(59%) of (+)-1 [bp 70 °C (10 mm); $[\alpha]^{24}_D$ +66.3 ± 3.5° (c 3.1, $CHCl_3$)] which was >99% pure by GLC on column A at 150 °C.

Cyclization of (−)-18 to (−)-1. Alcohol (−)-18 (28 mg, 0.14 mmol) in 0.5 mL of $CHCl_3$ was cyclized as above with PTSA to yield after distillation (−)-1 [14.5 mg (62%); $[\alpha]^{23}_D$ −71.6 ± 2.0° (c 3.6, $CHCl_3$)] which was >99% pure by GLC on column A at 150 °C.

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Registry No. (+)-1, 65035-34-9; (−)-1, 73649-91-9; (±)-1, 71899-16-6; **2**, 22954-83-2; (±)-**3**, 73433-57-5; (±)-**4a**, 73433-58-6; (±)-**4b**, 73494-07-2; (±)-**5a**, 73433-59-7; (±)-**5b**, 73494-08-3; (±)-**11a**, 73433-60-0; (±)-**11b**, 73494-09-4; (±)-**12**, 73433-61-1; (±)-**13**, 73433-62-2; (±)-**14**, 73433-63-3; **15**, 52545-77-4; **16**, 1192-33-2; **17**, 1192-14-9; (+)-**18**, 73433-64-4; (−)-**18**, 73494-10-7; (±)-**18**, 73494-11-8; (±)-**19**, 73433-65-5; (±)-**20**, 71899-15-5; (+)-**22a**, 73433-66-6; (−)-**22b**, 73494-12-9; (±)-**10**, 73433-67-7.

Synthesis of Chiral Conformationally Fixed Cyclohexanones[1]

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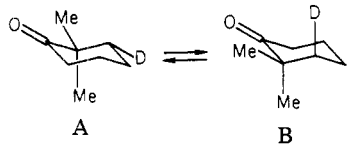
Received December 26, 1979

Two syntheses of (*R*)-(+)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**1**) are presented. Related 4-alkylcyclohexanones (intermediates in the syntheses) bear other (potential) conformational anchoring groups. The key steps in the syntheses are the opening of the cyclobutane ring of (+)-3,3-dimethylnopinone (**10**) by either pyrolysis or reaction with BBr_3. The high optical purity of the final compound was determined by analysis of the ^{19}F NMR spectrum of the diastereomeric ester mixture obtained from the reaction of alcohol (+)-**14b** with (*S*)-(+)-MTPA chloride.

Since the original publication of the octant rule in 1961,[2] optical rotatory dispersion (ORD) and circular dichroism (CD) have been used to obtain important information about the absolute stereochemistry and/or conformation of chiral ketones[3] and, as such, have become important research tools. Recently, we[4] and others[5] have become interested in the effects of isotopic substituents on CD spectra. The data already obtained have led to a greater understanding of the nature and origins of the induced Cotton effect,[6] and variable-temperature circular dichroism has been used successfully to study the conformational demands of isotopic substituents in conformationally mobile cyclohexanone systems.[4d,e] Thus from equilibrium 1, where the molecule bears a *gem*-dimethyl "chiral probe",[4d] it was determined that deuterium prefers to occupy the axial position. The enthalpy difference between the two conformations was calculated to be in the range of 5 ± 2 cal/mol.



(1)

This type of enthalpy calculation depends upon a reasonable assumption of the rotational strengths ([*R*] values) of the individual conformers A and B. These [*R*] values are determined from the CD spectrum of a "reference" compound which, while bearing the particular substituent of interest, is held in a fixed conformation due to either (1) sufficient rigidity in the carbon skeleton to preclude conformational change (e.g., the adamantane[5] or the steroid[7] skeleton) or (2) excessive bias of one conformation over another due to a large potential-energy difference (e.g., the *tert*-butylcyclohexane skeleton[4c,8]). We felt that cyclohexanones with a γ-*tert*-butyl group would serve as the most convenient and appropriate models for the conformationally mobile systems we are investigating and, therefore, searched for a general synthetic path to such chiral ketones.

In this paper, we report two syntheses of (*R*)-(+)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**1**). Several related 2,2-dimethylcyclohexanones with other 4-alkyl substituents which can be considered as conformational anchoring groups were prepared as intermediates to (+)-**1**. In a subsequent paper,[9] the syntheses of 4-*tert*-butylcyclohexanones having different substitution patterns will be presented, and the CD spectra of these reference ketones will be discussed in detail.

Initial Considerations and Synthesis. Generality was of paramount importance in the design of a synthesis of

(1) Taken from: Konopelski, J. P. Ph.D. Thesis, Stanford University, 1979.

