Assignment of the Absolute Configuration of α-Chiral Carboxylic Acids by ^{1}H NMR Spectroscopy

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Received October 26, 1999

The prediction of the absolute configuration of α-chiral carboxylic acids from the ^{1}H NMR spectra of their esters with (*R*)- and (*S*)-ethyl 2-hydroxy-2-(9-anthryl) acetate [(*R*)- and (*S*)-9-AHA, **5**] is discussed. Low-temperature NMR experiments, MM, semiempirical, and aromatic shielding effect calculations allowed the identification of the main conformers and showed that, in all esters studied, conformer *ap* is the most stable. A simple model for the assignment of the absolute configuration from NMR data is presented, and its reliability is corroborated with acids **6**−**31** of known absolute configuration. In addition to **5**, other auxiliary reagents with open (**32**−**38**) and cyclic (**39**−**42**) structures have also been studied. *trans*-(+)- and (−)-2-phenyl-1-cyclohexanol (**41**) was found to be particularly efficient and produced $\Delta\delta^{RS}$ values similar to those of **5**.

Introduction

Although the determination of absolute configuration by NMR spectroscopy is widely used in the cases of secondary alcohols and primary α-substituted amines,[1] the application of this technique to other functional groups has been scarcely investigated or is not fully reliable.

The method consists of the derivatization of the substrate with the (*R*)- and the (*S*)-enantiomer of a chiral auxiliary reagent usually containing an aryl ring (i.e., arylmethoxyacetic acids, AMAAs) that directs its anisotropic cone selectively toward one of the substituents L_1/L_2 of the asymmetric center of the substrate (Figure 1). The chemical shifts observed for the L_1/L_2 groups of the amine or alcohol under investigation reflect their spatial relationship with respect to the aryl ring, and therefore, the absolute configuration at the chiral center of the substrate can be correlated to that of the auxiliary reagent by means of the NMR spectra.

This phenomenon depends on the existence of a preferred conformation in the ester or amide derivatives (the same for the *R* and the *S* derivative), where the aryl ring is oriented to produce shielding selectively on just one of the substituents (L_1/L_2) of the amine/alcohol part. The conformational characteristics and the role of the aryl ring (ring current and orientation) are well understood in the case of the AMAA[2] derivatives of secondary alcohols[2a−h] and primary α-substituted amines.[2i,k] The esters of AMAAs with secondary alcohols are dominated by two main conformers[3] (*ap* and *sp*); in each one the aryl group selectively shields one of the substituents (L_1 or L_2) of the alcohol part. The average spectra can be related to the structure of conformer *sp*, which is the predominant one, and the assignment of the *R*/*S* stereochemistry can be obtained from the difference in the chemical shifts[4] of L_1/L_2 measured as $\Delta\delta^{RS}$.

We have recently demonstrated the application of this methodology to other substrates. In the case of β-chiral primary alcohols,[5] extensive energy calculations and conformational analysis of their 9-anthrylmethoxyacetic acid (9-AMA) esters were necessary to find the NMR-significant conformer and the model that correlates their absolute configuration with their ^{1}H NMR spectra. Nevertheless, a note of caution was stressed regarding the uncertainty of the configuration deduced by application of this method to substrates where the functional group serving as a handle to the auxiliary reagent is more than one bond away from the asymmetric center.

Carboxylic acids are also interesting substrates because they are frequently found in nature as optically active compounds and there are almost no general approaches for the determination of their stereochemistry. A few reports that correlate their absolute configuration with the NMR spectra of certain derivatives have been published in the past few years.[6] PGDA (**1**) and PGME

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(3) The *sp* and *ap* conformers are defined by the synperiplanar and antiperiplanar arrangements of the C_α−OMe and C=O groups, respectively. See ref 2c

(4) $\Delta\delta^{RS}$ represents the difference between the chemical shift of the same group of the substrate in the (*R*)- and (*S*)-derivative ($\Delta\delta^{RS} = \delta R - \delta S$).

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10.1021/jo9916838 CCC: $19.00
Published on Web 04/07/2000

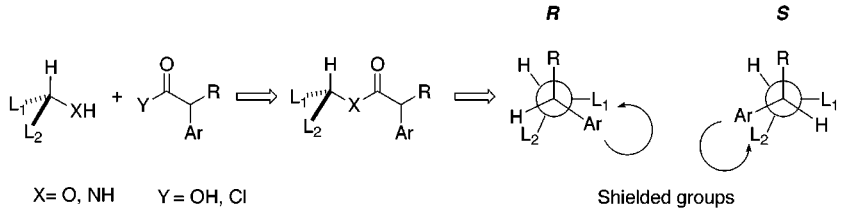
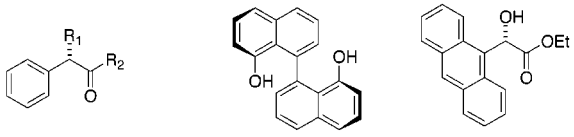


Figure 1.

(**2**) were proposed by Kusumi et al.,[6a,d] mandelic ester (MA, **3**) by Tyrrell et al.,[6b] and 1,1′-binaphthalene-8,8′-diol [BNDO (**4**)] was used by Fukushi et al.[6c]

Nevertheless, the $\Delta\delta$ values reported are very small, and the range of compounds of known absolute configuration used to test the stereochemical predictions is, in most cases, very limited. Moreover, no real understanding of the factors that determine the experimental results has been advanced; the conformations used to explain the NMR data obtained with **1**−**4** are simply empirical, and in fact, they could be substituted by other stereochemical dispositions that explain the results equally well.



An important decision that has to be taken into account in the development of new reagents concerns the selection of the bond employed to link the auxiliary reagent to the substrate (carboxylic acid). In the reports discussed above, amide (PGDA and PGME)[6a,d] and ester (MA and BNDO)[6b,c] bonds have been used. However, we reasoned that linking the carboxylic acid to the auxiliary reagent through an ester bond should be preferred to an amide because the equilibrium around the C_α−CO bond in amides has been shown to be highly dependent on the structure of the carboxylic acid (i.e., the nature of the aryl ring in the case of AMAA amides),[2j,k] significantly limiting the generality of the results. Moreover, the COC═O skeletal fragment shows a clear preference for the *Z* conformation, while the conformational distribution of CNHC═O is much more complex, with *Z*/*E* ratios ranging from 90:10 to 50:50.[7] The mobility around the C_α−CO bond and the absence of any strong conformational preference about the NH−CO bond of amides strongly suggest that less generality could be expected in the use of those reagents[6a,d,e] apart from the compounds tested and those with very closely related structures. The higher reliability of esters led us to concentrate our efforts on aryl alcohols rather than arylamines as chiral derivatizing reagents (CDA) for α-chiral carboxylic acids.

In this paper we present our results on the use of alcohol **5** [ethyl 2-hydroxy-2-(9-anthryl) acetate, 9-AHA] as a reagent for the determination of the absolute configuration of α-chiral carboxylic acids by comparison of the NMR spectra of their esters with (*R*) and (*S*)-**5**. MM[8] and AM1/PM3[9] methods were used to calculate the geometry and relative stability of the conformers; DNMR[10] was employed to prove experimentally the theoretical findings; and finally, aromatic shielding effect calculations[11] on each conformer and on the equilibrium mixture were carried out and the results were compared with the experimental NMR shielding. A preliminary account of this study has already been published.[12] In the last part of this article, the usefulness of aryl alcohols other than **5** is also described, with particular emphasis on the cyclohexane derivatives **41**−**45** and the role of the aryl ring in the effectiveness of these reagents.

