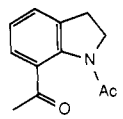
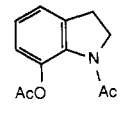
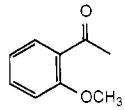
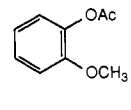
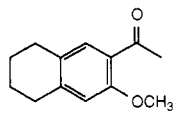
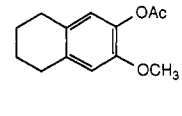
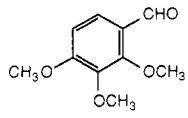
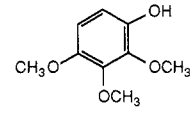
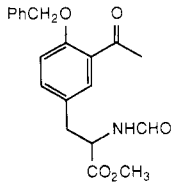
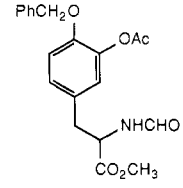
**Table II. Comparative Baeyer–Villiger Reactions**

| entry | substrate | conditions | product | yield, % |
|---|---|---|---|---|
| 1 |  | $CF_3CO_3H$, $Na_2HPO_4$, $CH_2Cl_2$[a] |  | 20–25 |
| 2[b] |  | $CF_3CO_3H$, $CHCl_3$, reflux, 5 h |  | 60 |
| 3[c] |  | *m*-CPBA, $CH_2Cl_2$, 25 °C, 22 h |  | 60 |
| 4[d] |  | *m*-CPBA, $CH_2Cl_2$, reflux; KOH, MeOH, room temp |  | 83 |
| 5[e] |  | *m*-CPBA, $CHCl_3$, reflux, 48 h |  | 33 |

[a] For preparation and use of this reagent system see ref 3. [b] See ref 11. [c] See ref 2b. [d] See ref 9. [e] See ref 15b.

**7-Acetoxyindole (7)**: $^1H$ NMR ($CDCl_3$, 80 MHz, ppm) 8.5 (br s, 1 H, NH), 6.4–7.5 (m, 5 H, ArH), 2.37 (s, 3 H, $OCOCH_3$); IR (neat) $\nu_{max}$ 3368, 3110, 3079, 2933, 1735, 1636, 1580, 1495, 1443, 1369, 1342, 1287, 1228, 1204, 1109, 1036, 907, 892, 846, 791, 722 $cm^{-1}$; EIMS, *m/e* (relative intensity) 175 ($M^+$, 38), 133 (base), 105 (25), 104 (29); CIMS (isobutane), *m/e* 176 ($M^+ + H$, base), 134 (8); HRMS, *m/e* 175.0635 ($C_{10}H_9NO_2$ requires 175.0633).

***O*-Benzyl-*O*-methylcatechol (10).** A solution of 90% $H_2O_2$ in $Et_2O$ (14.4 mmol in 2.0 mL) was added to **9** (108.7 mg, 0.654 mmol) followed by *p*-TsOH·$H_2O$ (11 mg, 0.06 mmol, 9 mol %). The resulting solution was stirred 5 h at 22 °C. The reaction mixture was poured onto 10 mL of 10% $Na_2CO_3$, and the mixture was extracted with $CH_2Cl_2$ (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo (bath temperature <25 °C) to afford crude 2-methoxyphenol as a light yellow oil. This crude oil dissolved in 1.5 mL of dry acetone was treated with $K_2CO_3$ (0.46 g, 3.3 mmol, 5 equiv), benzyl bromide (0.25 mL, 2.1 mmol, 3.2 equiv), and *n*-$Bu_4NI$ (catalyst). The reaction mixture was warmed to 55 °C under $N_2$ for 14 h, cooled to room temperature, and partitioned between 50 mL of $Et_2O$ and 15 mL of water. The $Et_2O$ layer was washed with 20 mL of brine and was dried over $MgSO_4$. Removal of the solvent in vacuo followed by chromatography (PCTLC, 2 mm $SiO_2$, hexane and then 50% $Et_2O$–hexane) afforded 124 mg of **10** [140 mg theor., (89%)] as a colorless oil: $^1H$ NMR ($CDCl_3$, 80 MHz, ppm) 7.2–7.4 (m, 5 H, $PhCH_2$), 6.89 (br s, 4 H, ArH), 5.14 (s, 2 H, $PhCH_2$), 3.88 (s, 3 H, $OCH_3$); IR (neat) $\nu_{max}$ 3034, 2951, 2935, 2919, 2838, 1591, 1508, 1456, 1290, 1258, 1220, 1185, 1125, 1022, 1010, 741, 699 $cm^{-1}$; EIMS, *m/e* (relative intensity) 214 ($M^+$, 4), 91 (base); CIMS (isobutane), *m/e* 215 ($M^+ + H$, base), 147 (6), 137 (14), 91 (12); HRMS, *m/e* 214.0999 ($C_{14}H_{14}O_2$ requires 214.0994).