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(3) For a general discussion, see: (a) Djerassi, C. *Proc. Chem. Soc., London* **1964**, 314-330. (b) Crabbé, P. "ORD and CD in Chemistry and Biochemistry"; Academic Press: New York, 1972.

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(6) Meyer, W. L.; Lobo, A. P.; Ernstbrunner, E. E.; Giddings, M. R.; Hudec, J. *Tetrahedron Lett.* **1978**, 1771-1774.

(7) Kirk, D. N.; Klyne, W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1076-1103.

(8) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562-5578.

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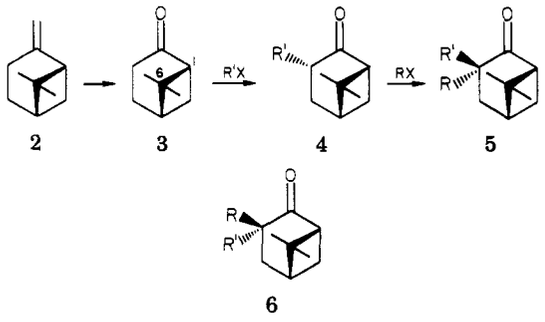
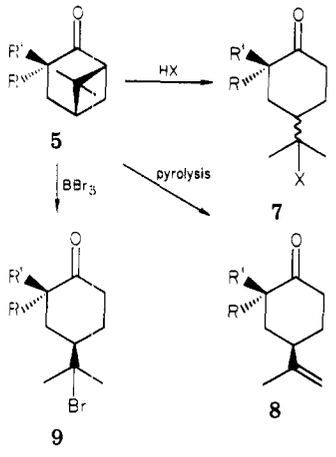
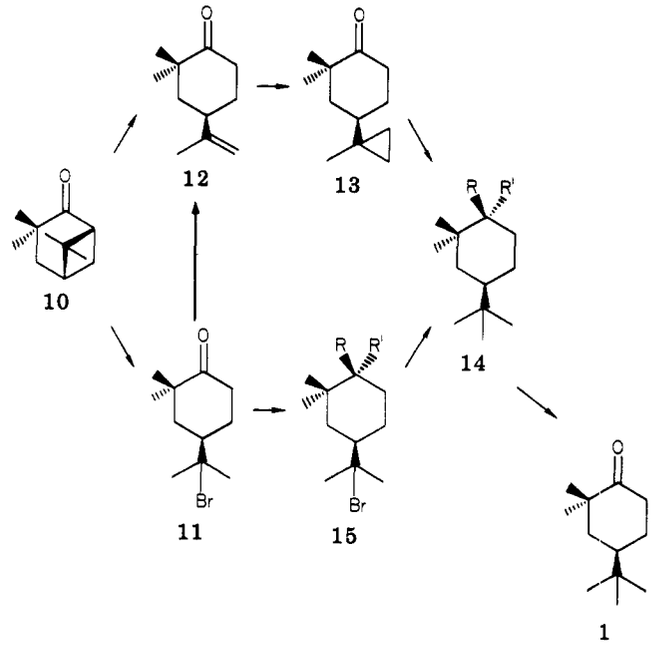
Scheme I



Scheme II



Scheme III



a, R = OH; R′ = H; b, R = H; R′ = OH

ketone (+)-1. Any synthetic route(s) must be adaptable to molecules bearing substituents other than α,α-dimethyl, including isotopic substituents. Since the CD effect of a molecule whose chirality is due solely to isotopic substitution is small,[4a,b,5] high optical purity is a necessity. Accordingly, it was decided to begin with a naturally occurring chiral compound of known absolute configuration rather than relying on a resolution step. We were also interested in studying the effectiveness of alkyl substituents other than *tert*-butyl as conformational anchoring groups. Therefore, the syntheses of ketone (+)-1 were designed to include a number of molecules with substituents at C-4 related to the desired *tert*-butyl group. The chiroptical properties of these intermediates and the final compound are described in a subsequent paper[9] and shed some light on a hitherto unrecognized limitation of the *tert*-butyl group.

(+)-Nopinone (3), available in large quantities by ozonolysis of (−)-β-pinene (2), is a very convenient and versatile starting material. The absolute configuration is known, and reliable data are available on the optical purity of both (−)-2 and (+)-3.[10,11] Also, as will be discussed shortly, nopinone-type molecules are known to undergo cleavage of the C-1–C-6 bond to give cyclohexanones substituted at C-4.

Nopinone can be alkylated α to the ketone (under kinetic control) to give exclusively the thermodynamically less stable exo isomer 4 (Scheme I).[12] The second alkylation is also stereospecific, with approach of the R group again from the less hindered side to give 5. The epimeric compound 6 (R ≠ R′) can be synthesized[14] by reversing the order of alkyl group introduction.