Results and Discussion

Conformational Composition and Preference. The main issue in relation to the potential use of chiral aryl alcohols such as 9-AHA (**5**) as reagents for the assignment of absolute configuration of carboxylic acids is to demonstrate the existence of an NMR-significant conformational preference that is the same in all of the esters and independent of the nature of the carboxylic acid.

To this end, we carried out MM and semiempirical calculations on a series of more than 20 α-substituted carboxylic acids (Figure 2). On the basis of previous studies,[2c] it is known that the alcohol part of an ester adopts a preferred conformation where H−C_α-O−C═O are in a plane and the C_α′H is in an *sp* disposition in relation to the C═O bond (Figure 3a). Therefore, we focused our attention on the rotation around the C_α−CO bond (Figure 3b), the most important process in these compounds.

The calculations revealed a consistent conformational composition over the whole series, with only two main

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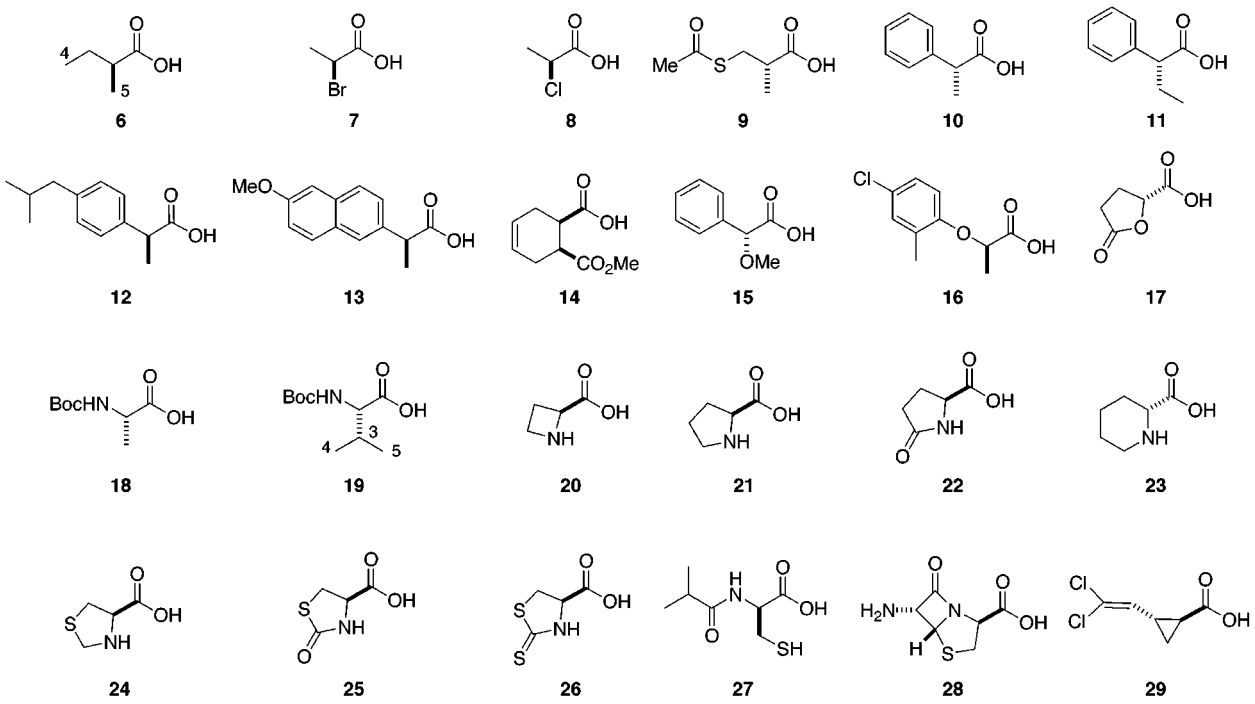

Figure 2. α-Chiral carboxylic acids studied by theoretical calculations.

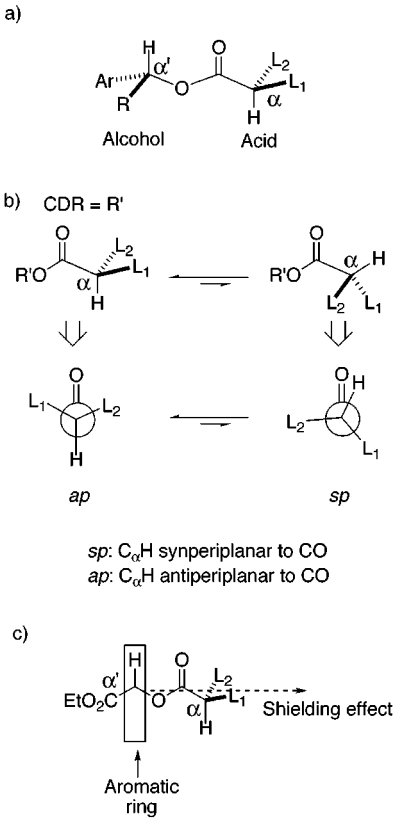

Figure 3. (a) Preferred conformation of the ester of ethyl 2-hydroxy-2-(9-anthryl) acetate (**5**) with an α-chiral carboxylic acid. (b) Main orientations in the acid fragment. (c) Low-energy orientation of the aromatic ring.

Table 1. Conformational Preference of α-Chiral Carboxylic Acids 6−29 (RCO_2H), Their Methyl Esters (RCO_2Me), and *N*-Methyl Amides (RCONHMe)[a]

	RCO_2H			RCO_2Me		RCONHMe	
acid	MM	AM1	PM3	MM	PM3	MM	PM3
6	0.64	0.37	0.54	0.53	0.69	0.49	−0.09
7	1.13	0.45	−0.91	0.99	−0.91[b]	0.40	−0.40
8	1.14	0.42	0.04	0.99	0.12	0.34	−1.98
9	0.85	0.31	0.63	0.73	0.80	0.39	0.42
10	1.41	0.57	0.71	1.23	0.94	0.77	−0.41
11	1.31	0.63	0.79	1.05	1.02	0.48	−0.13
12	0.42	0.56	0.52	1.24	0.95	0.79	−0.01
13	1.42	0.54	0.31	1.25	0.94	0.90	−0.43
14	0.91	0.00	0.75	1.29	0.95	0.88	−1.59
15	0.08	0.00	0.30	0.24	0.31	−0.12	−1.40
16	0.83	0.10	0.16	−0.10	0.14	0.37	−2.51
17	1.35	0.25	0.29	1.13	0.33	0.62	0.09
18	0.75	0.36	0.94	0.72	1.09	0.21	2.37
19	0.86	0.22	0.73	0.56	0.88	0.26	1.96
20	1.28	0.76	0.91	1.01	0.15	0.98	0.15
21	1.22	0.75	0.65	0.91	0.73	−0.05	−0.41
22	1.12	1.48	0.62	0.84	0.68	0.24	0.30
23	0.97	0.08	0.70	0.91	0.87	0.34	1.73
24	1.23	0.32	0.00	1.01	0.02	0.07	−2.60
25	0.94	0.00	0.30	0.73	0.63	0.09	0.13
26	0.93	0.46	0.00	0.62	0.70	0.98	0.42
27	0.37	0.37	0.99	0.14	1.17	0.13	1.78
28	1.69	0.76	0.56	1.37	0.63	2.23	0.16
29	2.11	0.44	0.86	1.83	1.04	*c*	1.09

