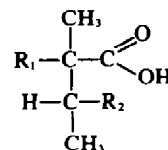


Table 1. Properties of the investigated acids



Compound	R ₁	R ₂	Source	Method of resolution	[α] _D ²⁵ exp.	[α] _D ²⁵ lit.	Optical purity by NMR ^a (%)	Absolute configuration	[α] _D ²⁵ corrected to 100% optical purity
1	H	H	KMnO ₄ oxidation of S ⁺ (-)-2-methyl-1-butanol		+ 18.9°	+ 19.8° (ref. 5)	100	S(+) (ref. 6)	+ 18.9°
2	H	OCH ₃	Dr K. Maskens Oxford ⁷	Quinine ETOH ⁷	+ 17.5° (ref. 7)		100	2S, 3R(+) (ref. 8)	+ 17.5°
3	OH	H	EGA	Brucine ETOH	- 3.4°	+ 3.75° (ref. 9)	not measurable	R(-) (ref. 10)	- 3.75°
4	OCH ₃	H	Synthesis ¹¹	Brucine acetone	- 7.3°		54	R(-) ^b	- 13.5°
5	n-C ₆ H ₅	H	Fluka	Brucine acetone	+ 1.52°	+ 1.23° (ref. 12)	30	S(+) ^c	+ 5.0°

^a Defined as (moles of 1 form - moles of d form) / (moles of 1 form + moles of d form) (ref. 13).

^b Established by NMR methods and correlation with (3), see this paper.

^c Established by comparison with 2-ethyl-2-methyleicosanoic acid¹⁴.

OPTICALLY ACTIVE 2-METHYL SUBSTITUTED ACIDS AND ESTERS: CHIROPTICAL PROPERTIES, CONFORMATIONAL EQUILIBRIA AND NMR WITH OPTICALLY ACTIVE SHIFT REAGENTS

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Abstract—CD spectra at 25° and -185° and in various solvents are reported for 5 2-methyl substituted carboxylic acids i.e.:

(R)-2-methylbutanoic acid
(R)-2-hydroxy-2-methylbutanoic acid
(R)-2-methoxy-2-methylbutanoic acid
(R)-2-ethyl-2-methylbutanoic acid
(2R, 3S)-3-methoxy-2-methylbutanoic acid.

The chiroptical properties are interpreted on the basis of reasonable assumptions about the rotamer populations and may be correlated with an empirical rule correlating the sign of the $n \rightarrow \pi^*$ CD band of the carboxylic acid group and the spatial configuration around this group.

NMR measurements on mixtures of the methyl esters and optically active shift reagents are described and use is made of these data to determine the optical purity.

INTRODUCTION

The chiroptical properties of carboxylic acids and esters have been studied extensively.¹ For simple acyclic carboxylic acids, the interpretation presents difficulties because of the well-established occurrence of conformational equilibria.² Nevertheless, investigations of the CD bands of the $n \rightarrow \pi^*$ transition of the carboxyl group in 2-hydroxy acids and some 2-alkyl acids on the one hand³ and a series of 2-halo acids⁴ on the other have resulted in identical empirical rules for the correlation of absolute configuration with the sign of ellipticity.

Rules of this kind are based on assumptions about the rotamer populations. Information about these conformational equilibria is still far from complete, so there always exists the danger of wrong conclusions resulting in incorrect empirical rules. Detailed knowledge of the chiroptical properties as a function of solvent and temperature is one of the ways to increase our knowledge of the rotamer equilibria in simple acyclic carboxylic acids. Moreover, a larger number of data increases the chance of correct empirical rules being established.

Therefore, in this paper a discussion is given of the chiroptical properties of some 2-methyl substituted carboxylic acids (Table 1):

(R)-2-methylbutanoic acid (1)

(2R, 3S)-3-methoxy-2-methylbutanoic acid (2)
(R)-2-hydroxy-2-methylbutanoic acid (3)
(R)-2-methoxy-2-methylbutanoic acid (4)
(R)-2-ethyl-2-methylhexanoic acid (5)

In order to test the published rules, the absolute configuration of the acids should be known unequivocally. For the determination of the absolute configuration of 3 (unknown in optically active form), NMR methods using optically active shift reagents were used. Subsequently, these methods were also used for the other acids studied for two reasons:

(1) to determine the applicability of these methods for the determination of the absolute configuration and to investigate the influence of structure.