Our synthetic strategy called for the modification of the nopinone skeleton into a cyclohexanone system bearing a γ substituent related to *tert*-butyl. Several reactions are known to mediate this type of transformation (Scheme II). Treatment of nopinones with mineral acids results in opening the cyclobutane ring with formation of a cyclohexanone substituted at C-4 with a three-carbon unit[15] (7, X varies depending upon the acid or combination of acids used). However, the product undergoes racemization, the extent of which is dictated by the reaction conditions, thus reducing the utility of this synthetic approach for chiroptical studies.[16] The cyclobutane ring of nopinones can also be cleaved by pyrolysis, which has been reported to give, among other products, 4-isopropenylcyclohexanones (8).[17] Although there is no racemization of the crucial γ position, the poor yield (15–30%) of the desired molecule limits the use of this reaction, especially for the synthesis of expensive isotopically labeled compounds.[18] Finally, Levine and Gopalakrishnan[19] have reported that the reaction of 3,3-dideuterionopinone (5, R = R′ = D) with BBr_3

(10) Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50–52.

(11) Comyns, A. E.; Lucas, H. J. *J. Am. Chem. Soc.* **1957**, *79*, 4339–4341.

(12) The assignment of the stereochemistry of 4 was based on the fact that when (+)-*trans*-3-methynopinone (4, R′ = Me) was treated with 5% methanolic potassium hydroxide at room temperature for 24 h, a new compound was isolated which had an NMR spectrum identical with that reported[13] for (+)-*cis*-3-methylnopinone (5, R′ = Me; R = H).

(13) Bessière-Chrétien, Y.; Meklati, B. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1969**, *269*, 1315–1318.

(14) Edgar, M. T.; Barth, G.; Lee, S.-F.; Pak, C. S.; Djerassi, C. *J. Am. Chem. Soc.*, in press.

(15) Van Der Gen, A.; Van Der Linde, L. M.; Witteveen, J. G.; Boelens, H. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1034–1044.

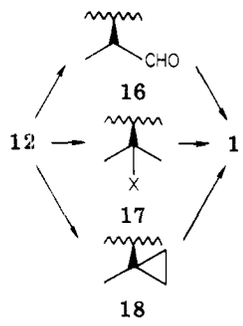
(16) This is not strictly true, since the racemization at C-4 does not affect other optical centers that may be present in the molecule. For example, removal, by suitable chemical means, of the γ substituent in 7 would result in the formation of a 2,2-disubstituted cyclohexanone whose optical activity (R ≠ R′) is determined solely by the optical purity of the starting β-pinene and the stereospecificity of the alkylation reactions used in the synthesis of 5. This type of synthesis has been used successfully in our laboratory. See ref 14.

(17) (a) Coxon, J. M.; Garland, R. P.; Hartshorn, M. P. *Aust. J. Chem.* **1972**, *25*, 2409–2415. (b) Mayer, C. F.; Crandall, J. K. *J. Org. Chem.* **1970**, *35*, 2688–2690. (c) Takagi, Y.; Nakahara, Y.; Matsui, M. *Tetrahedron* **1978**, *34*, 517–521.

(18) This does not hold true if the isotopic substitution occurs *after* the pyrolysis step. See ref 4a.

(19) Levine, S. G.; Gopalakrishnan, B. *Tetrahedron Lett.* **1979**, 699.

Scheme IV



gave (*R*)-2,2-dideuterio-4-(2-bromo-2-propyl)cyclohexanone (**9**, R = R′ = D) of substantial, but unknown, enantiomeric excess. This reaction could be of significant synthetic utility in the present study, provided it proceeds with high optical purity and is not affected by the presence of alkyl substituents.

It was decided to explore the reaction of BBr_3 with a substituted nopinone molecule and to compare these results with those obtained by pyrolysis (Scheme III). Treatment of (+)-3,3-dimethylnopinone (**10**), prepared according to Scheme I (R = R′ = Me), with BBr_3 gave (*R*)-(+)-2,2-dimethyl-4-(2-bromo-2-propyl)cyclohexanone (**11**) in 77% yield. When (+)-**10** was subjected to pyrolysis, it afforded (*R*)-(+)-2,2-dimethyl-4-isopropenylcyclohexanone (**12**) in 17% yield.

It should be noted that since both routes depicted in Scheme III begin with the same chiral molecule, simple comparison of the rotation and the CD spectrum of each final compound (**1**) will determine the relative stereospecificity of the two synthetic sequences. However, the relative stereochemical merit of the first reaction in each sequence can be ascertained by the conversion of bromide (+)-**11** to olefin (+)-**12**. When (+)-**11** was treated with $KOC(C_2H_5)_3$,[20] (+)-**12** was isolated in good yield. This newly synthesized sample of the olefin (+)-**12** was identical, by CD spectrum and rotation, with the substituted isopropenyl compound formed in the pyrolysis of ketone (+)-**10**. Therefore, the reaction of BBr_3 with (+)-**10** proceeds with the same degree of stereospecificity as does the pyrolysis of (+)-**10** to (+)-**12**.

