The Determination of Enantiomeric Purity Using Chiral Lanthanide Shift Reagents[1]

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Abstract: Chiral tris[β-diketonato]europium(III) chelates **1**–**14** have been synthesized and tested for their effectiveness in inducing chemical shifts ($\Delta\Delta\delta$) between corresponding resonances of enantiomeric organic substances. Judged by the dual criteria of generality of application as reagents for determining enantiomeric composition and ease of preparation, the most useful of these chiral shift reagents are tris[*d*,*d*-dicampholylmethanato]europium(III) (**1**, Eu(dcm)$_3$), tris[3-trifluoroacetyl-*d*-nopinonato]europium(III) (**9**), and tris[3-trifluoroacetyl-*d*-camphorato]-europium(III) (**10**). Compound **1**, Eu(dcm)$_3$, is the most effective reagent for the resolution of enantiotopic resonances; reagents **9** and **10** are considerably less effective, but are more easily prepared. It is not presently possible to predict in any detail the influence of a particular chiral shift reagent on a mixture of enantiomers, and achieving useful resolution between the signals of enantiotopic protons in complex, polyfunctional structures may require testing several chiral shift reagents, and varying sample concentrations and temperature. Chiral shift reagents are applicable in principle to the determination of enantiomeric composition of most "hard" organic bases; they are not effective with most "soft" bases, with acids, or with certain chelating agents. Conditions for use of these reagents are described.

The direct determination of enantiomeric purity is a central problem in the chemistry of chiral substances. Classical methods for these determinations are experimentally cumbersome;[3] the applicability of more convenient nmr procedures based on diastereomeric interactions between enantiomeric solutes and optically active solvents is limited by the small magnitude of the chemical shift differences induced between corresponding resonances of enantiomers.[4] We,[5,6] and others,[7] have demonstrated that nmr shift reagents[8] composed of tris chelates of chiral β-diketone ligands with europium(III) shift corresponding resonances of many enantiomeric organic substances to different extents. The magnitudes of the resulting differences in the chemical shifts of corresponding groups of the enantiomeric compounds (called "enantiomeric shift differences," $\Delta\Delta\delta$, in this paper) are usually much larger than those observed in procedures employing either optically active solvents,[4] or diastereomeric compounds,[9] and provide a useful alternative to these procedures.

The work reported here was practical in intent: we wished to establish which of the readily available types of chiral β-diketone ligands, when coordinated to europium, were most effective in inducing large values of $\Delta\Delta\delta$, to examine the range of applicability of these chiral shift reagents, and to define experimental conditions required to obtain maximum enantiomeric shift differences. It was not our primary purpose to establish in detail the mechanisms by which the chiral shift reagents exercise their influence. Nonetheless, to simplify the discussions that follow, it is worthwhile to outline several conclusions that have been reached concerning the mechanism of action of nonchiral europium shift reagents, and to indicate briefly ways in which these considerations are pertinent to the action of chiral shift reagents.

The magnetic interaction between a europium shift reagent and the protons of a Lewis base coordinated to the europium(III) ion is predominantly pseudocontact in character: the magnetic field produced by summation of the magnetic moments of the six unpaired electrons of the europium ion combines with that resulting from the orbital motion of the europium electrons and generates an anisotropic magnetic field in the vicinity of the shift reagent;[10] the protons of Lewis bases coordinated to the europium atom reflect this field in their chemical shifts. For achiral tris[β-diketonato]europium(III) complexes, it is not presently clear whether the conformational mobility of these complexes[11,12] is sufficient to generate an effectively axial magnetic symmetry around the europium atom, with the europium–Lewis base bond colinear with the

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(2) National Science Foundation Undergraduate Research Participant.

(3) M. Raban and K. Mislow, *Top. Stereochem.*, **2**, 199 (1967).

(4) W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **91**, 5150 (1969); W. H. Pirkle, R. L. Muntz, and I. C. Paul, *ibid.*, **93**, 2817 (1971), and references in each.

(5) G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, **92**, 6979 (1970).

(6) G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, **93**, 5914 (1971).

(7) H. L. Goering, J. N. Eikenberry, and G. S. Koermer, *J. Amer. Chem. Soc.*, **93**, 5913 (1971); R. R. Fraser, M. A. Petit, and J. K. Saunders, *Chem. Commun.*, 1450 (1971).

(8) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); J. K. M. Sanders, S. W. Hanson, and D. H. Williams, *ibid.*, **94**, 5325 (1972); W. DeW. Horrocks, Jr., and J. P. Sipe, III, *ibid.*, **93**, 6800 (1971); R. von Ammon and R. D. Fischer, *Angew. Chem., Int. Ed. Engl.*, **11**, 675 (1972); W. DeW. Horrocks, Jr., in "Chemical Applications of Nuclear Magnetic Resonance in Paramagnetic Molecules," G. N. La Mar, W. DeW. Horrocks, Jr., and R. H. Holm, Ed., Academic Press, New York, N. Y., 1973, Chapter 14; B. C. Mayo, *Chem. Soc. Rev.*, **2**, 49 (1973); A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973).

(9) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969), and references therein.

(10) The ground electronic state of europium(III) is $^7F_0$; strictly speaking, the pseudocontact interaction between metal and coordinated bases arises in the low-lying (~400 cm^{-1}) $^7F_1$ and higher excited states: S. I. Weissman, *J. Amer. Chem. Soc.*, **93**, 4928 (1971). R. G. Hayes and J. L. Thomas, *Organometal. Chem. Rev., Sect. A*, **7**, 1 (1971), particularly pp 38–44.

(11) I. M. Armitage, L. D. Hall, A. G. Marshall, and L. G. Werbelow, *J. Amer. Chem. Soc.*, **95**, 1437 (1973); S. L. Lippard, *Progr. Inorg. Chem.*, **8**, 109 (1967).

(12) A review of the chemistry of complexes of the lanthanide ions has been presented by T. Moeller, *MTP (Med. Tech. Publ. Co.) Inorg. Chem. Ser. One, Int. Rev. Sci.*, **7**, 275 (1972).

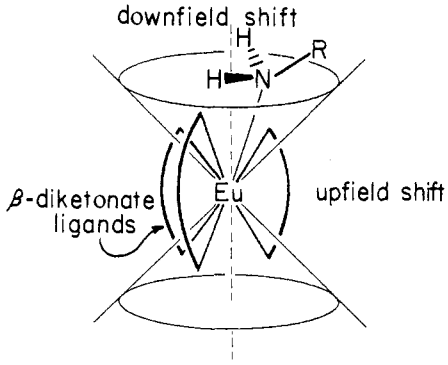


Figure 1. Deshielding occurs along the effective pseudosymmetry axis of tris[β-diketonato]europium(III) complexes, and shielding perpendicular to this axis.

principal axis of the chemical shift tensor;[8,13] the instantaneous symmetry of these complexes is lower (Figure 1).[14] The exceptional usefulness of europium(III) chelates as shift reagents originates in the unusually small extent to which the resonances of the ligands around europium are broadened by interaction with the paramagnetic metal ion; these line widths reflect the short spin–lattice relaxation time characterizing the unpaired electrons on europium. Exchange between substrate coordinated to europium and substrate free in solution is rapid.[15] In the presence of excess substrate, complexes containing either one or two substrate molecules coordinated to europium may be formed.[16]

The differences in chemical shifts observed for enantiomeric substrates in solutions containing chiral shift reagents might arise from at least two, probably mutually dependent, interactions; the equilibrium constants for formation of the various possible diastereomeric complexes between the enantiomeric substrates and the chiral chelate might differ, and the geometries of these complexes, once formed, might be distinct. The data that follow provide qualitative evidence that both the equilibrium constant for association of substrate with chelate and the geometry of the resulting diastereomeric complexes contribute to the observed values of $\Delta\Delta\delta$.

Results and Discussion

Synthesis of Chiral Lanthanide Shift Reagents. Chiral β-diketone ligands were prepared by condensation of the enolate anion of a chiral *tert*-alkyl ketone with a chiral or achiral carboxylic acid chloride or ester; a representative synthetic sequence is outlined

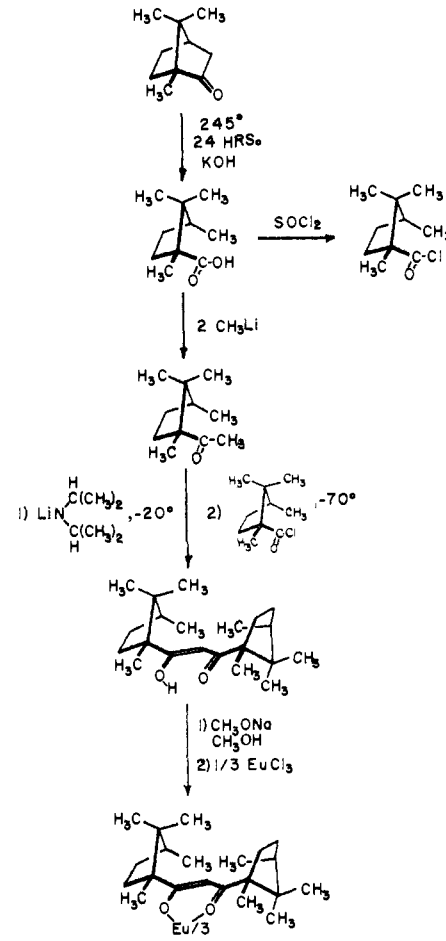


Figure 2. Tris[*d*,*d*-dicampholylmethanato]europium(III), Eu(dcm)$_3$ (**1**), is synthesized from *d*-camphor.

in Figure 2.[17] The choice of the base utilized in forming the enolate of the intermediate alkyl methyl ketone is important; the use of sodum hydride or sodium amide required vigorous reaction conditions (typically 85° for *ca.* 12 hr); substitution of lithium diisopropylamide[18] for these bases resulted in fewer self-condensation products and less O-acylation, and permitted the enolization reaction to be carried out under mild conditions (−20 to −50°, 0.5–2 hr). Although several procedures for synthesizing β-diketones were utilized during the course of the work and are reported in the Experimental Section, the procedures for *d*,*d*-dicampholylmethane and 3-trifluoroacetyl-*d*-nopinone should be considered representative of the most convenient routes to nonfluorinated and fluorinated β-diketones, respectively.

The conversion of β-diketones to tris[β-diketonato]europium(III) complexes has usually been accomplished by treating the β-diketone first with sodium hydroxide in aqueous methanol and then with europium trichloride hexahydrate. Dilution of the resulting solution with water frequently results in precipitation of an oily mixture of shift reagent and sodium β-diketonate.

(13) G. E. Hawkes, D. Leibfritz, D. W. Roberts, and J. D. Roberts, *J. Amer. Chem. Soc.*, **95**, 1659 (1973); R. E. Cramer and E. Dubois, *ibid.*, **95**, 3801 (1973); C. L. Honeybourne, *Tetrahedron Lett.*, 1095 (1972), and references cited in each.

(14) R. E. Cramer and K. Seff, *J. Chem. Soc., Chem. Commun.*, 400 (1972); J. C. A. Boeyens, *J. Chem. Phys.*, **54**, 75 (1971); W. DeW. Horrocks, Jr., J. P. Sipe, III, and J. R. Luber, *J. Amer. Chem. Soc.*, **93**, 5258 (1971); W. DeW. Horrocks, Jr., and J. P. Sipe, III, *Science*, **177**, 994 (1972).

(15) It has so far been possible to freeze this exchange only in isolated instances: D. F. Evans and M. Wyatt, *J. Chem. Soc., Chem. Commun.*, 312 (1972); 339 (1973); A. M. Grotens, J. J. M. Backus, F. W. Pijpers, and E. deBoer, *Tetrahedron Lett.*, 1467 (1973).

(16) J. W. ApSimon, H. Beierbeck, and A. Fruchier, *J. Amer. Chem. Soc.*, **95**, 939 (1973); J. S. Ghotra, F. A. Hart, G. P. Moss, and M. L. Staniforth, *J. Chem. Soc., Chem. Commun.*, 113 (1973), and references cited in each.

(17) Methods of preparing tris- and tetrakis[β-diketonato]europium(III) complexes are reviewed by S. J. Lyle and A. D. Witts, *Inorg. Chim. Acta*, **5**, 481 (1971). See also D. Seebach and V. Ehrig, *Angew. Chem., Int. Ed. Engl.*, **11**, 127 (1972); V. Shurig, *Tetrahedron Lett.*, 3297 (1972).

(18) Lithium tetramethylpiperidide might prove a useful alternative to lithium diisopropylamide: R. A. Olofson and C. M. Dongherty, *J. Amer. Chem. Soc.*, **95**, 582 (1973).

Table I. Enantiomeric Shift Differences ($\Delta\Delta\delta$, ppm)[a]

Compd	Resonance obsd	Shift reagent[b] 1	2	3	4	5	6	7	9	10
1-Phenylethylamine	$CHCH_3$	0.66	0.60	0.62	0.27	0.10	0.21	0.12	0.21	0.50
	$CHCH_3$	4.42	1.30	1.65	0.10	1.13	0.55	0.10	0.10	
	ortho *H*	0.15	0.13	0.13	0.13	0.0	0.13	0.00	0.12	0.05
N-Methyl-1-phenylethylamine[c]	$CHCH_3$	0.21	0.37	0.47	0.40	0.28	0.10	0.12	0.0	*f*
	NCH_3	1.46	0.10	0.22	1.13	0.25	0.50	0.18	0.00	*f*
	ortho *H*	1.45	0.30	0.43	0.23	0.14	0.09	0.00	0.0	*f*
N,N-Dimethyl-1-phenylethylamine[c]	$CHCH_3$	0.26	0.13	0.23	0.05	0.03		0.0	0.7	*f*
	$N(CH_3)_2$	0.85	0.17	0.43	0.17	0.24	0.05	0.0	0.15	*f*
sec-Butylamine	$CHNH_2$	2.93	0.57	0.75	0.20	0.30			0.0	0.0
	$CHCH_3$	0.36	0.30	0.23	0.15	0.20	0.25	0.11	0.10	0.52
	CH_2CH_3	0.36	0.03	0.05	0.05	0.00	0.04	0.00	0.05	0.25
Cyclohexylmethylcarbinol	$CHCH_3$	1.22	0.10	0.10	0.08	0.09	0.00	0.03	0.50	0.07
1-Phenylethanol	$CHCH_3$	0.70	0.23	0.25	0.0	0.0	0.00	0.1	0.55	0.40
	$CHCH_3$	0.61		0.00	0.02	0.10	0.00	0.0	0.45	0.00
	ortho *H*	0.06	0.10	0.05	0.02	0.0	0.00	0.0	0.05	0.00
1,3-Di-*tert*-butylpropargyl alcohol[c]	*CH*OH	2.50		1.30		1.03	0.10	0.11	2.02	0.59
	1-*tert*-butyl	2.43		0.13	0.00	0.21	0.05	0.0	0.48	0.09
Benzyl methyl sulfoxide	CH_3	1.21		0.40	0.14	0.12	0.0	0.0	0.05	0.0
sec-Butyl formate	*H*CO	0.48	0.10	0.06	0.00		0.0	0.03	0.20	0.0
	$CHCH_3$	0.40	0.10	0.10	0.00		0.00	0.03	0.06	0.04
	CH_2CH_3	0.25	0.05	0.02	0.0		0.0	0.03	0.10	0.03
sec-Butylformamide	*H*CO		0.05	0.05	0.10	0.20	0.03	0.05	0.00	0.0
	$CHCH_3$	0.30	0.05	0.09	0.05	0.03	0.05	0.05	0.00	0.10
	CH_2CH_3	0.22	0.05	0.04	0.02	0.02	0.03	0.05	0.02	0.05
Camphor[c]	CH_3	0.12	0.00	0.00	0.04		0.02	0.00	0.10	0.03
	$C(CH_3)_2$	0.75	0.00	0.00	0.00		0.00	0.00	0.16	0.12
		0.14	0.00	0.00	0.00		0.00	0.00	0.04	0.00
1-Methoxy-2-methylcyclohexane	OCH_3	0.98[d]	0.06	0.10	0.00	0.00	0.00	0.00	0.00	0.00
		1.02[e]	0.07	0.17	0.01	0.02	0.01	0.00	0.2	0.00

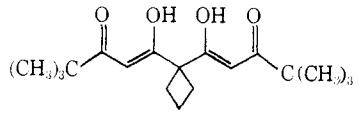
[a] The concentrations of shift reagent and substrate were approximately 0.3 ± 0.1 *M*. Small adjustments were made in each to maximize values of $\Delta\Delta\delta$. Spectra were recorded in carbon tetrachloride solution, except for those of 1-phenylethylamine, *N*-methyl-1-phenylethylamine, *N,N*-dimethyl-1-phenylethylamine, *sec*-butylamine, and benzyl methyl sulfoxide, all of which were obtained in chloroform-d_1. [b] Resonances for which no $\Delta\Delta\delta$ value is given could not be measured due to interfering resonances, broadened lines, or lack of shift reagent. All values of $\Delta\Delta\delta$ were measured at 27°. [c] Assignments of resonances to enantiomers were confirmed using samples enriched in one enantiomer. [d] Cis epimer. [e] Trans epimer. [f] Substrate resonances broadened on addition of even small quantities of **10**.