[a] Energies (kcal/mol) are relative to the *ap* conformer, as defined in Figure 3b. A positive value means that *sp* is higher in energy, whereas a negative one corresponds to lower energy states [b] cf. AM1 data −0.52. [c] *sp* nonstable.

orientations of the C_α−H bond relative to the C=O bond (Figure 3b): the *ap* conformation where the C_α−H bond is antiperiplanar in relation to the C=O bond and the *sp* conformation where these two bonds are in a synperiplanar disposition. The energy gap between these two main conformers, *sp* and *ap*, was estimated by semiempirical methods (AM1 and PM3, Table 1) and showed a preference of approximately 1 kcal/mol for the *ap* over the *sp* conformer for all of the acids investigated. This means that, in the most stable conformer, C_α−H and $C_{\alpha'}$−H are antiperiplanar. When L_1 or L_2 are polar groups (i.e.,alkoxy in **15**−**17**), some deviation from planarity is observed and the angle becomes smaller than 180° as a result of the tendency of the alkoxy group to become

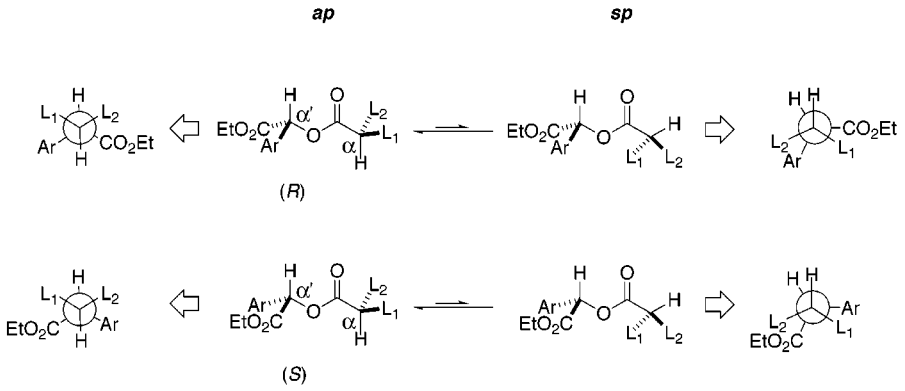

Figure 4. Conformational equilibrium in the esters of (*R*)- and (*S*)-9-AHA (**5**) with an α-chiral carboxylic acid.

closer to the C=O bond. Fortunately, this effect is small and does not represent a significant modification of the general disposition of L_1/L_2 in relation to the aryl group.

MM and PM3 calculations were also carried out on the methyl esters of acids **6**−**29**, and the same geometry and similar energy differences as in the free acids were found (Table 1). Furthermore, calculations on the esters of acid (*S*)-**6** with alcohols (*R*)- and (*S*)-**5** corroborated this conformational composition with a 0.5−0.9 kcal/mol preference for *ap* over *sp* (Figure 4).[13]

When the same calculations (MM and PM3, Table 1) were carried out on the methyl amides of acids **6**−**29**, the absence of a common conformational preference was found. In fact, rotation around the C_α−CO bond was found to be preferentially *sp* in 12 out of the 24 amides investigated and preferentially *ap* in the other 12 cases. This dependence of the conformational composition on the nature of the acid confirms our previous observations[2j,k] that alcohols should be preferred to amines as auxiliary reagents for carboxylic acids.

Because we used an ester derivative, the preferred conformation has the OR group synperiplanar (*sp*) to the C=O bond and the aryl ring is coplanar to the $C_{\alpha'}$−H bond[14] (Figure 3c), a situation that permits an effective transmission of the shielding effect to the substituents (L_1/L_2) of the acid.

All of these data allow us to assume that the conformational composition of any ester of **5** with an α-chiral carboxylic acid is as represented in Figure 4. Thus, the L_1 substituent in the (*R*)-9-AHA ester should be shielded in the *ap* conformation, while the L_2 substituent will remain unaffected (Figure 4). In contrast, in the *sp* conformation it is L_2 that is shielded, while L_1 remains unaffected. In the case of the (*S*)-9-AHA ester, it is L_2 that is shielded in the *ap* conformation and L_1 in the *sp* conformation. Because the population of the *ap* conformer is higher than that of the *sp* conformer, L_1 will be more shielded in the (*R*)-9-AHA ester than in the (*S*)-derivative ($\Delta\delta^{RS} < 0$), and conversely, L_2 will be more shielded in the (*S*)-9-AHA ester than in the (*R*)-ester ($\Delta\delta^{RS} > 0$). The signs of the $\Delta\delta^{RS}$ values will allow the assignment of the spatial position of L_1/L_2 by comparison of the ^{1}H NMR spectra of both diastereoisomers.

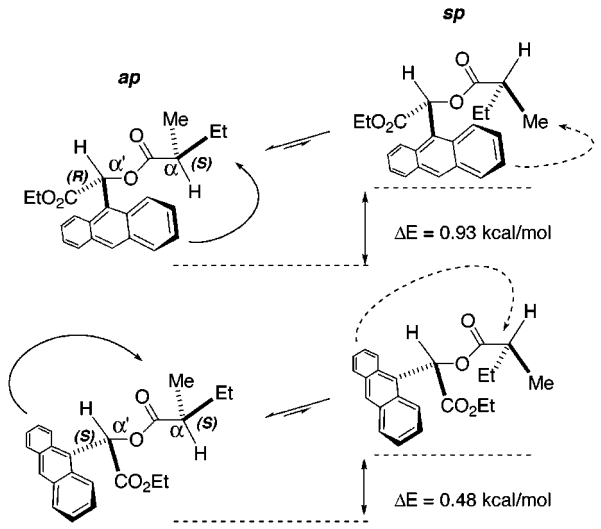

Figure 5. Conformational equilibrium in the esters of (*R*)- and (*S*)-9-AHA (**5**) with (*S*)-2-methylbutyric acid (**6**). Energy calculated by AM1.

NMR Results. Once the existence of an unequivocal conformational preference identical for all esters of α-carboxylic acids with chiral secondary aryl alcohols and the favorable orientation of the aryl ring with regards to substituents L_1/L_2 was theoretically well established, the next step was to find the necessary experimental evidence.