A solution of 30% $H_2O_2$ (0.8 mL, 7.8 mmol, 10.0 equiv) was added to a solution of **9** (129 mg, 0.78 mmol) in 0.8 mL of THF. *p*-TsOH·$H_2O$ (15 mg, 0.08 mmol, 10 mol %) was added and the reaction mixture was stirred 24 h at 22 °C. Workup, benzylation, and purification as described above afforded 132 mg of **10** [166 mg theor., (80%)].

**3-Methoxy-5,6,7,8-tetrahydro-2-naphthalenol (12)**: mp 80–81 °C (hexane); $^1H$ NMR ($CDCl_3$, 470 MHz, ppm) 6.62 (s, 1 H, C1-H), 6.54 (s, 1 H, C4-H), 5.40 (s, 1 H, OH), 3.84 (s, 3 H, $OCH_3$), 2.67 (m, 4 H, C5-H and C8-H), 1.74 (m, 4 H, C6-H and C7-H); IR (KBr) $\nu_{max}$ 3413, 2927, 2837, 1518, 1450, 1433, 1373, 1322, 1291, 1266, 1249, 1209, 1109, 1020, 865, 846, 808 $cm^{-1}$; EIMS, *m/e* (relative intensity) 178 ($M^+$, base), 163 (15), 150 (36), 135 (31), 117 (12), 107 (24), 91 (18); CIMS (isobutane), *m/e* 179 ($M^+ + H$, base), 177 (6); HRMS, *m/e* 178.0993 ($C_{11}H_{14}O_2$ requires 178.0994).

***N*-(Carbobenzyloxy)-4-*O*-benzyl-3-hydroxy-L-tyrosine methyl ester (19)**: $^1H$ NMR ($CDCl_3$, 200 MHz, ppm) 7.39 (br s, 5 H, $PhCH_2O$), 7.34 (br s, 5 H, $PhCH_2O$), 6.81 (d, 1 H, $J$ = 8.2 Hz, C5-H), 6.69 (d, 1 H, $J$ = 2.0 Hz, C2-H), 6.54 (dd, 1 H, $J$ = 8, 2 Hz, C6-H), 5.64 (s, 1 H, OH), 5.22 (d, 1 H, $J$ = 7.7 Hz, NH), 5.10 (s, 2 H, $PhCH_2O$), 5.06 (s, 2 H, $PhCH_2O$), 4.60 (m, 1 H, $NHCHCH_2$), 3.72 (s, 3 H, $OCH_3$), 3.01 (d, 2 H, $J$ = 5.6 Hz, $CHCH_2$); IR (neat) $\nu_{max}$ 3518, 3364, 3064, 3033, 2952, 1718, 1592, 1510, 1455, 1438, 1382, 1343, 1275, 1215, 1129, 1061, 1025, 738, 698 $cm^{-1}$; EIMS, *m/e* (relative intensity) 435 ($M^+$, 1), 392, 374, 332, 303, 284, 268, 241, 224, 213, 211, 204, 195, 181, 91 (base); CIMS (isobutane), *m/e* 436 ($M^+ + H$, 14), 392 (base).