In preparations of nonfluorinated shift reagents, the use of sodium methoxide as base and methanol as solvent resulted in precipitation of the shift reagents directly from solution in good purity; fluorinated shift reagents still required addition of water to precipitate from methanol. Further purification of the shift reagent and dehydration at 100° (0.1 Torr) for *ca.* 24 hr, following procedures detailed in the Experimental Section, improved the ability of these materials to induce large enantiomeric shift differences.

All the shift reagents prepared during the course of this work are thermally stable, oxygen-insensitive, glasses or solids; all have good solubility in organic solvents. They are decomposed by acids, and by materials capable of chelating with the europium ion (*e.g.*, α-diketones, α-dioximes).[19]

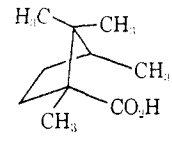
Influence of Structure of the β-Diketonate Ligands on the Effectiveness of the Chiral Shift Reagents. A number of shift reagents were synthesized to determine which chiral alkyl substituents were most effective in inducing large enantiomeric shift differences. In order to simplify the preparations, the only ketones and carboxylic acids that were examined were those that could be obtained from natural sources in optically active form, or that could be easily derived from an optically active natural product; materials requiring chemical resolution were not used. Further, only organic compounds bearing no basic functionalities other than the carbonyl to be incorporated into the β-diketone were considered, in the untested belief that Lewis basic centers in the β-diketonate ligand would compete with the substrate of interest for coordination sites on europium. Camphor, fenchone, and β-pinene were tractable and readily available starting materials;[20] lanosterol and menthone were used in some preparations, but proved to be less convenient; attempts to prepare ligands

(19) Praesodymium analogs of certain of these reagents were prepared, and also showed useful properties. However, the downfield shifts induced by europium shift reagents are almost always more convenient to work with than the upfield shifts produced by praesodymium, and these materials were not examined in any detail. Holmium analogs showed unacceptable line broadening, as expected. Attempts to decrease the electronic T_1 of holmium by adding heavy atoms or paramagnetic species, or by trying to couple the electronic states of two holmium atoms through complex formation with bis-β-diketones such as i, were not successful (see the Experimental Section for details).



i

(20) The common names given to the carboxylic acids derived from camphor and fenchone by basic cleavage are campholic acid (ii) and fencholic acid (iii), respectively. Throughout we will refer the configuration of these organic moieties to the configuration of the starting ketones: for example, campholic acid derived from *d*-camphor will be called *d*-campholic acid.



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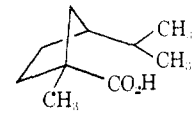

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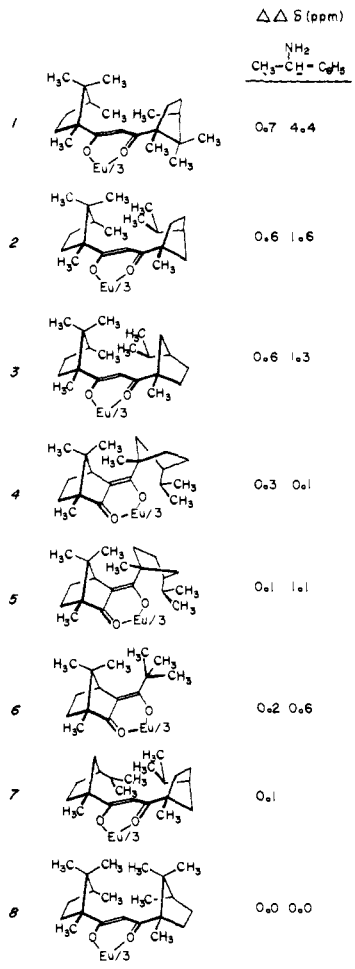


Figure 3. Nonfluorinated chiral shift reagents are listed roughly in the order of effectiveness in inducing shift differences between corresponding resonances of enantiomers of 1-phenylethylamine. These enantiomeric shift differences ($\Delta\Delta\delta$) are reported for chloroform-d_1 solutions at concentrations of shift reagents (*ca.* 0.2–0.5 *M*) and 1-phenylethylamine (*ca.* 0.3 *M*) which approximately maximize the value of $\Delta\Delta\delta$ for the CH_3 resonances.

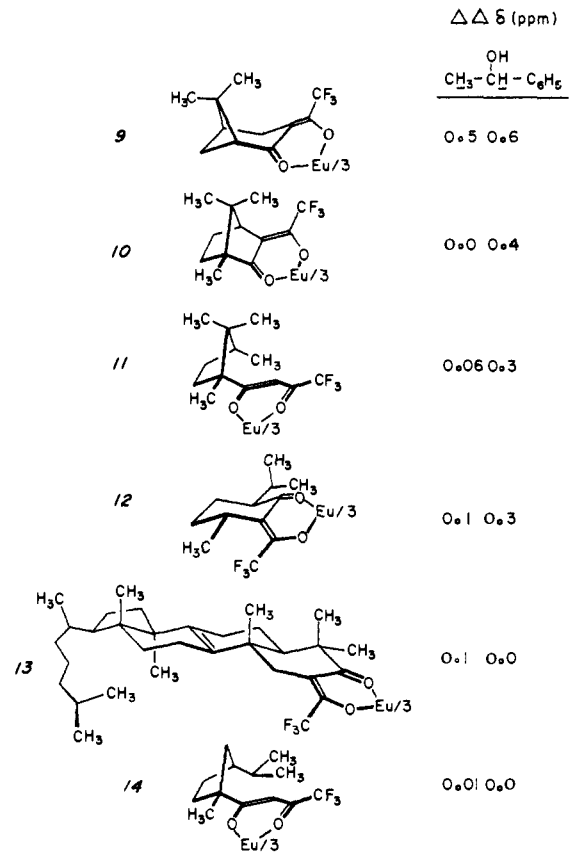


Figure 4. Fluorinated chiral shift reagents are listed in the order of effectiveness in inducing enantiomeric shift differences ($\Delta\Delta\delta$) for 1-phenylethanol. Shift differences ($\Delta\Delta\delta$) are reported for carbon tetrachloride solutions at concentrations of shift reagents (*ca.* 0.2–0.5 *M*) and 1-phenylethanol (*ca.* 0.3 *M*) which approximately maximize the value of $\Delta\Delta\delta$ for the CH_3 resonances.

containing patchouleone and cedranone moieties were not successful.

Figure 3 lists chiral shift reagents derived from nonfluorinated β-diketonate ligands; Figure 4 lists those derived from fluorinated ligands. Each list is arranged roughly in the order of decreasing general effectiveness of the shift reagent in inducing large values of $\Delta\Delta\delta$; magnitudes of this parameter in ppm for the methyl and methine protons of two representative substrates, 1-phenylethylamine and 1-phenylethanol, are included in these figures for brief comparison. To establish this order of effectiveness, values of $\Delta\Delta\delta$ for enantiomers of a number of compounds were obtained: a selection of these data is summarized in Table I.[21] The spectra from which these data were abstracted were obtained under conditions that approximately maximized the values of $\Delta\Delta\delta$ for that particular combination of shift reagent and substrate. In general, $\Delta\Delta\delta$ was determined experimentally by a procedure that consisted of adding successive small quantities of shift reagent to a solution containing a racemic mixture of the substrate being examined, and examining the spectrum of the solution at 27° after each addition. The resonances of the substrate shifted (usually downfield) and separated into doublets as the concentration of shift reagent increased. The frequency separation between the components of the doublets was taken as the enantiomeric shift difference. At high concentrations of shift reagent, values of $\Delta\Delta\delta$ were usually obtained that did not change significantly with further increases in the concentration of shift reagent. These limiting values of $\Delta\Delta\delta$ may or may not have been the maximum values observed. In many cases, it was possible to confirm the assignment of the components of the doublets to groups that were enantiotopic by external comparison[22] by adding a portion of one pure enantiomer to the sample, and identifying the peaks whose intensities were enhanced.

If addition of a chiral shift reagent to a sample splits certain resonances of the sample into two components, the frequency separation between these components can normally be assumed to be $\Delta\Delta\delta$, except in one important instance: *viz.*, when the protons giving rise to these resonances are enantiotopic[22] by internal comparison (for example, the methylene protons of benzyl methyl sulfoxide or of *sec*-butylamine). A doubling of the resonances of protons of this type might in principle be due to magnification of the enantiotopic shift difference by the shift reagent, or by several different types of diastereomeric interaction between the substrate and

(21) The data reported in Table I of ref 6 contain an error: values of $\Delta\Delta\delta$ listed as having been obtained with tris[*d,l*-difencholylmethanato]-europium(III) (labeled **7** in ref 6) were actually obtained with tris[*d*-campholyl-*l*-fencholylmethanato]europium(III) (labeled **6** in ref 6).

(22) M. Raban and K. Mislow, *Top. Stereochem.*, 1, 7 (1967).

Table II. Enantiomeric Shift Differences Induced by Shift Reagents **1** and **9** ($\Delta\Delta\delta$, ppm) Are Compared for 2-Butyl Derivatives, $CH_3CHXCH_2CH_3$

	$\Delta\Delta\delta$ (ppm)							
	1[c]				**9**[d]			
X[a]	H[b]	$CHCH_3$	CHX	CH_2CH_3	H[b]	$CHCH_3$	CHX	CH_2CH_3
NH_2		0.36	2.90	0.36		0.10	0.0	0.05
$NHCH_3$	1.20	1.45		0.70	0.00[e]	0.00[e]		0.00[e]
$N(CH_3)_2$	1.38	0.30			0.09[e]	0.00[e]		0.00[e]
OH		0.76		0.50		0.40	0.0	0.12
CH_2OH		0.02		0.02		0.16	0.0	0.00
$COCH_3$	0.12	0.27	0.0	0.11	0.16	0.08		0.00
$OCHO$	0.48	0.40	0.0	0.25	0.20	0.06	0.0	0.10
$OCOCH_3$	0.29	0.35	0.37	0.06	0.11	0.12	0.40	0.12
$OCOC_6H_5$, (ortho H)	0.42	0.05	0.37	0.07		0.10		0.00
$NHCHO$		0.30		0.22	0.00	0.02		0.00
$CO_2CH_2CH_3$		0.21			0.08	0.12		0.05
OCH_3	0.45	0.19	0.0		0.00	0.03		0.00
HgCNO		0.06		0.0		0.0[e]	0.0[e]	0.0[e]
CN		0.00		0.03		0.04	0.0	0.00
SH		0.00	0.00	0.00		0.00	0.0	0.00
$SCH(CH_3)CH_2CH_3$		0.00	0.00	0.00		0.00	0.00	0.00
NO_2		0.00	0.00	0.00		0.00	0.0	0.00
Br		0.00	0.00			0.00	0.00	0.00

[a] The concentration of substrate was 0.3 M; the solvent was CCl_4, except for X = amine, in which instances the solvent was $CDCl_3$. The concentration of **1** ranged between 0.2 and 0.6 M. Values of $\Delta\Delta\delta$ are approximately maximized for the given solvent at 27°. [b] These values of $\Delta\Delta\delta$ are for the indicated resonances of the group X. [c] After purification by trituration with methanol, **1** was dried at 56° (0.01 Torr) for 48 hr. [d] Shift reagent **9** was not purified, but was dried (56° (0.01 Torr)) for 48 hr. [e] These resonances broadened considerably with the addition of even small quantities of **9**.

the shift reagent.[23-25] Unambiguous identification of signals arising from enantiomeric substrates is most directly accomplished by examination of a sample enriched in one enantiomer; lacking an enriched sample, examination of spin decoupling experiments can occasionally be used to assign signals. We have simply avoided assigning values of $\Delta\Delta\delta$ to groups at a prochiral center[22] unless it proved possible to make unambiguous assignments.

Two principal conclusions emerge from the data of Figures 3 and 4 and Table I: first, all of these shift reagents, with the exception of the achiral compound **8**, are able to resolve resonances of enantiomers for a wide range of organic substrates; second, although all of the shift reagents are capable of yielding observable values of $\Delta\Delta\delta$ for certain substrates, reagent **1**, tris-[*d,d*-dicampholylmethanato]europium(III) (Eu(dcm)$_3$), is clearly the single best reagent. Reagent **9**, tris[3-trifluoroacetyl-*d*-nopinonato]europium(III), seems to be second in utility, with **10**, tris[3-trifluoroacetyl-*d*-camphorato]europium(III), and **2**, tris[*d*-campholyl-*l*-fencholylmethanato]europium(III), also useful materials. Considering both effectiveness as shift reagents and ease of preparation, **1**, **9**, and **10** appear to be the most useful substances.

Applicability of Chiral Shift Reagents. The principle restriction on the applicability of chiral europium shift reagents is that common to all europium shift reagents: to be influenced by a europium shift reagent, the substrate must contain one or more atoms capable of coordinating to the europium ion. Europium(III) in tris[β-diketonate] complexes is a "hard" ion:[26] it complexes strongly with amines, alcohols, carbonyls, epoxides, sulfoxides, and related basic functional groups; it complexes weakly with ethers, sulfides, nitroalkanes, and nitriles; and it complexes not at all with olefins, aromatic residues, halides, and similar "soft" bases. Table II gives values of $\Delta\Delta\delta$ for a range of derivatives of the 2-butyl moiety, obtained using shift reagents **1** and **9**, that illustrate these generalizations. Within the limitations imposed by the requirement that the substrate coordinate with europium, the application of chiral europium shift reagents in determination of enantiomeric purity is broad: almost every enantiomeric organic base we have examined seems to give useful separations of resonances with some shift reagent, provided that the chiral center is reasonably close to the site that coordinates to the europium ion. In this connection, it is important to emphasize that it may be necessary to try several shift reagents to achieve a useful value of $\Delta\Delta\delta$ for an intractable substrate. At present, it is difficult to predict which shift reagent will yield the best enantiomeric shift differences for a given substrate.

The determination of enantiomeric purity is practical for substances having more than one functional group capable of coordinating to europium, as well as for those bearing a single basic group. As expected, the former class of substrates give rise to a single, shifted, spectrum in the presence of a shift reagent, rather than to a number of superimposed spectra resulting from coordination of europium at a number of different sites. This single spectrum is presumably a weighted average, resulting from rapid interchange of the europium ion among the possible coordinating sites. Figures 5 and 6 illustrate portions of the spectra of two polyfunctional molecules, each in the presence of two different shift reagents. Although no effort was made to resolve ambiguities in the assignment of resonances to particular groups in the substrate molecules, in both instances resonances due to different enantiomers were identified unambiguously by noting the enhancement

(23) G. E. Wright, *Tetrahedron Lett.*, 1097 (1973); H. Gerlach and B. Zagalak, *J. Chem. Soc., Chem. Commun.*, 274 (1973).

(24) R. R. Fraser, M. A. Petit, and M. Miskow, *J. Amer. Chem. Soc.*, **94**, 3253 (1972).

(25) (a) M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Amer. Chem. Soc.*, **94**, 5924 (1972); (b) C. J. Reich, G. R. Sullivan, and H. S. Mosher, *Tetrahedron Lett.*, 1505 (1973).

(26) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963); R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967); G. Klopman, *ibid.*, **90**, 223 (1968).