(2) to determine the optical purity. This is most conveniently deduced from the NMR spectrum of one of the methyl esters using a chiral solvent¹⁵ or a chiral complexing reagent.¹⁶ The usefulness of these chiral reagents was greatly increased by the introduction of both a paramagnetic ion and a group that increases the Lewis acid character of the reagent.¹⁷ Because of the scarcity of data which define the scope of application of these reagents¹⁸ we measured their actions on the series of 2-methyl substituted acids described in this paper.

The chiroptical properties of **1** have been discussed previously in ethanol¹⁵ and in various other solvents together with a discussion of possible rotamers.³

To investigate the influence of a change from carboxyl to carboxy-methyl, CD data were also collected for the methyl esters.

RESULTS

The CD results on the $n \rightarrow \pi^*$ transition of the carboxyl group of the acids and esters are tabulated in Table 2.

The shift reagent Eu-optishift I* induces shifts that are roughly half as large for the investigated 2-methyl esters as those induced by Eu-optishift II.* This is in agreement with the stronger Lewis acid character of II.¹⁷

Induced shifts were useless for compound **3** due to line broadening.

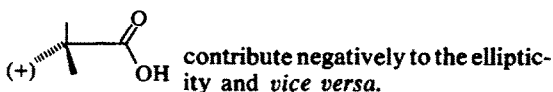
Table 3 summarizes the low field shifts ($\Delta\delta$) induced by shift reagent II and the enantiomeric differences of these shifts ($\Delta\Delta\delta$).

DISCUSSION

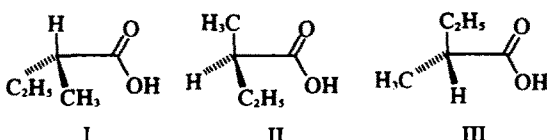
CD and conformation

Acyclic carbonyl compounds have been found to have a threefold barrier to rotation around the $C_\alpha-C_\beta$ bond, one of the three groups attached to the α -C atom being in an eclipsed position with respect to the carbonyl oxygen.²⁰ In this paper these three eclipsed conformations will also be the starting point of our discussions of the carboxylic acids, as has been done before.^{3,4,21} It must be realized, however, that such a line of reasoning constitutes a simplification particularly because exactly eclipsed conformations will probably not occur. This may have consequences for the chiroptical properties especially in those cases where the three groups on the β -carbon atom are very similar as in **5**. Our knowledge of the conformations in these simple molecules is not sufficient to include these details in the discussion.

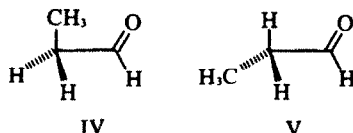
The data on the individual compounds are discussed below on the basis of reasonable assumptions about the conformations and in relation with an empirical rule. This rule^{3,4} states that substituents projecting to the viewer in



2-Methylbutanoic acid (1). Three conformations play a role in 1:



For propionaldehyde it has been found that the most favourable conformation is the one where methyl and carbonyl group are eclipsed:³



the preference of IV over V is 3349 J/mol. Replacing the Me group by an Et group decreases this preference to 2930 J/mol.

If the aldehydic proton is replaced by a larger atom or group, V is even more destabilized with respect to IV because of non-bonded interactions between the Me group and this new group. Quantitative data about this influence are not available.

Returning now to **1**, it is clear that II and III will be more favourable than I in two respects:

- (1) the carbonyl group is eclipsed with an alkyl group;
- (2) non-bonded interactions between alkyl groups and hydroxyl groups are minimized.

On the basis of the above-mentioned facts, it is not easy to make predictions about the relative stabilities of II and III. Listowsky³ assumes that II is slightly preferred over III, but it is not clear what the basis of this assumption is.

The CD shows a sign inversion from negative to positive and a 7-fold increase in ellipticity upon cooling to -185° , indicating a change in the conformational equilibrium.

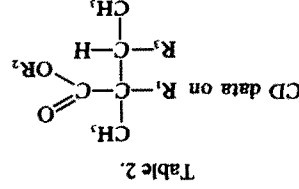
On the basis of the empirical rule, I and III should exhibit positive ellipticity and II negative ellipticity. The CD spectrum should then arise from a mixture of II and III at room temperature and mainly III at -185° . This implies that III is more stable than II (in contrast with Listowsky's assumption), apparently because the gain in energy by the eclipsed position of the methyl in II is overcompensated by the loss in energy resulting from the non-bonded interaction between Et and OH groups.