Several approaches were considered for the transformation of the isopropenyl (or 2-bromo-2-propyl) side chain into the desired *tert*-butyl group. For example, olefin (+)-**12** could be hydroborated and oxidized to aldehyde **16** (Scheme IV), using the method of Meinwald and Jones.[21] Methylation α to the aldehyde (after proper protection of the cyclohexanone ketone) followed by reduction of the aldehyde to the hydrocarbon would give the ketone **1**. Although this sequence is straightforward, it was thought to be somewhat lengthy for our purposes and was not pursued. A shorter synthetic approach would begin with Markownikoff-type hydration or hydrohalogenation of (+)-**12**, resulting in **17** (a molecule similar to or identical with **11**, depending upon the heteroatom). The tertiary heteroatom could then be replaced with a methyl group by using $Al(Me)_3$.[22] A third route to the desired final product involves the cyclopropanation of olefin (+)-**12** to give cyclopropane **18**.[23] Hydrogenolysis of the least substituted bond of the cyclopropane ring[24] would result in the *tert*-butyl substituted molecule **1**.

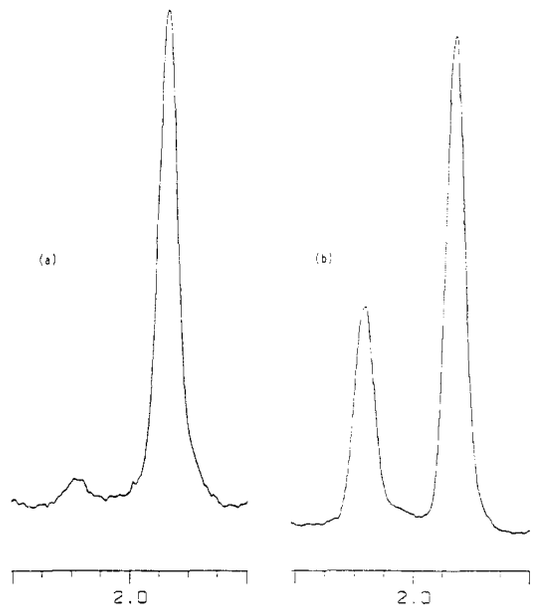


Figure 1. ^{19}F NMR spectra of the MTPA esters from (a) (1*R*,4*R*)-(+)-2,2-dimethyl-4-*tert*-butylcyclohexan-1-ol (**14b**) and (b) partially racemized **14b**.

As seen in Scheme III, these latter two approaches were developed for the synthesis of (+)-**1**. Reaction of olefin (+)-**12** with CH_2I_2 in the presence of zinc–copper couple formed in situ[23b] resulted in the formation of cyclopropane (+)-**13**, which was hydrogenated with PtO_2 in AcOH[24] to give two compounds identified as the epimeric alcohols **14**.[25] Oxidation using Jones reagent afforded the desired (*R*)-(+)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**1**) in ca. 7% yield from (+)-**10**. The second synthesis of (+)-**1** also proceeded without incident. Reduction of bromide (+)-**11** with $NaBH_4$ gave a mixture of bromo alcohols (**15**), which was treated without purification with $Al(Me)_3$ to give the *tert*-butyl alcohols (+)-**14**. Again, Jones oxidation gave the desired ketone (+)-**1** in 45% yield from (+)-**10**. The higher yield of this second synthesis makes it the method of choice.

Optical Purity. As discussed previously, the relative stereospecificity of the two syntheses in Scheme III was easily established. An inspection of the CD spectrum and the rotation of the final compound from each sequence showed them to be identical within experimental error. Although this result would tend to indicate that both synthetic routes proceeded with little or no racemization, it was necessary to establish the absolute optical purity of (+)-**1**.

This was accomplished by treating the equatorial alcohol (+)-**14b** with (*S*)-(+)-MTPA[26] chloride in pyridine.[27] Figure 1a shows the ^{19}F NMR spectrum of the diastereomeric MTPA esters derived from (+)-**14b**. The spectrum of the MTPA esters synthesized from a sample of partially racemized **14b**[28] is given in Figure 1b. Integration of the