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**Registry No.** **1**, 104019-19-4; **2**, 105205-61-6; **3**, 105205-62-7; **4**, 105205-63-8; **5**, 104019-20-7; **6**, 105205-64-9; **7**, 5526-13-6; **7** (alcohol), 4770-38-1; **8**, 13513-82-1; **9**, 21022-73-1; **10**, 835-79-0; **11**, 105205-65-0; **12**, 3579-88-2; **13**, 105205-66-1; **14**, 642-71-7; **15**, 41038-42-0; **16**, 19676-64-3; **17**, 105205-67-2; **18**, 105205-68-3; **18** (3-acetyl), 105205-69-4; **19**, 105229-41-2; *p*-TsOH, 104-15-4; $PhCH_2Br$, 100-39-0; *o*-$MeOC_6H_4OH$, 90-05-1; *o*-$MeOC_6H_4COMe$, 579-74-8; indoline, 496-15-1; methyl 2-methoxy-5,6,7,8-tetrahydronaphthalene-3-carboxylate, 78112-34-2; methyl 3,4,5-trimethoxybenzoate, 1916-07-0; 2,3,4-trimethoxybenzaldehyde, 2103-57-3.

**Supplementary Material Available:** Preparative information and full spectral and physical characterization of substrates **2**, **3**, **5**, **6**, **8**, **9**, **11**, **13**, **15**, **17**, and **18** (5 pages). Ordering information is given on any current masthead page.

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# Use of Chiral Lanthanide Shift Reagents in the Determination of Enantiomer Composition and Absolute Configuration of Epoxides and Arene Oxides

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The metabolism of olefins and arenes in plants, animals, and fungi often proceeds via epoxide and arene oxide intermediates[1,2] which are frequently formed in high optical yields. Earlier studies from these laboratories have been concerned with the synthesis and determination of optical purity and absolute configuration of epoxides[3-5] and arene oxides[2] using a wide range of methods. Chiral shift reagents have been used previously to estimate the optical purity of acyclic epoxides[6-13] including keto epoxides[13] but have not been used in the determination of absolute con-

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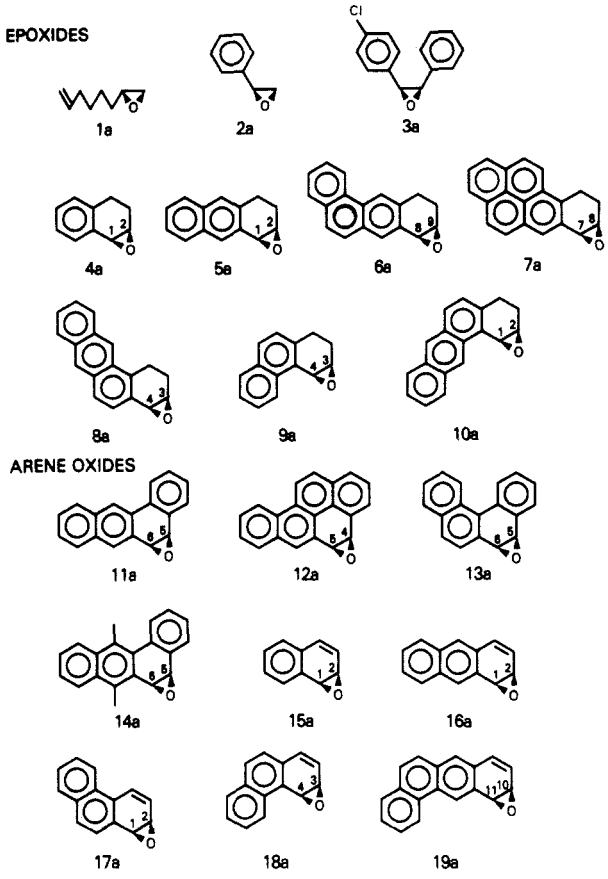
**Scheme I**




figuration. The present report provides a method which allows both enantiomeric excess and absolute configuration to be obtained for a wide range of chiral epoxides and arene oxides.

Enantiomers of cyclic and acyclic epoxides **1–10** and *K*-region arene oxides **11–14** (Scheme I) were found to be distinguishable by NMR using the chiral lanthanide shift reagent tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(tfc)$_3$] as an additive to solutions of these compounds in $CDCl_3$. The induced downfield shift of the oxirane ring proton signals and the anisochronous signals corresponding to each enantiomer are indicated in Table I. Magnitudes of the induced downfield shifts of the oxirane hydrogens are expressed in terms of the gradient (*G*) of the initial straight line