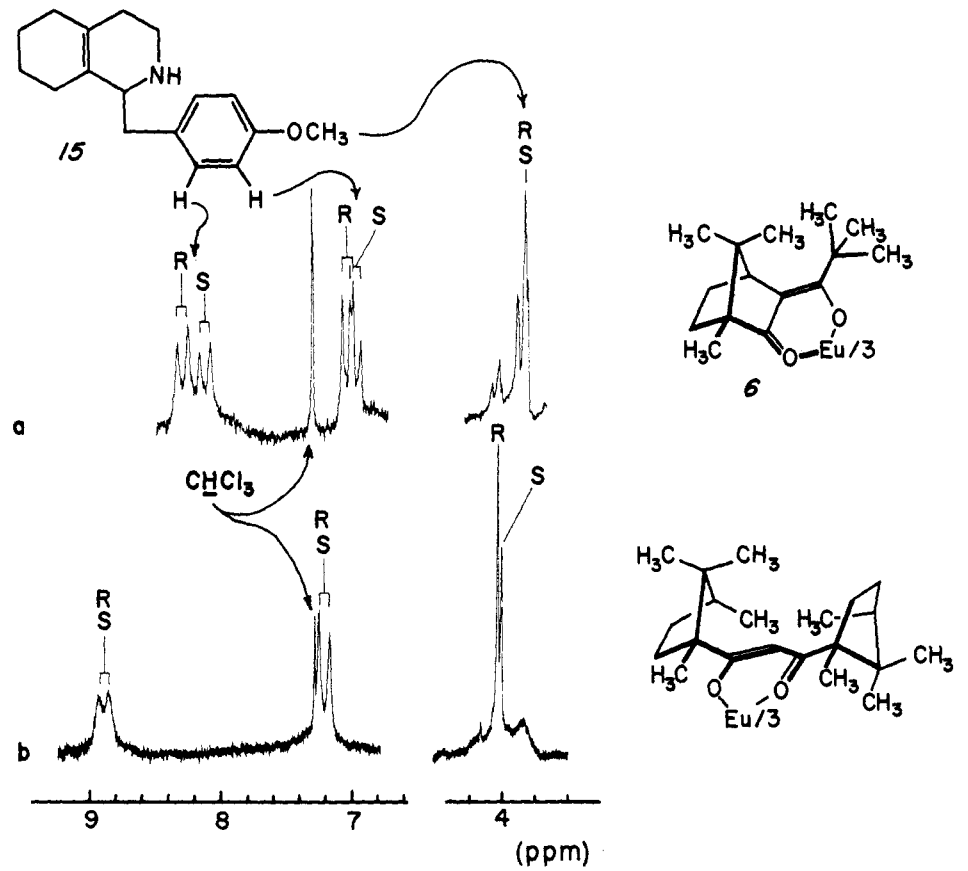


Figure 5. Resolved methoxy and aromatic resonances are observed (100 MHz) for the enantiomers of amine **15** in the presence of shift reagents **1** and **6**; chemical shifts are referenced to tetramethylsilane ($T = 31°$). The *R* enantiomer of **15** is present in higher concentration than the *S* enantiomer. (a) The concentration of substrate is 0.5 *M* and that of **6** is *ca.* 0.3 *M* in $CDCl_3$; (b) the concentration of substrate is 0.5 *M* and that of **1** is *ca.* 0.2 *M* in $CDCl_3$.

of peaks on addition of one pure enantiomer. These spectra were obtained using concentrations that seemed to maximize values of $\Delta\Delta\delta$ at 31°. The marked difference in the effects of the indicated shift reagents again points to the desirability of testing enantiomeric separations using several shift reagents, particularly in instances in which it is desirable to estimate quantitatively the enantiomeric purity of the substance being examined; these patterns are not predictable, and the generation of a shifted spectrum containing well-separated, isolated resonances that are suitable for integration is primarily a matter of trial and error.[27]

Solvent and Temperature Effects; Sample Preparation; Concentration. Determinations of enantiomeric purity using chiral shift reagents should be carried out in nonbasic solvents; because the solvent is present in large excess over the substrate, even weakly basic solvents are capable of competing effectively with substrate for coordination sites on the europium, and consequently of lowering the observed values of the chemical shift δ and the enantiomeric shift difference $\Delta\Delta\delta$. The best solvents for these studies are pentane (or other hydrocarbons), 1,1,2-trichloro-1,2,2-trifluoroethane, and carbon tetrachloride. For comparable concentrations of two representative substrates (2-butanol and 3-methyl-2-pentanone) and shift reagent **1**, pentane and 1,1,2-trichloro-1,2,2-trifluoroethane solutions gave significantly larger values for both δ and $\Delta\Delta\delta$ than did solutions of fluorotrichloromethane, carbon tetrachloride, carbon disulfide,[28] benzene, chloroform, and methylene chloride (Table III). Presumably the range of values for δ and $\Delta\Delta\delta$ for these solvents reflects different degrees of association of the substrate with the shift reagent, and perhaps changes in conformation of the substrate–shift reagent complex, in each solvent. Whether differences in the equilibrium constant for association in these solvents result from solvation of the alcohol or the europium ion, or a general medium effect, is a question that cannot be fully answered at present.

The use of pentane as a solvent for shift reagent studies has the obvious disadvantage of masking weakly shifted substrate resonances.[29] Fluorotrichloromethane is inconvenient because of its high volatility, although

(27) In instances in which it is difficult to achieve satisfactory separations of enantiomeric resonances using any of the available shift reagents, it is sometimes possible to obtain useful data by manipulation of the structure of the substrate. Thus, for example, citronellol yielded values of $\Delta\Delta\delta$ less than 0.001 ppm in the presence of **7**, **9**, or **10** (27°), and only the $CHCH_3$ resonance could be conveniently observed. Acylation of the alcohol provided derivatives that could be examined more conveniently: acetate ($COCH_3$, $\Delta\Delta\delta = 0.00$), trifluoroacetate ($COCF_3$, $\Delta\Delta\delta = 0.00$), pivalate ($COC(CH_3)_3$, $\Delta\Delta\delta = 0.01$), and 3,3-dimethylbutanoate ($COCH_2C(CH_3)_3$, $\Delta\Delta\delta = 0.01$). Thus, small but observable values of $\Delta\Delta\delta$ were obtained for the two most hindered compounds; moreover, these esters have the advantage of possessing methyl groups near the basic functionality that appear as strong, well-shifted, easily integrated singlets in the presence of shift reagents. In general, carboxylic acids (which decompose europium chelates) are most conveniently converted to methyl esters before use with shift reagents.

(28) For a discussion of the advantages of carbon disulfide as a solvent for tris[dipivaloylmethanato]europium(III), see D. B. Walters, *Anal. Chim. Acta.*, 60, 421 (1972).

(29) Although soluble in pentane, **1** is quite insoluble in cyclohexane-d_{12}.

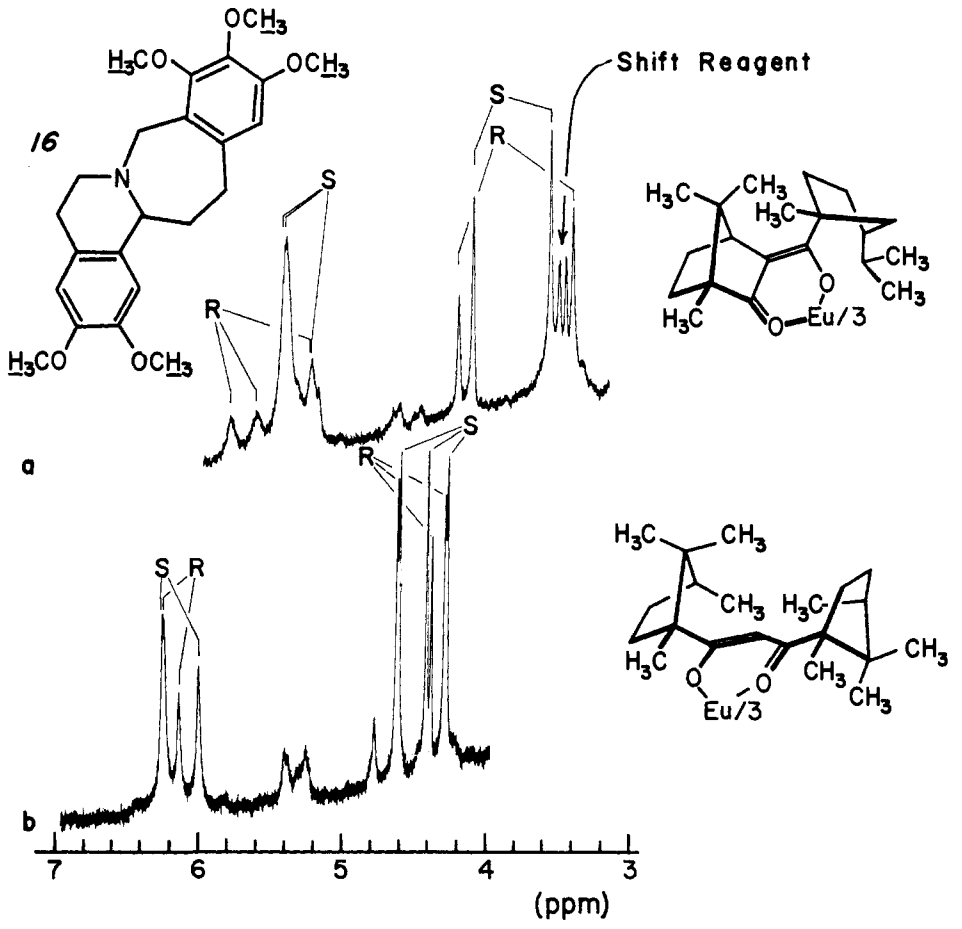


Figure 6. Resolved methoxy resonances are observed (100 MHz) for the enantiomers of amine **16** in the presence of shift reagents **5** and **1**. Chemical shifts are referenced to tetramethylsilane ($T = 31°$). The *S* enantiomer of **16** is present in higher concentration than the *R* enantiomer. (a) The concentration of substrate is 0.5 *M* and that of **5** is *ca.* 0.3 *M* in $CDCl_3$; (b) the concentration of substrate is 0.5 *M* and that of **1** is *ca.* 0.4 *M* in $CDCl_3$.

Table III. Solvent Effects on $\Delta\Delta\delta$ for 2-Butanol and 3-Methyl-2-pentanone in the Presence of Shift Reagent **1**

Solvent	Wt of **1**, mg[a]	$\Delta\Delta\delta(\delta)$ (ppm)[b] CH_3–CHOH–CH_2–CH_3		CH_3–CO–CH(CH_3)–CH_2–CH_3		
C_5H_{12}	100[c]	1.05 (15.78)	0.61 (9.72)	0.11 (13.38)	0.30 (9.32)	0.13 (6.03)
CCl_2FCF_2Cl	100[c]	0.86 (15.55)	0.58 (9.58)	0.11 (12.75)	0.28 (8.75)	0.12 (5.68)
$CFCl_3$	100[c]	0.80 (15.17)	0.52 (9.33)	0.11 (11.85)	0.23 (8.06)	0.09 (5.23)
CCl_4	100	0.76 (15.00)	0.50 (9.23)	0.11 (11.50)	0.23 (7.80)	0.08 (5.07)
CS_2	100	0.69 (14.47)	0.42 (8.88)	0.11 (10.92)	0.16 (7.30)	0.04 (4.72)
C_6D_6	100	0.67 (13.57)	0.43 (8.37)	0.11 (10.47)	0.25 (7.05)	0.09 (4.58)
$CDCl_3$	100	0.63 (12.18)	0.37 (7.55)	0.09 (6.48)	0.11 (4.18)	0.02 (2.80)
CD_2Cl_2	100	0.46 (9.83)	0.24 (6.12)	0.07 (5.85)	0.10 (3.67)	0.00 (2.50)
Dioxane-d_8	100[c]	0.0 (1.50)	0.0 (1.10)	0.00 (2.21)	0.00 (1.16)	0.00 (0.94)
80% $CO(CD_3)_2$ 20% CCl_4	100[c]	0.00 (1.67)	0.0 (1.23)	0.00 (2.30)	0.00 (1.28)	0.0 (0.99)
50% C_5D_5N 50% CCl_4	100[c]	0.00 (1.27)	0.0 (1.01)	0.00 (2.01)	0.00 (1.01)	0.0 (0.83)
CCl_4	*d*	0.79 (15.75)	0.53 (9.70)	0.09 (13.77)	0.27 (9.45)	0.12 (6.10)
$CDCl_3$	*d*	0.80 (15.90)	0.55 (9.78)	0.10 (12.50)	0.25 (8.48)	0.11 (5.50)
CD_2Cl_2	*d*	0.70 (15.78)	0.50 (9.71)	0.11 (11.85)	0.22 (7.82)	0.10 (5.02)

[a] Solutions were made up by adding the specified weight of **1** to 350 μl of solvent and 7.5 μl of 2-butanol or 10 μl of 3-methyl-2-pentanone. Shift reagent **1** was purified by trituration with methanol, and then dried at 56° (0.01 Torr) for 48 hr. [b] Values of δ are given relative to TMS internal standard at 32°. The chemical shifts are very sensitive to temperature. [c] This amount was approximately the maximum weight of **1** soluble in 350 μl of the specified solvent (plus 7–10 μl of substrate) at 32°. [d] The concentration of **1** was adjusted so that the chemical shifts (δ) of the substrate in CCl_4, $CDCl_3$, and CD_2Cl_2 were as close as possible to the values of δ obtained for the substrate with 100 mg of **1** in pentane. The amounts of **1** added to 2-butanol in CCl_4, $CDCl_3$, and CD_2Cl_2 were 130, 230, and 270 mg, respectively. The amounts of **1** added to 3-methyl-2-pentanone in CCl_4, $CDCl_3$, and CD_2Cl_2 were 140, 320,[c] and 290 mg,[c] respectively.

this property can be useful for some applications. Maximum values of $\Delta\Delta\delta$ using shift reagents with nonfluorinated ligands are limited somewhat in pentane, 1,1,2-trichloro-1,2,2-trifluoroethane, and fluorotrichloromethane by the solubility of the shift reagent; shift reagents with fluorinated ligands are quite soluble

in these solvents.[30] Carbon tetrachloride is a particularly convenient solvent for shift reagent studies since shift reagents with either fluorinated or nonfluorinated ligands are quite soluble in it, and the maximum values of $\Delta\Delta\delta$ and δ obtained in carbon tetrachloride for a given concentration of shift reagent are relatively large.

Although the majority of spectra examined in this work were obtained at ambient temperature, a study of the influence of temperature on the magnitude of enantiomeric shift differences demonstrated that low-temperature spectroscopy offers important advantages for relatively weakly coordinating substrates (Table IV). Compounds such as 2-methylbutanol, 2-nitrobutane, 2-butanethiol, and 2-cyanobutane show negligible enantiomeric shift differences at ambient temperature ($\Delta\Delta\delta$ = 0.00–0.02 ppm) but large shift differences at −50 to −75° ($\Delta\Delta\delta$ = 0.14–1.06 ppm). Line widths may remain as small as *ca.* 0.07 ppm down to −85° in CS_2 for very weakly basic substrates such as 2-butanethiol. Values of $\Delta\Delta\delta$ for strongly coordinating substrates, such as amines, usually increase only slightly, and substrate resonances broaden rapidly as the temperature is lowered. Figure 7 illustrates the influence of temperature on the spectrum of 2-methylbutanol. Both δ and $\Delta\Delta\delta$ increase substantially as the temperature of the sample is decreased. At high temperatures, the resonances of **1** resemble those for the shift reagent in the absence of substrate (Figure 11), while at low temperature the resonances of **1** resemble those for the shift reagent in the presence of a strongly coordinating substrate. Since the resonances of **1** in the presence of a substrate move upfield as the temperature is lowered, it is often possible to observe weakly shifted substrate resonances that are masked by the resonances of **1** at ambient temperature.

Table IV. Temperature Dependence of Enantiomeric Shift Differences ($\Delta\Delta\delta$) Induced by **1**

Substrate[a]	Resonance obsd	$\Delta\Delta\delta$ (ppm) 25°	Maximum useful $\Delta\Delta\delta$[b]	Maximum $\Delta\Delta\delta$[c]
2-Butyl acetate	$COCH_3$	0.13	0.65 (−25°)	1.50 (−50°)
	$CHCH_3$	0.18	0.47 (−25°)	0.74 (−50°)
Methyl 3,7-dimethyl-octanoate	CH_2CH_3	0.03	0.13 (−25°)	0.28 (−50°)
	$CHCH_3$	0.10	0.60 (−50°)	1.04 (−75°)
	OCH_3	0.07	0.07 (25°)	0.12 (−25°)
2-Butyl methyl ether	OCH_3	0.21	0.21 (25°)	1.36 (−25°)
	$CHCH_3$	0.12	0.98 (−25°)	1.75 (−50°)
	CH_2CH_3	*d*	0.45 (−50°)	0.45 (−50°)
Camphor	CH_3	0.0	0.14 (0°)	0.34 (−25°)
	$C(CH_3)_2$	0.39	1.06 (−25°)	1.06 (−25°)
	$C(CH_3)_2$	0.06	0.28 (−25°)	0.42 (−50°)
2-Methyl-1-butanol	$CHCH_3$	0.02	1.06 (−75°)	1.06 (−75°)
	$CHCH_3$	0.02	0.60 (−75°)	0.60 (−75°)
2-Nitrobutane	$CHCH_3$	0.00	0.15 (−75°)	0.30(−100°)
	CH_2CH_3	0.00	0.00 (−50°)	0.0 (−100°)
2-Cyanobutane	$CHCH_3$	0.00	0.05 (−50°)	0.05 (−50°)
	CH_2CH_3	0.03	0.29 (−50°)	0.98 (−75°)
2-Butanethiol	$CHCH_3$	0.00	0.14 (−75°)	0.14 (−75°)
	CH_2CH_3	0.00	0.00 (−75°)	0.0 (−75°)

[a] The concentration of substrate was *ca.* 0.3 *M* in CS_2 (dried over 3A molecular seives). The concentration of **1** was *ca.* 0.15 *M* for *sec*-butyl acetate and 2-nitrobutane; *ca.* 0.3 *M* for 2-butyl methyl ether, camphor, and 2-methyl-1-butanol; and *ca.* 0.45 *M* for 2-cyanobutane, methyl 3,7-dimethyloctanoate, and 2-butanethiol. [b] Line widths are *ca.* 1–5 Hz. [c] Line widths are 3–40 Hz. [d] Substrate resonance cannot be observed due to interfering resonances of **1**.