The results for the methyl ester show similar trends. However, the intensities are lower.

3-Methoxy-2-methylbutanoic acid (2). The importance of substituents for the chiroptical properties clearly shows up by inspection of the chiroptical properties of 3-methoxy-2-methylbutanoic acid.[†] For the (2R, 3S) compound **2** the

*Abbreviations are explained in the experimental section.

†This acid was kindly supplied by Dr K. Maskens, Oxford Polytechnic, whose results⁷ indicate that the absolute configuration is (+) 2S, 3R. The CD data presented here are for the enantiomer.



Compound	R_1	R_2	R_3	λ (nm)	$\Delta\epsilon$	EPA 25°	EPA - 185°	Hexane	Dioxan	Methanol
1	H	H	H	212	-0.061	215	+0.416			
2	H	H	H	215	-0.022	215	+0.144			
	H	H	OCH ₃	213	-0.056	213	-2.24			
	H	OCH ₃		212	-0.200	212	-2.44			
3	OH	H	H	211	-0.101	214	+0.114		210	-0.036
	OH	CH ₃	OCH ₃	212	-0.200	212	-2.44		210	-0.036
	OH	H	H	240	+0.013	240			240	
	OH	CH ₃	H	210	-0.077	218	+0.126			
4	OCH ₃	H	H	222	-0.166	225	-0.100	223		
	OCH ₃	CH ₃	H	222	-0.166	225	+0.126	-0.143		
	OCH ₃	CH ₃	CH ₃	218	-0.185	221	-0.081			
5	n-C ₄ H ₉	n-C ₄ H ₉	H	221	-0.03	221	+0.153			
	n-C ₄ H ₉	CH ₃	H	220	+0.105					

All data are corrected to 100% optical purity.

All data apply to the 2 R(-) enantiomers.

Low temperature data have been corrected for shrinkage of the solvent.

Table 3. Low field shifts ($\Delta\delta$) and enantiomeric chemical shift differences ($\Delta\Delta\delta$) for the methyl esters of 2-methyl substituted carboxylic acids in CDCl_3 with Eu-optishift II

Acid	Group	δ	$\Delta\delta^a$	$\Delta\Delta\delta^b$
1	COOCH_3	3.70	4.45	0.01 ^c
	$\alpha\text{-CH}_3$	1.11 ($J = 7.0$) ^d	3.26 (S)	
			3.35 (R)	0.09
	$\alpha\text{-H}$	2.3	6.05	
2	t-CH_3^e	0.89 ($J = 7.0$)	2.05	0.02 ^c
	COOCH_3	3.68	1.90	
	OCH_3	3.32	2.87 (2R, 3S)	1.00
			2.97 (2S, 3R)	
	$\beta\text{-H}$	3.50	4.62	
	$\alpha\text{-H}$	2.57	6.08	
	$\alpha\text{-CH}_3$	1.19 ($J = 7.0$)	2.81	
	t-CH_3	1.17 ($J = 6.3$)	3.48	
4	COOCH_3	3.76	1.80 (R)	0.35
			2.15 (S)	
	OCH_3	3.30	9.76 (S)	
			10.80 (R)	-1.04
	CH_2	1.80	7.8	
			10.0	(2.2)
	$\alpha\text{-CH}_3$	1.42	6.84 (S)	
			7.34 (R)	-0.50
	t-CH_3	0.90	6.46 (R)	
			6.86 (S)	0.40
5	COOCH_3	3.70	2.06	0.007 ^c
	$\alpha\text{-CH}_3$	1.12	1.70	
			1.875	0.005
	$\text{C}_2\text{H}_5\text{-CH}_3$	0.90	1.156 (S)	
			1.168 (R)	0.012
	t-CH_3	0.86	0.1706 (R)	
			0.1715 (S)	-0.009

^a Induced shifts $\Delta\delta$ were calculated for molar ratios 1:1, assuming a linear concentration dependence and are always down field.

^b $\Delta\Delta\delta$ is arbitrarily taken to be negative if $\Delta\delta$ is larger for (R) than (S) isomer signal.

^c Line width increase at half maximum peak height, in ppm.

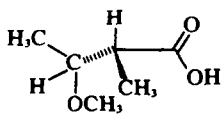
^d Coupling constants were not affected by association with Eu-optishift II.

^e t-CH_3 means terminal methyl group.

