Nuclear Magnetic Resonance Determination of Enantiomeric Composition and Absolute Configuration of γ-Lactones Using Chiral 2,2,2-Trifluoro-1-(9-anthryl)ethanol

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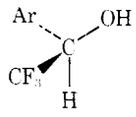
Since lactone functionality is ubiquitous among nature's molecules, the determination of absolute configuration and enantiomeric purity of variously substituted chiral lactones is one that is periodically encountered by those synthesizing or elucidating the structures of natural products. Chiroptic methods are useful for determining absolute configurations of some lactones depending upon the substitution patterns.[1] X-ray structural analysis is valuable (in the case of suitably crystalline materials) but time consuming and hence expensive. In this paper, we describe an NMR method for simultaneously determining absolute configurations and enantiomeric purities of δ-lactones that is, in principle, applicable regardless of substitution pattern.

Chiral aryltrifluoromethylcarbinols, **1**, are known to render the NMR spectra of enantiomers "nonequivalent" for a



1, Ar = phenyl
b, Ar = α-naphthyl
c, Ar = 9-anthryl

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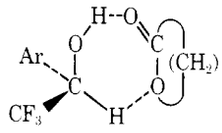
number of solute types. The observation of separate signals for each enantiomer allows determination of enantiomeric purity *without reference to an external standard of enantiomeric purity.*[2] This is done by measurement of the relative intensities of the two sets of signals.

The induced spectral nonequivalence arises from the formation of short-lived diastereomeric solvates that have nonidentical spectra as a consequence of the population of rather specific conformations. Knowledge of the structures of these conformations and the absolute configuration of the carbinol allows assignment of absolute configuration to each of the solute enantiomers on the basis of the sense of nonequivalence[3] induced by chiral **1**. While the phenylcarbinol **1a** or the naphthylcarbinol **1b** have been used most frequently for the NMR determination of enantiomeric purity and absolute configuration, we have found that, for such determinations, the next higher analogue, 2,2,2-trifluoro-1-(9-anthryl)ethanol (**1c**), is superior to either **1a** or **1b** in several ways. Most importantly, **1c** has the ability to induce greater spectral nonequivalence between enantiomeric solutes than either **1a** or **1b** despite its modest solubility compared to **1a** and **1b**. While nonequivalence magnitudes depend upon the solute involved and the experimental conditions utilized, it is not uncommon to observe nonequivalence magnitudes of 0.1 ppm. In addition, fluoro alcohol **1c** is readily prepared and resolved and is conveniently handled. It is not sensitive toward moisture and can be easily recovered after use.

Solvation Models. Experience has shown that one fundamental solvation model accounts for the nonequivalence observed for the enantiomers of a variety of solute types. Both the hydroxyl and carbinyl hydrogen of **1** are capable of bonding interactions with basic sites, the former giving rise to the stronger interaction. A priori, one expects some chelatelike solvation of a lactone by **1** as shown in **2**. The stronger primary hydrogen bond is expected to occur between the hydroxyl of **1** and the carbonyl oxygen of the lactone, in view of the greater basicity of this oxygen compared to the ring oxygen.[5] Subsequent to this primary *intermolecular* interaction, the weaker carbinyl hydrogen bond,[6] being *intramolecular*, can effectively control conformer population so that **2** represents a major solution conformer. Substituents on either face of the lactone respond differently to the shielding effect of the aromatic substituent of **1**. For example, in the generalized drawings **3** and **4**, it will be seen that, in the absence of additional carbinol–lactone interactions, the only difference between the two diastereomeric solvates (to a first approximation) is that R_2 is cis to Ar in **3** but trans in **4**. The converse occurs for R_1. Consequently, the enantiomer incorporated into **3** will have its time averaged R_2 resonance upfield and its R_1 resonance downfield relative to the same signals of the other enantiomer.[7] Possible effects of dissimilar extents of solvation can be minimized through use of a severalfold excess of **1**.



