The Use of Chiral Solvating Agents for Nuclear Magnetic Resonance Determination of Enantiomeric Purity and Absolute Configuration of Lactones. Consequences of Three-Point Interactions

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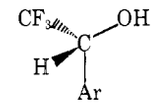
Received October 21, 1976

Diastereomeric solvates result from the solvation of enantiomeric lactones by chiral 2,2,2-trifluoro-1-(9-anthryl)ethanol (1). In most instances, these solvates are of similar general structure and energy as a consequence of "two-point only" interaction. The nature of the time-averaged NMR spectral differences of these diastereomeric solvates is a reliable guide to the absolute configurations of the lactone enantiomers. Additional (i.e., "three-point") interactions require modification of the generalizations of the "two-point" model. Several lactones bearing nitrophenyl or nitrobenzyl substituents have been shown to depart from the two-point model as a consequence of π–π interaction between the nitrated aromatic substituent of the lactone and the anthryl substituent of 1. These π–π interactions cause the diastereomeric solvates to be of different stabilities as evidenced by Eu(fod)$_3$ studies and direct chromatographic resolution of the nitrated lactone enantiomers on silica gel using solutions of chiral 1 as an eluent. ^{13}C NMR studies offer additional insight into the structures of these diastereomeric solvates.

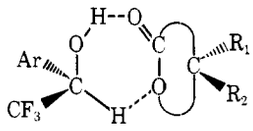
The intermediacy of short-lived molecular complexes has been invoked in such diverse areas as rationalization of reaction mechanisms, separation methods, biological activity, and physical and spectral properties. Diastereomeric complexes, produced through interactions of chiral molecules, often show considerable stereochemical dependence of their chemical, spectral, and physical properties. Such behavioral differences are not always well understood even though the practical applications of such differences are legion.

We have been concerned about the details of interaction between certain "chiral solvating agents" and a diverse series of enantiomeric solutes.[1a-j] In many cases, both enantiomeric purity and absolute stereochemistry can be determined for the solutes on the basis of such interactions. For example, we recently reported[2] that "two-point" interaction between chiral 2,2,2-trifluoro-1-(9-anthryl)ethanol (1) and γ-lactone enantiomers, as shown in **2a,b,** is responsible for the nonequivalence of the NMR spectra of the enantiomers. The shielding effect of the anthryl substituent causes the resonances of the R_1 substituent(s) to occur at higher field for the enantiomer incorporated into **2a** than for that incorporated into **2b.** The converse situation holds for the resonances of R_2 substituents located on the other face of the lactone. Implicit in this solvation model is the assumption that no additional interactions occur between the alcohol and the lactone. It was suggested that additional interactions might perturb the model and alter the correlation between stereochemistry and observed senses of nonequivalence. In this paper, we address ourselves to the consequences of one type of "additional interaction" between lactones and chiral carbinol **1.**

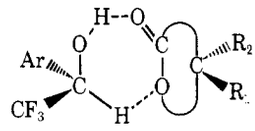


Ar = 9-anthryl

1

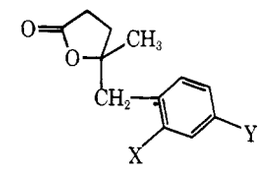


2a



2b

Diastereomeric solvates **2a** and **2b** can be considered to be of essentially equal stability if no appreciable lactone–carbinol interactions occur beyond the hydrogen bonding–carbinyl hydrogen bonding[1b] interactions depicted. Additional interactions will be stereochemically dependent and can result in differential stability of the solvates. They may even alter the structure of the solvates. Consider, for example, the diastereomeric solvates derived from (*R*)-(−)-1 and the enantiomers of γ-benzyl-γ-methylbutyrolactone (**3**) and the *o*-nitro, *p*-nitro, and 2,4-dinitro analogues, **4, 5,** and **6.** In the presence



3, X = Y = H
4, X = NO_2; Y = H
5, X = H; Y = NO_2
6, X = Y = NO_2

of a severalfold excess of (*R*)-(−)-1, a (−)-enriched sample of **3** shows low-field nonequivalence for the benzyl methylene hydrogens and high-field nonequivalence fo the methyl hydrogens. In accord with the model, this lactone has been assigned the (*S*)-(−) configuration. Addition of the achiral shift reagent Eu(fod)$_3$ to the preceding sample causes the lactone resonances to move downfield (Figure 1 shows this for the benzyl methylene hydrogens) as the Eu(fod)$_3$ "strips" the lactone from carbinol **1.**[3] Figure 2, a plot of nonequivalence magnitude (i.e., $\delta R - \delta S$) as a function of Eu(fod)$_3$:lactone ratio, shows a smooth attenuation of nonequivalence toward zero. This is a consequence of the similar stabilities of the two diastereomeric lactone–carbinol solvates in the absence of "additional" interactions.[3]

