, 3 H), 1.37 (s, 3 H), 4.8 (m, 1 H); MS *m/z* 137 (36), 136 (37), 95 (53), 94 (60), 83 (83), 82 (90), 55 (100).

Anal. Calcd for $C_9H_{13}BrO$: C, 49.97; H, 6.01. Found: C, 49.84; H, 6.15.

**(+)-*trans*-Verbanone (21).** A solution of the bromide (+)-**19** (0.046 mol, 10 g) in dimethyl sulfoxide (100 mL) was treated with anhydrous lithium bromide (20 g) and lithium carbonate (17.5 g) and heated at 140–150 °C for 60 h. The reaction mixture was cooled and filtered. The filtrate was diluted with water and extracted with ether. The combined ether extracts were washed with water and brine, dried over anhydrous $Na_2SO_4$, concentrated, and chromatographed (eluting with 5% acetone-hexane) to give 3.45 g of an approximately 5:1 mixture of the enone **20** and (+)-nopinone (**8**). This mixture proved difficult to separate and therefore was used without purification in the synthesis of the ketone (+)-**21**. A suspension of copper(I) iodide (30 mmol, 5.6 g) in anhydrous ether (60 mL) was cooled to −78 °C over nitrogen, and methyllithium (30 mmol, 19.4 mL of a 1.55 M solution) was added. The mixture was warmed to 0 °C, a second equivalent of MeLi (19.4 mL) was added, and the mixture was stirred for 30 min at 0 °C. A solution of the mixture obtained from the previous reaction (2 g) in a small amount of ether was added and the resulting solution was stirred for 1 h at 0 °C. The mixture was poured into 5% HCl (600 mL) and extracted with ether. The ether extracts were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated. Purification by LC (eluting with 3% ethyl acetate-hexane) provided the pure ketone (+)-**21** (2.0 g): $[\alpha]^{20}_D$ +29.0°( *c* 0.97) [lit.[26] $[\alpha]^{21}_D$ +22.4° (*c* 10% in benzene)]; IR (neat) 1715 $cm^{-1}$; NMR $\delta$ 0.85 (s, 3 H), 1.05 (d, 3 H, $J$ = 6 Hz); 1.34 (s, 3 H); MS *m/z* 152 (15, $M^+$), 109 (32), 95 (48), 83 (100), 55 (64); mol wt 152.120 10 (calcd for $C_{10}H_{16}O$, 152.120 11).

**(3*R*,4*R*)-(+)-3-Methyl-4-(2-bromo-2-propyl)cyclohexanone (22).** Following the procedure for the synthesis of the bromide (+)-**11**, (+)-*trans*-verbanone (**21**, 2.9 mmol, 440 mg) was treated with $BBr_3$ (3.2 mmol, 295 $\mu$L) for 1.5 h at −78 °C. Normal workup, followed by rapid chromatography (eluting with 10% ethyl acetate-hexane under ca. 10 lb nitrogen pressure), gave 200 mg of a 5:1 mixture of starting ketone (+)-**21** and the olefin (−)-**23,** respectively, along with 250 mg (37%) of the bromide (+)-**22** as a colorless oil which crystallized at −15 °C: $[\alpha]^{20}_D$ +140.6° (*c* 0.68); IR (neat) 1720 $cm^{-1}$; NMR $\delta$ 1.07 (d, 3 H, $J$ = 6 Hz), 1.78 (s, 3 H), 1.83 (s, 3 H); MS *m/z* 234 (2, $M^+$ for Br = 81), 232 (2, $M^+$ for Br = 79), 153 (24), 97 (42),83 (48), 69 (100), 55 (88).

Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.51; H, 7.35. Found: C, 51.08; H, 7.99.