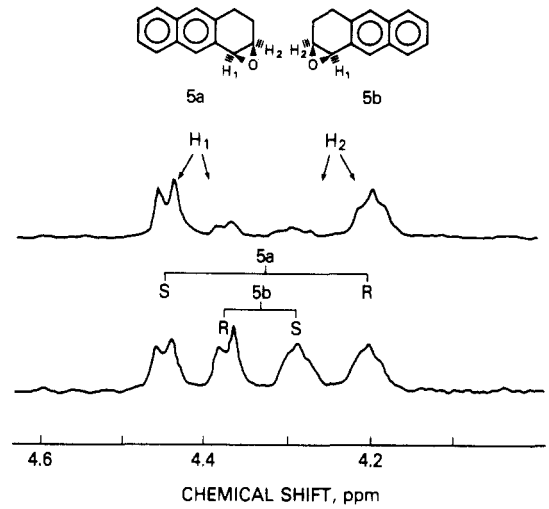
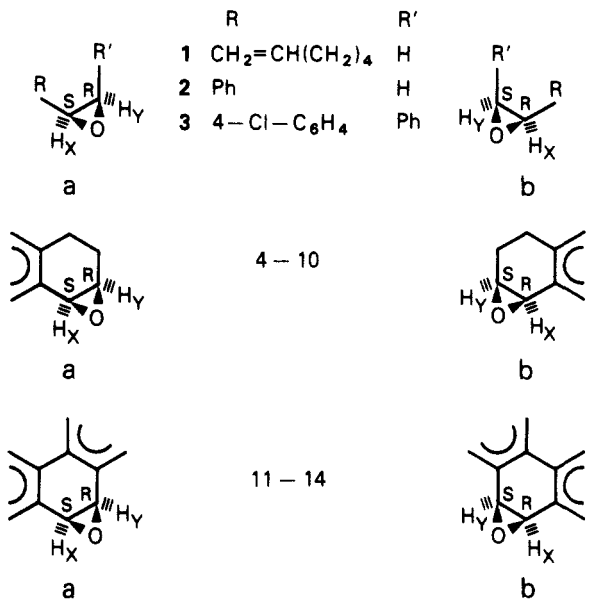



**Figure 1.** NMR spectra of the oxirane hydrogens of 1,2,3,4-tetrahydroanthracene 1,2-oxide (**5**, 0.10 M in $CDCl_3$) in the presence of the chiral lanthanide shift reagent Eu(tfc)$_3$ (0.01 M). Upper trace: 90% 1*S*,2*R* enantiomer **5a** ($[\alpha]_D$ −101°). Lower trace: **5a** + **5b**, (±)-enantiomers.

**Scheme II**




section of a plot of $\delta$ (ppm) vs. the ratio [Eu(tfc)$_3$]/[epoxide].[14]

Absolute configuration of the acyclic epoxides **1–3**, tetrahydro epoxides **4–10**, and K-region arene oxides **11–14** in both the a and b enantiomer series (Scheme II) can be correlated with the induced shift values (*G*). Positioning the enantiomer in this way (Scheme II) provides a convenient means for comparing the effects of the shift reagents on the relevant oxirane protons. Protons $H_x$ were found to have *smaller G values* than $H_y$ in the a enantiomer series (**1a–3a**), and the absolute configuration at the chiral carbon atom (R, $H_x$ substituents) was consistently found to be *S* for these acyclic epoxides. Since cyclic epoxides were of major interest to the present study, further examples of acyclic epoxides were not examined.

An opposite trend was observed for the cyclic epoxides **4–10** and arene oxides **11–14**. Thus, protons $H_x$ have *larger G values* than $H_y$ in the a enantiomer series when the absolute configurations are as shown (*S* and *R*, respec-

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Table I. Eu(tfc)$_3$ Induced $G$ Values for Epoxides 1–10 and K-Region Oxides 11–14[a]