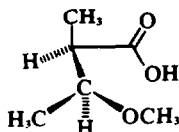
^f Due to overlap no $\Delta\Delta\delta$ value could be determined.

room temperature data are not significantly different from those of 1. However, lowering of the temperature does not give a sign inversion, but produces an increase in negative ellipticity by a factor of 10. Consideration of the three rotamers and application of the empirical rule predicts for VI and VIII positive CD bands and for VII

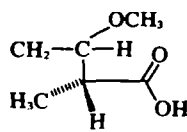
OME and the OH of the carboxyl group. The other most probable contributor is VI, where a similar H-bond is possible. VIII probably is destabilized with respect to III because of the size of the group that replaces the ethyl group of 1. The ester shows comparable results, although the room temperature intensity is much more negative than for the acid.



VI



VII

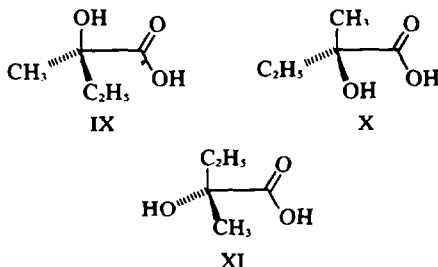


VIII

a negative one. This implies that VII is the most stable conformation, probably the stability is increased by an intramolecular H bond between the

This may reflect destabilization of VI with respect to VII because the intramolecular hydrogen bond is not longer possible in the ester.

2 - Hydroxy - 2 - methylbutanoic acid (3). For the 2-hydroxy acid (3) the following three rotamers may be involved:



The CD spectrum at room temperature shows two CD bands (at 211 and 240 nm), a feature that is generally seen in 2-hydroxy acids.²² The two bands are interpreted as belonging to different rotamers, one of them generally being ascribed to a rotamer like IX, where a possibility for intramolecular hydrogen bonding from the 2-hydroxyl to the carbonyl group exists.

IR evidence²³ indicates that in 3 at concentrations of 10^{-3} mol/l in CCl₄ (comparable with our measurements in concentration) an appreciable amount of intramolecular H-bonding occurs. CD measurements in an apolar solvent (hexane) are impossible for solubility reasons, but changing the solvent from dioxan, via EPA to methanol produces a gradual increase in intensity of the 240 nm band and a decrease of the band at 210 nm. This may be rationalized as follows: In a polar hydroxylic solvent, the amount of intermolecular hydrogen bonding with the solvent increases, thereby destabilizing rotamer IX relative to X and XI. This implies that the 210 nm band should be ascribed to rotamer IX, the positive band at 240 nm to X and/or XI. The assignment of the low wavelength band to IX is in agreement with the fact that hypsochromic shifts in the electronic spectrum are well known to occur, if the chromophore acts as acceptor for the hydrogen bond.²⁴

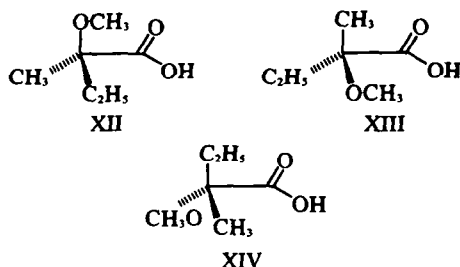
The disappearance of the negative 210 nm band in EPA at -185° would then imply that in EPA intermolecularly H-bonded rotamers i.e. solvated X and XI are more stable than the intramolecularly H-bonded rotamer IX.

On the basis of the empirical rule, we would indeed expect a negative ellipticity for IX and a positive one for XI. X is a more difficult case because it is not *a priori* clear whether the ethyl or the hydroxyl group predominates in determining the sign of the ellipticity.

The methyl ester shows only one negative band at 210 nm, which changes sign upon cooling to -185° . The occurrence of only one band may be incidental and arise from a negligible difference in wavelength of absorption between the ester rotamers.

2-Methoxy-2-methylbutanoic acid (4). Compound 4 has not been described in optically active form. The determination of its absolute configuration was carried out in the following way. Treatment of 3 with Ag₂O in methyl iodide gives a mixture of the methyl esters of 3 and 4 that is difficult to separate. NMR with optishift II and comparison of the NMR spectra of the so formed product and the synthesized 4 (Table 1) allows one to deduce the absolute configuration of 4, making the reasonable assumption that the absolute configuration of 3 is not changed during the methylation procedure.