**(3*R*,4*R*)-(−)-3-Methyl-4-isopropenylcyclohexanone (23).** Following the procedure for the synthesis of the bromide (+)-**11**, (+)-*trans*-verbanone (**21,** 19,9 mmol, 1.5 g) was treated with $BBr_3$ (10.9 mmol, 1.0 mL) for 1 h at −78 °C. Normal workup, followed by chromatography (eluting with 5% ethyl acetate-hexane), gave 1.3 g of a 2:1 mixture of starting ketone (+)-**21** and the olefin (−)-**23.** Chromatography on silver nitrate impregnated silica gel (eluting with 7% ethyl acetate-hexane) provided the pure olefin (−)-**23**: $[\alpha]^{20}_D$ −27.7° (*c* 0.66); IR (neat) 3060, 1715, 1645 $cm^{-1}$; NMR $\delta$ 0.91 (d, 3 H, $J$ = 5 Hz), 1.67 (m, 3 H), 4.8 (m, 2 H); MS *m/z* 152 (40, $M^+$), 137 (30), 110 (31), 82 (42), 68 (100), 67 (42); mol wt 152.120 23 (calcd for $C_{10}H_{16}O$, 152.120 11).

**(3*R*,4*R*)-(−)-3-Methyl-4-(1-methyl-1-cyclopropyl)cyclohexanone (24).** Following the procedure for the synthesis of the cyclopropane (−)-**17**, the olefin (−)-**23** (0.99 mmol, 150 mg) gave 65 mg (40%) of the cyclopropane (−)-**24**: $[\alpha]^{20}_D$ −51.4° (*c* 0.42); IR (neat) 3080, 1715 $cm^{-1}$; NMR $\delta$ 0.37 (m, 4 H), 0.95 (s, 3 H), 1.15 (d, 3 H, $J$ = 6 Hz); MS *m/z* 166 (1, $M^+$), 111 (76), 110 (54), 82 (41), 67 (43), 55 (100); mol wt 166.135 62 (calcd for $C_{11}H_{18}O$, 166.135 76).

**(3*R*,4*R*)-(+)-3-Methyl-4-*tert*-butylcyclohexanone (4).** Following the procedure for the synthesis of (−)-**5**, the cyclopropane (−)-**24** (0.3 mmol, 49 mg) was hydrogenated to a mixture of *tert*-butyl alcohols, which was oxidized using Jones reagent to give 42 mg (85%) of the ketone (+)-**4**: $[\alpha]^{20}_D$ +247.8° (*c* 0.45); IR (neat) 1720 $cm^{-1}$; NMR $\delta$ 0.93 (s, 9 H), 0.98 (d, 3 H, $J$ = 5 Hz); MS *m/z* 168 (26, $M^+$), 112 (91), 97 (42), 83 (59), 57 (100), 55 (44); mol wt 168.151 12 (calcd for $C_{11}H_{20}O$, 168.151 41).

**4-*tert*-Butyl-2-cyclohexen-1-one (26).** A solution of 4-*tert*-butylcyclohexanone (**25,** 0.02 mol, 3.08 g) in ethylene glycol (40 mL) was treated with anhydrous HBr (1.62 g) at 50 °C for 2 h. The mixture was saturated with NaCl and extracted with ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution, water, and brine, dried over anhydrous $Na_2SO_4$, and distilled to give a product (4.4 g) which NMR indicated to be the ethylene ketal of 2-bromo-4-*tert*-butylcyclohexanone, with singlets of nine and four protons at $\delta$ 0.87 and 3.63, respectively, and a multiplet of one proton at $\delta$ 4.2. A solution of the bromo ketal (5.8 mmol, 1.6 g) in dimethyl sulfoxide (7 mL) was treated with sodium methoxide (1.1 g) and the mixture was kept at 80 °C for 2.5 h, poured into water, and extracted with hexane. The hexane extracts were washed with brine, dried over anhydrous $Na_2SO_4$, concentrated, and distilled, Hydrolysis of the

distillate with 15% sulfuric acid (2 mL) in dioxane (1 mL) gave the enone **26** (490 mg): UV $\lambda_{max}$ 228 nm (log $\epsilon$ 4.01); IR (neat) 1685 $cm^{-1}$; NMR $\delta$ 0.98 (s, 9 H), 5.98 (d of d, $J$ = 10 and 2 Hz), 6.95 (d of t, $J$ = 10 and 2 Hz); MS *m/z* 152 (3, $M^+$), 96 (100), 57 (74); mol wt 152.119 95 (calcd for $C_{10}H_{16}O$, 152.120 11).