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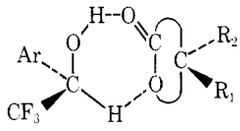

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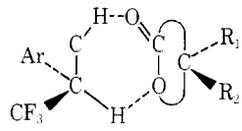

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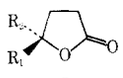
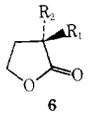
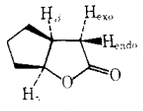
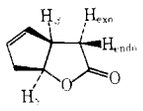
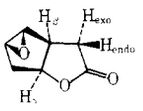
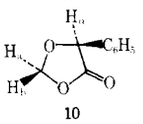
These expectations are born out by the data in Table I. All of the lactones in Table I exhibit nonequivalence for at least one set of enantiomeric protons in the presence of a severalfold excess of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**1c**). Enantiomeric purities could be accurately determined for all lactones except **6b** and **6c**, which exhibit partial overlap of enantiomeric resonances. Enantiomeric purities could, however, be estimated for these lactones.

The ring protons of type **5** and **6** lactones couple extensively and give rise to spectral patterns that complicate the interpretation of the induced nonequivalence. This problem, less severe when substituents simplify the ring pattern (as in **7**, **8**, and **9**), can often be avoided by observing the nonequivalence of nonring protons. Nonequivalence has been observed for protons separated from the chiral center by as many as four carbons (e.g., **6c**).

In each case, the protons that show perceptible nonequivalence exhibit nonequivalence senses consistent with the generalized solvation model **3**–**4**. When the major lactone enantiomer has the configuration depicted in Table I, (*R*)-(−)-**1c** causes R_1 (or H_{endo}) to show high-field nonequivalence. Conversely, R_2 (and H_{exo} and H_γ) show low-field nonequivalence. Except for **5c** and **5d**, the configurations of which we now assign, the absolute configurations of the lactones in Table I are known and have been used to establish the validity of the solvation model.

An additional aspect of the solvation model is that it can assist in making spectral assignments. For example, it was the low-field sense of nonequivalence observed for the high-field α proton of **9** that first suggested that this proton was H_{exo}. Close inspection of coupling constants confirmed this assignment. Similarly, the observation of a high-field sense of nonequivalence for the high-field α-proton resonances of **7** and **8** suggested that these resonances stemmed from endo hydrogens. Apparently the epoxide ring alters the magnetic environment of the α protons so as to change their relative positions[8] with respect to the other lactones. Dioxolanone **10**, derived[9] from (*S*)-(+)-enriched mandelic acid, also shows the utility of the solvation model in making spectral assignments. The NMR spectrum of **10** contains 1 H singlets at δ 5.04, 5.40, and 5.48. The first of these was shown to stem from the hy-

Table I

Lactone		Absolute configuration of major enantiomers R_1	R_2		Nonequivalence amt[b]/sense[3] R_1	R_2	[α]	Enantiomeric excess, %	Ref
 5	a	CH_3	H	(S)	2.0/high		−3.00 (neat)	9	21
	b	CH_3	CH_3CH_2	(R)	1.0/high	4.2/low[e]	+1.31 (c 21.8, $CHCl_3$)	11	22
	c	CH_3	$(CH_3)_2CH$	(S)	2.0/high	4.5 3.5/low[e]	+1.89 (c 28.5, $CHCl_3$)	21	a
	d	$C_6H_5CH_2$	CH_3	(R)	3.0/high	7.0/low	+1.17 (c 29.1, $CHCl_3$)	9	a
 6	a	CH_3CH_2	H	(R)	3.8/high		−7.65 (c 9.8, EtOH)	72	17
	b	$CH_3CH_2CH_2$	H	(R)	3.8/high		−8.05 (c 5.7, EtOH)	c	17
	c	$CH_3(CH_2)_3$	H	(R)	0.5/high		−7.31 (c 9.7, EtOH)	c	17
 7			H_{endo} 5.0/high		H_{exo} 3.0/low	H_γ 0.5/low		33[d]	18
 8			4.0/high		2.5/low	3.0/low		33[d]	21
 9			~0		1.2/low	7.0/low		33[d]	21
 10			H_b 0.9/high		H_a 3.1/low	H_α 5.0/low		14	9