Lowering the temperature influences the magnitude of the pseudocontact shift produced by a chiral europium shift reagent in at least four ways: by increasing the degree of association between the substrate and the shift reagent, by changing the equilibrium populations of the various conformers that almost certainly exist for any complex of shift reagent with substrate, by increasing the magnetic susceptibility of the shift reagent–substrate complexes present in the magnetically active $^7F_1$ and higher states, and by decreasing the population of these excited states. It will be very difficult, either experimentally or theoretically, to disentangle these effects, and to understand the ways in which they balance to produce the enantiomeric shift differences; we have made no effort to do so.[31] Nonetheless, it is clear that the utility of this experimental procedure as a method of increasing the enantiomeric shift differences offers important potential advantages for samples in which association between shift reagent and substrate appears to be small at ambient temperature.

The influence of concentration of shift reagent and substrate on the resolution obtainable between enantiomeric resonances is again a subject in which it is presently difficult to make clear predictions. Figure 8 illustrates the effect of increasing concentrations of $Eu(dcm)_3$ (**1**) on the spectrum of 1-phenylethylamine in chloroform-d_1. Several features of these spectra are noteworthy. First, although the magnitude of $\Delta\Delta\delta$ for the methine proton increases smoothly as the concentration of **1** is increased, the magnitude of $\Delta\Delta\delta$ for the methyl protons passes through a maximum over the same range of concentrations of **1** and decreases to essentially zero at the highest concentration, and $\Delta\Delta\delta$ for the ortho aromatic protons reaches a maximum, decreases, and finally changes sign. Choosing the concentration of shift reagent and substrate yielding the best spectrum for quantitative analysis of enantiomeric composition requires taking these types of variations in $\Delta\Delta\delta$ into account, along with the relatively uniform increase in line width with increasing δ, the general increase in line width that accompanies the increased sample viscosity as shift reagent concentration increases, and the requirement that signals to be used for integration should not be close to other strong signals. The correct balance of concentrations is best achieved by trial and error, but it is important to keep in mind that high concentrations of shift reagent do not necessarily yield the best spectra for analytical purposes.

A factor as important as those already discussed in obtaining spectra suitable for quantitative analysis of enantiomeric purity is the method by which the sample solution is prepared. Solutions are made up using dry spectrograde solvents. Although the shift reagents (particularly those having trifluoroacetyl moieties) are

(30) About 100 mg (0.09 mmol) of **1** is soluble in 350 μl of these solvents (32°), while more than 300 mg (0.35 mmol) of **9** is soluble under the same conditions. All of the shift reagents **1**–**14** were soluble in carbon tetrachloride to the extent of at least 300 mg of shift reagent per 350 μl of solvent (25°). Generally, addition of a soluble substrate significantly increases the solubility of the shift reagent. Conversely, sparingly soluble substrates are often "pulled" into solution by the shift reagent.

(31) For references to the temperature dependence of δ in the presence of achiral shift reagents, see A. M. Grotens, J. J. M. Backus, and E. de Boer, *Tetrahedron Lett.*, 1465 (1973).

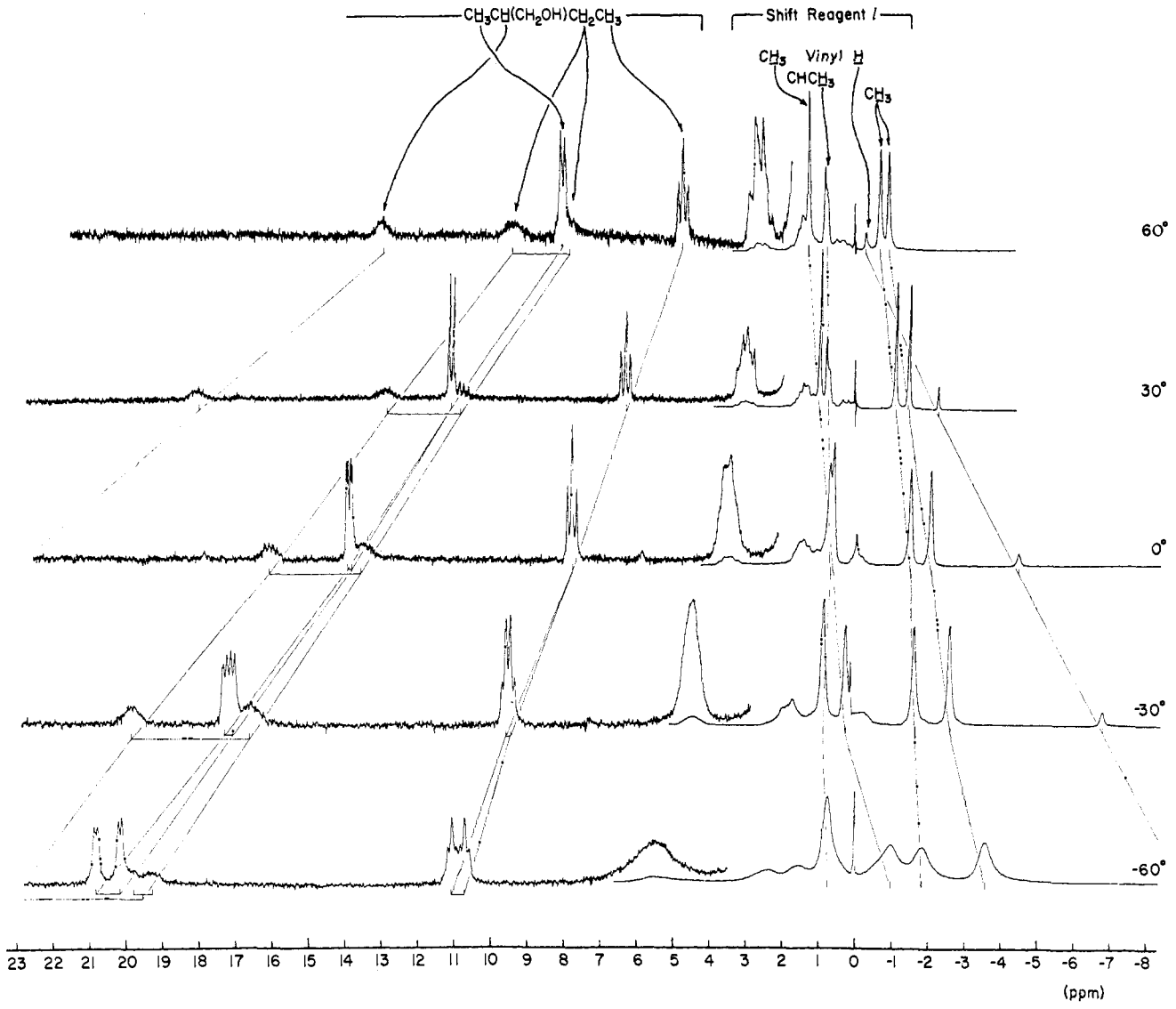


Figure 7. The magnitudes of $\Delta\Delta\delta$ increase for 2-methyl-1-butanol with decreasing temperature in the presence of **1**. The concentrations of substrate and **1** in CS_2 in these spectra are 0.3 and 0.15 *M*, respectively.

sensitive to water and should be stored in a desiccator after drying, their transfer and manipulation for short periods in air presents no difficulty. In qualitative work, the influence of shift reagent concentration on the spectrum is explored simply by adding ~15-mg samples of solid shift reagent to a solution of the sample in an nmr tube, and obtaining successive spectra. Addition of even carefully purified shift reagents sometimes results in a significant increase in line width and a serious decrease in resolution. Samples in which resolution has deteriorated can usually be restored by filtration through a well-rinsed cotton plug in a disposable pipet or through a Micropore nmr filter.[32] We speculate that the solid responsible for the effects may be finely divided paramagnetic europium oxide, resulting from hydrolysis of the shift reagent, but we have never tested this speculation. Regardless, it is essential to keep the sample solutions free of filterable solids to achieve high resolution.

Observations Pertinent to the Structure of the Complexes between Shift Reagent and Substrate. A basic question in considering details of the structure of the complexes formed between europium shift reagents and substrates is that of stoichiometry: *viz.*, are the complexes formed in substantial quantity in solutions of shift reagent and substrate those which are composed of two molecules of substrate and one shift reagent, or are the only complexes present in significant quantity those of one to one stoichiometry? Although a variety of techniques based on determination of the concentration dependence of chemical shifts have been devised to test for 2:1 complexes,[16] examination of solutions containing mixtures of chiral substrates offers an interesting, if limited, alternative method of exploring this problem. Figure 9 shows the spectrum of a mixture of both *R* and *S* enantiomers of 1-phenylethylamine, enantiomerically pure (*R*)-*N*-methyl-1-phenylethylamine, and the achiral shift reagent tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione]europium(*III*), Eu(fod)$_3$. This spectrum exhibits a small but real difference in the shifts of corresponding resonances of the enantiomers of the 1-phenylethylamine. The simplest explanation of this phenomenon is that coordination of (*R*)-*N*-methyl-1-phenylethylamine to Eu-

(32) Obtainable from Stohler Isotope Chemicals, Inc., Waltham, Mass. 02154 as a filter disk holder (SFH-10) and filter disks (SFD-5).

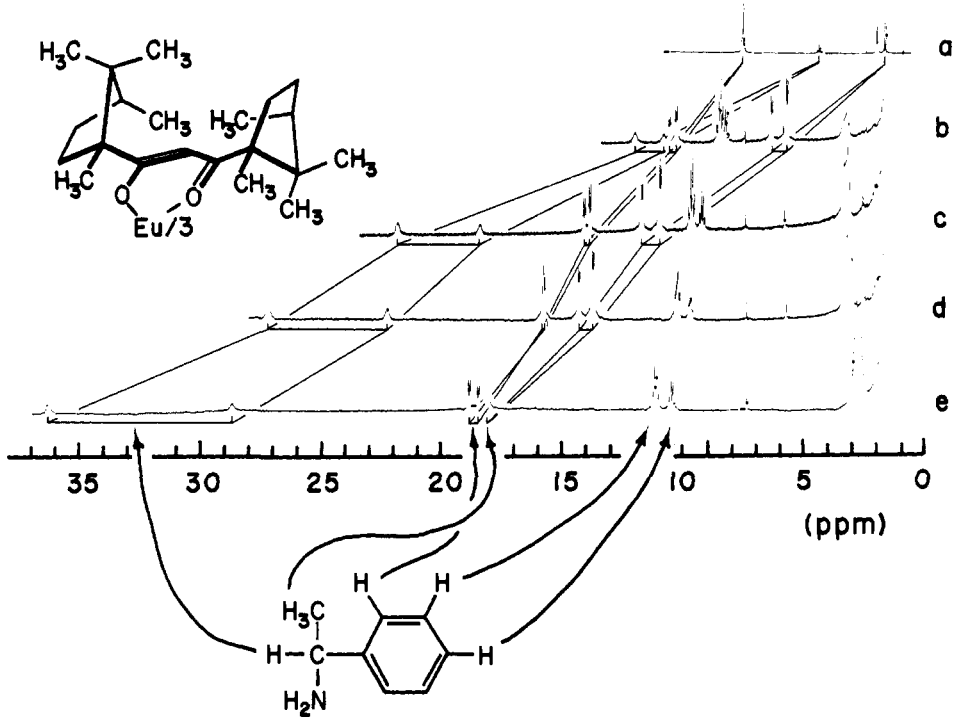


Figure 8. Spectra (100 MHz) of (*R*)- and (*S*)-1-phenylethylamine in the presence of increasing concentrations of **1** demonstrate that the magnitude of the enantiomeric shift differences ($\Delta\Delta\delta$) does not always correlate with that of the chemical shift differences ($\Delta\delta$). The concentration of substrate in these spectra is 0.3 *M* in $CDCl_3$, and that of **1** is *ca.* (a) 0.0 *M*, (b) 0.1 *M*, (c) 0.2 *M*, (d) 0.3 *M*, and (e) 0.5 *M*. The *R* enantiomer is present in higher concentration than the *S* enantiomer. The resonances above 4 ppm are due to the protons of the β-diketonate ligands.

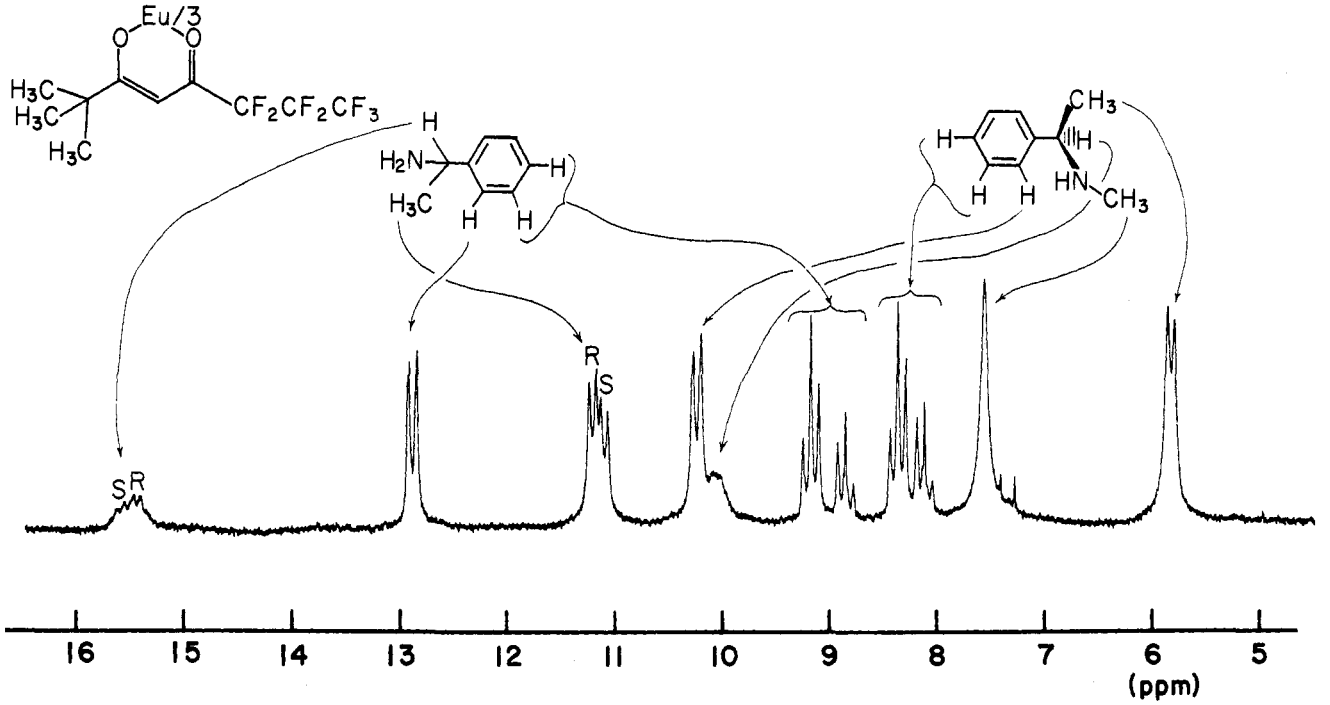


Figure 9. The resonances of corresponding protons of (*R*)- and (*S*)-1-phenylethylamine are distinct in the presence of a nonchiral shift reagent and an optically active amine: [(*R*)-1-phenylethylamine] ~ 0.3 *M*, [(*S*)-1-phenylethylamine] ~ 0.2 *M*, [(*R*)-*N*-methyl-1-phenylethylamine] ~ 0.6 *M*, and $Eu(fod)_3$ is 0.6 *M* in $CDCl_3$. The spectrum was taken at 100 MHz (31°).