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(21) Meinwald, J.; Jones, T. H. *J. Am. Chem. Soc.* **1978**, *100*, 1883–1886.
(22) (a) Harney, D. W.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1974**, *27*, 1639–1653. (b) Kennedy, J. P. *J. Org. Chem.* **1970**, *35*, 532–535. (c) Kennedy, J. P.; Desai, N. V.; Sivaram, S. *J. Am. Chem. Soc.* **1973**, *95*, 6386–6390.
(23) (a) Woodworth, C. W.; Buss, V.; Schleyer, P. v. R. *Chem. Commun.* **1968**, 569–570. (b) Rawson, R. J.; Harrison, I. T. *J. Org. Chem.* **1970**, *35*, 2057–2058.
(24) (a) Gröger, C.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 373–374. (b) Oppolzer, W.; Godel, T. *J. Am. Chem. Soc.* **1978**, *100*, 2583–2584.
(25) Richer, J.-C.; Perrault, G. *Can. J. Chem.* **1965**, *43*, 18–23.
(26) MTPA = α-methoxy-α-(trifluoromethyl)phenylacetic acid.
(27) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549. We are grateful to Professor H. S. Mosher for a sample of (*S*)-(+)-MTPA chloride.

spectrum (a) leads to a value of 88% enantiomeric excess (ee) for alcohol (+)-**14b** and, therefore, for ketone (+)-**1**. Since the (−)-β-pinene used as starting material has an optical purity of 92%,[11,29] the synthetic pathways presented in this paper proceed with very high (if not complete) stereochemical control, and comparison of the chiroptical properties of the various 4-alkylated cyclohexanones can thus be performed with confidence. These results, together with their conformational implications, are described in a subsequent paper.[9]

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. 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. ^{1}H NMR spectra were obtained on a Varian T-60 (60 MHz) spectrometer or the Bruker HXS 360 (360 MHz) spectrometer of the Stanford Magnetic Resonance Laboratory, using deuteriochloroform as solvent and tetramethylsilane as internal reference. ^{19}F NMR spectra were recorded on a Varian XL-100 spectrometer by Dr. L. J. Durham. Low-resolution mass spectra 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 with a direct inlet system. Elemental analyses were determined by Mr. E. Meier of the Stanford Microanalytical Laboratory.

High-pressure liquid chromatography (high-pressure LC) was performed on a Waters Associates Prep LC/System 500 using silica gel columns. Column chromatography was done with E. Merck silica gel 60 (230–400 mesh ASTM). Gas chromatography (GC) was performed on a Varian Aerograph 2700 with a thermal conductivity detector on 0.25 in. × 10 ft aluminum columns of either 10% SE-30 on Chromosorb W or 15% Carbowax 20M on Chromosorb W.

All temperatures are given in degrees Celsius.

(+)-Nopinone (3). Ozone was bubbled through a solution of (−)-β-pinene (**2**, 35.0 g, $[\alpha]_D$ −21° (neat), 92% optical purity) in 600 mL of absolute methanol at −78 °C. Excess ozone was purged with nitrogen at −78 °C, and dimethyl sulfide (29 mL) was added. The mixture was stirred overnight at room temperature and concentrated. The resulting oil was diluted with hexane, washed with water and brine, dried over anhydrous $MgSO_4$, concentrated, and distilled to give (+)-nopinone (**3**, 25.6 g, 72%): $[\alpha]^{20}_D$ +35.3°(*c* 0.99), +36.6°(*c* 1.6, MeOH) (lit.[10] $[\alpha]_D$ +39.9°(MeOH)); IR (neat) 1702, 1460, 1200 cm^{-1}; NMR δ 0.85 (s, 3 H), 1.33 (s, 3 H); mass spectrum, *m/z* 138 (20%, M$^+$), 109 (22%), 95 (29%), 83 (100%), 81 (25%), 55 (45%); mol wt calcd for $C_9H_{14}O$ 138.10446, found 138.10623.

(+)-*trans*-3-Methylnopinone (4, R′ = Me). To a 100-mL two-neck round-bottom flask (nitrogen inlet, serum stopper, magnetic stirrer) was added THF (35 mL) under nitrogen. The flask was cooled to 0 °C and diisopropylamine (33.0 mmol, 4.61 mL) was added, followed by *n*-BuLi (33.0 mmol, 13.3 mL of a 2.5 M solution). The flask was cooled to −78 °C and a solution of (+)-nopinone (**3**, 25.4 mmol, 3.5 g) in a small amount of THF was added dropwise. The resulting solution was stirred for 2 h at −78 °C and then allowed to warm to 0 °C. MeI (49.5 mmol, 3.08 mL) was added and stirring was continued for another 6 h at room temperature. The reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed with 5% HCl, water, and brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting oil was chromatographed (eluting with 4% ethyl acetate–hexane) and distilled to give (+)-*trans*-3-methylnopinone (**4**, R′ = Me, 2.7 g, 70%): $[\alpha]^{20}_D$ +57.8° (*c* 6.08); IR (neat) 1710, 1460, 1370, 980 cm^{-1}; NMR δ 0.88 (s, 3 H), 1.20 (d, 3 H), 1.33 (s, 3 H); mass spectrum, *m/z* 152 (28, M$^+$), 110 (28), 109 (29), 95 (39), 83 (100), 55 (36); mol wt calcd for $C_{10}H_{16}O$ 152.12011, found 152.12047.