Repetition of these NMR experiments for (*S*)-enriched samples of nitrated lactones **4, 5,** and **6** affords different results. First, the senses of methyl nonequivalence for these lactones are inverted and are of the same sense as that of the benzyl methylene groups. Secondly, Eu(fod)$_3$ seems less able to "disrupt" the lactone–carbinol solvates, especially in the case of the dinitro analogue, **6** (Figure 1). Thirdly, Eu(fod)$_3$ preferentially "disrupts" the (*R,S*) solvate, as evidenced (Figure 2) by the greater downfield shifts of both the methyl and benzyl methylene resonances of the *S* enantiomer than the *R* enantiomer. Again, this effect is more pronounced for dinitro **6** than for *p*-nitro **5** or *o*-nitro **4.** These curves are best explained by invoking a stereochemically dependent π–π interaction between the anthryl substituent of **1** and the nitrated benzyl substituents of the lactones. The strengths of these π–π interactions are dinitro **6** > *p*-nitro **5** > *o*-nitro **4.**[5] For steric

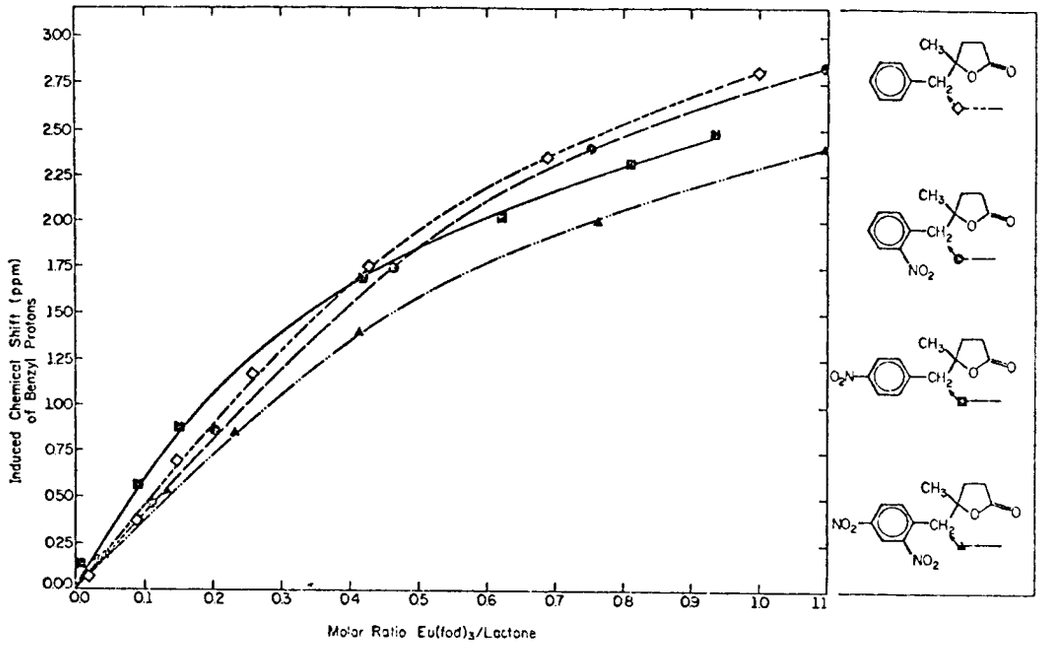


Figure 1. The influence of $Eu(fod)_3$ concentration on the (averaged) induced chemical shifts of the benzyl protons of lactones 3–6. Lactone concentrations are ca. 0.07 M; carbinol 1 concentration is ca. 0.21 M.