$(fod)_3$ results in formation of a shift reagent that is chiral by virtue of the coordinated enantiomerically pure amine, and that this amine–europium complex is capable of further coordination by 1-phenylethylamine, and in consequence, of inducing a chemical shift between the enantiomers of this amine. This rationalization of the enantiomeric shift difference observed in Figure 9 implies that molecules of both (*R*)-*N*-methyl-1-phenylethylamine and 1-phenylethylamine are able to coordinate simultaneously to the $Eu(fod)_3$. An al-

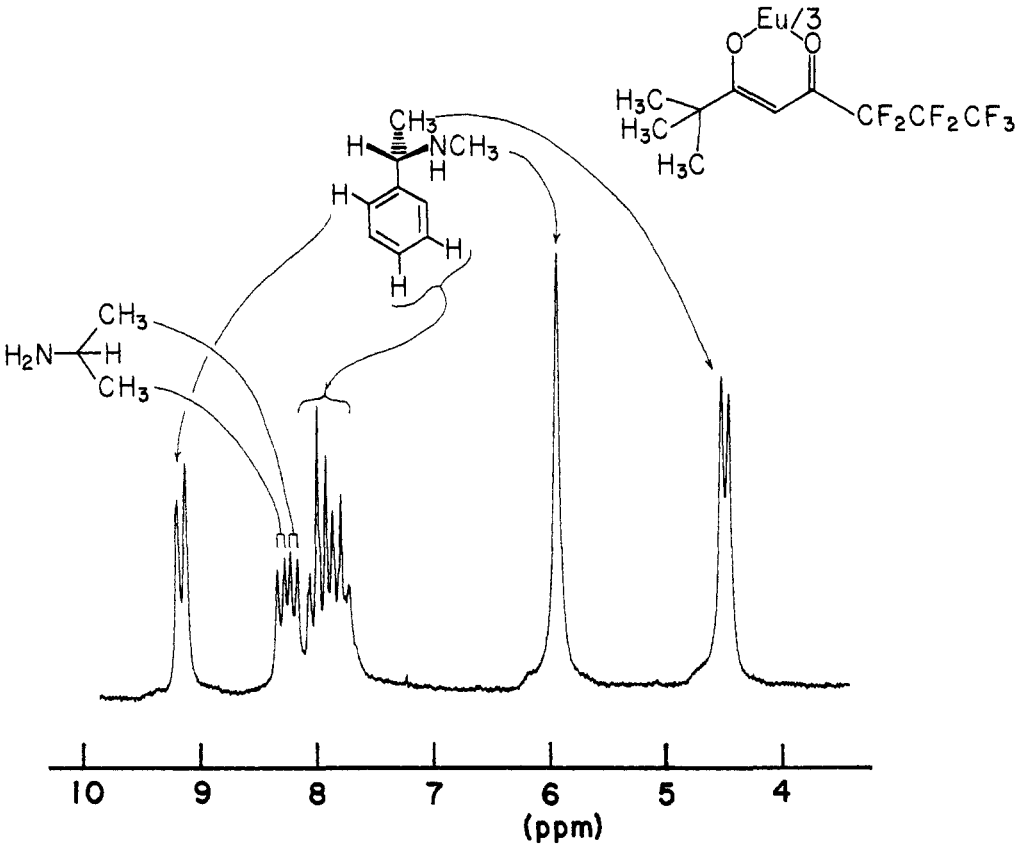


Figure 10. The resonances of the two methyl groups of isopropylamine (~0.3 *M*) are distinct in a $CDCl_3$ solution containing (*R*)-*N*-methyl-1-phenylethylamine (~0.8 *M*) and $Eu(fod)_3$ (~0.8 *M*). This spectrum was taken at 100 MHz (31°).

ternative explanation, that the enantiomeric shift difference reflects interactions between the two amines free in solution, with the shift reagent acting simply by complexing more strongly with the enantiomer of the 1-phenylethylamine that interacts less strongly with the (*R*)-*N*-methyl-1-phenylethylamine, is rendered less likely by the results of a related experiment summarized in Figure 10. This figure shows the spectrum of a mixture of (*R*)-*N*-methyl-1-phenylethylamine, isopropylamine, and $Eu(fod)_3$. The nonequivalence of the methyl groups of the isopropylamine again argues for the ability of an optically active amine to induce chirality in the complex formed between $Eu(fod)_3$ and two amine molecules.

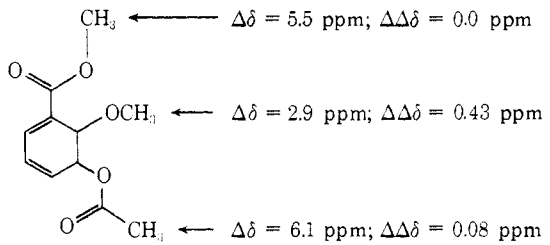
Induced chirality of the type implied by these spectra is not sufficiently general to be analytically useful: the magnitudes of the enantiomeric shift differences observed in similar experiments with substrates that coordinate with europium less strongly than amines were usually too small to be of any quantitative value.[33] These experiments are, however, of value in suggesting that 2:1 complexes of substrate to chiral shift reagent might be of sufficient importance to influence values of $\Delta\Delta\delta$, and in implying that the β-diketonate ligand framework around the europium atom has enough flexibility to transmit a diastereomeric interaction between two chiral substrate molecules coordinated to the same europium atom.[34]

This implication of flexibility to the ligand framework is supported qualitatively by the behavior of the resonances of the β-diketonate ligands of **1** on adding 1-phenylethylamine (Figure 11). Addition of 1 equiv of 1-phenylethylamine to a solution of **1** results in an upfield shift of the methyl resonances of the dcm ligand of *ca.* 2 ppm; addition of a second equivalent of 1-phenylethylamine produces only a small further upfield shift. It seems more likely that the shifts observed in going from $Eu(dcm)_3$ to $Eu(dcm)_3 \cdot S$ reflect a reorganization of the β-diketonate ligands around the metal to accommodate the additional ligand than a change in the magnetic characteristics of the complex on coordination of this ligand. We believe that the positions of the β-diketonate ligands should be more closely restricted to an equatorial belt ringing the principal effective magnetic symmetry axis of the complex in the presence of additional ligands than in their absence; the signs of the observed shifts are consistent with this belief, and their magnitude is sufficiently large to suggest that the extent of the reorganization is appreciable. The observation that only a small change in the spectrum of the dcm ligand accompanies addition of a second equivalent of 1-phenylethylamine is not incompatible with the suggestion that these complexes are capable of coordinating two substrate molecules simultaneously, since the geometry of the dcm ligands relative to the magnetic susceptibility tensor of the complex during the transformation from $Eu(dcm)_3 \cdot S$ to $Eu(dcm)_3 \cdot 2S$ may change relatively little.

(33) Spectra of various racemic amines in the presence of (*R*)-1-phenylethylamine and $Eu(fod)_3$ exhibited values of $\Delta\Delta\delta$ between 0.01 and 0.10 ppm. Racemic ketones, alcohols, sulfoxides, and amides showed no detectable enantiomeric shift difference under comparable conditions.

(34) Attempts to increase significantly the maximum $\Delta\Delta\delta$ values of various amines, ketones, esters, and sulfoxides in the presence of **1** by the addition of optically active *N*-methyl-1-phenylethylamine were unsuccessful.

The available data do not resolve the relative contributions to the enantiomeric shift differences resulting from inequality of the various association constants between chiral shift reagent and enantiomeric substrates, and that resulting from differences in the geometries of the diastereomeric complexes formed between shift reagent and these enantiomers. However, qualitatively, a number of observations indicate that the latter effect is important. First, when the concentration of shift reagent is high relative to that of a strongly basic substrate, $\Delta\Delta\delta$ may remain large. If differences in association constant were solely responsible for $\Delta\Delta\delta$, this parameter should vanish when the substrate is completely coordinated to shift reagent. Second, there is no general correlation between the magnitudes of $\Delta\delta$ and $\Delta\Delta\delta$, as might be expected if diastereomeric complexes had similar geometries but different association constants. Thus, in the substituted cyclohexadiene **17**,[35] the protons shifted the



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smallest amount on coordination to **1** show the largest value of the enantiomeric shift difference; a similar effect is evident in certain of the spectra reproduced in Figure 8. Further, the sign of $\Delta\Delta\delta$ may vary from one peak to another in a spectrum. For example, in spectrum c of Figure 8, the signal of the methyl group of the *R* enantiomer occurs at higher field than that of the *S* enantiomer group, while this order is reversed for the methine resonances. All of these observations argue for significantly different geometries for the diastereomeric complexes formed between a chiral shift reagent and enantiomeric substrates.

Conclusions

Chiral tris[β-diketonato]europium(III) complexes provide practical reagents for direct spectroscopic determination of the enantiomeric purity of a large number of organic Lewis bases. They have both advantages and disadvantages relative to other spectroscopic procedures proposed for this purpose: *viz.*, nmr spectroscopy of enantiomeric mixtures in optically active solvents,[4] and ^1H and ^{19}F nmr of diastereomeric esters.[9,22] The principal virtue of procedures based on chiral shift reagents is the convenience of the experimental procedure and the relative ease of interpretation offered by the spectra; no chemical manipulation of the sample is required and even the less readily prepared of the chiral shift reagents are more easily obtained than quantities of the useful optically active solvents; more importantly, both the enantiomeric shift differences ($\Delta\Delta\delta$) and the chemical shifts (δ) obtained using these reagents are usually larger than the corresponding parameters in the other methods. Thus, it is possible to carry out a quantitative determination of the enantiomeric composition of structures having sufficient complexity that analysis of their unshifted spectrum would be difficult. The principle disadvantage of the shift reagent procedures is that the organic substrate must coordinate with the europium chelates. Although many organic structures fulfill this requirement, a number of important classes of organic compounds—particularly Lewis acids and soft Lewis bases—do not.[36] Reagents other than chiral shift reagents are most convenient for establishing the enantiomeric purity of these substances, and for assigning absolute configurations.[4,25b,37,38]

(35) This substance was obtained from our colleagues, Drs. G. Berchtold and C. Filer.

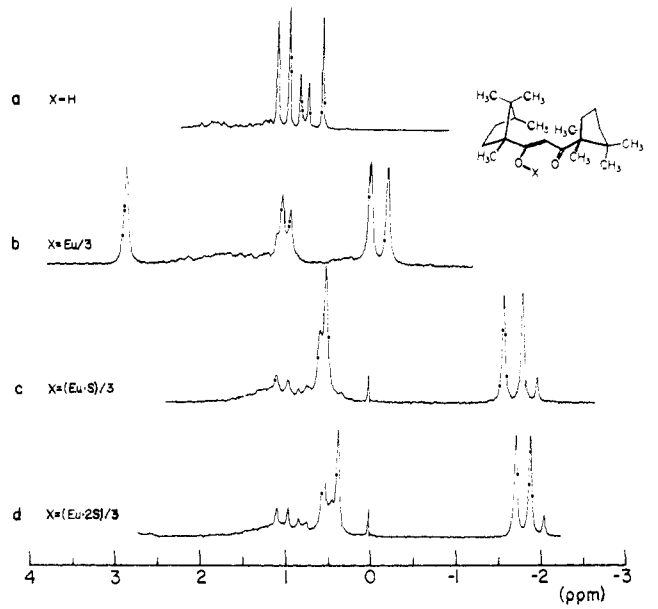

Figure 11. $Eu(dcm)_3$ resonances move to higher field upon addition of a strongly coordinating substrate: (a) *d,d*-dicampholylmethane; (b) tris[*d,d*-dicampholylmethanato]europium(III) ($Eu(dcm)_3$, **1**); (c) 1 equiv of $Eu(dcm)_3$ and 1 equiv of (*S*)-1-phenylethylamine; (d) 1 equiv of $Eu(dcm)_3$ and 2 equiv of (*S*)-1-phenylamine. Equilibrium constants for association between the amine and the europium chelate have not been measured; the labels of the spectra (*e.g.*, X = (Eu·2S)/3) should be taken to refer only to the composition of the solution, rather than to the stoichiometry of the complex. The sharp resonance at 0 ppm is TMS. Spectra (60 MHz) were taken in $CDCl_3$.

Experimental Section

General. All melting points and boiling points are uncorrected. Infrared spectra were determined with Perkin-Elmer Model 237 or 237B grating spectrophotometers. Unless otherwise stated, nmr spectra were determined at 60 MHz with a Varian Model T-60 spectrometer. Chemical shift values are expressed as δ (ppm) relative to a tetramethylsilane internal standard. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Unless otherwise stated, ir, nmr, and optical rotation data were all determined in carbon tetrachloride. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind.

Reaction mixtures were dried with anhydrous magnesium sulfate. Distillations were usually performed with a 35-cm, vacuum-jacketed Holzmann column. Ozonolyses were accomplished with a Wels-

(36) Appropriate derivates of uranium offer promise as shift reagents for soft Lewis bases: *cf.* R. von Ammon, R. D. Fischer, and B. Kanellakopulos, *Chem. Ber.*, 104, 1072 (1971); C. Wiedenheft, *Inorg. Chem.*, 8, 1174 (1969).

(37) W. H. Pirkle, *Chem. Commun.*, 1525 (1970).

(38) Although we have not been encouraged to attempt absolute configuration assignment by the data reported in this paper, K. Ajisaka, M. Kamisaku, and M. Kainosho [*Chem. Lett. Jap.*, 857 (1972)] have been able to correlate the sign of $\Delta\Delta\delta$ obtained using shift reagent **10** and the absolute configuration of a closely related series of substrates.

bach T-23 ozone generator. Reactions involving air-sensitive compounds were carried out under prepurified nitrogen using standard techniques.[39] Solvents for reactions involving organometallic reagents were distilled prior to use, and were transferred under nitrogen by stainless steel cannula or hypodermic syringe to the dried reaction flask. Ether was distilled from calcium hydride, while benzene and 1,2-dimethoxyethane were distilled from a deep purple solution of sodium benzophenone dianion.

Materials. Commercial starting materials were used without purification unless stated otherwise. *d*-Camphor, $[\alpha]^{25}D$ +43.9° (*c* 4.6, C_2H_5OH) [lit.[40] $[\alpha]^{16}D$ +44.2° (*c* 16.5, C_2H_5OH)], was obtained from Eastman Organic Chemicals, while *l*-camphor, $[\alpha]^{25}D$ −41.8° (*c* 4.2, C_2H_5OH) [lit.[40] $[\alpha]^{16}D$ −43.6° (*c* 16.5, C_2H_5OH)], was obtained from Aldrich Chemical Co.[41] *d*-Fenchone, $[\alpha]^{25}D$ +40.1° (*c* 9.45, C_2H_5OH) [lit.[42] $[\alpha]^{16}D$ +68.9° (*c* 8.1, C_2H_5OH)], and *l*-fenchone, $[\alpha]^{25}D$ −57.3° [lit.[43] $[\alpha]^{23}D$ −66.94° (*c* 14.3, C_2H_5OH)], were obtained from K and K Labs. *l*-β-Pinene, $[\alpha]^{25}D$ −16.8° (neat) [lit.[44] $[\alpha]D$ −19.5° (neat)], and *l*-methanol, $[\alpha]^{25}D$ −49.4° (*c* 10, C_2H_5OH) [lit.[45] $[\alpha]^{18}D$ −49.5° (*c* 5, C_2H_5OH)], were obtained from Aldrich Chemical Co. Commercial lanosterol was purchased from both Aldrich Chemical Co. (mp 131–135°, $[\alpha]^{25}D$ +60° (*c* 1.0, $CHCl_3$) [lit.[46] $[\alpha]^{20}D$ +58° (*c* 1.6, $CHCl_3$), mp 140–141°]) and Pfaltz and Bauer (mp *ca.* 120°, $[\alpha]^{25}D$ +38° (*c* 1.4, $CHCl_3$)).

Benzene-d_6, acetone-d_6, chloroform-d_1, methylene-d_2 chloride, and pyridine-d_5 were supplied by Stohler Isotope Chemicals. Dioxane-d_8 was supplied by Norell Chemical Co. Carbon tetrachloride and carbon disulfide were reagent grade and 1,1,2-trichloro-1,2,2-trifluoroethane, fluorotrichloromethane, and pentane were Spectroquality when used as solvents for shift reagent studies. Drying the carbon tetrachloride, carbon disulfide, and chloroform-d_1 did not increase the maximum $\Delta\Delta\delta$ values for substrates in the presence of **1** in these solvents.

Diisopropylamine (Aldrich) was distilled from barium oxide and from calcium hydride and then stored with molecular sieves under a nitrogen atmosphere. Citronellol and optically active derivatives of 1-phenylethylamine were obtained from Hoffmann-La Roche, Inc. Sodium hydride (57% dispersion in mineral oil) and sodium amide were purchased from Alfa Inorganics, Inc. Sodium methoxide was obtained from Matheson Coleman and Bell and was stored under a dry nitrogen atmosphere. Methyllithium in ethyl ether, also from Matheson Coleman and Bell, was analyzed for active methyllithium using the Gilman double titration procedure.[47]

Europium trichloride hexahydrate, praseodymium trichloride heptahydrate, and holmium trichloride hexahydrate were purchased from American Potash and Chemical Co. (Kerr-McKee), West Chicago, Ill., as 99.9% pure material. Platinum oxide (83–86% platinum) was obtained from Englehard Industries.