(+)-3,3-Dimethylnopinone (10). By the above procedure, (+)-*trans*-3-methylnopinone (**4**, R′ = Me, 0.078 mol, 11.8 g) gave, along with recovered starting material (3.4 g), (+)-3,3-dimethylnopinone (**10**, 8.4 g, 65%): $[\alpha]^{20}_D$ +75.0° (*c* 1.16); IR (neat) 1710, 1390, 1200 cm^{-1}; NMR δ 0.83 (s, 3 H), 1.23 (s, 3 H), 1.30 (s, 3 H), 1.32 (s, 3 H); mass spectrum, *m/z* 166 (38, M$^+$), 151 (5), 110 (75), 95 (95), 83 (100); mol wt calcd for $C_{11}H_{18}O$ 166.13576, found 166.13604.

(*R*)-(+)-2,2-Dimethyl-4-(2-bromo-2-propyl)cyclohexanone (11). This procedure follows that of Levine and Gopalakrishnan.[19] To a 50-mL two-neck round-bottom flask (argon inlet, serum stopper, magnetic stirrer) was added (+)-3,3-dimethylnopinone (**10**, 7.23 mmol, 1.2 g) and CH_2Cl_2 (10 mL, distilled from P_2O_5) under argon. The flask was cooled to −78 °C and BBr_3 (7.95 mmol, 738 μL) was added dropwise. The mixture was stirred for 30 min, and pyridine (24 mmol, 1.93 mL) was added, followed by MeOH (72 mmol, 3.0 mL). The solution was poured in water and extracted with ether. The combined extracts were washed in 5% oxalic acid and brine, passed through a portion of anhydrous Na_2SO_4, concentrated, and chromatographed rapidly (eluting with 5% ethyl acetate–hexane under ca. 10-lb nitrogen pressure) to give the bromide (+)-**11** (1.37 g, 77%) as a white crystalline solid: mp 46–47 °C; $[\alpha]^{20}_D$ +78.3° (*c* 0.83); IR (solution) 1705 cm^{-1}; NMR δ 1.10 (s, 3 H), 1.20 (s, 3 H), 1.8 (s, 6 H); mass spectrum, *m/z* 248 (2.5, M$^+$ for ^{81}Br), 246 (2.4, M$^+$ for ^{79}Br), 167 (16), 111 (38), 83 (61), 69 (100), 55 (87).

Anal. Calcd for $C_{11}H_{19}BrO$: C, 53.45; H, 7.75. Found: C, 53.43; H, 7.59.

(*R*)-(+)-2,2-Dimethyl-4-isopropenylcyclohexanone (12). Method I. Ketone (+)-**10** (0.03 mol, 5.0 g) was pyrolyzed at 450 °C in a Pyrex tube (25-mm diameter, 30-cm length) packed with glass beads (5-mm diameter) at a rate of 375 μL/min with a nitrogen carrier gas flow of 30 mL/min. The crude product (4.5 g) was separated by using high-pressure LC (eluting with 3% ethyl acetate–hexane) to give the unsaturated ketone (+)-**12** (0.87 g, 17%), $[\alpha]^{20}_D$ +110.0° (*c* 0.54).

Method II. This is the procedure of Acharya and Brown.[20] A 3.0 M solution of potassium triethylmethoxide was prepared by dissolving potassium (0.1 mol, 3.9 g) in 28 mL of 3-ethyl-3-pentanol under nitrogen with stirring for 2 h at 140 °C. The solution was a viscous red liquid at 60 °C and a solid at room temperature.

The bromo ketone (+)-**11** (0.64 mmol, 158 mg) was cooled to 0 °C and the alkoxide solution (3.0 mmol, 1 mL) was added at 60 °C under a nitrogen blanket. The flask was stoppered and heated at 60 °C for 14 h. Bulb-to-bulb vacuum distillation resulted in a mixture of 3-ethyl-3-pentanol and alkenes. The alcohol was removed by passing the mixture through a short silica gel column. Analysis by GC showed the alkene mixture (85 mg, 80%) to be >90% (+)-**12** Preparative GC afforded the pure olefin (+)-**12**: $[\alpha]^{20}_D$ +112.8° (*c* 0.58); IR (neat) 1710, 1385 cm^{-1}; NMR δ 1.07 (s, 3 H), 1.23 (s, 3 H), 1.73 (m, 4 H), 4.77 (m, 2 H); mass spectrum, *m/z* 166 (68, M$^+$), 110 (62), 109 (38), 95 (34), 82 (36), 68 (100), 67 (49), 55 (35); mol wt calcd for $C_{11}H_{18}O$ 166.13575, found 166.13574.