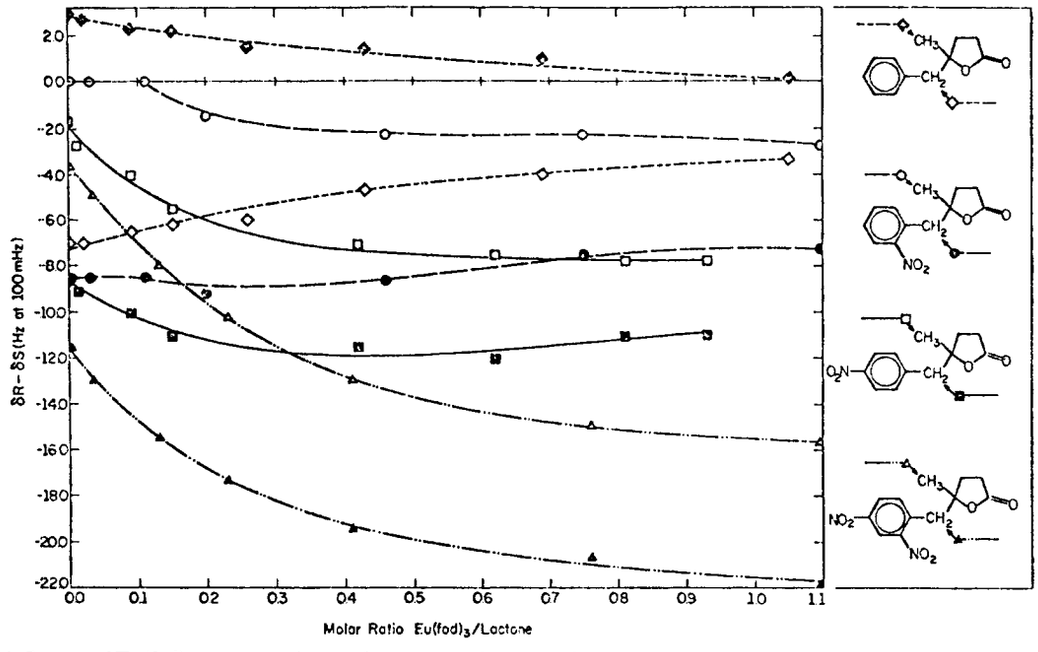


Figure 2. The influence of $Eu(fod)_3$ concentration on the senses and magnitudes of nonequivalence of the lactones 3–6. Samples used to generate these data were those described for Figure 1.

reasons, the *o*-nitro group of **4** is less apt to be coplanar with the phenyl ring and is consequently a less effective π acid. Solvates **7a,b** make it evident that the *R,R* solvate can simultaneously experience three bonding interactions whereas the *R,S* solvate can simultaneously experience but two.

As a further test of this "differential stability" concept, 30 mg of racemic **6** was chromatographed on silica using a carbon tetrachloride solution of (*R*)-(−)-**1** as eluent. The progress of the colored π complexes was followed visually and, after development, the section of the column containing this band was divided into high R_f, mid R_f, and low R_f fractions.[6] Recovery and chromatographic purification of the high and low R_f fractions afforded optically active samples of **6**, the enantiomeric compositions and absolute configurations (Table I) of which were established by NMR in the presence of (*R*)-(−)-**1**. The high R_f fraction (8.8 mg) was 50% enriched in the (*R*)-(−) enantiomer; the low R_f sample (17.4 mg), 18% enriched in the (*S*)-(+) enantiomer. This elution order is that expected if the mechanism of chromatographic resolution reflects the relative stabilities of the two diastereomeric solvates.

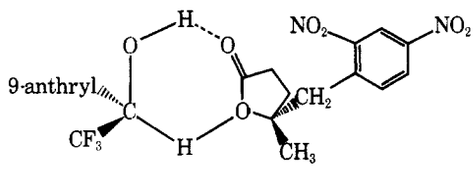
The assignment of the (*S*)-(+) configuration to **6** was independently established. After chromatographic separation of the chiral diastereomeric hydroxy amides **8**, hydrolysis of the low R_f isomer followed by cyclization leads to (*S*)-(−)-**3** in high enantiomeric purity. Nitration with nitronium tetrafluoroborate affords (*S*)-(+) samples of **4**, **5**, and **6** with moderate racemization (Scheme I). Lactones **4**, **5**, and **6** were separated chromatographically.

To gain further insight into the structures of the diaste-

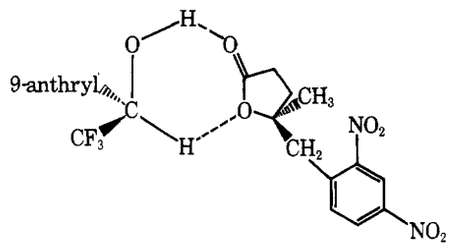
Table I. Rotational and NMR Nonequivalence Data for Lactones 6, 9, and 10 Enantiomerically Enriched by Chromatography Using (*R*)-(−)-1 as Eluent