To that end, we selected for our study the aryl alcohol (*R*)- and (*S*)-9-AHA (**5**) and tested its ability to separate the signals of (*S*)-2-methylbutyric acid (**6**). The ^{1}H NMR spectra of the resulting diastereomeric (*R*)- and (*S*)-9-AHA esters showed clear differences in the chemical shifts of the protons located around the asymmetric center of the acid (L_1/L_2). The ethyl group in the (*R*)-ester resonates at higher field than in the (*S*)-9-AHA ester, whereas the signal for the methyl group moves in the opposite sense and is observed at higher field in the (*S*)-9-AHA ester in comparison to the (*R*)-9-AHA ester. Therefore, the ethyl group corresponds to L_1, and the methyl group corresponds to L_2 (Figure 5). This means that if we compare the chemical shift of these groups in both esters, the difference, $\Delta\delta^{RS}$, is positive (+0.10 ppm) for the methyl protons and negative (−0.16, −0.10, and −0.09 ppm) for the ethyl group in accordance with the *S* absolute configuration of the acid **6**. These results are fully coherent with the conformational composition and

(13) (a) For the (*R*)-9-AHA ester of **6**: DE = 0.93 (AM1), 0.93 (PM3). (b) For the (S)-9-AHA ester of **6**: DE = 0.48 (AM1), 0.39 (PM3).

(14) To maintain consistency with previous works, $C_{\alpha'}$ refers to the carbon bearing the hydroxy group in the alcohol moiety, although it is C_2 in the systematic name. In those works, the *sp* conformer was defined by the synperiplanar disposition of the CαOMe and C=O groups.

Table 2. ^{1}H NMR Chemical Shifts of (*R*)- and (*S*)-9-AHA (5) Esters of (*S*)-2-Methylbutyric Acid (6) at Different Temperatures

T, K	$C_\alpha\underline{H}$	$C\underline{H_2}-CH_3$	$CH_2-C\underline{H_3}$	$C\underline{H_3}$(5)
		(*R*)-AHA		
300	2.427	1.663/1.418	0.802	1.191
263	2.430	1.655/1.410	0.800	1.199
233	2.433	1.649/1.405	0.799	1.204
203	2.438	1.641/1.397	0.796	1.212
173	2.443	1.628/1.386	0.790	1.218
		(*S*)-AHA		
300	2.430	1.728/1.532	0.950	1.091
193	2.446	1.732/1.566	0.980	1.065

Table 3. ^{1}H NMR Chemical Shifts of (*R*)- and (*S*)-9-AHA (5) Esters of *N*-*t*-Boc-L-Valine[16] (19) at Different Temperatures

T, K	$C_\alpha H$	CH(3)	CH_3(4)	CH_3(5)
		(*R*)-AHA		
300	4.267	1.982	0.816	0.603
243	4.304	1.974	0.799	0.522
193	4.375	1.956	0.754	0.397
		(*S*)-AHA		
300	4.167	2.322	1.001	0.962
243	4.178	2.393	1.016	0.970
193	4.200	2.459	1.022	0.978

preference for the *ap* form derived from the calculations (Figure 5).

Additional support for these findings was obtained from low-temperature NMR experiments on the esters of acid (*S*)-**6** with (*R*)- and *(S)*-**5** (Table 2), where an increase in the shielding was observed in accordance with the greater population of the preferred conformer *ap*. Thus, in the NMR spectrum of the ester of (*S*)-**6** with (*R*)-**5** the ethyl group resonances were shifted to higher field ($\Delta\delta^{T1,T2} = 0.022_{CH2}$ and 0.006_{CH3} ppm)[15] when the probe temperature was decreased from 300 to 203 K, whereas in the ester of (*S*)-**6** with (*S*)-**5** it was the methyl group signal that was shifted to higher field ($\Delta\delta^{T1,T2} =$ 0.026 ppm) when the temperature was decreased to 193 K. These shifts indicate beyond doubt that the ethyl group is located on the same side as the aryl ring in the most stable *ap* conformer of the ester of (*S*)-**6** with (*R*)-**5**, whereas in the (*S*)-**5** ester this side is occupied by the methyl group. Signal broadening was not observed, meaning that the rotation around the $C_\alpha-CO$ bond continues to be rapid, and this explains the small $\Delta\delta^{RS}$ values obtained.

Analogous behavior was observed in the esters of (*R*)- and (*S*)-9-AHA with acid (*S*)-**19** (Table 3) where larger shielding of the isopropyl group of its ester with (*R*)-9-AHA was observed at lower temperatures.

Moreover, the NMR signals due to the $C_\alpha H$ proton of (*R*)- and (*S*)-9-AHA esters of **6** and **19** are shifted to lower field at low temperatures (see Tables 2 and 3). This effect is perfectly consistent with the equilibrium represented in Figure 4 and can be explained by the increase in the population at lower temperatures of a conformer in which the $C_\alpha H$ is out of the shielding cone of the carbonyl group. This condition is fulfilled only by the *ap* conformer, which is the most stable.

The calculated aromatic shielding effects for the *ap* and *sp* conformers of the esters of (*R*)- and (*S*)-**5** with (*S*)-2-methylbutyric acid (**6**) compare well with the experimental values and confirm that the most important contributions to the average NMR spectra come from the *ap* conformer (Table 4).

Table 4. Calculated Aromatic Shielding Effects for the Esters of 5 and 41 with (*S*)-2-methylbutyric Acid (6)

config	conf	Me(5)	Me(4)
		CDA **5**	
R	*sp*	0.89	−0.14
	ap	−0.20	0.10
S	*sp*	−0.17	0.30
	ap	0.95	−0.04
		CDA **41**	
R	*sp*	0.40	0.64
	ap	1.01	0.09
S	*sp*	0.92	0.08
	ap	0.04	0.36

Full experimental support for this interpretation of the DNMR data and a demonstration that the conformational characteristics of the (*R*)- and (*S*)-9-AHA esters of **6** and **19** are general for other substrates were obtained after examination of many other carboxylic acids[17] (**6**−**31**) of known absolute configuration and with widely varied structures.

The structures and $\Delta\delta^{RS}$ values are shown in Figure 6 and serve to illustrate two important facts. First, the distribution of the signs of $\Delta\delta^{RS}$ is perfectly homogeneous along the series[18] and consistent with the absolute configuration of these compounds and with the conformational composition shown in Figure 4. Second, the data also show that reagent 9-AHA (**5**) is much better than other reagents (i.e.,**1**−**3**) because it produces $\Delta\delta^{RS}$ values that are much higher (see ref 6) and its influence is exerted over much longer distances.

Model for Assignment of the Absolute Configuration of Carboxylic Acids. As we have shown, the sign of the $\Delta\delta^{RS}$ values of the esters of 9-AHA (**5**) is an indicator of the spatial location of L_1/L_2 relative to the aryl group and therefore allows the determination of the *R*/*S* absolute configuration of the carboxylic acid. Experimentally, this entails the preparation of the (*R*)- and (*S*)-9-AHA esters of the acid of unknown configuration and comparison of their ^{1}H NMR spectra.

This information should be interpreted in the light of the equilibrium and structures shown in Figure 4. Nevertheless, as the average spectrum is dominated by conformer *ap*, the equilibrium can be simplified by considering this form (Figure 7) as the only relevant one and by using it to fix the spatial location of L_1 and L_2. According to this model, the substituent that is more shielded in the (*R*)-9-AHA ester than in the (*S*)-9-AHA ester ($\Delta\delta^{RS} < 0$) should be ascribed to L_1 in the figure, and conversely, the substituent that is more shielded in the (*S*)-9-AHA ester than in the (*R*)-9-AHA ester ($\Delta\delta^{RS} > 0$) corresponds to L_2. Identification of L_1/L_2 and their placement around the asymmetric center can then be directly obtained from the signs of $\Delta\delta^{RS}$ as shown in Figure 7.