| compd | config | $[\alpha]_D$ | ref | epoxide conc, M | chem shift, ppm | $G$ = chem shift, ppm / [Eu(tfc)$_3$]/[epoxide] |
|---|---|---|---|---|---|---|
| **1a** | 7*S*[b] | | | | $H_7$ 2.70 | 4.05[c] |
| **1b** | 7*R* | +12° | 12 | | $H_7$ 2.70 | 4.18[c] |
| **2a** | 1*S*[b] | | | 0.132 | $H_1$ 3.85 | 3.19 |
| | | | | | $H_2$ 3.14[d] | 3.44 |
| **2b** | 1*R* | −22° | 15 | 0.132 | $H_1$ | 3.46 |
| | | | | | $H_2$ | 2.87 |
| **3a** | 1*S*,2*R* | −8.4° | 5 | 0.195 | $H_1$ 4.21 | 4.82 |
| | | | | | $H_2$ 4.14 | 5.34 |
| **3b** | 1*R*,2*S*[b] | | | 0.195 | $H_1$ | 5.52 |
| | | | | | $H_2$ | 4.91 |
| **4a** | 1*S*,2*R* | −131° | 16 | 0.137 | $H_1$ 3.84 | 4.48 |
| | | | | | $H_2$ 3.73 | 4.39 |
| **4b** | 1*R*,2*S*[b] | | | 0.105 | $H_1$ | 2.52 |
| | | | | | $H_2$ | 3.56 |
| **5a** | 1*S*,2*R* | −151° | 16 | 0.107 | $H_1$ 4.03 | 3.63 |
| | | | | | $H_2$ 3.79 | 3.50 |
| **5b** | 1*R*,2*S*[b] | | | 0.051 | $H_1$ | 3.06 |
| | | | | | $H_2$ | 4.28 |
| **6a** | 8*S*,9*R*[b] | | | 0.034 | $H_8$ 4.08 | 1.06 |
| | | | | | $H_9$ 3.84 | 1.05 |
| **6b** | 8*R*,9*S* | +130° | 17 | 0.045 | $H_8$ | 0.85 |
| | | | | | $H_9$ | 1.15 |
| **7a** | 7*S*,8*R* | −144° | 18 | 0.037 | $H_7$ 4.29 | 1.51 |
| | | | | | $H_8$ 3.95 | 1.50 |
| **7b** | 7*R*,8*S* | +144° | 18 | 0.037 | $H_7$ | 1.29 |
| | | | | | $H_8$ | 1.69 |
| **8a** | 4*S*,3*R* | −97° | 2, 19 | 0.025 | $H_4$ 4.01 | 0.75 |
| | | | | | $H_3$ 3.89 | 0.70 |
| **8b** | 4*R*,3*S*[b] | | 19 | 0.045 | $H_4$ | 0.91 |
| | | | | | $H_3$ | 1.19 |
| **9a** | 3*R*,4*S* | −160° | 20 | 0.060 | $H_4$ 4.69 | 2.29 |
| | | | | | $H_3$ 3.86 | 1.99 |
| **9b** | 3*S*,4*R* | +156° | 20 | 0.060 | $H_4$ | 1.93 |
| | | | | | $H_3$ | 2.24 |
| **10a** | 1*S*,2*R* | −171° | 21 | 0.022 | $H_1$ 4.87 | 1.15 |
| | | | | | $H_2$ 3.93 | 1.12 |
| **10b** | 1*R*,2*S* | +177° | 21 | 0.016 | $H_1$ | 0.46 |
| | | | | | H2 | 0.57 |
| **11a** | 5*R*,6*S* | −119° | 22 | 0.043 | $H_5$ 4.56 | 0.56 |
| | | | | | $H_6$ 4.70 | 0.67 |
| **11b** | 5*S*,6*R*[b] | | | 0.022 | $H_5$ | 0.37 |
| | | | | | $H_6$ | 0.32 |
| **12a** | 4*R*,5*S* | −123° | 23 | 0.030 | $H_4$ 4.81 | 0.58 |
| | | | | | $H_5$ 4.90 | 0.64 |
| **12b** | 4*S*,5*R* | +123° | 23 | 0.030 | $H_4$ | 0.68 |
| | | | | | $H_5$ | 0.55 |
| **13a** | 5*R*,6*S* | −432° | 24 | 0.060 | $H_5$ 4.81 | 0.48 |
| | | | | | $H_6$ 4.67 | 0.55 |
| **13b** | 5*S*,6*R*[b] | | | 0.060 | $H_5$ | 0.55 |
| | | | | | $H_6$ | 0.49 |
| **14a** | 5*R*,6*S* | −117° | 25 | 0.059 | $H_5$ 4.58 | 0.58 |
| | | | | | $H_6$ 5.01 | 0.69 |
| **14b** | 5*S*,6*R*[b] | | | 0.059 | $H_5$ | 0.65 |
| | | | | | $H_6$ | 0.61 |