[a] Absolute configuration assignments based on NMR model reported in this paper. [b] Hertz at 100 MHz. [c] Accurate values of enantiomeric composition not obtainable owing to partial overlap of enantiomeric resonances. [d] Determined by combining known amounts of each pure enantiomer. [e] Values for methyl resonances of R_2.

drogen α to the carbonyl by means of deuterium labeling. It is, however, difficult to determine which of the remaining two singlets arises from H_a and which from H_b. Addition of the shift reagent Eu(fod)$_3$ moves the H_α resonance downfield rapidly but has only a minor nondifferential effect on those of H_a and H_b. In the presence of a severalfold excess of (*R*)-(−)-**1c**, H_α shows the sense of nonequivalence expected on the basis of the solvation model. The sense of nonequivalence of the upfield geminal hydrogen is the same as that of H_α whereas that of the downfield geminal hydrogen is opposite. Hence, the upfield geminal hydrogen is presumed to be on the same face of the lactone ring as H_α and the assignment in Table I is made accordingly.

Comments on the limitations of the model are in order. Additional basic sites in a lactone (e.g., the epoxide ring in **9**) may interfere with "normal" solvation by chiral **1** as might additional modes of lactone–carbinol interaction. Since knowledge of lactone structure arms one for anticipation of possible "additional interactions", the model should be reliable for assignment of absolute configurations to lactones if intelligently applied.[7] While only γ-lactones are presently described, the model is expected to be applicable to lactones of other ring sizes.[7]

Synthesis, Resolution, and Configurational Assignment of Fluoro Alcohol 1c. Borohydride reduction of trifluoromethyl 9-anthryl ketone (**11**), obtained by high-temperature trifluoroacetylation of anthracene with trifluoroacetic anhydride, yields racemic **1c**. This alcohol is readily resolved via the chromatographic procedure developed[10a] for fluoro alcohol **1b**. For those lacking the automated multigram HPLC system[10b] that makes this resolution routine, we suggest the asymmetric synthesis of (*R*)-(−)-**1c** from **11** using a reagent prepared by Meyers[11] from lithium aluminum hydride and the commercially available (4*S*,5*S*)-(−)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline.[12] While the fluoro alcohol typically obtained by this procedure possesses an optical purity of only 50%, we find that partially resolved **1c** is easily crystallized to enantiomeric purity and that the overall yield of enantiomerically pure (*R*)-(−)-**3** from this acetylation–reduction–crystallization sequence is ca. 25–30%. Even so, the chromatographic resolution of **1c** is more efficient, affording both enantiomers in higher yields.

Resolved fluoro alcohol **1c** is a thermally stable, off-white crystalline solid, stable to dilute acids and bases. If given routine protection from light and oxygen, this fluoro alcohol possesses excellent shelf life. As a consequence of its stability, it can be recovered after use by chromatography on silical gel and/or recrystallization from petroleum ether.

In the presence of (*R*)-(+)-1-(1-naphthyl)ethylamine, the ^1H and ^{19}F NMR spectra of (*S*)-(+)-enriched **1a**,[13] (*S*)-(+)-enriched **1b**,[10,14] and (+)-enriched **1c** show anisochronous resonances for the enantiomeric carbinyl hydrogens and trifluoromethyl groups. Since the three fluoro alcohols show the same senses of nonequivalence, it follows that all are of the same [i.e., (*S*)-(+)] absolute configuration.[14]

When the (+) enantiomers of fluoro alcohols **1a–c** are used as chiral solvating agents for partially resolved solutes such as methyl ethyl sulfoxide,[15,4d] α-methylbenzyl alcohol, α-methylbenzylamine,[4a] or methyl alaninate,[4b] all three induce the same senses of nonequivalence in the NMR spectra of the enantiomeric solutes. Again, this indicates that all three fluoro alcohols have the same absolute configuration, (*S*)-(+).