(15) $\Delta\delta^{T1,T2}$ represents the difference between the δ value (ppm) at the higher (T_1) and lower (T_2) temperature [$\Delta\delta^{T1,T2} = \delta(T_1) - \delta(T_2)$].

(16) Some indication of coalescence in the ^{1}H NMR spectra was observed at ca. $T = 243$ K. Only data for the major form are given in the table. Assignment of the minor component is ambiguous because of its very low population.

(17) (*R*)-*O*-Phenyllactic acid was synthesized from (*S*)-ethyl lactate; see: Tottie, L.; Baeckstrom, P.; Moberg, C.; Tegenfeldt, J.; Heumann, A. *J. Org. Chem.* **1992**, *57*, 6579−6587.

(18) The ^{1}H NMR data of the NHBoc group are very sensitive to experimental conditions and should not be used to derive the configuration (see ref 2h).

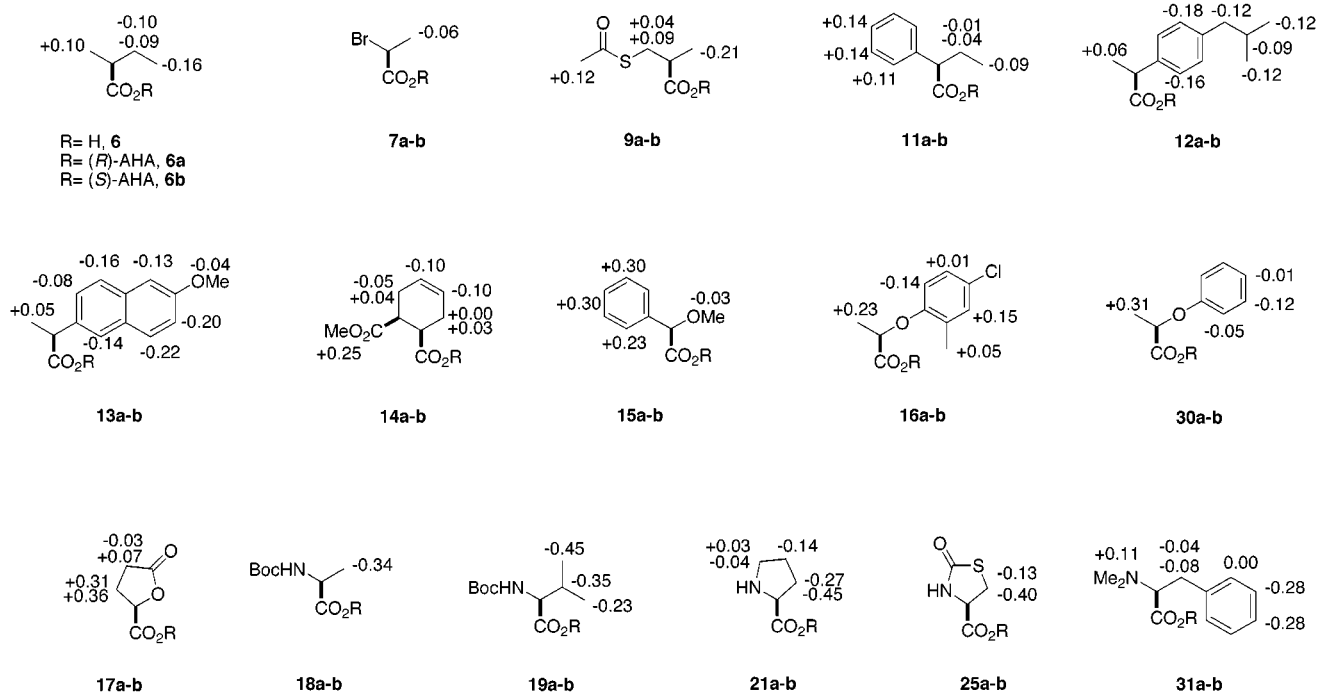

Figure 6. $\Delta\delta^{RS}$ values in the esters of 9-AHA (**5**) with the acids shown.

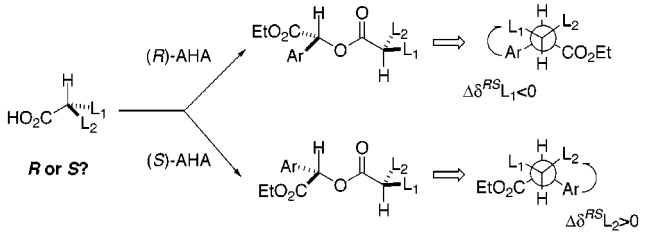

Figure 7. Conformational model for the assignment of the absolute configuration of α-chiral carboxylic acids by NMR spectroscopy.

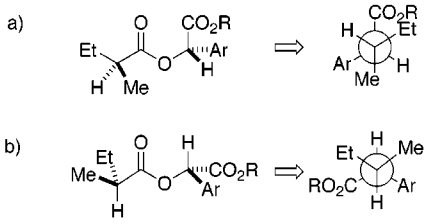

Figure 8. Simplified model for arylalkoxyacetic acid esters of the acid **6** according to (a) ref 6b (MA) and (b) our data (9-AHA).

In contrast to the equilibrium and structures described in Figure 4 for the esters of 9-AHA (**5**), the results reported using MA (**3**) as the reagent have been interpreted[6b] assuming a completely different preferred conformation ($C_{\alpha'}$−H not coplanar with C=O and L_1/L_2 *cis* to the C=O group, see Figure 8a). This model is, however, inconsistent with the well documented[2c] coplanarity of $C_{\alpha'}$−H with C=O and with our calculations (Table 1) and NMR data (Figure 6), and indeed, no specific experimental data has been advanced to support it. Notwithstanding, the application of this model has yielded correct *R*/*S* assignments because those two errors cancel each other, and the spatial location of L_1/L_2 relative to the aryl ring is roughly the same as if the more likely simplified model shown in Figure 8b were considered.

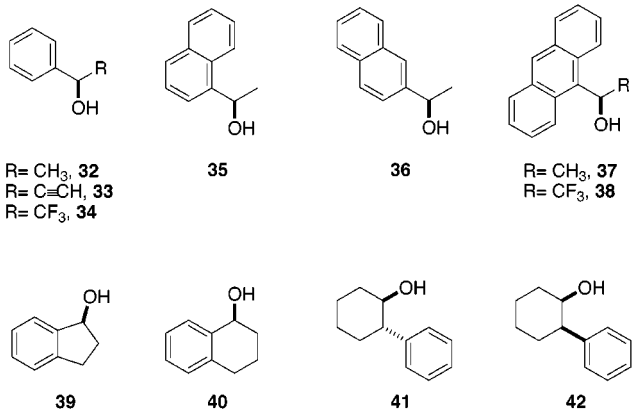

Figure 9.

Other Aryl Alcohols as Auxiliary Reagents. According to earlier observations in AMAA esters,[2c,d] the conformational equilibrium around the C_α−CO bond is practically independent of the nature of the alcohol. This means that it is reasonable to expect that other secondary aryl alcohols would behave as 9-AHA and could therefore potentially be used as auxiliary reagents for NMR configuration assignment of carboxylic acids.