***trans*-3-Methyl-4-*tert*-butylcyclohexanone (Racemic 4).** Following the procedure for the synthesis of the ketone (+)-**21**, the enone **26** (1.97 mmol, 300 mg) was treated with a solution of $Me_2CuLi$ to give racemic **4** (275 mg, 83%): IR (neat) 1720 $cm^{-1}$; NMR $\delta$ 0.93 (s, 9 H), 0.98 (d, 3 H, $J$ = 5 Hz); MS *m/z* 168 (25, $M^+$), 112 (91), 97 (40), 83 (59), 57 (100), 55 (45); mol wt 168.151 61 (calcd for $C_{11}H_{20}O$, 168.151 41).

**4,4-Dimethylnopinone (27).** 4,4-Dimethylnopinone (**27**) was synthesized by the literature procedure[28] from (+)-verbenone (**14**): $[\alpha]^{20}_D$ +47.3° (*c* 5.7); IR (neat) 3080 (C=CH), 1720 (C=O), 1640 (C=C), 1370-1390 ($C(CH_3)_2$) $cm^{-1}$; NMR $\delta$ 1.00 (s, 3 H), 1.06 (s, 3 H), 1.23 (s, 3 H), 1.33 (s, 3 H); MS *m/z* 166 (25, $M^+$), 124 (33), 109 (62), 95 (37), 83 (100), 69 (45), 55 (30); mol wt 166.135 85 (calcd for $C_{11}H_{18}O$, 166.135 76).

**(*S*)-(−)-3,3-Dimethyl-4-isopropenylcyclohexanone (28).** Following the procedure for the synthesis of (−)-**16**, the ketone (+)-**27** (60 mmol, 10 g) was pyrolyzed to yield a mixture of products, from which 1.46 g (8.8 mmol, 14%) of the olefin (−)-**28** was isolated by preparative LC: $[\alpha]^{20}_D$ −12.6° (*c* 1.9); IR (neat) 1720 (C=O), 1390-1370 ($C(CH_3)_2$) $cm^{-1}$; NMR $\delta$ 0.86 (s, 3 H), 1.03 (s, 3 H), 1.80 (t, 3 H, $J$ = 2 Hz), 4.70 (bs, 1 H), 4.90 (t, 1 H, $J$ = 2 Hz); MS *m/z* 166 (12, $M^+$), 110 (26), 82 (21), 68 (100), 67 (38); mol wt 166.135 80 (calcd for $C_{11}H_{18}O$, 166.135 75).

**(*S*)-(−)-3,3-Dimethyl-4-(1-methyl-1-cyclopropyl)cyclohexanone (29).** Following the procedure for the synthesis of the cyclopropane (−)-**17**, the olefin (−)-**28** (2.4 mmol, 400 mg) gave, in addition to the unreacted starting material (0.6 mmol, 100 mg), 45 mg (11%) of the cyclopropane (−)-**29**: $[\alpha]^{20}_D$ −23.1° (*c* 6.7); IR (neat) 1720 (C=O), 1390-1370 ($C(CH_3)_2$) $cm^{-1}$; NMR $\delta$ 0.0-0.9 (m, 4 H), 1.05 (s, 6 H), 1.21 (s, 3 H); MS *m/z* 180 (27, $M^+$), 125 (93), 124 (25), 95 (37), 83 (60), 82 (100), 69 (38), 67 (91), 55 (61); mol wt 180.152 19 (calcd for $C_{12}H_{20}O$; 180.151 41).

**(*S*)-(−)-3,3-Dimethyl-4-*tert*-butylcyclohexanone (6).** Following the procedure for the synthesis of (−)-**5**, the cyclopropane (−)-**29** (0.22 mmol, 40 mg) was hydrogenated to a mixture of *tert*-butyl alcohols, which was oxidized using Jones reagent to give 35 mg (85%) of the ketone (−)-**6**: $[\alpha]^{20}_D$ −2.4° (*c* 1.9); IR (solution) 1720 (C=O) $cm^{-1}$; NMR $\delta$ 1.00 (s, 3 H), 1.05 (s, 9 H), 1.21 (s, 3 H), 1.58 (s, 2 H); MS *m/z* 182 (6, $M^+$), 98 (23), 93 (28), 69 (31), 59 (20), 57 (100); mol wt 182.166 28 (calcd for $C_{12}H_{22}O$, 182.167 05).

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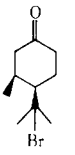


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