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. NMR spectra were obtained with Varian Associates A-60A or HA-100 spectrometers. Infrared spectra were obtained with a Beckman IR-12. Optical rotations were determined in a Zeiss visual polarimeter using a 1.0-dm tube. Mass spectra were obtained with a Varian MAT CH-5 instrument. Microanalyses were performed by J. Nemeth and Associates, University of Illinois. For nonequivalence measurements, spectra were determined at 100 MHz and 27 °C using carbon tetrachloride solutions 0.2 M in lactone and 0.6 M in **1c**. Lowering the carbinol: lactone molar ratio or the use of $CDCl_3$ as solvent lessens the nonequivalence, sometimes helpful in reducing signal overlap.

Trifluoromethyl 9-Anthryl Ketone (11). A thick-walled glass tube (or stainless steel bomb) was charged with anthracene (17.8 g, 0.10 mol), trifluoroacetic anhydride (22.0 g, 0.105 mol), and benzene (75 ml), sealed, heated at 200 °C for 15 h, cooled to room temperature, and cautiously opened. The dark reaction mixture was poured onto a column of silica gel (100 g) and eluted with pentane (ca. 1.5 l.). The reddish-orange eluent was concentrated and rechromatographed on silica gel (100 g). Elution with pentane gave a small amount of anthracene followed closely by a long, yellow band of ketone, crude yield 20 g (73%). Recrystallization from methanol gave bright yellow granules: mp 81–84 °C; IR (Nujol) 1750 (C=O), 1200 and 1150 cm^{-1} (CF_3); NMR (CCl_4) δ 7.23–7.95 (m, 8 ArH) and 8.43 (broad, 1 H, ArH at position 10); mass spectrum (70 eV) *m/e* (rel intensity) 274 (M^+, 77.2), 205 (100.0), 177 (79.6), and 176 (44.7).

Anal. Calcd for $C_{16}H_9F_3O$: C, 70.08; H, 3.31; F, 20.78. Found: C, 69.85; H, 3.37; F, 20.42.

2,2,2-Trifluloro-1-(9-anthryl)ethanol (1c). Portionwise addition of excess sodium borohydride (0.25 g, 6.5 mmol) to a stirred methanol solution of **11** (1.5 g, 5.5 mmol) followed by partition between water and methylene chloride and evaporation of the dried (anhydrous $MgSO_4$) organic layer afforded racemic **1c** (1.5 g, 99%): mp 140–142 °C (MeOH–H_2O, 3:1 v/v); NMR (CCl_4) δ 3.42 (d, 1 H, exchangeable OH, J = 5.2 Hz), 6.28 (d of q, 1 H, J_d = 5.2, J_q = 8.0 Hz), 7.15–7.45 (m, 4), 7.62–7.85 (m, 2), 7.6–9.1 (m, very broad, 2, peri H) and 8.20 (s, 1, ArH at position 10); mass spectrum (70 eV) *m/e* (rel intensity) 276 (M^+, 76.5), 207 (100.0), 179 (86.6), and 178 (73.8).

Anal. Calcd for $C_{16}H_{11}F_3O$: C, 69.56; H, 4.01. Found: C, 69.61; H, 3.91.

Racemic **1c** was resolved by the method of Pirkle and Hoekstra.[10a] Treatment of the high R_f diastereomer with excess methoxide ion in methanol liberated the (+) fluoro alcohol enantiomer which was then chromatographed on silica gel (pentane–benzene, 1:1 v/v) affording (+)-**1c**, mp 142–145 °C, $[\alpha]^{26}D$ 27.2 ± 1.1° (*c* 6.25, $CHCl_3$).

Asymmetric Reduction of Trifluoromethyl 9-Anthryl Ketone. The procedure of Meyers and Kendall[11] was followed with minor modifications. Thus, in a typical run, a 1-l., three-necked, round-bottom flask fitted with a mechanical stirrer, nitrogen inlet, and low-temperature thermometer and charged with tetrahydrofuran (375 ml), diethyl ether (375 ml), and lithium aluminum hydride (2.4 g, 0.063 mol) was cooled to ca. −20 °C in a well-insulated liquid nitrogen–pentane slush bath. To the stirred reaction mixture was then added solid (4*S*,5*S*)-(−)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline (28.0 g, 0.137 mol) as rapidly as convenient. After a few minutes the reaction mixture was cooled to −75 °C, ketone **11** added (8.2 g, 0.030 mol), and the reaction allowed to warm to −65 °C. After stirring for 3 h at −65 °C, the reaction mixture was allowed to warm to −40 °C and hydrolyzed with aqueous ammonium chloride. The organic layer was collected, washed with water, and extracted with 0.4 N hydrochloric acid (3 × 100 ml) to recover the oxazoline. After separation, the acid layer was promptly poured over NaOH pellets and the oxazoline extracted into ether (2 × 200 ml). After drying, concentration of the ethereal solution followed by cooling to −70 °C afforded recovered crystalline oxazoline, 12.8 g (46%), $[\alpha]^{23}D$ −124.5° (*c* 10.0, $CHCl_3$).