To test this idea we decided to explore the usefulness of other alcohols with different substituents, skeletal structures, and aryl rings as chiral reagents. To this end, (*S*)-2-methylbutyric acid (**6**) was selected as the substrate, and the $\Delta\delta^{RS}$ values of its esters with alcohols **32**−**42** (Figure 9) were analyzed as before.

The results presented in Table 5 show that the $\Delta\delta^{RS}$ are, in most cases, smaller than those obtained with 9-AHA (**5**). Among the open chain 1-aryl alcohols examined, only two, **37**[19] and **38**, produced shifts comparable to those of **5**, demonstrating once again[2b,g] the superiority

Table 5. $\Delta\delta^{RS}$ Values for the Esters of Aryl Alcohols 32−42 with (*S*)-2-Methylbutyric Acid (6)

	32a,b	33a[a]	34a[a]	35a,b	36a,b	37a[a]	38a,b	39a[a]	40a[a]	6c,d	42a[a]	6a,b
Me(5)	−0.30	−0.03	0.04	−0.03	−0.03	0.09	+0.10	0.01	0.00	−0.10	0.04	+0.10
Me(4)	+0.06	0.07	0.05	+0.07	+0.07	0.18	−0.16	0.02	0.01	+0.15	0.06	−0.16

[a] These compounds were used in racemic form, and $\Delta\delta$ values were measured from the spectra of the mixture.

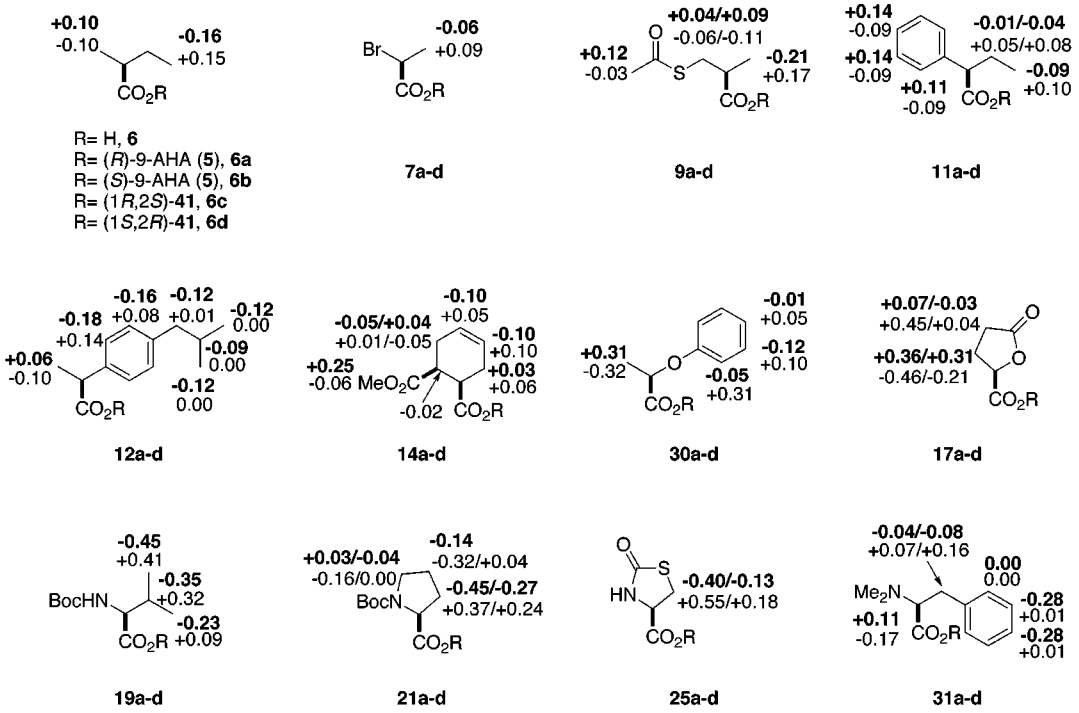

Figure 10. $\Delta\delta^{RS}$ values for the esters of the carboxylic acids shown with *trans*-2-phenyl-1-cyclohexanol (**41**) (lightface) and 9-AHA (**5**) (**bold**).

of the anthryl ring in this kind of reagent. The cyclic analogues **39** and **40** produced almost no separation of signals, and a similar result was obtained with the cyclohexane derivative **42**.[20] However, the commercially available (1*R*,2*S*)- and (1*S*,2*R*)-2-phenyl-1-cyclohexanol (**41**) gave $\Delta\delta^{RS}$ values[21] very close to those observed with 9-AHA (**5**), although this reagent bears a phenyl rather than an anthryl ring.

Corroboration of the effectiveness of (1*R*,2*S*)- and (1*S*,2*R*)-2-phenyl-1-cyclohexanol (**41**) as a reagent was obtained after esterification with the α-chiral carboxylic acids of known absolute configuration shown in Figure 10. The data shown can be summarized in the following conclusions: (a) The signs of the shifts produced by **41** are regularly distributed in all of the compounds examined, so that $\Delta\delta^{RS}$ values are positive for protons in L_2 and negative for protons in L_1. (b) The signs obtained are opposite to those obtained with **5** (positive for L_1 and negative for L_2). (c) The $\Delta\delta^{RS}$ values obtained with **41** are, in terms of absolute values, similar to those produced by **5** for protons close to the chiral center. These facts indicate that both **41** and **5** show basically the same ability to separate the resonances of the enantiomeric

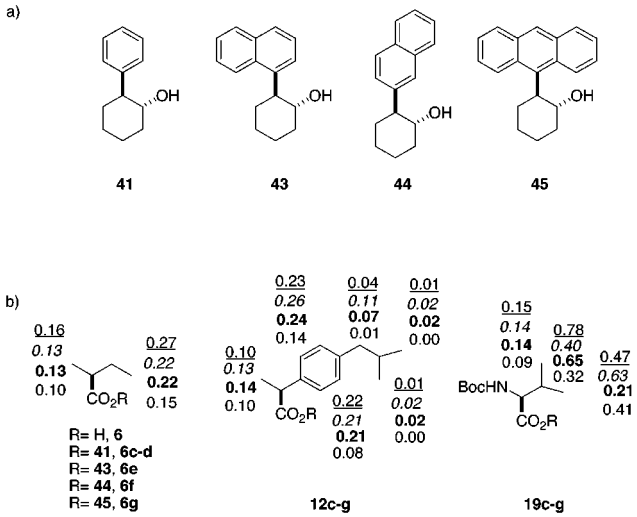

Figure 11. (a) *trans*-2-Aryl-1-cyclohexanols and (b) $|\Delta\delta^{RS}|$ values for the esters of the acids **6**, **12**, and **19** with alcohols **41** (lightface), **43** (**bold**), **44** (*italic*) and **45** (underlined).

protons of the substrates. Aromatic shielding effects have been calculated for the *ap* and *sp* conformations of the esters of (*S*)-2-methylbutyric acid (**6**) with reagents **41** and **5**, and the results of these calculations are also similar (Table 4).

To study the role of the aryl ring in **41** and to explore the possibility of increasing the $\Delta\delta^{RS}$ values by changing the aromatic ring, the 1-naphthyl (**43**), 2-naphthyl (**44**), and 9-anthryl (**45**) derivatives (Figure 11) were synthe-

(19) Racemic 1-(9-anthryl)-1-ethanol (**37**) was obtained by reduction of 9-acetylanthracene with $NaBH_4$ in MeOH.