(*d*)-*trans*-1,2,2,3-Tetramethylcyclopentanecarboxylic Acid (*d*-Campholic Acid). This compound was prepared by a method similar to that of Schmidt.[48] A mixture of *d*-camphor (404 g, 2.66 mol) and potassium hydroxide pellets (809 g, 14 mol) was heated in a 3-l. rocking steel bomb at 245° for 24 hr. The bomb was cooled, and the solid was removed with steam and hot water. The aqueous solution was filtered through Celite with suction while warm, washed with two 1.5-l. portions of ether, made acidic with concentrated hydrochloric acid, and extracted with six 1.5-l. portions of ether. The combined organic layers were dried and concentrated. Distillation[49] of the resulting crude yellow solid through a short Vigreux column yielded a pale yellow wax (bp 120–127° (2.2 Torr)), which was recrystallized twice from pentane to give 226 g (50%) of a white crystalline solid: mp 92–100°; $[\alpha]^{25}D$ +45.4° (*c* 2.5, C_2H_5OH) [lit.[48] mp 104–105°; $[\alpha]D$ +46.3°]; ir 1690 (C=O) and 2300–3400 cm^{-1} (C–H and OH); nmr δ 0.76, 1.04, and 1.24 (s, 3 each, CCH_3), 0.89 (d, 3, J = 6.0 Hz, $CHCH_3$), 11.84 (s, 1, COOH), and 0.6–2.8 (m). The *l* enantiomer was prepared by a similar procedure.

***d*-Nopinone.** A solution of 80 g (0.59 mol) of *l*-β-pinene in 720 ml of absolute methanol was ozonized according to the procedure of Meinwald and Gassman.[50] After work-up and distillation, 60 g (73%) of the ketone was isolated as a colorless oil: bp 86–88° (10 Torr); $[\alpha]^{25}D$ +16.9° (neat) [lit.[50] bp 83–88° (12 Torr), $[\alpha]^{25}D$ +18.4 (neat)]; ir 1710 cm^{-1} (C=O); nmr δ 1.4–2.8 (m, 8), 1.35 (s, 3, CH_3), and 1.85 (s, 3, CH_3).

(*d*)-*trans*-1,2,2,3-Tetramethylcyclopentanecarbonyl Chloride (*d*-Campholyl Chloride.) To a flame-dried, nitrogen-purged, 500-ml, round-bottomed flask fitted with reflux condenser, magnetic stirring bar and calcium chloride drying tube was added 60.0 g (0.35 mol) of *d*-campholic acid, 64 ml of thionyl chloride (2.5-fold excess), and 200 ml of dry benzene. The mixture was stirred vigorously while refluxing for 16 hr. The reaction mixture was then concentrated at reduced pressure, and the resulting yellow oil was distilled to give 60.0 g (91%) of the acid chloride as a colorless liquid: bp 94° (12 Torr); ir 1790 cm^{-1} (C=O); nmr δ 0.82, 1.11, and 1.34 (s, 3, each, CCH_3), 0.90 (d, 3, J = 6.4 Hz, $CHCH_3$), and 1.4–2.8 (m). The *l* enantiomer was prepared by a similar procedure.

(*d*)-1-Acetyl-1,2,2,3-tetramethylcyclopentane (*d*-Campholylmethane). *d*-Campholic acid (131 g, 0.771 mol) was dissolved in 700 ml of freshly distilled 1,2-dimethoxyethane in a flame-dried, nitrogen-purged, 3-l. flask equipped with a mechanical stirrer and a reflux condenser.[51] An atmosphere of prepurified nitrogen was maintained in the reaction apparatus throughout the reaction. A 1.6 *M* solution of methyllithium in ether (1.00 l.) was allowed to drip into the reaction mixture at a rate that sustained a gentle reflux (*ca.* 1 l./1.5 hr). Methane was evolved during the addition of the first equivalent of methyllithium. After refluxing and stirring for 18 hr, the cloudy-white reaction mixture was transferred *via* cannula into 3 l. of well-stirred water. The aqueous phase was extracted with three 1-l. portions of ether, and the combined organic phase was washed with 700 ml of water, dried, and concentrated. Distillation afforded 85.6 g (66%) of the ketone as a colorless liquid: bp 94–96° (13.5 Torr); $[\alpha]^{25}D$ +59.5° (*c* 10.0, CCl_4); ir 1700 cm^{-1} (C=O); nmr δ 0.61, 1.06, and 1.14 (s, 3 each, CCH_3), 0.85 (d, 2, J = 7.0 Hz, $CHCH_3$), 2.05 (s, 3, $COCH_3$), and 0.6–2.8 (m).[52]

***d,d*-Dicampholylmethane (H(dcm)).**[53] To a flame-dried, nitrogen-purged, 2-l., round-bottomed flask equipped with a mechanical stirrer, nitrogen inlet, and low temperature thermometer was added a crystal of 2,2′-bipyridyl indicator and 380 ml (0.615 mol) of 1.62 *M* methyllithium in ether.[54] The solution was cooled to −20° and 62.3 g (0.615 mol) of diisopropylamine was added *via* syringe. Gas was evolved and the solution changed in color from red-orange to orange. After stirring the lithium diisopropylamide for 30 min

(39) D. F. Shriver, "The Manipulation of Air-Sensitive Compounds," McGraw-Hill, New York, N. Y., 1969, Chapter 7.

(40) J. D. M. Ross and I. C. Somerville, *J. Chem. Soc.*, 2770 (1926).

(41) The absolute configuration of the enantiomers of camphor has been defined: F. H. Allen and D. Rogers, *J. Chem. Soc. B*, 632 (1971); J. A. Wunderlich, *Acta. Crystallogr.*, **23**, 846 (1967); M. G. Northolt and J. H. Palm, *Recl. Trav. Chim. Pays-Bas*, **85**, 143 (1966).

(42) W. Hückel, *Justus Liebigs Ann. Chem.*, **549**, 186 (1941).

(43) O. Wallach, *Justus Liebigs Ann. Chem.*, **272**, 99 (1893).

(44) R. Padmanabhan and S. K. K. Jatkar, *J. Indian Chem. Soc.*, **12**, 518 (1935).

(45) H. G. Rule and J. Smith, *J. Chem. Soc.*, **127**, 2188 (1925).

(46) H. Wieland, H. Pasedach, and A. Ballauf, *Justus Liebigs Ann. Chem.*, **529**, 68 (1937).

(47) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967); H. Gilman, F. K. Cartledge, and S.-Y. Sim, *ibid.*, **1**, 8 (1963); G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Amer. Chem. Soc.*, **93**, 1379 (1971).

(48) H. Schmidt, *Riechst. Aromen*, **7**, 161 (1957); *Chem. Abstr.*, **52**, 1108b (1958).

(49) The condenser was heated with steam and a heat lamp to prevent solidification of the distillate.

(50) J. Meinwald and P. G. Gassman, *J. Amer. Chem. Soc.*, **82**, 5445 (1960). An attempt to use a dimethyl sulfide work-up [J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966); also P. S. Bailey, S. S. Bath, F. Dobinson, F. J. Garcia-Sharp, and C. D. Johnson, *J. Org. Chem.*, **29**, 697 (1964)] for this reaction lead to a serious explosion on distillation of the product. K. H. Overton and P. Owen [*J. Chem. Soc., Perkin Trans. 1*, 226 (1973)] have recently isolated a particularly stable bisperoxide of nopinone from ozonolysis of β-pinene; the stability of this peroxide is presumably attributable to steric crowding around the peroxidic site. This, and other experiences with ozonolyses of hindered olefins, have convinced us that the dimethyl sulfide work-up procedure does not adequately destroy ozonides and peroxides of sterically hindered olefins.

(51) M. J. Jorgenson, *Org. React.*, **18**, 14 (1970).

(52) Elemental analyses for carbon and hydrogen were within 0.3% for this compound.

(53) This synthesis was patterned after a general procedure by House: (a) H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971); (b) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Amer. Chem. Soc.*, **95**, 3310 (1973).

(54) When commercial methyllithium containing 1 equiv of lithium halide was used, most of the halide crystallized at −20°, making the reaction mixture difficult to stir for small scale reactions for which magnetic stirring may be conveniently used. Halide-free methyllithium may be purchased from Matheson Coleman and Bell, or the halide may be removed by precipitation with dioxane and filtration prior to use.

at −20°, *d*-campholylmethane (103.6 g, 0.616 mol) dissolved in 100 ml of freshly distilled ether and cooled to −20° was rapidly added to the reaction solution *via* cannula. The solution (now more intensely orange) was stirred at −20° for 25 min and was then cooled to −60°.

d-Campholyl chloride (116 g, 0.615 mol) was dissolved in 50 ml of freshly distilled ether, cooled to −60° and added to the enolate *via* cannula as rapidly as possible. After stirring at −50 to −70° for 30 min, the reaction mixture was warmed to −20° over a period of 30 min and was transferred *via* cannula into a well-stirred mixture of 1 *M* hydrochloric acid (1.2 l.) and ice. The aqueous phase (acidic to pH paper) was extracted with four 1.2-l. portions of ether, and the combined organic phase was washed with two 1-l. portions of sodium chloride solution, dried, and concentrated. Distillation of the crude red oil gave a white, opaque paste (bp 100–118° (*ca.* 0.06 Torr)). Two recrystallizations from methanol–ethanol gave 69.2 g (35%) of the diketone as a white crystalline solid: mp 64.5–65.0°; $[\alpha]^{25}D$ +88.9° (*c* 0.62, C_2H_5OH); ir 1790 (C=O) and 1720 cm^{-1} (C=O); nmr δ 0.61, 1.03, and 1.15 (s, 6 each, CCH_3), 0.85 (d, 6, J = 7.2 Hz, $CHCH_3$), 5.60 (s, 1, vinyl H), 16.90 (s, 1, OH), and 0.6–2.7 (m).[52]

Copper Chelate Purification of β-Diketonates. The following method illustrates a general procedure for purifying β-diketones.[55] To a solution of 11 g of *tert*-butylhydroxymethylene-*d*-camphor, (H(*t*-bhmc), *vide infra*), in 20 ml of methanol was added a hot, filtered solution of 8.0 g of copper(II) acetate in 70 ml of water. The mixture was allowed to stand until it had cooled to room temperature. The dirty green copper salt of the diketone was collected on a sintered glass filter funnel, washed with water, sucked dry, and washed with two 20-ml portions of cold pentane to give a light green powder, mp 234.0–235.5°.

Pure diketone was recovered by shaking the copper salt with a mixture of 50 ml of cold 10% sulfuric acid and 50 ml of cold ether. More acid was added until a light blue color in the aqueous phase appeared, and the black color in the organic phase disappeared. The aqueous phase was separated, and extracted with one 50-ml portion of ether. The combined organic layers were then washed with one 50-ml portion of sodium bicarbonate solution and two 50-ml portions of water, and dried. After removing the solvent, 9.9 g (90%) of a light yellow liquid was obtained and identified as pure (H(*t*-bhmc) by nmr, ir, and tlc.

Tris[*d,d*-dicampholylmethanato]europium(III) (1). *d,d*-Dicampholylmethane (25.9 g, 0.081 mol) was dissolved in 600 ml of reagent grade methanol (40°) in a nitrogen-purged, round-bottomed flask equipped with a mechanical stirrer and nitrogen inlet.[56] A solution of 4.37 g (0.081 mol) of sodium methoxide in 50 ml of methanol was added, and the solution was stirred 20 min, at 40°. Upon addition of a filtered solution of 9.89 g (0.27 mol) of europium(III) chloride hexahydrate in 200 ml of methanol, a cream-white precipitate immediately formed. The suspension was stirred vigorously at 35–40° for 2 hr, cooled to 0°, and filtered with suction to give several brittle beige lumps and a cream-colored amorphous solid. The product was dissolved in pentane, filtered to remove the insoluble material, concentrated, and dried at 100° (0.1 Torr) for 36 hr to give 18.8 g (63%) of **1** as a white powder: mp 222.0–227.5°; $[\alpha]^{25}D$ +28.6° (*c* 5.4, CCl_4);[57] ir 1540 m^{-1}; nmr δ (broad) −0.02, 0.09, and 3.63 (s, 3 each, CH_3), and 1.10 (d, 3, J = 6 Hz, $CHCH_3$).[52,58]

3-Trifluoroacetyl-*d*-nopinone. The enolate of *d*-nopinone (13.8 g, 0.10 mol) was prepared and allowed to react with ethyl trifluoroacetate (14.2 g, 0.10 mol) by the procedure described for the synthesis of H(dcm). The crude reaction mixture was quenched in 250 ml of cold 1 *M* hydrochloric acid, and the aqueous phase was extracted with four 175-ml portions of ether. The combined organic phase was washed with two 50-ml portions of saturated aqueous sodium chloride solution, and then extracted with two 50-ml portions of cold 1 *M* sodium hydroxide. The combined basic extracts were made acidic with 1 *M* hydrochloric acid and extracted with three 100-ml portions of ether. The combined ethereal layers were washed with saturated aqueous sodium chloride, dried, concentrated, and distilled to give 8.9 g (42%) of the pure diketone as a colorless liquid: bp 68° (2.5 Torr); $[\alpha]^{24}D$ +21.7° (neat), $[\alpha]^{24}D$ +12.9° (*c* 2.0, CCl_4); ir 1790, 1720, and 1650 (strong) cm^{-1} (keto and enol C=C and C=O); nmr δ 0.95 and 1.40 (s, 3 each, CH_3), 2.2–3.0 (m), and 14.8 (s, broad, 1, OH).[52]

3-Trifluoromethylhydroxymethylene-*d*-camphor was prepared from the enolate of *d*-camphor (12.3 g, 0.081 mol) and ethyl trifluoroacetate (11.5 g, 0.081 mol) by the procedure described for the synthesis of H(dcm). Distillation of the crude product afforded 17 g (85%) of the diketone as a colorless liquid: bp 89–92° (7 Torr); $[\alpha]^{24}D$ +178° (neat), $[\alpha]^{24}D$ +144° (*c* 2.0, CCl_4); ir 1740, 1705 (strong), and 1650 cm^{-1}; nmr δ 0.87, 1.00, and 1.01 (s, 9 total, CH_3), 1.2–2.2 (m, 4), 2.85 (m, 1, CH_2CH), and 11.22 (s, 1, OH).[52]

Tris[3-trifluoroacetyl-*d*-nopinato]europium(III) (9) was synthesized from 17.5 g (0.075 mol) of 3-trifluoroacetyl-*d*-nopinone by the procedure used for **1** with the following exception. After stirring the reaction mixture for 1 hr, 200 ml of water was added, and the product was extracted from the resulting oily mixture with three 150-ml portions of pentane. The combined organic layers were washed with water, concentrated, dried for 36 hr at 100° (0.1 Torr), and powdered to give 18.2 g (84%) of **9** as a bright yellow amorphous solid: mp *ca.* 80–100°; $[\alpha]^{24}D$ −67.2° (*c* 2.0, CCl_4); ir 1600–1660 cm^{-1}; nmr δ 0.6–3.0 (s, broad).

Attempts to prepare a sample of **9** for elemental analysis by tlc, molecular distillation, and sublimation resulted in decomposition of the chelate.

Tris[3-trifluoroacetyl-*d*-camphorato]europium(III) (10) was synthesized by a procedure analogous to that used for **9** from 2.48 g (10.0 mmol) of 3-trifluoroacetyl-*d*-camphor. The product (1.6 g, 50%) was a bright yellow amorphous solid, mp *ca.* 220°. A sample of **10** was purified for elemental analysis by fractional molecular distillation, 180–200° (0.004 Torr): softens *ca.* 130°, mp *ca.* 180°; $[\alpha]^{24}D$ +152° (*c* 2.0, CCl_4); ir 1630–1680 cm^{-1}; nmr δ (broad) −1.3 to −0.5, −0.08 (s), 0.41 (s), 1.6–2.3, and 3.39 (s).[52,59]

***tert*-Butylhydroxymethylene-*d*-camphor (H(*t*-bhmc)).** The procedure for making H(*t*-bhmc) was modeled after Kopecky's synthesis of hindered diketones.[60] Sodium amide (11.0 g, 0.275 mol) was added to 150 ml of anhydrous 1,2-dimethoxyethane (DME) in a flame-dried, 500-ml, three-necked, round-bottomed flask fitted with an efficient mechanical stirrer, a 250-ml pressure equalized dropping funnel, reflux condenser, and nitrogen inlet. The DME suspension of sodium amide was warmed to reflux temperature, and a solution of *d*-camphor (41.9 g, 0.275 mol) in 100 ml of anhydrous DME was added to the refluxing solution over 1 hr.[61] The reaction mixture was refluxed for an additional 30 min, and then cooled to room temperature. Dry nitrogen was bubbled through the grey-green suspension of enolate for 2 hr to remove the dissolved ammonia. The reaction mixture was again heated to reflux, and a solution of pivaloyl chloride (11.1 g, 0.092 mol) in 50 ml of DME was added through the dropping funnel to the solution over a period of 5 min. After allowing the reaction mixture to reflux for an additional 12 hr, it was cooled and poured into a mixture of 150 g of ice and 25 ml of concentrated hydrochloric acid. The pH of the aqueous phase was adjusted to 6–7 with the addition of more acid; the orange organic layer was separated and the aqueous layer was extracted with two 150-ml portions of ether. The combined organic layers were washed with five 100-ml portions of water, dried, and concentrated. Excess camphor was removed by sublimation at 100° (20 Torr), and the residual oil was distilled to give H(*t*-bhmc) (10 g, 46%) as a light yellow oil: bp 66–82° (0.05 Torr); ir 1760, 1705, 1665, and 1610 cm^{-1} (keto and enol C=O and C=C); nmr δ 1.21 (s, 9, keto and enol $C(CH_3)$), and 13.1 (s, OH). Pure diketone was isolated as white flakes from the diketone–enol mixture by recrystallization from methanol: mp 66–68°; ir 1760 and 1700 cm^{-1} (C=O); nmr δ 0.84, 0.89, and 1.00 (s, 3 each, CH_3), 1.12 (s, 9, $C(CH_3)_3$), and 3.70 (d, 1, J = 4 Hz, vinyl H).[62]

Tris[3-(*tert*-butylhydroxymethylene)-*d*-camphorato]europium(III) (6). This synthesis was modeled after a standard procedure for making rare earth chelates.[62] *tert*-Butylhydroxymethylene-*d*-

(55) C. R. Hauser, *et al.*, *Org. React.*, **8**, 122 (1954).