The original organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated to afford fluoro alcohol **1c** as a yellow oil, 5.5 g (67%), $[\alpha]^{23}D$ −13.8° (*c* 6.0, $CHCl_3$) (51% e.e.) after purification by chromatography on silica gel.

Optical Purification of Partially Enriched (−)-1c. A solution of partially resolved (−)-**1c** (11.0 g, ca. 50% e.e.) in high-boiling petroleum ether (700 ml) was concentrated to 500 ml and held at 55 °C. After 12 h, small yellow crystals of essentially racemic alcohol (4.1 g, $[\alpha]^{24}D$ −1.3 ± 1.0°, corresponding to an approximate optical purity of 5%) were collected. In this particular experiment, 2.1 g of large, off-white crystals of enantiomerically enriched alcohol were also collected and quickly separated by hand. Enantiomerically enriched alcohol does not always crystallize at this stage. The mother liquors, concentrated to 300 ml by boiling, deposited a second crop of off-white crystals (1.4 g) upon slow cooling to room temperature. Cooling to 0 °C yielded yet another crop of white crystals that, when combined with crops one and two, amounted to 4.5 g of (−)-**1c** having $[\alpha]^{23}D$ −23.3 ± 1.0° (*c* 6.0, $CHCl_3$) corresponding to an optical purity of 86%. Subsequent recrystallization of this material afforded optically pure (−)-**1c**, mp 130.5–133 °C.

Enantiomerically Enriched Lactones. Samples of type **6** lactones were generously provided by Meyers and co-workers[17] and lactones **7, 8,** and **9** were kindly provided by Partridge and co-workers.[18] Type **5** lactones were obtained as described below.

Asymmetric Synthesis of γ-Valerolactone (5a). Ethyl levulinate (5.05 g, 0.035 mol) was reduced by addition to a stirred solution of diisopinocampheylborane[19] [0.05 mol from (−)-α-pinene] in 50 ml of diglyme at 0 °C. Cooling and stirring were maintained for 18 h followed by the addition of 35 ml of 2.5 M NaOH and 16 ml of 30% H_2O_2 and heating to 50 °C for 2 h. The cooled solution was extracted with diethyl ether (3 × 40 ml), acidified with 3 M hydrochloric acid, and the lactone extracted into diethyl ether (5 × 40 ml). After concentration the enantiomerically enriched lactone was purified by preparative GLC (0.375 in. × 25 ft, 5% Carbowax 20M on 60/80 Chromosorb G, 135 °C): NMR (CCl_4) δ 4.56 (m, 1, γ-H), 2.4 (m, 3, α- and β-H), 1.83 (m, 1, α-H), 1.38 (d, 3, J = 6.0 Hz, CH_3).