	High R_f fraction		Low R_f fraction	
Lactone (wt chromatographed)	Wt, mg $[\alpha]^{25}_D$ ($CHCl_3$) ee[a] by NMR	Proton (amt noneq),[b] sense[c]	Wt, mg $[\alpha]_D$ ($CHCl_3$) ee[a] by NMR	Proton (amt noneq),[b] sense[c]
6 (30 mg)	8.8 −12.2°[d] (*c* 0.98) 50%	H_6 (18.0), H Benzyl (10.0), H $-CH_3$ (3.5), H	17.4 +6.7° (*c* 1.93) 18%	H_6 (20.0), L Benzyl (11.0), L $-CH_3$ (2.2), L
9 (30 mg)	14.2 +5.6° (*c* 1.58) 15%	H_3 (3.0), H; H_5 (18.0), H H_γ (11.0), H	8.8 −14.2° (*c* 0.98) 36%	H_3 (3.2), L H_5 (22.5), L H_6 (22.0), L H_γ (13.0), L
10[e] (49 mg)	50%	H_3 (3.0), H; H_5 (26.0), H	24 +72.9° 50%	H_3 (3), L; H_5 (26), L

[a] Enantiomeric excess as determined by relative peak heights of enantiomeric resonances. [b] Amount of nonequivalence in hertz at 100 MHz. Variations in nonequivalence magnitudes between high and low R_f fractions reflect somewhat different sample concentrations. [c] H = highfield; L = lowfield. [d] Sample used for rotation later found to contain a trace of (*R*)-(−)-**1**. [e] This lactone was actually resolved using (*S*)-(+)-**2**. Signs of rotation and senses of nonequivalence have been inverted in the table for uniformity with the other entries.



7a *R,R* solvate



7b *R,S* solvate

reomeric solvates derived from carbinol **1** and the enantiomers of **6**, ^{13}C NMR nonequivalence studies were carried out. In the presence of a severalfold excess of (*R*)-(−)-**1**, every carbon of (*S*)-(+)-enriched **6**, except the methyl carbon, shows nonequivalence (Table II). Note that all carbon resonances shift upfield in the presence of **1** except the carbonyl and carbinyl carbons. The downfield shifts noted for the latter are consistent with a diminution of electron density at these carbons attendant with hydrogen bonding and carbinyl hydrogen bonding to the adjacent oxygens. As expected, the carbonyl carbon shows the greater effect. Upfield shifts of the remaining carbons are rationalized on the basis of diamagnetic shielding by the anthryl substituent of **1** and by its electron donation via π–π complexing to **6**. The low-field sense of nonequivalence shown by all carbons in the 2,4-dinitrobenzyl substituent is in accord with a greater degree of π–π (charge transfer) interaction in the *R,R* solvate than in the *R,S* solvate. Similarly, the high-field nonequivalence shown by the carbonyl, α, β, and γ carbons suggests a greater degree of hydrogen bonding and carbinyl hydrogen bonding for the *R,R* than for the *R,S* diastereomer.

The data presented are consistent with **7a** being representative of the time-averaged structure of the *R,R* solvate. It is not clear that **7b** is equally representative of the *R,S* solvate since, should the π–π interaction be competitive with carbinyl hydrogen bonding, structure **7c** might well compete with or dominate **7b**. Structure **7c** could well be responsible for the "inverted" sense of nonequivalence shown by the methyl group of **6**. Since **7b** is the conformation expected to provide the shielding responsible for the "normal" upfield sense of methyl nonequivalence of *S*-enriched **6**, the "absence" of **7b**