[a] Spectra were recorded at 220 or 300 MHz in $CDCl_3$. [b] Data obtained from racemates by comparison to optically active material [c] Chemical shifts of $H_7$ observed at a concentration ratio of 0.137 mol Eu(tfc)$_3$ per mole of epoxide as stated in ref 12. [d] Proton $H_2$ cis to proton $H_1$.

tively). Although the absolute configuration of each enantiomer may be assigned on the basis of the $G$ values of its oxirane ring protons, assignment can be difficult when the two $G$ values are similar. In practice, observation of the effect of the shift reagent on a mixture of enantiomers is more useful than determination of $G$ values. Introduction of the chiral lanthanide shift reagent affords a spectrum with two pairs of oxirane ring proton signals. The outer pair of signals arises from the two oxirane ring protons of the enantiomer with the low- and high-field signals corresponding to protons bearing $S$ and $R$ configurations, respectively. The inner pair of signals, on the other hand, arises from the enantiomer with the low- and high-field signals corresponding to protons bearing $R$ and $S$ configurations, respectively. An example of the separation of signals due to enantiomers of **5** is shown in Figure 1. On the basis of the trend found for the cyclic epoxides **4–10** and arene oxides **11–14**, whose absolute configuration have been established by independent methods, the present approach appears to provide a useful technique for the assignment of configuration to both the tetrahydro epoxide and K-region arene oxide derivatives of polycyclic aromatic hydrocarbons.

One limitation upon the use of chiral lanthanide shift reagents to differentiate between epoxide enantiomers is the acid lability of some epoxides and arene oxides. Thus,

**Table II. Effects of Eu(hfc)$_3$ on the Chemical Shifts (250 MHz, $CDCl_3$) of the Oxirane Protons in the Unstable Benzo-Ring Arene Oxides 15–19**[a]

| | chem shifts, ppm | | | | | |
|---|---|---|---|---|---|---|
| | benzylic | | allylic | | arene oxide | ratio [Eu(hfc)$_3$]/ |
| compd | *b* | *c* | *b* | *c* | conc, M | [arene oxide] |
| 15 | 4.47 | 4.99 | 4.10 | 4.74, 4.58 | 0.17 | 0.040 |
| 16 | 4.55 | 4.97 | 4.08 | 4.57, 4.44 | 0.05 | 0.139 |
| 17 | 4.69 | 5.02 | 4.31 | 4.68, 4.58 | 0.13 | 0.075 |
| 18 | 4.69 | 4.88 | 4.17 | 4.36, 4.33 | 0.06 | 0.140 |
| 19 | 5.28 | 5.63 | 4.38 | 4.64, 4.55 | 0.09 | 0.037 |

[a] Syntheses of the arene oxides are given in ref 16, 27, and 28. [b] Before addition of Eu(hfc)$_3$. [c] After addition of Eu(hfc)$_3$.

7,8,9,10-tetrahydrobenzo[*a*]pyrene 9,10-oxide and chrysene 5,6-oxide were found to aromatize rapidly upon addition of Eu(tfc)$_3$, which appears to act as a weak acid. Prior filtration of the $CDCl_3$ through alumina to remove traces of acid did not prevent these isomerizations, and thus *G* values could not be obtained. Benzo-ring arene oxides are generally less stable in acidic conditions than K-region arene oxides. Stereo differentiation between the enantiomers of arene oxides **15–19** was possible upon addition of small quantities of anhydrous shift reagent in acid free $CDCl_3$. Attempts to add more shift reagent resulted in isomerization to phenols, thus preventing the determination of *G* values for these labile arene oxides. Resolution of signals due to each enantiomer of arene oxides **15–19** proved to be more efficient with tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$] compared to Eu(tfc)$_3$. Notably, the allylic proton signals on the oxirane ring enantiomers **15–19** were clearly distinguishable while the benzylic proton signals remained unresolved.

The signals due to each enantiomer of arene oxide **17** are clearly evident when Eu(hfc)$_3$ was added (Figure 2). Since this sample had been obtained from diastereomerically pure (1*R*,2*R*)-*trans*-2-bromo-1-(2-methoxy-2-phenyl-2-(trifluoromethyl)acetoxy)-1,2,3,4-tetrahydrophenanthrene ($[\alpha]_D$ −93°),[16] the NMR spectrum obtained in the presence of Eu(hfc)$_3$ clearly indicated that the initially formed arene oxide racemized at ambient temperature.