Asymmetric Synthesis of γ,γ-Dialkyl-γ-butyrolactones (5b–d). Enriched samples of **5b–d** were obtained by the method of Reid and Turner[20] via the low-temperature reaction of Grignard reagents with (−)-menthyl levulinate followed by lactonization. A typical procedure follows. A solution of 5.0 g (19.7 mmol) of (−)-menthyl levulinate in 50 ml of anhydrous ether was cooled to −78 °C. The Grignard reagent (24 mol) in ether (2–3 M) was added dropwise with stirring over a 30-min period. The stirred solution was allowed to warm to −20 °C over 4 h and held at −20 °C for 12 h. The solution was then warmed to 0 °C, 50 ml of Et_2O added, and the solution extracted with dilute H_2SO_4 (3 × 30 ml, 1.5 M). The ether was evaporated and the hydroxy ester hydrolyzed by addition of 50 ml of 3 M NaOH and 40 ml of ethanol with heating to reflux for 2 h. The EtOH was removed by distillation and the aqueous solution washed with CH_2Cl_2 (3 × 30 ml) to remove menthol. Acidification with dilute H_2SO_4 and extraction with CH_2Cl_2 (4 × 30 ml) afforded the hydroxy acid which was lactonized by the azeotropic removal of water with benzene (80 ml). The concentrated lactone solution was diluted with CH_2Cl_2 (80 ml) and washed with 10% $NaHCO_3$ (2 × 10 ml). The dried ($MgSO_4$) CH_2Cl_2 solution was concentrated in vacuo to yield the lactone (40–60%).

Proton Assignments of 5b–d (CCl_4). 5b: δ 2.47 (m, 2, β-H), 2.05 (m, 2, α-H), 1.68 (q, 2, J = 7.5 Hz, CH_2CH_3), 1.36 (s, 3, CH_3CO), 0.98 (t, 3, J = 7.5 Hz, CH_2CH_3). **5c:** δ 2.47 (m, 2, β-H), 1.92 (m, 3, α-H and CH_3CHCH_3), 1.28 (s, 3, CH_3), 1.00 (d, 3, J = 6.5 Hz, CH_3), 0.93 (d, 3, J = 6.5 Hz, CH_3). **5d:** δ 7.17 (m, 5, aromatic), 2.87 (q, 2, J = 14 Hz, benzyl), 2.4–1.7 (m, 4, α-H and β-H), 1.17 (s, 3, CH_3).

Proton Assignments of 7, 8, and 9 (CCl_4). Assignments and coupling constants were sometimes ascertained in separate experiments using $Eu(fod)_3$. **7:** δ 4.87 (m, 1, γ-H), 2.8 (m, 1, β-H), 2.68 (d of d, 1, J_{gem} = 15 Hz, J_{vic} = 10 Hz, H_{exo}), 2.12 (d, 1, J_{gem} = 15 Hz, H_{endo}), 2.2–1.4 (m, 6, $-CH_2CH_2CH_2-$). **8:** δ 5.76 (m, 1, −CH=), 5.54 (m, 1, −CH=), 5.00 (m, 1, γ-H), 3.45 (m, 1, β-H), 2.68 (m, 2, $-CH_2CH=CH-$), 2.63 (d of d, 1, J_{gem} = 17.5, J_{vic} = 9.5 Hz, H_{exo}), 2.25 (d of d, 1, J_{gem} = 17.5, J_{vic} = 2.0 Hz, H_{endo}). **9:** δ 4.90 (m, 1, γ-H), 3.54 (m, 2, epoxide ring), 2.92 (m, 1, β-H), 2.60 (m, 2, CH_2CO), 2.47 (d, 1, J_{gem} = 16 Hz, H_{endo}), 2.07 (d of d of d, 1, J_{gem} = 16, J_{vic} = 7.0, J_{HCCCH} = 1.5 Hz, H_{exo}).

Enantiomerically Enriched 5-Phenyl-1,3-dioxolan-4-one (10). A mixture of 2.7 g (17.7 mmol) of (*S*)-(+)-mandelic acid, 6.4 g (42.1 mmol) of racemic mandelic acid, 6.0 g (74.5 mmol) of chloromethyl methyl ether, 9.8 g (150 mmol) of mossy zinc, and 150 ml of diethyl ether was stirred for 7 h, allowed to stand overnight, and washed with water and 10% aqueous $NaHCO_3$. After a final water wash, the organic layer was dried and the ether removed in vacuo, affording crude **10** (4.4 g, 48%), bp 105 °C (0.4 mmHg) [lit.[9] 143 °C (17 mmHg)], which was purified by two recrystallizations from hexane at −20 °C (liquefies on warming to room temperature). The NMR sample studied was a mixture of approximately equal amounts of enriched and racemic dioxolanone having $[\alpha]^{24}D$ 3.6 ± 0.4° (*c* 10.4, CCl_4), 14 ± 3% optically pure by the NMR method.