(56) Syntheses of lanthanide chelates carried out under nitrogen lead to higher yields and purity than those carried out without excluding air, presumably by preventing oxidation of the β-diketone ligands. Magnetic stirrers are conveniently used for this reaction on a smaller scale.

(57) Values of optical rotation for all the europium chelates vary markedly with concentration.

(58) Nmr line widths and chemical shifts for all the europium chelates are quite variable, depending both on the temperature and on the presence of excess ligand.

(59) Compound 10 has also been prepared by B. Feibush, M. F. Richardson, R. E. Sievers, and C. S. Springer, Jr., *J. Amer. Chem. Soc.*, **94**, 6717 (1972).

(60) K. R. Kopecky, D. Nonhebel, G. Morris, and G. S. Hammond, *J. Org. Chem.*, **27**, 1036 (1962).

(61) This reaction should be conducted in an efficient hood since large quantities of ammonia are liberated during the formation of the camphor enolate.

(62) K. J. Eisentraut and R. E. Sievers, *J. Amer. Chem. Soc.*, **87**, 5254 (1965).

camphor (1.94 g, 8.20 mmol) was dissolved in 10 ml of 95% ethanol in a 100-ml, nitrogen-purged flask containing a Teflon-covered magnetic stirring bar. A solution of sodium hydroxide (0.4 g, 10 mmol) in 15 ml of 50% aqueous ethanol was added, and the mixture was stirred for 2 min. Europium trichloride hexahydrate (1.00 g, 2.74 mmol) was dissolved in 15 ml of 50% aqueous ethanol and then rapidly added to the vigorously stirred yellow enolate. The product immediately precipitated as a light yellow solid. The reaction mixture was stirred for 30 min, and then was diluted with 30 ml of ice–water. The precipitate was separated by suction filtration, dried in a vacuum dessicator for 6 hr (0.1 Torr) at room temperature, and broken into a fine powder. The powder was further purified by dissolving it in 200 ml of absolute ethanol, separating the insoluble solids by centrifugation, and precipitating the product by diluting the resulting homogeneous solution with 200–400 ml of ice–water. The precipitate was collected by filtration, dried for 12 hr at room temperature (0.1 Torr), and purified by fractional molecular distillation (134–140° (0.01 Torr)) to give 1.6 g (68%) of **6** as a yellow solid: mp 131–134° (discolors 108–112°); $[\alpha]^{25}D$ +38.2° (*c* 4.9, CCl_4); ir 1560–1620 and 1460–1480 cm^{-1}; nmr δ 0.95 (s, 6, 2 CH_3) and 1.2 (s, 9, $C(CH_3)_3$).[52]

1,1-Bis(4,4-dimethyl-1,3-dioxopentyl)cyclobutane (i). This compound was synthesized using the procedure for the synthesis of H(dcm). Starting with pinacolone (10.0 g, 0.10 mol) and cyclobutanedicarboxylic acid dichloride[63] (10.6 g, 0.05 mol), a yellow oil was obtained after distillation (95–120° (0.004 Torr)) which was crystallized twice from methanol to give the tetraketone (3.6 g, 24%) as pure white needles: mp 60.0–60.5°; ir 1500–1680 cm^{-1} (enol C=O and C=C); nmr δ 1.14 (s, 18, $CC(CH_3)_3$), 1.6–2.7 (m, 6, ring CH_2), 5.38 (s, 2, vinyl H), and 15.6 (s, broad, OH).[52]

1-Methyl-3-isopropylcyclopentyl-1-carboxamide (*d*-Fencholylamide). Semmler's procedure[64] was used as a model for the synthesis of fencholylamide. To a 250-ml flame-dried round-bottomed flask equipped with a magnetic stirring bar and reflux condenser was added *d*-fenchone (25 g, 0.16 mol), sodium amide (6.4 g, 0.16 mol), and 50 ml of dried benzene under nitrogen. The solution was allowed to reflux overnight under nitrogen. The resulting black oil was poured into 100 g of crushed ice and the brown solid was separated by filtration. Extraction of the mother liquors with ether yielded more brown solid after removal of the solvent. The product was recrystallized from methanol–water as white flakes (24 g, 86%): mp 109–111° [lit.[64] 109°]; ir 1675 cm^{-1} (C=O); nmr δ 1.0 (s, 3, CCH_3), 1.2 (d, 6, $CH(CH_3)_2$), and 1.65 (s, 2, NH_2). The *l* enantiomer was prepared by a similar procedure.

(*d*)-1-Methyl-3-isopropylcyclopentanecarboxylic Acid (*d*-Fencholic Acid). The procedure followed was a modified version of Humbert's synthesis.[65] To a well-stirred solution of *d*-fencholylamide (24.0 g, 0.142 mol) in 75 ml of ethanol in a 300-ml, round-bottomed, flask with magnetic stirring bar and reflux condenser was added a solution of potassium hydroxide (12.6 g, 0.225 mol) in 50 ml of ethanol and 10 ml of water. After refluxing for 18 hr, the reaction mixture was poured into 200 ml of water, and extracted with three 100-ml portions of ether to yield *ca.* 10 g of unreacted amide from the concentrated organic phase. The aqueous phase was made acidic with concentrated hydrochloric acid and extracted with three 200-ml portions of ether. The combined organic layers were dried, concentrated, and distilled to give 14 g (58%) of the acid as a clear colorless liquid: bp 113–115° (1.5 Torr) [lit.[39] bp 110–112° (1.0 Torr)]; $[\alpha]^{24}D$ +2.2° (neat); ir 1700 (C=O), and 2600–3400 cm^{-1} (COOH); nmr δ 0.90 (d, 6, $CH(CH_3)_2$), 1.30 (s, 3, CCH_3), and 12.6 (s, 1, COOH). The *l* enantiomer was prepared by a similar procedure.

***l*-Menthone.** The procedure of Hussey and Baker[66] was used to synthesize 95 g (95%) of pure *l*-menthone: bp 95–97° (15 Torr); $[\alpha]^{25}D$ −25.3° (*c* 10.0, CCl_4), $[\alpha]^{25}D$ −25.8° (neat) [lit.[41] bp 116–119° (41 Torr), $[\alpha]^{27}D$ −28.9°, $[\alpha]^{27}D$ −25.6 (neat)]; ir 1710 cm^{-1} (C=O); nmr δ 0.8–1.0 (m, CH_3 and $CH(CH_3)_2$) and 1.0–2.2 (*m*).

***d*-Dihydrolanosterol.** Commercial lanosterol (100 g) was stirred with boiling acetone (2.5 l.) and methanol (500 ml) until most of the solid had dissolved. The insoluble material was removed by filtration through a hot Buchner funnel. Upon cooling, a white precipitate formed which was recrystallized from acetone–methanol to give 62 g of pure lanosterol: mp 136–139°; ir (KBr pellet) 3100–3600 (OH) and 1030 cm^{-1} (C–OH). The procedure of Wieland, Pasedach, and Ballauf[46] was used to reduce 62 g of *d*-lanosterol with 1.5 g of platinum oxide to 60 g (97%) of pure *d*-dihydrolanosterol: mp 143–144° [lit.[46] mp 145-146°]; $[\alpha]^{25}D$ +58.1° (*c* 10.0, CCl_4); ir ($CHCl_3$) 3100–3600 (OH) and 1010 cm^{-1} (C–OH).

***d*-Dihydrolanosterone (Δ⁸-Lanosten-3-one).** The procedure of Wieland, Pasedach, and Ballauf[46] was used to oxidize 33.3 g (0.078 mol) of *d*-dihydrolanosterol. The crude product was crystallized twice from ethanol–water to give 20.9 (63%) of *d*-dihydrolanosterone, mp 113–115°. Additional crystallizations did not significantly raise the melting point of the ketone and resulted in excessive loss of material. A 3-ft, 2-in., dry alumina column[67] with methylene chloride was used to further purify 12 g of the ketone to give 6.2 g of colorless crystals: mp 117.5–119° [lit.[46] mp 117–118°]; $[\alpha]^{25}D$ +74.6° (*c* 10.4, CCl_4); ir 1710 cm^{-1} (C=O).

1-Methyl-3-isopropylcyclopentanecarbonyl chloride (*d*-fencholyl chloride) was synthesized by the procedure described for the synthesis of *d*-campholyl chloride. Starting with 13 g (0.076 mol) of *d*-fencholic acid and 15 ml (*ca.* 0.17 mol) of thionyl chloride, 13.2 g (92%) of the acid chloride was obtained as a colorless liquid: bp 72° (3.4 Torr) [lit.[68] bp 68–72° (4.0 Torr)]; ir 1800 cm^{-1} (C=O); nmr δ 1.4 (s, 3, CCH_3) and 0.8 (d, 6, J = 8 Hz, $CH(CH_3)_2$). The *l* enantiomer was prepared by a similar procedure.

(*l*)-1-Acetyl-1-methyl-3-isopropylcyclopentane (*d*-Fencholylmethane). Starting with 38.3 g (0.22 mol) of *d*-fencholic acid and 0.45 mol of methyllithium, *d*-fencholylmethane was synthesized by the procedure described for the synthesis of *d*-campholylmethane. A voluminous white solid precipitated as the methyllithium was added. The ketone was isolated as a clear liquid: bp 85.5–89.5° (9.0 Torr); $[\alpha]^{24}D$ −2.9° (neat), $[\alpha]^{20}D$ −1.55° (*c* 10.0, CCl_4); ir 1715 cm^{-1} (C=O); nmr δ 0.85 (d, 6, J = 8 Hz, $CH(CH_3)_2$), 1.20 (s, 3, CCH_3), and 2.05 (s, 3, $COCH_3$).[52] The *l* enantiomer[52] was prepared by a similar procedure.

***d,l*-Dicampholylmethane** was synthesized by the procedure described for the synthesis of H(dcm). Starting with 7.21 g (38.3 mmol) of *l*-campholyl chloride and 6.43 g (38.3 mmol) of *d*-campholylmethane, 5.6 g (45%) of the product was isolated as white crystals: mp 61.5–62.0°; bp 125–132° (0.005 Torr); $[\alpha]^{20}D$ 0.0° (*c* 6.0, CCl_4); ir and nmr indistinguishable from those of H(dcm).[52]

Trifluoroacetyl-*d*-campholylmethane. The enolate of *d*-campholylmethane (11.0 g, 0.065 mol) was prepared and allowed to react with ethyl trifluoroacetate (9.24 g, 0.065 mol) using the procedure described for the synthesis of H(dcm). The reaction mixture was quenched (150 ml of 1 *M* hydrochloric acid and ice) and was extracted with four 175-ml portions of ether. The combined organic layers were washed with saturated aqueous sodium chloride, dried, concentrated, and carefully distilled to give 7.9 g (46%) of the diketone as a colorless liquid: bp 89–96° (5.5 Torr); $[\alpha]^{20}D$ +55.6° (*c* 10.0, CCl_4); ir 1640 and 1585 cm^{-1} (broad and strong enol C=C and C=O); nmr δ 0.68, 1.06, and 1.22 (s, 3 each, CH_3), 0.88 (s, 3, J = 6 Hz, $CHCH_3$), 5.94 (s, 1, vinyl H), and 14.5 (s, enol OH).[52]

2-Trifluoroacetyl-*d*-dihydrolanosterone. The enolate of *d*-dihydrolanosterone (4.12 g, 9.68 mmol) was prepared and allowed to react with ethyl trifluoroacetate (1.37 g, 9.68 mmol) by the procedure described for the synthesis of H(dcm). The reaction mixture was quenched (50 ml of 1 *M* hydrochloric acid and ice) and then extracted with four 100-ml portions of ether. The combined organic layers were washed with saturated aqueous sodium chloride, dried, and concentrated to give a yellow opaque oil. *Ca.* 3 g of the oil was chromatographed using *ca.* 500 ml of methylene chloride on a 30 in. × 2 in. silica gel dry column.[67] Extraction of the bottom 6 in. of the column with chloroform and concentration of the extract gave the product as an orange oil, free from dihydrolanosterone as determined by tlc; nmr δ 0.7–1.23 (m, $CHCH_3$ and CH_3) and 15.70 (s, OH).

6-Trifluoroacetyl-*l*-menthone was prepared from *l*-menthone (15.4 g, 0.10 mol) and ethyl trifluoroacetate (7.10 g, 0.05 mol), by the procedure described for the synthesis of H(dcm). Distillation of the crude product afforded 3.2 g (27%) of the product as a light yellow liquid: bp 100–115° (8 Torr); $[\alpha]^{24}D$ +56.2° (neat),

(63) Cyclobutane-1,1-dicarboxylic acid dichloride was prepared from commercial cyclobutane-1,1-dicarboxylic acid (Aldrich) by standard procedures: W. A. Nevill, D. S. Frank, and R. D. Trepka, *J. Org. Chem.*, **27**, 422 (1962).

(64) F. W. Semmler, *Chem. Ber.*, **39**, 2577 (1906).

(65) F. Humbert and G. Guth, *Bull. Soc. Chim. Fr.*, 2867 (1966).

(66) A. S. Hussey and R. H. Baker, *J. Org. Chem.*, **25**, 1434 (1960).

(67) For a good discussion of dry-column chromatography techniques, see B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

(68) P. L. Pickard and E. F. Engles, *J. Amer. Chem. Soc.*, **74**, 4607 (1952).