(*R*)-(+)-2,2-Dimethyl-4-(1-methyl-1-cyclopropyl)cyclohexanone (13). This procedure follows that of Rawson and Harrison.[23b] A mixture of zinc dust (3.13 mmol, 205 mg) and cuprous chloride (3.13 mmol, 310 mg) in anhydrous ether (5 mL) was heated to reflux for 30 min with stirring under nitrogen. The olefin (+)-**12** (1.2 mmol, 200 mg) was added, followed by methylene diiodide (1.56 mmol, 126 μL), and the mixture was refluxed for 24 h. Filtration followed by chromatography on silver nitrate impregnated silica gel (eluting with 5% ether–hexane) to remove unreacted starting material gave cyclopropane (+)-**13** (100 mg, 46%): $[\alpha]^{20}_D$ +113.4° (*c* 0.58); IR (neat) 3080 (cyclopropane), 1705, 1390 cm^{-1}; NMR δ 0.28 (s, 4 H), 0.92 (s, 3 H), 1.05 (s, 3 H), 1.13 (s, 3 H); mass spectrum, *m/z* 180 (48, M$^+$), 152 (56), 110 (86), 95 (44), 82 (55), 81 (50), 67 (43), 55 (100); mol wt calcd for $C_{12}H_{20}O$ 180.15141, found 180.15163.

(28) The synthesis of this molecule began with (+)-**10**, which was treated with H_2SO_4/HCl[12] to give **7** (R = R′ = Me, X = Cl). Reaction with $NaBH_4$ followed by treatment with $Al(Me)_3$ and Jones reagent gave **1**, which had an enantiomeric excess of 37% by polarimetry. Integration of the spectrum in Figure 1b gave a value of 34% ee.

(29) Determined by polarimetry.

(1S,4R)-(+)-2,2-Dimethyl-4-*tert*-butylcyclohexan-1-ol (14a) and (1R,4R)-(+)-2,2-Dimethyl-4-*tert*-butylcyclohexan-1-ol (14b). Catalytic hydrogenation of cyclopropane (+)-13 (0.48 mmol, 86 mg) with 3 mg of PtO_2 in 1.5 mL of acetic acid at room temperature and 1 atm 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. The resulting oil was chromatographed (eluting with 10% ether–hexane) to give a crystalline compound (20 mg, identified as the cis alcohol (+)-**14a**) and a semicrystalline compound (61 mg, identified as the trans alcohol (+)-**14b**). (+)-**14a**: mp 77–78 °C; $[\alpha]^{20}_D$ +51.6° (*c* 0.92); IR (solution) 3620, 2460, 1360, 1230 cm^{-1}; NMR δ 0.85 (s, 9 H), 0.91 (s, 3 H), 0.96 (s, 3 H), 3.4 (s, 1 H); mass spectrum, *m/z* 184 (10, M^+), 151 (14), 111 (56), 110 (89), 109 (91), 57 (100); mol wt calcd for $C_{12}H_{24}O$ 184.18270, found 183.18314. (+)-**14b**: mp 69–70 °C; $[\alpha]^{20}_D$ +27.1° (*c* 1.01); IR (solution) 3610, 3450, 1360 cm^{-1}; NMR δ 0.83 (s, 9 H), 0.88 (s, 3 H), 0.99 (s, 3 H), 3.24 (d of d, 1 H); mass spectrum, *m/z* 166 (12), 123 (28), 110 (100), 82 (26), 57 (80).

Anal. Calcd for $C_{12}H_{24}O$: C, 78.19; H, 13.12. Found: C, 77.51; H, 12.87.

(R)-(+)-2,2-Dimethyl-4-*tert*-butylcyclohexanone (1). Method I. A solution of alcohol (+)-**14a** (0.11 mmol, 20 mg) in 600 μL of acetone was treated with excess Jones reagent[30] (ca. 30 μL) and stirred for 30 min at room temperature. The reaction mixture was diluted with water and extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated to yield ketone (+)-1 (19 mg, 90%) as a colorless oil, $[\alpha]^{20}_D$ +104.7° (*c* 0.62).