In a similar manner, mandelic acid-d_1, obtained via the sodium borodeuteride reduction of benzoylformic acid in dilute Na_2CO_3, afforded 5-phenyl-1,3-dioxolan-4-one-*5-d:* NMR (CCl_4) δ 5.40 (s, 1), 5.48 (s, 1), 7.37 (s, 5).

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Registry No.—(±)-**1c**, 60686-64-8; (+)-**1c**, 60646-30-2; (−)-**1c**, 53531-34-3; **5a**, 19041-15-7; **5b**, 60686-65-9; **5c**, 60646-31-3; **5d**, 60646-32-4; **7**, 43119-29-5; **8**, 43119-28-4; **9**, 59829-44-6; **10**, 60646-33-5; **11**, 784-04-3; anthracene, 120-12-7; trifluoroacetic anhydride, 407-25-0; (4*S*,5*S*)-(−)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline, 51594-33-3; ethyl levulinate, 539-88-8; diisopinocampheylborane, 1091-56-1; (*S*)-(+)-mandelic acid, 17199-29-0; chloromethyl methyl ether, 107-30-2; mandelic acid-d_1, 60646-34-6; 5-phenyl-1,3-dioxolan-4-one-5-*d*, 60646-35-7.

References and Notes

(1) (a) The assignment of absolute configuration of γ-lactones has met with some success by the use of circular dichroism (CD).[1b] Beecham[1c] found a relationship between the sign of the n–π* absorption band and the configuration about the α-carbon atom for a series of γ-lactones. The magnitude and sign of the CD appeared to be independent of ring substitution in other positions. Kuriyama[1d] noted a correlation between chirality at the γ-carbon atom of some α,β-unsaturated γ-lactones and the sign of the π–π* Cotton effect. (b) For a brief review see A. F. Beecham, *Tetrahedron Lett.*, 3591 (1968). (c) A. F. Beecham, *ibid.*, 2355 (1968). (d) I. Uchida and K. Kuriyama, *ibid.*, 3761 (1974).

(2) The use of an NMR method giving distinguishable enantiomeric resonances has other inherent advantages over polarimetric methods for determination of enantiomeric composition. For example, for compounds of low specific rotation, typical of lactones of type **5** and **6**, small amounts of optically active impurities can cause errors in polarimetrically determined optical purities with misleading consequences. [For an example see T. Hiyama, T. Mishima, H. Sawada, and H. Nozaki, *J. Am. Chem. Soc.*, **98**, 641 (1976)].

(3) *Sense of nonequivalence* is defined as the field position of a particular signal of the major enantiomer relative to that of the minor enantiomer and is referred to as high field or low field.

(4) Models of the carbinol–substrate interaction causing this nonequivalence have been proposed for (a) aromatic amines, W. H. Pirkle, T. G. Burlingame, and S. D. Beare, *Tetrahedron Lett.*, 5849 (1968); (b) amino esters, W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **91**, 5150 (1969); (c) aryl amine oxides, W. H. Pirkle, R. L. Muntz, and I. C. Paul, *ibid.*, **93**, 2817 (1971); (d) sulfoxides, W. H. Pirkle, S. D. Beare, and R. L. Muntz, *Tetrahedron Lett.*, 2295 (1974); and (e) sulfinates, W. H. Pirkle and M. S. Hoekstra, *J. Am. Chem. Soc.*, **98**, 1832 (1976).

(5) (a) Electron densities at the carbonyl and ring oxygens of **5a** have been calculated[5b] to be 1.482 and 0.893, respectively. Infrared evidence of hydrogen bonding of adenine, uracil derivatives, and *N*-methylacetamide to some γ-lactones at the carbonyl oxygen has been presented.[5c] Furthermore, we find that addition of the shift reagent Eu(fod)$_3$ to carbon tetrachloride solutions of **7** or **8** induces much greater chemical shifts for the protons on the α carbons than for those in the γ position. This indicates coordination of the Eu(fod)$_3$ to the carbonyl oxygen. (b) H. G. Raubenheimer and D. H. DeKock, *J. S. Afr. Chem. Inst.*, **25**, 70 (1972). (c) *ibid.*, **25**, 321 (1972).