$[\alpha]^{24}D$ +49.0° (*c* 2.0, CCl_4); ir 1770 and 1710 cm^{-1}; nmr δ 16.0 (s, OH).[52]

Trifluoroacetyl-*l*-fencholylmethane was prepared from *l*-fencholylmethane (6.67 g, 0.0403 mol) and ethyl trifluoroacetate (5.71 g, 0.0403 mol) by the procedure described for the synthesis of H(dcm). Distillation of the crude product afforded 4.9 g (46%) of the product as a colorless liquid: bp 97° (7 Torr); $[\alpha]^{20}D$ −12.0° (*c* 10.0, CCl_4); ir 1650 and 1585 cm^{-1} (enol C=C and C=O); nmr δ 0.91 (d, 6, *J* = 6 Hz, $CH(CH_3)_2$), 1.27 (s, 3, CH_3), 5.92 (s, 1, vinyl H), and 14.77 (s, broad, 1, OH).[52]

3-(*d*-Fencholyl)-*d*-camphor. The procedure used to synthesize H(*t*-bhmc) was used to prepare 3-(*d*-fencholyl)-*d*-camphor from *d*-camphor (32 g, 0.21 mol) and *l*-fencholyl chloride (13 g, 0.069 mol). The product (16 g, 77%) was obtained as a light yellow liquid: bp 115–150° (1.0 Torr): ir 1750, 1695, 1660, and 1605 cm^{-1} (keto and enol C=O); nmr δ 12.8 (s, OH).[52]

3-(*l*-Fencholyl)-*d*-camphor. The procedure used to synthesize H(*t*-bhmc) was used to prepare 3-(*l*-fencholyl)-*d*-camphor from *d*-camphor (39 g, 0.25 mol) and *l*-fencholyl chloride (15.7 g, 0.083 mol). The product (19 g, 74%) was obtained as a light yellow liquid, bp 122–134° (0.10 Torr), having nmr and ir spectra indistinguishable from those of 3-(*d*-fencholyl)-*d*-camphor.[52]

***l,l*-Difencholylmethane. (H(dfm)).** Approximately 3 g of a sodium hydride dispersion in mineral oil (1.7 g of NaH, 0.071 mol) was added to a 500-ml, flame-dried, round-bottomed flask equipped with two pressure-equalizing dropping funnels, an efficient mechanical stirrer, and a reflux condenser with a calcium sulfate drying tube attached to a bubbler. The sodium hydride was washed with 100 ml of dried ether and 100 ml of anhydrous DME. *Ca.* 150 ml of dried DME was added to the flask along with 0.1 ml of ethanol and 0.1 ml of *tert*-butyl alcohol as catalysts. In one dropping funnel was placed 5.05 g (0.30 mol) of *l*-fencholylmethane, and in the other funnel was placed 5.67 g (0.030 mol) of *l*-fencholyl chloride; each was diluted with 20 ml of anhydrous DME. After heating the well-stirred suspension of sodium hydride to gentle reflux and adding *ca.* 20% of the acid chloride, the methyl ketone and acid chloride were dropped simultaneously into the refluxing solution over the course of 2 hr, maintaining a slight excess of acid chloride throughout the reaction. Gas evolution was monitored so that a few additional drops of *tert*-butyl alcohol could be added if the reaction slowed or stopped.[69] After refluxing overnight, the cooled orange solution was poured onto 200 g of crushed ice and 200 ml of ether, and then made acidic with concentrated hydrochloric acid. The aqueous phase was extracted with four 150-ml portions of water, dried, concentrated, and distilled to give 4.2 g (45%) of H(dfm) as a light yellow liquid: bp 128–140° (0.02 Torr); $[\alpha]^{25}D$ −17.0° (*c* 10.0, CCl_4); ir 3200–2550 (weak shoulder, OH), 1695, and 1600 cm^{-1} (C=O); nmr δ 0.85 (d, 12, *J* = 8 Hz, $CH(CH_3)_2$), 1.2 (s, 6, CH_3), 5.55 (s, 1, vinyl H), and 16.2 (s, 1, OH).[52]

***d*-Campholyl-*d*-fencholylmethane.** The procedure used to synthesize H(dfm) was used to prepare *d*-campholyl-*d*-fencholylmethane from *d*-campholylmethane (5.89 g, 0.035 mol) and *d*-fencholyl chloride (6.60 g, 0.035 mol). The product (7.1 g, 63%) was obtained as a light yellow liquid:[70] bp 117–135° (0.035 Torr); ir 1600 and 1700 (C=O) and 3200–2350 cm^{-1} (weak, O—H); nmr δ 5.5 (s, 1, vinyl H) and 16.5 (s, 1, OH).[52]

***d*-Campholyl-*l*-fencholylmethane.** The procedure used to synthesize H(dfm) was used to prepare *d*-campholyl-*l*-fencholylmethane from *d*-campholylmethane (3.6 g, 0.022 mol) and *l*-fencholyl chloride (4.1 g, 0.022 mol). The product (3.4 g, 49%) was obtained as a light yellow liquid (bp 128–140° (0.05 Torr)) with nmr and ir spectra indistinguishable from those of *d*-campholyl-*d*-fencholylmethane.[52]

Tris[*d,l*-dicampholylmethanato]europium(III) (8). To a 50-ml round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet[51] was added 0.55 g (1.73 mmol) of *d,l*-dicampholylmethane and 15 ml of methanol. The mixture was stirred at room temperature until most of the diketone had dissolved, and then 0.093 g (1.73 mmol) of sodium methoxide in 7 ml of methanol was added by cannula. Stirring for 2 min resulted in a clear, slightly yellow solution. Europium chloride hexhydrate (0.21 g, 0.58 mmol) dissolved in 7 ml of methanol was transferred by cannula into the very well stirred enolate solution. A yellow solid precipitated immediately (sometimes in the form of a single sticky lump). The mixture was vigorously stirred for 2 hr, cooled to 0°, filtered with suction, and rinsed with a small amount of cold methanol to give a white powder and several lumps.[71] The powder was dissolved in pentane and centrifuged to remove the insoluble material, the solvent was removed under vacuum, and the resulting solid was dried at 100° (0.1 Torr) for 36 hr and then crushed to give **8** (0.26 g, 40%) as a fine powder: mp 222.5–225.0°; $[\alpha]^{25}D$ 0.0° (*c* 5.0, CCl_4); ir 1540 cm^{-1}; nmr δ −0.38, 0.00, and 3.20 (s, 3 each, CCH_3) and 1.05 (d, 3, *J* = 6 Hz, $CHCH_3$).

Tris[*d,d*-dicampholylmethanato]holmium(III) was synthesized by a procedure analogous to that used for **8** from 5.09 g (15.9 mmol) of H(dcm) and 2.00 g (5.29 mmol) of holmium trichloride hexahydrate. The product (4.5 g, 76%) was a white amorphous solid; mp *ca.* 250°. A sample was purified for analysis by fractional molecular distillation (250–270° (0.005 Torr)): mp 264–268°; $[\alpha]^{24}D$ +40.2° (*c* 10, CCl_4); ir 1770 and 1710 cm^{-1}; nmr δ (broad) −1.5 (s), 1.1 (m), 2.2 (m), 4.2–6.1, and 9.6–11.9.[52]

Tris[*d,d*-dicampholylmethanato]praseodymium(III) was synthesized by a procedure analogous to that used for **8** from 3.20 g (10 mmol) of H(dcm) and 1.16 g (3.3 mmol) of praseodymium trichloride heptahydrate. The product (1.16 g, 44%) was a mint green solid. A sample was purified for analysis by fractional molecular distillation (190–210° (0.003 Torr)): mp *ca.* 80°, $[\alpha]^{24}D$ +54.5° (*c* 2.0, CCl_4); ir (broad) 1510–1650 and 1505 cm^{-1}; nmr δ −0.15 (s, CH_3), 0.65 (d, *J* = 6 Hz, $CHCH_3$), and 0.8–4.6 (m, broad).[52]

Tris[*d*-campholyltrifluoroacetylmethanato]europium(III) (11) was synthesized by a procedure analogous to that used for **9** from 2.64 g (10.0 mmol) of *d*-campholyltrifluoroacetylmethane. The crude product (2.2 g, 71%) was purified for elemental analysis by fractional molecular distillation (170–180° (0.004 Torr)) to give **11** as an amorphous yellow solid: mp *ca.* 100°; $[\alpha]^{24}D$ +36.8° (*c* 2.0, CCl_4); ir 1580–1650 cm^{-1}; nmr δ (broad) 1.33 (s), 1.41 (s), and 2.65 (m).[52]

Tris[*l*-fencholyltrifluoroacetylmethanato]europium(III) (14) was synthesized using a procedure analogous to that used for **9** starting with 1.32 g (5.0 mmol) of *l*-fencholyltrifluoroacetylmethane. The product (1.0 g, 65%) was obtained as a viscous yellow glass that softened below ambient temperature: $[\alpha]^{24}D$ −9.5° (*c* 1.5, CCl_4); ir 1580–1660 cm^{-1}; nmr δ (broad) 1.32, 1.9–3.0, and 3.3–4.1. Attempts to purify **14** for elemental analysis by tlc, molecular distillation, and sublimation resulted in decomposition of the chelate.

Tris[6-trifluoroacetyl-*l*-methanato]europium(III) (12) was synthesized using a procedure analogous to that used for **9** from 2.40 g (10.0 mmol) of 6-trifluoromethylhydroxymethylene-*l*-menthone. The product (1.8 g, 63%) was isolated as a yellow glass that softened below ambient temperature: $[\alpha]^{24}D$ −131° (*c* 1.3, CCl_4); ir 1580–1640 and 1710 cm^{-1}; nmr δ (broad) −2.2 to 4.5 (m). Attempts to purify **12** for elemental analysis by tlc, molecular distillation, and sublimation resulted in decomposition of the chelate.

Tris[*d*-campholyl-*l*-fencholylmethanato]europium(III) (2) was synthesized using a procedure analogous to that used for **9** from 0.874 g (2.73 mmol) of *d*-campholyl-*l*-fencholylmethane. The product (0.62 g, 62%) was a viscous yellow glass: $[\alpha]^{25}D$ +27.8° (*c* 5.4, CCl_4); ir similar to **6**; nmr δ 0.4–2.7 (broad envelope). A pure sample of **2** for elemental analysis was obtained by fractional molecular distillation (200–250° (0.01 Torr)).[52]

Tris[*l*-campholyl-*l*-fencholylmethanato]europium(III) was synthesized by a procedure analogous to that used for **9** from 1.61 g (5.04 mmol) of *l*-campholyl-*l*-fencholylmethane. The product (1.1 g, 60%) was a viscous yellow glass: $[\alpha]^{20}D$ −39.2° (*c* 9.3, CCl_4); nmr and ir indistinguishable from **2**.[52]

Tris[3-(*tert*-butylhydroxymethylene)-*d*-camphorato]praseodymium(III) was prepared by a procedure analogous to that for **6** from 1.91 g (8.1 mmol) of H(*t*-bhmc) and 1.00 g (2.7 mmol) of praseodymium trichloride heptahydrate. The product (1.75 g, 76%) was purified by fractional molecular distillation (150–200° (0.01 Torr)) to give pure product as a light green powder: softens at 145–150°, becomes a clear liquid 230–243°; $[\alpha]^{25}D$ +46.0° (*c* 3.5, CCl_4); nmr and ir similar to **6**.[52]

Tris[3-(*d*-fencholyl)-*d*-camphorato]europium(III) (4) was prepared by a procedure analogous to that used for **6** from 2.5 g (8.2 mmol) of 3-(*d*-fencholyl)-*d*-camphor. After purification by molecular distillation (150–200° (0.01 Torr)), 2.1 g (72%) of **4** was obtained as yellow needles that could be powdered: mp 113–115° (softens 80–90°); $[\alpha]^{25}D$ +72.4° (*c* 4.4, CCl_4); ir 1560–1620 cm^{-1}; nmr δ 0.6–1.9 (m).[52]

Tris[3-(*l*-fencholyl)-*d*-camphorato]europium(III) (5) was synthesized using the same procedure and scale as that for **4**. The product

(69) The alcoholic catalysts reacted slowly with the acid chloride.

(70) Because the *d*-fenchone starting material was optically impure, this diketone contained *ca.* 23% of *l*-campholyl-*d*-fencholylmethane.

(71) The activity of these lumps as a shift reagent was slightly inferior to the rest of the precipitate, and the lumps could be separated mechanically at this point.

(1.9 g, 65%) was a yellow glass: mp 112–114° (softens at 80°); $[\alpha]^{25}D$ +57.4° (*c* 3.8, CCl_4); nmr and ir identical with **4**.[52]

Tris[*l,l*-difencholylmethanato]europium(III) (7). The procedure used to synthesize **1** was used, with the following exceptions, to prepare this material from 2.63 g (8.24 mmol) of *l,l*-difencholylmethane. The reaction mixture was diluted with 20 ml of ice–water and filtered with suction at 0°. The gummy residue was dried for 6 hr at 20° (0.1 Torr) and dissolved in ether, and the insoluble solid was removed by centrifugation. After removing the ether at reduced pressure, the yellow, oily crude product was purified by fractional distillation (200–250° (0.01 Torr)) using a Dry Ice–acetone collecting finger to give a light yellow glass (1.3 g, 43%) that softened below 25°. An analytical sample was further purified by fractional molecular distillation (180–250° (0.01 Torr)): $[\alpha]^{25}D$ −18.8° (*c* 5.8, CCl_4); ir 1575 cm^{-1}; nmr δ 0.7–2.0.[52]

Tris[*d*-campholyl-*d*-fencholylmethanato]europium(III) (3) was synthesized using a procedure analogous to that for **7**. The product (1.6 g, 52%) was a viscous yellow glass: $[\alpha]^{25}D$ +33.6° (*c* 7.4, CCl_4); nmr and ir indistinguishable from **2**.[52]

Tris[*d,l*-difencholylmethanato]europium(III) was synthesized using the same procedure and scale as that for **7**. The product (1.4 g, 46%, $[\alpha]^{25}D$ −5.2° (*c* 9.6, CCl_4)) had physical and spectroscopic properties similar to those of **7**.[52]

Tris[2-trifluoroacetyl-*d*-dihydrolanosteronato]europium(III) (13). *Ca.* 0.45 g of 2-trifluoroacetyl-*d*-dihydrolanosterone (as an orange oil) was dissolved in 5 ml of ether and shaken with 2 ml of 10% aqueous sodium hydroxide. Then 2 ml of 10% aqueous $BaCl_2$ solution was added and the solution was again shaken. The mixture was stored overnight at 0°, and the resulting white precipitate of the barium chelate was separated by filtration, washed with distilled water, and washed with a small portion of methanol. The dried white powder had mp *ca.* 260°, softening at 215°.

To a 50-ml, round-bottomed, flask equipped with magnetic stirring bar and nitrogen inlet was added 0.30 g (0.26 mmol) of bis-[2-trifluoroacetyl-*d*-dihydrolanosteronato]barium(II) and 0.063 g (0.17 mmol) of europium trichloride hexahydrate. The flask was flushed with nitrogen and 30 ml of ethanol was added. The ethanol solution was heated to 70° and vigorously stirred for 1 hr to give a pale yellow solution and a white precipitate. This mixture was cooled to 0°, filtered to remove the precipitated barium chloride, diluted with 30 ml of water, and extracted with pentane. The combined pentane extracts were washed once with water, concentrated, and dried for 24 hr at 100° (0.01 Torr) to give 0.2 g of the product as a bright yellow solid: mp *ca.* 220°; ir (strong) 1610 cm^{-1}; nmr δ −1 to +4 (broad envelope) (resembling the parent ligand) and 0.8 (m).

Anal. Calcd for $C_{96}H_{144}EuF_9O_6$: C, 67.14; H, 8.46. Found: C, 66.75; H, 8.46.

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Hydrogen–Deuterium Randomization in 7-Methyl-4-octanone-7-d_1 at Times of 10^{-11}–10^{-5} Sec Following Field Ionization

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Abstract: Partial hydrogen–deuterium (H–D) randomization occurs prior to the McLafferty rearrangement in 7-methyl-4-octanone-7-d_1 following field ionization (FI) even at times as short as the order of 10^{-11} sec. This behavior contrasts sharply with that of straight-chain ketones in which no H–D randomization occurs prior to the McLafferty rearrangement at times $<7 \times 10^{-10}$ sec. At times of 10^{-11}–10^{-10} sec following FI the rate of the McLafferty rearrangement is an order of magnitude smaller in 7-methyl-4-octanone than in a typical straight-chain ketone 2-octanone, but at $\sim 10^{-6}$ sec the situation is reversed with the rate being an order of magnitude smaller in the straight-chain ketone. The difference in kinetics is consistent with the McLafferty rearrangement at times > a few $\times 10^{-11}$ sec following FI being a stepwise rather than a concerted process. It is proposed that H–D randomization in the 7-methyl-4-octanone-7-d_1 ion involves γ-D transfer to the oxygen forming a tertiary radical, followed by reverse D transfer from the oxygen to the alkyl chain. The reverse transfer is facilitated by the stability of the tertiary radical.

The unimolecular gas-phase reactions induced by electron impact (EI) of aliphatic ketones have been studied intensively.[2] The behavior of aliphatic ketones following field ionization (FI) has also received considerable attention.[3–6] Mass spectra of partially deuterated straight-chain aliphatic ketones produced by EI at ordinary ionizing voltages (70 eV) reveal little hydrogen–deuterium (H–D) randomization,[7] although a degree of randomization is manifested in the metastable region[8] (corresponding to molecular ion lifetimes of 10^{-6} sec). At very low ionizing voltages (10–12 eV) a degree of H–D randomization is also evident in the normal EI mass spectra.[7,8] These observations have been rationalized on the basis that the randomization reactions in straight-chain aliphatic ketones have low

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(2) For a review of the early studies, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, Chapter 3.

(3) A. J. B. Robertson and B. W. Viney, *Advan. Mass Spectrom.*, **3**, 23 (1966).

(4) F. W. Röllgen and H. D. Beckey, *Surface Sci.*, **23**, 69 (1971).

(5) E. M. Chait and F. G. Kitson, *Org. Mass Spectrom.*, **3**, 533 (1970).

(6) P. J. Derrick, A. M. Falick, S. Lewis, and A. L. Burlingame, *Org. Mass Spectrom.*, **7**, 887 (1973).

(7) W. Carpenter, A. M. Duffield, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 160 (1968).

(8) (a) A. N. H. Yeo, R. G. Cooks, and D. H. Williams, *Chem. Commun.*, 1269 (1968); (b) A. N. H. Yeo and D. H. Williams, *J. Amer. Chem. Soc.*, **91**, 3582 (1969).