(20) Transformation of the *trans*-alcohol (**41**) into the diastereomeric *cis*-alcohol (**42**) was carried out by the Mitsunobu reaction; see: Takahashi, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1617−1620.

(21) For a given proton of the acid, $\Delta\delta^{RS}$ represents the difference between its chemical shift in the (1*R*,2*S*)-derivative and that in the (1*S*,2*R*)-derivative.

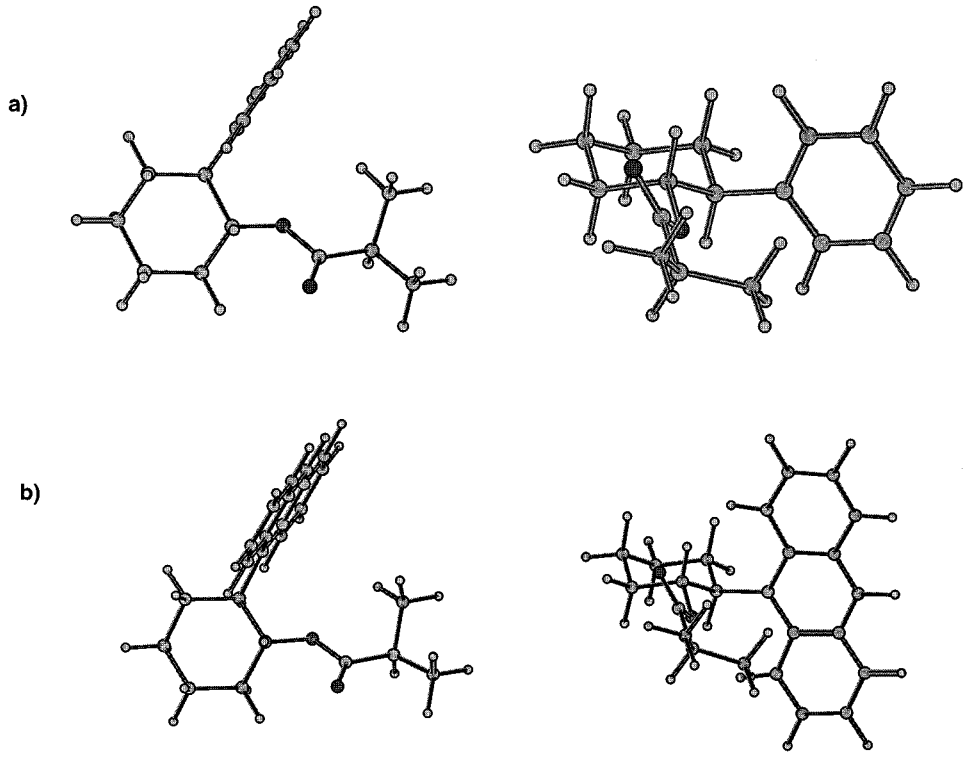

Figure 12. Frontal and side views of the calculated minimum energy conformers of the (a) *trans*-2-phenyl-1-cyclohexanol and (b) *trans*-2-anthryl-1-cyclohexanol esters of 2-methylpropionic acid.

sized from the corresponding arylbromides and cyclohexene oxide,[22] and their ability to produce selective shifts was tested with acids **6**, **12**, and **19**, of known absolute configuration. The results shown in Figure 11 indicate that no significant improvement in $\Delta\delta^{RS}$ values is associated with the presence of naphthyl or anthryl rings.

MM calculations showed why *trans*-2-aryl-1-cyclohexanols are more qualified than their *cis* counterparts as CDA reagents for acids. In both cases, the chair conformers with an equatorial aryl group proved to be the most stable ones, but in the *trans* isomers only the aromatic ring is placed to cause maximum shielding effect on the acid substituents (equatorial−equatorial relationship). Furthermore, the aryl rings were roughly coplanar with the C(2′)H bond, with the fragment $C_{\alpha'}$-$HOCOC_{\alpha}H$ adopting the same conformation as in the esters of **5** ($C_{\alpha}H-CO$ and $C_{\alpha'}H$ coplanar and *ap* as in Figure 7). In the case of **43**−**45**, the only modification observed when compared with **41** was a small rotation of the aryl plane, which departs by about 10° from coplanarity with C(2′)H. Figure 12 shows frontal and side views of the calculated minimum energy conformers of the *trans*-2-phenyl-1-cyclohexanol and *trans*-2-anthryl-1-cyclohexanol esters of 2-methylpropionic acid where the above structural features can be observed.

The fact that **43**−**45**, with naphthyl and anthryl rings, do not produce higher shifts than **41**, which has a practically identical conformation, seems to be in conflict with data obtained for 9-AMA esters. Nevertheless, inspection of the structures of esters of **5** indicates that

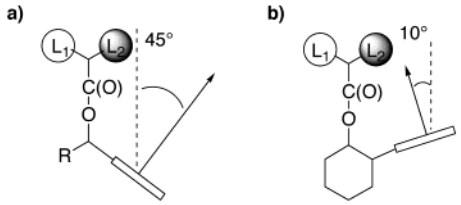

Figure 13. Schematic representation of the direction of maximun shielding in the esters of (a) **5** and (b) **41**.

the direction of maximum shielding points to positions 4 or 5 bonds away from the asymmetric center,[2g] whereas in the esters of **41**, the maximum shielding is focused on the immediate surroundings of the asymmetric carbon (Figure 13). Thus, if the phenyl group of **41** is replaced by a larger aromatic system, as in **43**−**45**, the area of shielding becomes very much larger. This should now affect not only the substituent on the same side (L_2) but also to some extent the other substituent (L_1), and so on average the $\Delta\delta^{RS}$ values will not be as high as expected. In the case of **5**, the focus of the anisotropic ring is so far away that even if its effect is greatly increased, it will never affect more than one substituent in each conformer.

Figure 14 shows a graphic summary that illustrates how the absolute configuration of an α-chiral carboxylic acid can be deduced from the signs of the experimental $\Delta\delta$ values in their esters with any *trans*-2-aryl-1-cyclohexanol.

Conclusions

In summary, we have demonstrated that the esters of α-substituted carboxylic acids with aryl secondary alcohols such as 9-AHA (**5**) are composed of two conformers in equilibrium, with the $CH_{\alpha'}-O-C(=O)-CH_{\alpha}$ system in the same plane and the form defined by an *anti* relationship between CH_{α} and C=O groups being predominant.

(22) (a) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693−3694. (b) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699−10708. Compounds **43**−**45** were used in their racemic form. The $\Delta\delta^{RS}$ values of the esters **19e**, **12f**, **19f**, **12g**, and **19g** were measured after HPLC separation, whereas those of **6e**, **12e**, **6f**, and **6g** were directly measured from the spectra of the corresponding mixture.