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(7) It should be recognized that these chemical shift generalizations are possible for γ-lactones since the latter are relatively planar. These generalizations may not hold for relatively nonplanar lactones even though the fundamental postulates of the model are sound. In such instances, lactone conformation must be considered when determining the relationship between stereochemistry and chemical shift pertubation.

(8) Pertinent NMR studies of the effects of epoxide rings on the chemical shifts of neighboring protons include K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Lett.*, 559 (1964); K. Tori and T. Komeno, *ibid.*, 1157 (1974); D. R. Paulson, F. Y. N. Tang, G. F. Moran, A. S. Murray, B. P. Pelka, and E. M. Vasquez, *J. Org. Chem.*, **40**, 184 (1975); S. G. Davies and G. H. Witham, *J. Chem. Soc., Perkin Trans. 2*, 861 (1975).

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The Facile, Regiospecific Protonation of Alkenes. A Model System

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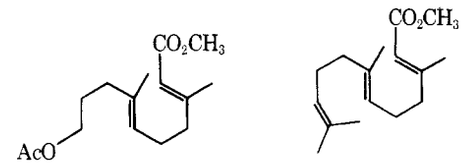
The protonation of olefins generally is accomplished only by relatively strong acids; in contrast, the enzymic protonation of a double bond presumably takes place under much milder conditions. Toward understanding of the mechanisms by which the latter can occur, it is of interest to examine chemical systems in which unusually facile double bond protonation takes place. We report herein such an example which we have uncovered.

To investigate the stability of *E*-α,β-unsaturated methyl esters with respect to double bond isomerization in acidic media,[2] **1** and **2** were treated with 85% phosphoric acid at room

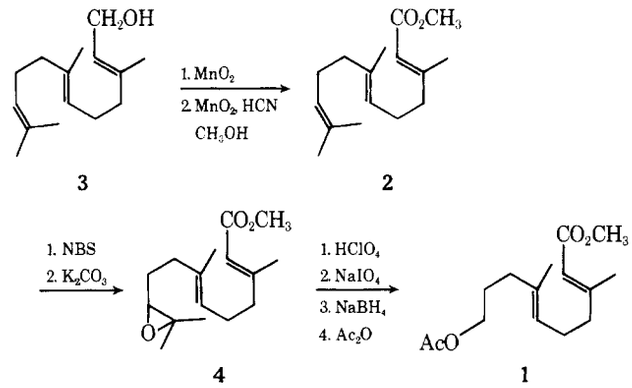


1 **2**

temperature. In contrast to compound **2**, which was recovered unchanged after 30 min, compound **1** underwent rapid and complete transformation. For this study, *E,E*-**1** was prepared stereospecifically, as described below.

Utilizing active MnO_2 as the oxidant, transformation of (*E,E*)-farnesol (**3**) into **2** was accomplished via the corresponding aldehyde following the two-step procedure developed by Corey.[3] Silica gel chromatography afforded the analytically pure methyl ester with >98% isomeric purity. The ester **2** was then selectively epoxidized to give the known epoxy ester **4** using van Tamelen's NBS reaction, followed by treatment with base.[4] Epoxide **4** was transformed into the desired acetoxy ester **1** by standard means as outlined in Scheme I.

Scheme I



Dissolution of compound **1** for 15 min in 85% phosphoric acid at room temperature resulted in the formation of three major products, as determined by TLC (R_f 0.41, 0.36, 0.04; 5% ethyl acetate in benzene). Separation of these by silica gel chromatography and spectroscopic characterization showed them to be the cyclized epimers **5** and **6** and the acyclic, tertiary alcohol **7** (yields of 45% for **5** and **6** and 38% for **7**). The structural assignments were made on the basis of spectrometric properties. Thus, the NMR spectra of **5** and **6** each show an unsplit methyl at 0.88 ppm, a broadened, vinylic