The following three rotamers are taken into account:

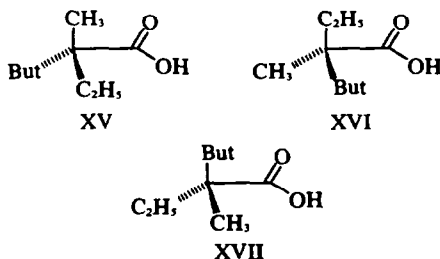


The two-band spectrum of the 2-hydroxy acid 3 disappears when the OH group is methylated to the OMe group in 4. This is in contrast with Listowskys experimental data. He finds two bands also in 2-alkoxy acids. However, his examples possess an α -H-atom. In 4, there is an important solvent effect (from $\Delta\epsilon = -0.048$ in methanol to $\Delta\epsilon = -0.143$ in hexane) in the same direction as in 3. The fact that only one band is observed may therefore be incidental and only reflect the fact that the wavelength of maximal absorption for the rotamers involved coincides. Decreasing the temperature to -185° does not give a sign inversion as in 3, the intensity however changes in the same direction i.e. to less negative.

In terms of the empirical rule one would expect XII and XIII to give negative contributions and XIV a positive one. This would imply that XII and XIII (conformations comparable to IX and X) are important in 4.

Again, the methyl ester gives similar results.

2-Ethyl-2-methylhexanoic acid (5). The following rotamers may be involved:



Following the discussion about 2-methylbutanoic acid **4**, it is clear there are two factors of importance for the distribution of the rotamer distribution: the nature of the eclipsed group and the non-bonded interactions between the other groups at C_β with the carboxyl OH group. The three alkyl groups are in this case so similar that a reasonable prediction about the relative stabilities of the rotamers can hardly be made. The low intensity of the CD at room temperature indicates that stability differences are small. At -185° in EPA, a positive ellipticity of reasonable magnitude is found.

On the basis of the empirical rule, positive ellipticity is predicted for XV and XVII, and negative for XVI. This implies that either XV or XVII is the most stable rotamer. However, at room temperature also XVI is present.

In the methyl ester a similar situation prevails.

The occurrence of sign inversions illustrates that it is extremely dangerous to apply the empirical rule to classes of acids for the determination of the absolute configuration without knowledge of the rotamer distribution.

NMR and optical purity. Optical purity determination of the methyl ester of **1** can easily be carried out by the use of NMR with the chiral shift reagent II. From Table 3 it is obvious that both the 2-Me and the terminal Me signals can be used for this purpose. The integrated intensity ratios represent directly the molar enantiomer ratio in mixtures. Although the ester Me signal shows a large downfield displacement it is not split but only slightly broadened.

The methyl ester of **2** does not show any splitting of signal, which considering the low molar ratio of **2** to reagent II and in the context of the present results, indicates 100% optical purity. Of interest is the large induced signal shift for the α -proton, comparable to the analogous shift for **1**. The importance of steric factors for the interaction is striking: the signal displacements for the OMe, 2-Me and terminal Me groups are 2–3 times larger in **4** than in **2**. In **2**, the slightly larger Me proton coupling of 7 Hz is associated with the larger

chemical shift ($\delta = 1.19$) as compared with $J = 6.3$ Hz for the Me doublet at $\delta = 1.17$. This confirms previous measurements⁷ on the erythro isomer.

Interaction of the hydroxy compound **3** with shift reagent II produced only broadened signals in contrast to the results obtained on 2-methylbutanol.⁷

The signal assignment in **4** is of interest (Fig 1). By adding the shift reagent in quantities of 10 mg and plotting the observed shifts it appears that the OMe signals are displaced to lower field at the highest rate and "overtake" the methyl ester signals. Also the 2-Me signals shift at a higher rate than the ester Me signals. The latter two groups exhibit the largest chemical shift differences when comparing the two antipodes.

The still larger value of 2.2 ppm for $\Delta\Delta\delta$ of the methylene group is most probably due to an enhancement of the intrinsic magnetic non equivalence of its two protons,²⁵ which is observable even in the absence of shift reagent. This is confirmed by the equal intensities of the multiplets at δ -values of 9.6 and 11.8 and further by the difference in pattern of these multiplets which is most clearly observed in the spectrum of a solution containing less shift reagent than for Fig 1. This inequality is caused by unequal coupling constants between the Me protons and each of the non-equivalent methylene protons.²⁵ Thus each multiplet is ascribed to a different proton in the methylene group, whilst the enantiomeric shift $\Delta\Delta\delta$ only broadens the multiplets. From Table 3 it may be noted that larger signal displacements occur with **4** than with **1** in spite of the smaller molar ratio of shift reagent to substrate. This is ascribed to the association of **4** as a double Lewis base with the lanthanide complex.