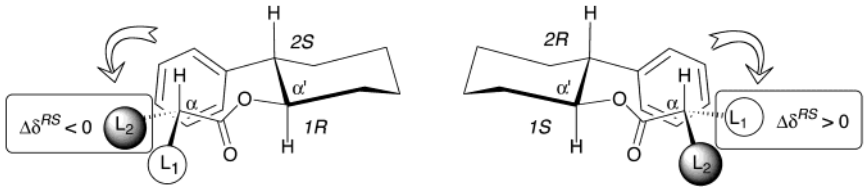

Figure 14. Conformational model for the determination of the absolute configuration of α-chiral carboxylic acids by NMR of their *trans*-2-phenyl-1-cyclohexanol esters. $\Delta\delta^{RS}$ defined as in ref 21.

The shielding produced by the aryl ring is selectively directed to the substituent of the acid located on the same side of the plane, and this shielding allows a correlation to be established between the absolute configuration of the alcohol and that of the acid. In practice, the esters of the acid with the both enantiomers of ethyl 2-hydroxy-2-(9-anthryl) acetate (**5**) have to be prepared, their ^{1}H NMR spectra compared, and the sign of $\Delta\delta^{RS}$ interpreted according to the model shown in Figure 7.

In addition to **5**, other aryl alcohols with open (**32**−**38**) and cyclic (**39**−**42**) structures have also been studied as auxiliary reagents, and (1*R*,2*S*)- and (1*S*,2*R*)-2-phenyl-1-cyclohexanol (**41**) was found to be particularly efficient, producing $\Delta\delta^{RS}$ values similar to those of **5**. Because of the geometry of compound **41**, replacement of its phenyl ring by naphthyl or anthryl (**43**−**45**) does not produce a significant improvement in its capability to separate the signals of the substrate. Thus, both **5** and **41** are reagents of similar effectiveness for the assignment of absolute configuration of α-chiral carboxylic acids by ^{1}H NMR spectroscopy. However, **41** produces much more complicated ^{1}H NMR spectra as a result of the presence of the cyclohexane signals, which may overlap significant protons of the substrate, and its effect on hydrogens placed at long distances from the chiral center is weaker than the effect generated by **5**.

Experimental Section

Computational Methods. Molecular mechanics (employing the PC91 force field[8]) and AM1[9] (PM3) calculations were performed using the Insight II package on a Silicon Graphics Iris (SGI) computer. Initial molecular geometries were originated from the Builder Module of Insight II; 3D coordinates were then generated from the bond lengths, bond angles, and dihedral angles using the DG-II package.[23] The conformational space of each compound was scanned by MM optimization of the sterically allowed conformations around key single bonds. The MM simulations were carried out in vacuo. Analysis of conformational transitions, identification of the low-energy conformers, and calculation of the energy barriers between these conformers were all carried out by MM. The energies of conformations were minimized in Cartesian coordinate space by the block diagonal Newton−Raphson method; minima corresponded to rms energy gradients less than 0.001 kcal/mol Å. The ground-state energies of the geometries were then calculated by AM1 (PM3) using the MOPAC 6.0 program. For all compounds, full geometry optimization used the Broyden−Fletcher−Goldfarb−Shanno (BFGS) method and the PRECISE option.[9]

Shielding Effect. Calculations were carried out on a SGI computer using a program (writen on Fortran 77) based on the semiclassical model of Bovey and Johnson.[11] No corrections for local anisotropic contributions[11d,e] were implemented. Calculations were performed with π-current loops separation of 1.39 Å.[11b,f]

NMR Spectroscopy. ^{1}H and ^{13}C NMR spectra of samples in 4:1 CS_2/CD_2Cl_2 or $CDCl_3$ (ca. 2−3 mg in 0.5 mL) were recorded on 500, 300, or 250 MHz NMR spectrometers. Chemical shifts (ppm) are internally referenced to the tetramethylsilane signal (0 ppm) in all cases. One- and two-dimensional NMR spectra were measured with standard pulse sequences. 2D Homo- (COSY) and heteronuclear (HMQC) shift correlation experiments were carried out using pulsed field gradient technique. Apodization with a shifted sine bell and baseline correction was implemented to process 2D spectra. 1D ^{1}H NMR spectra: size 32 K, pulse length 2.8 ms (30°), 16 acquisitions. 2D COSY spectra: sequence D1-90-t1-G_1-90-G_2-AQ, relaxation delay D1 = 1 s, 90° pulse 8.5 μs, gradient ratio 1:1. 2D TOCSY spectra: relaxation delay D1 = 2 s; mixing time 41.3 ms; 90° pulse 8.5 μs; TPPI-mode, NS = 64. 2D Proton-detected heteronuclear multiple quantum correlation (HMQC) experiments: sequence D190(^{1}H)-D2-90(^{13}C)-t_1/2-G1-180(^{1}H)-G2-t_1/2-90(^{13}C)-G3-D2-AQ (GARP(^{13}C)), relaxation delay D1 = 2s, D2 = 3.45 ms, 90° pulse (^{1}H) 8.5 μs; 90° pulse (^{13}C) 10.5 μs, gradient ratio 5:3:4. For DNMR spectroscopy, the probe temperature was controlled by a standard unit calibrated using a methanol reference; samples were allowed to equilibrate for 15 min at each temperature before recording spectra.

General. (*R*)- and (*S*)-ethyl 2-hydroxy-2-(9-anthryl)acetate (**5**) were obtained by asymmetric reduction of ethyl (9-anthryl)-glyoxylate with (*R*)- and (*S*)-ALPINE BORANE, respectively, (prepared in situ from 9-BBN and (+)- and (−)-pinene by the usual procedure).[24] It was methylated to measure the ee by HPLC (Chiral column) and then hydrolyzed to compare the stereochemistry with that of 9-AMA. The absolute stereochemistry was confirmed by CD. (*R*): yield = 85%, ee (OMe) = 90.36, $[\alpha]_D = -75.9$. (*S*): yield = 80%, ee (OMe) = 60.6, $[\alpha]_D = +50.9$.

Preparation of diastereomeric esters from the corresponding carboxylic acids was carried out with DCC and DMAP in CH_2Cl_2.[25] The reaction mixture was filtered and purified by flash chromatography on silica gel. Final purification was achieved by HPLC (μ-Porasil, 3 mm × 250 mm or Spherisorb S5W 5 μm, hexanes−ethyl acetate).

Acknowledgment. This work was financially supported by grants from CICYT (PM98-0227) and from the Xunta de Galicia (XUGA-20908B97 and XUGA: PGIDT99PXI20906B). S.K.L. acknowledges the Spanish Ministry for Education and Science for a postdoctoral research grant. M.J.F. thanks the Xunta de Galicia for a grant.

Supporting Information Available: Experimental data (HPLC, NMR, MS, etc.) relative to compounds **6a,b**, **7a,b**, **9a,b**, **11a,b**, **12a,b**, **13a,b**, **14a,b**, **15a,b**, **16a,b**, **30a,b**, **17a,b**, **18a,b**, **19a,b**, **21a,b**, **25a,b**, **31a,b**, **32a,b**, **33a**, **34a**, **35a,b**, **36a,b**, **37**, **37a**, **38a,b**, **39a**, **40a**, **6c,d**, **42**, **42a**, **7c,d**, **9c,d**, **11c,d**, **12c**, **11d**, **14c,d**, **30c,d**, **17c,d**, **19c,d**, **21c,d**, **31c,d**, **25c,d**, **43**, **6e**, **12e**, **19e**, **44**, **6f**, **12f**, **19f**, **45**, **6g**, **12g**, and **19g**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9916838

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