Scheme I

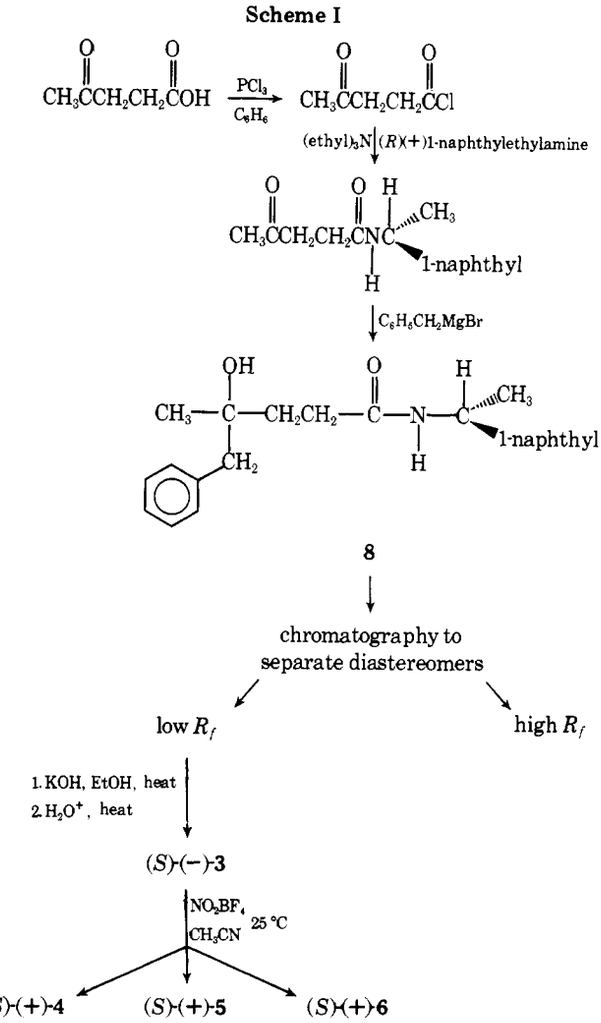
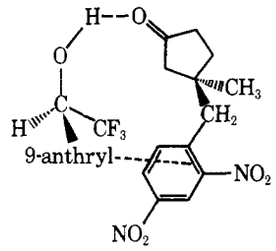


Table II. ^{13}C NMR Chemical Shifts and Nonequivalence of (*S*)-(+)-Enriched 6 in the Presence of (*R*)-(−)-1

		In the presence of (*R*)-(−)-1		
Carbon	Without 1, ppm[a]	ppm[a]	Δppm	Nonequivalence magnitude, Hz (sense)[b]
C=O	174.798	177.267	+2.469	8.62 (H)
α	33.315	32.744	−0.571	1.98 (H)
β	28.576	28.291	−0.285	Shoulder (H?)
γ	84.944	86.078	+1.134	4.66 (H)
$-CH_3$	25.850	24.815	−1.035	0.0
Benzyl	41.672	40.663	−1.009	4.13 (L)
Aromatic				
C-1	137.464	136.618	−0.846	4.13 (L)
C-2	150.660	149.608	−1.052	4.12 (L)
C-3	120.293	119.740	−0.553	3.05 (L)
C-4	147.278	146.407	−0.871	4.67 (L)
C-5	126.616	Not assignable		
C-6	135.466	134.623	−0.842	3.24 (L)

[a] Downfield from Me_4Si. [b] H = highfield, L = lowfield sense.

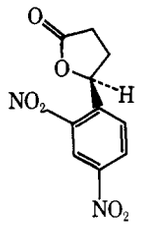
would thwart predictions predicated upon its substantial population.



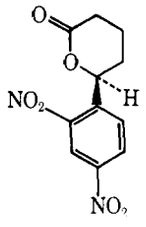
7c

Similar reasoning leads one to anticipate a stability difference in the diastereomeric solvates derived from (*R*)-(−)-1 and the enantiomers of dinitrophenyl lactones **9** and **10**. Indeed, chromatographic resolution of the enantiomers of these lactones can be effected as it was for lactone **6**. These results are summarized in Table I. It should also be noted that the senses of nonequivalence of the carbinyl hydrogens of **9** and **10** are (presumably) "inverted" since they are of the same sense as the nonequivalence of the protons on the 2,4-dinitrophenyl groups. These "inversions" appear to have the same general origin as those of lactones **5** and **6**. Thus, the differential chromatographic and spectroscopic behavior of the enantiomers of lactones **9** and **10** [in the presence of (*R*)-(−)-**1**] appear very similar to that of lactone **6**. Hence, the *S* configuration is assigned to the enantiomer preferentially included in the low R_f chromatographic fractions shown in Table I for each of these lactones.[7]

For lactones **4–6, 9,** and **10,** it was immediately apparent (from the similar senses of nonequivalence of substituents on



9



10

either face of the lactone ring) that the usual lactone–carbinol solvation model was being perturbed. This is of no consequence for enantiomeric purity determinations but did raise questions concerning assignments of absolute configuration based upon the observed senses of nonequivalence. It has been demonstrated that this perturbation comes from the presence of a third lactone–carbinol interaction (π–π bonding in these instances) that is stereochemically dependent. Since knowledge of lactone structure will often allow anticipation of such "third interactions", rational interpretation of observed senses of nonequivalence will often be possible even for "abnormal solutes". In general, the observation of opposite senses of nonequivalence for substituents on opposite faces of the lactone ring will be the hallmark of the normal solvation model.