On the basis of the present results obtained with 11

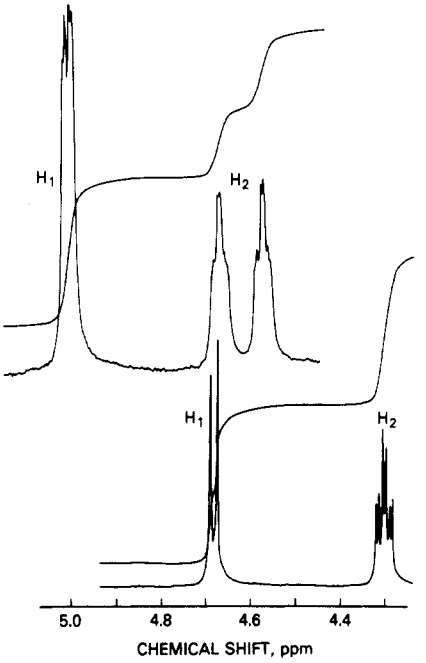
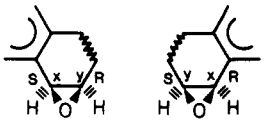



**Figure 2.** NMR spectra of oxirane hydrogens of phenanthrene 1,2-oxide (**17**, 0.13 M in $CDCl_3$) in the absence (lower trace) and presence (upper trace) of Eu(hfc)$_3$ (9.8 mM).

oxiranes of known stereochemistry, Eu(tfc)$_3$ may be used to predict the absolute configuration of other cyclic epoxides and K-region arene oxides: In the presence of




a b

chiral shift reagent, both oxirane ring proton signals ($H_x$ and $H_y$) are shifted downfield. The magnitude of induced shift (*G*) for the $H_x$ will be greater than $H_y$ in the a enantiomer series ($R_y$,$S_x$) and less than $H_y$ in the b series ($R_x$,$S_y$) as illustrated in Figure 1. Since the opposite trend found in acyclic epoxides was based upon only three examples **1–3**, predictions in the acyclic series can be made with less confidence.

## Experimental Section

NMR spectra were recorded in acid-free $CDCl_3$ solvent with tetramethylsilane as reference on Varian HR-220 and XL300 and Bruker WH 90 and 250 instruments. Tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(tfc)$_3$] and tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III) [Eu(hfc)$_3$] were purchased from the Aldrich Chemical Co. and stored under anhydrous conditions. The literature concerning the synthesis, resolution, and assignment of absolute configuration to individual enantiomers is given in Tables I and II. Phenanthrene 1,2-oxide (**17**) and 3,4-oxide (**18**) were

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found to racemize very rapidly at ambient temperature, and thus NMR data were obtained on the racemates.

The magnitude of the lanthanide induced shift of epoxides **1–10** and arene oxides **11–14** is expressed in terms of the parameter $G$, the gradient of the initial straight line section of a plot of observed induced shift vs. mole ratio of shift reagent to substrate, obtained from eq 1–3,[14] where $\Delta\delta_{lim}$ is the limiting shift of the

$$G = \Delta\delta_{lim}\frac{KS}{1 + KS} \quad (1)$$

$$K = A/(S - A)(C - A) \quad (2)$$

$$\Delta\delta_{obs} = \Delta\delta_{lim}A/S \quad (3)$$

1:1 complex ($\Delta\delta_{lim} = \delta_{adduct} - \delta_{substrate}$), $K$ is the equilibrium constant for the complex, $S$ is the initial concentration of epoxide, $A$ is the concentration of complex, and $C$ is the concentration of added shift reagent. Values of $\Delta\delta_{lim}$ and $K$ were determined by fitting the data of observed induced shifts ($\Delta\delta_{obs}$) as a function of the concentration of added shift reagent into eq 2 and 3 with a least-squares curve fitting routine of the MLAB program[29] in an interative mode. For each compound, five to eight concentrations up to a 0.8 M ratio, at which point the plots of $\Delta\delta_{lim}$ vs. the concentration ratio had begun to curve, were examined. Initial volumes of 0.70 mL increased to 0.85 mL in the course of adding the shift reagent, and appropriate corrections were made for the volume changes.