The enantiomeric shift differences for the 2-Me and 2-OMe groups, that are directly attached to the asymmetric C atom are reversed for the terminal Me and ester Me groups.

A similar reversal was found in methyl 2-methyl-2-phenylbutanoate. This implies that $\Delta\Delta\delta$ results from intrinsically different magnetic environments for diastereomeric associates of the two enantiomers.²⁶

In optically impure **5**, a larger molar ratio of reagent II/substrate than for **1** and **4** is required to induce separation of enantiomeric signals.

The Me group in the 2-Et substituent is most sensitive to the chiral effect of association with reagent II and the ester methyl least sensitive (Table 3). Fig 2 shows the spectrum of a racemic mixture at a molar ratio for which the 2-Me signal ($\delta = 9.1$) is slightly broadened and the ethyl-Me ($\delta = 5.9$) is already split. The measurable differential induced shifts for the terminal Me group show that a pseudo contact shift mechanism governs the interaction with the europium ion.

It may be concluded that in all compounds except **3** the 2-Me signal shifts are of the same order of

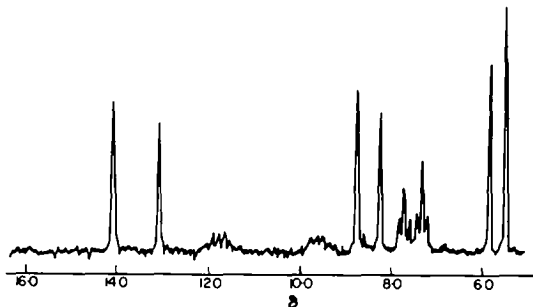


Fig 1. Low field part of 60 MHz PMR spectrum of compound **4** in the presence of reagent II (0.18 mol each in $CDCl_3$).

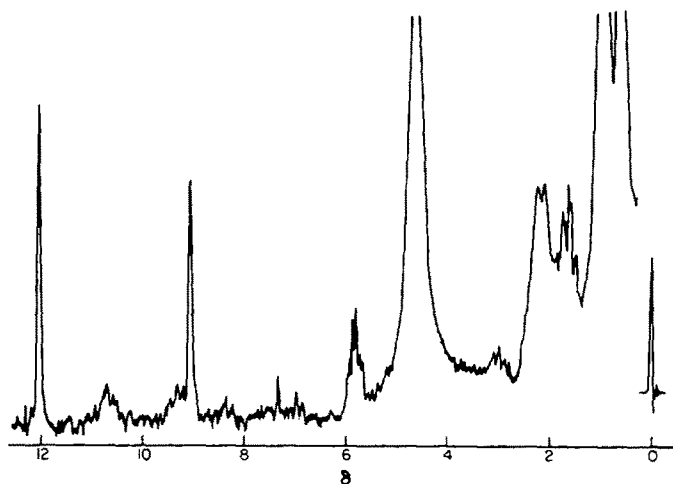


Fig 2. 60 MHz PMR spectrum of compound 5 (racemic) in the presence of reagent II (0.18 and 0.75 mol. resp. in CDCl_3).

magnitude (2–3 ppm at molar ratio 1) and may conveniently be used to determine the optical purity quantitatively.

EXPERIMENTAL

Details about the acids are given in Table 1. The esters were prepared by the diazomethane method.

Cd spectra were measured on a Jouan Dichrograph 185¹¹ equipped with a low temp accessory.

The low temp spectra have been corrected for shrinkage of the solvent.¹² EPA is a mixture of isopentane, diethyl ether and ethanol (5:5:2, v/v/v).

PMR spectra were measured on Varian A 60 and Bruker WH 90 spectrometers at 35° in dilute CDCl_3 solns (about 0.1 mol/l). Eu-optischift I [tris - (3 - trifluoromethylhydroxymethylene - d - camphorato) europium (III)] and Eu-optischift II [tris - (3 - heptafluoropropylhydroxymethylene - d - camphorato) europium (III)] were obtained from Willow Brook Lab, Inc. USA. Chemical shifts are given in ppm downfield from internal TMS (δ -values) and absolute values of coupling constants in Hz.

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