Experimental Section

General. Melting points were taken on a Buchi apparatus and are uncorrected. Optical rotations were determined at 589 nm in a Zeiss visual polarimeter using a 1.0-dm tube. ^1H NMR data were obtained with a Varian HA-100 or HR-220 spectrometer at 27 or 25 °C, respectively. Proton-decoupled carbon-13 spectra were obtained with a Varian XL-100-15 spectrometer equipped with a Digilab NMR-3 data system. The 25.2-MHz natural abundance spectra were obtained at 30 °C in the FT mode using a 32K point transform. The off-resonance proton-decoupled carbon-13 spectrum was obtained with a JEOL JNM FX-60 spectrometer in the FT mode. Microanalysis were performed by J. Nemeth and his colleagues.

The synthesis, resolution, and absolute configuration of **1** have been previously reported[2] as has an alternate synthesis of enantiomerically enriched **3**.[2]

Racemic Nitrated Lactones 4, 5, and 6. Nitration of racemic lactone **3** was effected by addition of a fourfold excess of nitronium tetrafluoroborate to the lactone (0.1 M) in dry acetonitrile at 0 °C followed by stirring for 1–2 h at 25 °C. Addition of H_2O and extraction with CH_2Cl_2 gave a mixture of *o*-nitro-, *p*-nitro-, and 2,4-dinitrophenyl substituted lactones **4, 5,** and **6** which were separated by column chromatography on silica gel with CH_2Cl_2. The elution order was **4,** followed by **5,** and then **6**. All three lactones were recrystallized from a mixture of CCl_4 and CH_2Cl_2 (5:1, v:v). Characterization data and yields are reported in Table III.

Table III

Lactone (mp, °C) yield, %	100-MHz NMR	Microanal. Calcd	Found
4 (110) 5–10	(CCl_4–$CDCl_3$ 2.1, v:v) 7.88 (m, 1), 7.65–7.30 (m, 3), 3.36 (s, 2), 2.73–1.97 (m, 4), 1.43 (s, 3)	$C_{12}H_{13}NO_4$ C, 61.27 H, 5.57 N, 5.95	C, 61.47 H, 5.72 N, 6.02
5 (110) 30	($CDCl_3$) 8.17 (d, 2, J = 8.5 Hz), 7.42 (d, 2, J = 8.5 Hz), 3.06 (s, 2), 2.63–1.97 (m, 2), 1.42 (s, 3)	$C_{12}H_{13}NO_4$ C, 61.27 H, 5.57	C, 60.99 H, 5.37
6 (98) 40	(CCl_4–$CDCl_3$ 3:1, v:v) 8.69 (d, 1, J = 2.3 Hz), 8.40 (d of d, 1, J = 2.3, 9.0 Hz), 7.75 (d, 1, J = 9.0 z), 3.43 (s, 2), 2.70–1.90 (m, 4), 1.38 (s, 3)	$C_{12}H_{12}N_2O_6$ C, 51.43 H, 4.32 N, 10.00	C, 51.63 H, 4.36 N, 10.05

Enriched Lactones 3, 4, 5, and 6. To a stirred solution of levulenic acid (23 g, 0.19 mol) in benzene (180 mL) was added phosphorus trichloride (16 g, 0.117 mol). After the initial exothermic reaction, the solution was stirred at 25 °C for 2.5 h. Evaporation of the solution under reduced pressure to 90 mL volume removed unreacted PCl_3 (bp 78 °C) and cooling and decantation separated the soluble acid chloride from the insoluble phosphorus-containing by-products. Care was taken to keep the solution cool since a previous attempt at distillation of the acid chloride had resulted in formation of α,β- and β,γ-unsaturated lactones.

The entire C_6H_6 solution of acid chloride was slowly added to a stirred and cooled (0 °C) solution of (*R*)-(+)-α-naphthylethylamine (20 g, 0.117 mol) and triethylamine (12 g, 0.119 mol) in C_6H_6 (100 mL). After the addition, the solution was allowed to warm to 25 °C and stirred for 12 h. The resulting amine hydrochloride was removed by filtration after addition of CH_2Cl_2 (400 mL). The filtrate was washed with dilute hydrochloric acid (1.5 M, 4 × 50 mL) and with dilute sodium bicarbonate (5%, 3 × 40 mL), dried ($MgSO_4$), and distilled under reduced pressure to yield 25.2 g of residue assumed to be mainly the keto amide.