**Registry No.** **1a**, 105205-70-7; **1b**, 52485-73-1; **2a**, 20780-54-5; **2b**, 20780-53-4; **3a**, 66701-19-7; **3b**, 62137-64-8; **4a**, 24825-01-2; **4b**, 58800-12-7; **5a**, 58717-28-5; **5b**, 58680-03-8; **6a**, 77550-46-0; **6b**, 95911-24-3; **7a**, 68906-81-0; **7b**, 68906-75-2; **8a**, 89618-18-8; **8b**, 89618-17-7; **9a**, 89772-83-8; **9b**, 78549-58-3; **10a**, 89618-15-5; **10b**, 89618-16-6; **11a**, 74444-65-8; **11b**, 74444-64-7; **12a**, 72010-12-9; **12b**, 72010-13-0; **13a**, 100017-09-2; **13b**, 100017-08-1; **14a**, 94729-53-0; **14b**, 94729-54-1; (±)-**15**, 84608-95-7; (±)-**16**, 92343-85-6; (±)-**17**, 66226-25-3; (±)-**18**, 66239-76-7; (±)-**19**, 105307-18-4; Eu(hfc)$_3$, 34788-82-4; Eu(tfc)$_3$, 34830-11-0.

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## Synthesis of (-)- and (+)-Frontalin

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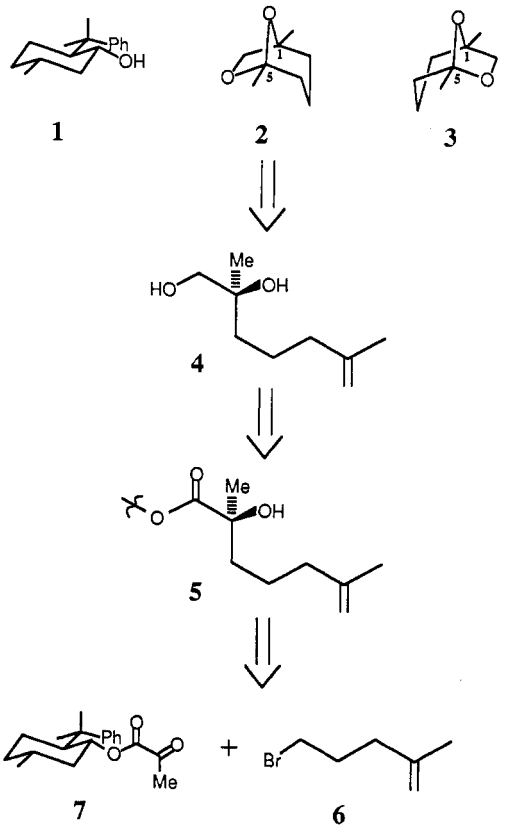
Recently we reported[1] on the high level of induction obtained in the Grignard additions to and in ene reactions of the glyoxylate ester of 8-phenylmenthol (**1**). We now report the application of this method for absolute stereochemical control in the separate syntheses of each of the enantiomers of frontalin.

Frontalin, first isolated by Kinzer,[2] is a component of the aggregation pheromone of the southern pine beetle *Dendroctonus frontalis* Zimmerman, and western pine beetle, *Dendroctonus brevicomis* Le Conte. Through unambiguous syntheses of both enantiomers and biological testing, Mori[3] has shown that the absolute configuration of the biologically active species **2** is 1*S*,5*R*. Its antipode **3** was found to be inactive. Other syntheses and studies[4] of frontalin have also been published.

**Scheme I**




**(*S*)-(-)-Frontalin (2).** Although frontalin contains two asymmetric centers, only the stereochemistry of C1 needs to be specifically addressed in the planning stages of a synthesis since the correct configuration at C5 is dictated by that of C1 during the formation of the bicyclic, ketal system. Thus, tertiary alcohol **4** (Scheme I), which contains suitable functionality for elaboration to (*S*)-frontalin, represents an ideal precursor. In turn, **4** could be obtained from hydroxy ester **5** by reduction, itself the product of addition of the Grignard reagent prepared from bromide **6** to the pyruvate ester **7** of 8-phenylmenthol.[5,6]

In the event, conversion of **6** to the Grignard reagent followed by reaction with the ester **7** at −78 °C provided

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