Method II. Bromo ketone (+)-**11** (1.2 mmol, 300 mg) was added to a solution of $NaBH_4$ (1.82 mmol, 69 mg) in MeOH 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 with anhydrous Na_2SO_4, and concentrated. The resulting oil (272 mg) was added to a 100-mL three-neck round-bottom flask (argon inlet, serum stopper, dry ice condenser, magnetic stirrer) under argon. The flask was cooled to −78 °C and CH_3Cl (ca. 10 mL) was added, followed by $Al(Me)_3$ (16.4 mmol, 6.8 mL of a 2.41 M solution, Alfa-Ventron). The cooling bath was removed and the reaction mixture was allowed to reflux for 3 h. The flask was cooled to −78 °C and cold MeOH (7 mL) was added dropwise. The flask and dry ice condenser were warmed to room temperature to allow the CH_3Cl to boil off. Dilute HCl (10 mL) was added dropwise and the mixture was extracted with ether. The ether extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated, and chromatographed (eluting with 10% ethyl acetate–hexane) to give alcohol (+)-**14a** (5 mg) and alcohol (+)-**14b** (123 mg, 57% from (+)-**11**). A solution of alcohols (+)-**14a** and (+)-**14b** in 5 mL of acetone was treated with excess Jones reagent (ca. 200 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 ketone (+)-1 (125 mg, 99%): $[\alpha]^{20}_D$ +107.1° (*c* 0.80); IR (neat) 1705, 1360 cm^{-1}; NMR δ 0.90 (s, 9 H), 1.05 (s, 3 H), 1.17 (s, 3 H); mass spectrum, *m/z* 182 (32, M^+), 167 (6), 126 (50), 82 (41), 57 (100), 55 (46); mol wt calcd for $C_{12}H_{22}O$ 182.16705; found 182.16812.

Preparation of MPTA Esters. Dry pyridine (300 μL) was injected into a dry reaction vial (fitted with a serum stopper), followed by injection of (*S*)-(+)-MTPA chloride[26,27] (0.12 mmol, 20.4 μL). An equal volume of CCl_4 was used to rinse out each syringe and was added to act as solvent. A solution of alcohol (+)-**14b** (ca. 6 mg) in a small amount of CCl_4 was added, and the reaction vessel was shaken briefly and allowed to stand at room temperature. After 24 h, (3-(dimethylamino)propyl)amine (0.09 mmol, 12 μL) was added, and the mixture was allowed to stand for 5 min. The reaction mixture was diluted with ether and washed with cold 5% HCl, cold saturated $NaHCO_3$ solution, and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was dissolved in CCl_4 and reevaporated several times to remove the last traces of ether. The ^{19}F NMR spectrum (Figure 1a) was taken without purification of the product (15 mg). The above procedure was repeated with partially racemized alcohol **14b**[28] to give 14 mg of product (see Figure 1b).

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Registry No. (*R*)-(+)-1, 73395-38-7; (−)-**2**, 18172-67-3; (+)-**3**, 38651-65-9; (+)-*trans*-**4** (R′ = Me), 29362-79-6; (+)-**10**, 36203-40-4; (*R*)-(+)-**11**, 73368-32-8; (*R*)-(+)-**12**, 69153-91-9; (*R*)-(+)-**13**, 73368-33-9; (1*S*,4*R*)-(+)-**14a**, 73395-39-8; (1*R*,4*R*)-(+)-**14b**, 73395-40-1; (1*R*,4*R*)-(+)-**14b** MTPA ester, 73368-34-0; **14b** isomer MTPA ester, 73395-41-2; (*S*)-(+)-MTPA chloride, 20445-33-4.

(30) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39–45.

Synthesis of 8-Hydroxy- and 11-Hydroxy-7,12-dimethylbenz[*a*]anthracenes.[1] Tin(II) Chloride Mediated Reductions

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8-Methoxybenz[*a*]anthracene-7,12-dione (**3**) and 11-methoxybenz[*a*]anthracene-7,12-dione (**4**) were converted in high yields to the corresponding 7,12-bis(epoxides) (**14a** and **14b**) (not isolated because of instability) by treatment with the ylide formed from trimethylsulfonium iodide. Reduction with lithium aluminum hydride afforded 7,12-dihydro-7,12-dihydroxy-8-methoxy-7,12-dimethylbenz[*a*]anthracene (**5**) and 7,12-dihydro-7,12-dihydroxy-11-methoxy-7,12-dimethylbenz[*a*]anthracene (**6**), respectively, in excellent yields. Treatment of **5** and **6** with stannous chloride and hydrogen chloride (or hydrochloric acid) in ether, ethyl acetate, dioxane, and tetrahydrofuran gave over 90% yields of 8-methoxy-7,12-dimethylbenz[*a*]anthracene (**1**) and 11-methoxy-7,12-dimethylbenz[*a*]anthracene (**2**), respectively. A discussion of the mechanism of these reductions focuses on the formation of an organotin intermediate and not a free carbenium ion.

In continuation of a program[3] to make all of the hydroxy-7,12-dimethylbenz[*a*]anthracenes available to workers interested in studying the metabolism of 7,12-dimethylbenz[*a*]anthracene (DMBA),[4] we describe herein

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