A solution of benzylmagnesium bromide, prepared by addition of α-bromotoluene (32.2 g, 0.188 mol) to magnesium turnings (9.1 g, 0.376 mol) in anhydrous ether (150 mL) followed by reflux (30 min), was added to a cold (5 °C) solution of the above keto amide (13 g, 0.048 mol) in dry ether (600 mL) with stirring. A solid formed immediately. After stirring at 25 °C for 3.5 h, hydrolysis with saturated aqueous ammonium chloride (350 mL) followed by ether extraction afforded, after drying and concentration of the extracts, an orange-brown oil (22.3 g). Chromatography of this oil on silica gel with CH_2Cl_2 afforded a 3:1 mixture (14.6 g) of the desired hydroxy amides and unreacted keto amide.

Chromatography of a portion of this mixture [silica gel with CH_2Cl_2–Et_2O (4:1, v:v)] resulted in separation of all three components (keto amide and the two diastereomers). The low R_f diastereomer (2.0 g, 5.54 mmol) was hydrolyzed by heating to reflux for 10 h with KOH (4.2 g, 75 mmol) in ethanol (50 mL). Subsequent addition of H_2O (200 mL) and extraction with CH_2Cl_2 (4 × 40 mL) removed the amine and acidification (3 M HCl) followed by extraction afforded the hydroxy acid which was lactonized by azeotropic removal of H_2O with benzene.

Nitration was effected as described earlier for the racemate and results in some racemization. In one case, **3** of 61% enantiomeric purity yielded **6** of 35% enrichment. To increase the yield of the *o*-nitrophenyl substituted lactone, a sample of the nitration reaction mixture was removed and worked up 10 min after addition of NO_2BF_4 while the solution was still cold. This sample was added to the final product before chromatography. The dinitrated lactone obtained in this manner was used for the carbon-13 study. Optical rotations and enantiomeric purities of the samples thus obtained follow: **4**, $[\alpha]^{24}_D$ +10.70° (*c* 4.60, $CHCl_3$), 34% ee; **5**, $[\alpha]^{24}_D$ +8.33° (*c* 9.72, $CHCl_3$), 31% ee; **6**, $[\alpha]^{24}_D$ +6.21° (*c* 9.50, $CHCl_3$), 31% ee. The NMR spectra of these lactones are identical with those of the racemic lactones.

Racemic γ-2,4-Dinitrophenyl-γ-butyrolactone (9). A solution of 4-phenylbutanoic acid (0.01 mol) in concentrated nitric (10 mL) and sulfuric (5 mL) acids was heated on a steam bath for 12–16 h. Cooling, followed by careful addition of H_2O (100 mL), caused precipitation of the nitrated acid which was extracted into CH_2Cl_2 (3 × 30 mL) and washed with H_2O. Evaporation of the solvent from the dried ($MgSO_4$) extract afforded 4-(2,4-dinitrophenyl)butanoic acid (>90%). γ-Bromination of the nitrated acid (5 mmol) was effected with *N*-bromosuccinimide (5 mmol) in CCl_4 (125 mL) through heating at reflux for 5 h in the presence of dibenzoyl peroxide (0.05 mmol). Succinimide precipitated on cooling and was removed by filtration. The filtrate, containing a mixture of the desired lactone, bromo acid, and unbrominated acid, was washed with 10% aqueous sodium bicarbonate to remove the acids from lactone **9**. Heating the aqueous extract converted the bromo acid salt to the hydroxy acid salt. Acidification of the aqueous solution followed by extraction with benzene and azeotropic removal of water by distillation effected lactonization. Acidic impurities were removed by extraction with 10% $NaHCO_3$. Both fractions of lactone **9** were combined and crystallized from a mixture of CCl_4 and CH_2Cl_2 (5:1, v:v): mp 109 °C; NMR ($CDCl_3$) δ 9.05 (d, 1, *J* = 2.3 Hz), 8.65 (d of d, 1, *J* = 9.0, 2.3 Hz), 8.12 (d, 1, *J* = 9.0 Hz), 6.30 (t, 1, *J* = 7.0), 3.20–1.90 (m, 4). Anal. Calcd for $C_{10}H_8N_2O_6$: C, 47.63; H, 3.20; N, 11.11. Found: C, 47.59; H, 3.32; N, 10.95.

Racemic δ-2,4-Dinitrophenyl-δ-valerolactone (10). This lactone was prepared from 5-phenylpentanoic acid in the manner described above for lactone **9**. Lactone **10** was not readily crystalline and was characterized only by 100-MHz NMR: NMR ($CDCl_3$) δ 8.82 (d, 1, *J* = 2.3 Hz), 8.55 (d of d, 1, *J* = 9.0, 2.3 Hz), 8.05 (d, 1, *J* = 9.0 Hz), 6.07 (d of d, 1), 3.00–1.50 (m, 6).

Acknowledgment. This work has been partially supported by the National Science Foundation and by the National Institutes of Health.

Registry No.—(*R*)-(−)-**1**, 53531-34-3; (±)-**3**, 61520-92-1; (*S*)-(−)-**3**, 61477-77-8; (±)-**4**, 61477-78-9; (*S*)-(+)-**4**, 61520-93-2; (±)-**5**, 61477-79-0; (*S*)-(+)-**5**, 61520-94-3; (±)-**6**, 61477-80-3; (*S*)-(+)-**6**, 61520-95-4; (*R*)-(−)-**6**, 61520-96-5; **8**, 61477-81-4; (±)-**9**, 61477-82-5; (*S*)-(−)-**9**, 61520-97-6; (*R*)-(+)-**9**, 61520-98-7; (±)-**10**, 61477-84-7; (*S*)-(+)-**10**, 61521-47-9; (*R*)-(−)-**10**, 61520-99-8; levulinic acid, 123-76-2; levulinoyl chloride, 1490-24-0; (*R*)-(+)-α-naphthylethylamine, 3886-70-2; *N*-(1-napthylethyl)levulinamide, 61477-85-8; benzyl bromide, 100-39-0; 4-phenylbutanoic acid, 1821-12-1; 5-phenylpentanoic acid, 2270-20-4.

References and Notes

(1) (a) W. H. Pirkle and M. S. Hoekstra, *J. Am. Chem. Soc.*, **98**, 1832 (1976); (b) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **41**, 801 (1976); (c) W. H. Pirkle and D. L. Sikkenga, *J. Chromatogr.*, **123**, 400 (1976); (d) W. H. Pirkle and M. S. Hoekstra, *J. Magn. Reson.*, **18**, 396 (1975); (e) W. H. Pirkle, S. D. Beare, and R. L. Muntz, *Tetrahedron Lett.*, 2295 (1974); (f) W. H. Pirkle and R. L. Muntz, *J. Am. Chem. Soc.*, **93**, 2817 (1971); (g) W. H. Pirkle, S. D. Beare, and R. L. Muntz, *J. Am. Chem. Soc.*, **91**, 4575 (1969); (h) W. H. Pirkle and S. D. Beare, *ibid.*, **91**, 5150 (1969); (i) W. H. Pirkle, T. G. Burlingame, and S. D. Beare, *Tetrahedron Lett.*, 5847 (1968); (j) W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **89**, 5485 (1967).

(2) W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, **42**, 384 (1977).

(3) In a solution containing enantiomeric lactones, R and S, chiral carbinol, C, and shift reagent, L, a *partial* accounting of the ensuing interactions is as follows:

$$R + C \underset{}{\overset{k_1}{\rightleftharpoons}} RC$$

$$S + C \overset{k_2}{\rightleftharpoons} SC$$

$$R + L \overset{k_3}{\rightleftharpoons} RL$$

$$S + L \overset{k_3}{\rightleftharpoons} SL$$

$$R + C + L \overset{k_4}{\rightleftharpoons} RLC$$

$$S + C + L \overset{k_5}{\rightleftharpoons} SLC$$

There are at least four mechanisms which might contribute to the time-averaged NMR nonequivalence shown by R and S: (a) the spectrum of RC ≠ SC; (b) [RL] ≠ [SL], i.e., $k_1 \neq k_2$; (c) the spectrum of RLC ≠ SLC; (d) [RLC] ≠ [SLC], i.e., $k_4 \neq k_5$. A more detailed explanation of a similar situation dealing with enantiomeric sulfoxides has been presented.[4]

(4) W. H. Pirkle and D. L. Sikkenga, *J. Org. Chem.*, **40**, 3430 (1975).

(5) The curves shown in Figure 2 are qualitatively similar in shape to those observed for several ring-substituted phenyl methyl sulfoxides in ref 4. The observation that higher concentrations of Eu(fod)$_3$ are required to produce the maximum perturbation in the spectrum of **6** than for **5** or **4** presumably indicates the greater magnitudes of k_1 and k_2 in the case of **6**. A smaller value for k_3 would afford a similar observation. Eu(fod)$_3$ competition experiments show that k_3 is smaller for lactone **6** than for **3**.

(6) A more detailed account of the chromatographic procedure is given in ref 1c.

(7) Similar arguments have been used to assign absolute configurations to methyl 2,4-dinitrophenyl sulfoxide and methyl *p*-nitrophenyl sulfoxide.[1c,4]